Great expectations of IVF patients: the role of gender, dispositional optimism and shared IVF prognoses

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Abstract

Study question: What success rates do male and female IVF patients expect? What determines patients' expectations? Might patients reconsider their expectations after receiving their individual IVF prognosis and does receiving their prognosis trigger anxious reactions?

Summary answer: Female and male IVF patients have unrealistic high expectations which are positively associated with their dispositional optimism, and which are only reconsidered by patients receiving a less than average IVF prognosis, the latter leading to more anxious reactions in females.

What is known already: Female patients undergoing IVF are known to have unrealistic expectations of the success of their own IVF cycle. The available evidence suggests women expect above average performance of their fertility clinic and (family) reproductive systems. The association of gender and personality trait dispositional optimism, with expectations of IVF success and the impact of providing couples with their IVF prognosis has not been studied previously.

Study design, size, duration: A total of 148 partnered individuals participated in this prospective survey at two separate points in treatment: following oocyte aspiration (T1) and embryo transfer (T2) (2019-2020, participation rate=85%). At the time of embryo transfer, gynaecologists provided couples with their IVF prognosis, calculated with the Adapted van Loendersloot model. Women and their male partners completed questionnaires independently and immediately following oocyte aspiration and embryo transfer.

Participants/materials, setting, methods: Dispositional optimism ('LOT-R' questionnaire) and expectations of IVF success (numerical rating scale) were assessed in eligible couples commencing a 2^{nd}-6^{th} IVF cycle on T1. Expectations of IVF success and anxiety ('Spielberger State-Anxiety Inventory') were (re)assessed on T2. The inter-partner correlation of expectations of IVF success was examined. Linear mixed models examined hypothesized determinants of expectations of IVF success (T1) and explored (determinants of) whether participants reconsidered their expectations after receiving their IVF prognosis (T1-T2) and whether couple's IVF prognosis was associated with anxious reactions (T2).

Main results and role of chance: The mean of the IVF success rates expected by patients immediately after oocyte aspiration was 59.1% (±20.0), irrespective of gender (p=0.077). Partners expectations of IVF success were moderately correlated (r=0.483; p<0.001). Expectations of IVF success were positively associated with the participant's dispositional optimism (p<0.001), but were not associated with their partner's dispositional optimism, women's age and their previous (un)successful IVF experiences. Gynaecologists gave couples their calculated IVF prognosis ranging from 4.8 to 69.2% (mean=30.9%) at the time of embryo transfer. Gender did not influence whether participants reconsidered their expectations after receiving their prognosis. In contrast to the subgroup (n=78), who received at least an average IVF prognosis and that did not reconsider their expectations of IVF success, the subgroup (n=70) receiving a below average IVF prognosis lowered their expectations of IVF success (interaction effect: p<0.001) from 55% to 46%. A below average IVF prognosis was associated with anxious reactions in women but not in men (interaction effect: p=0.011).

Limitations, reasons for caution: The study design and sample size were more optimal for examining hypothesised determinants of patient's expectations of IVF success than for studying the impact of sharing prognoses with patients. Whether (reconsidering) expectations influences IVF discontinuation rates and achieved live birth rates has yet to be followed-up.

Wider implications of the findings: Clinics are advised to offer patients the opportunity of receiving their IVF prognosis. Providing prognoses is in line with patient preferences and tempers the unrealistic high expectations of (fe)males with a less than average prognosis. A sensitive communication style is indicated, as lower prognoses are associated to anxious reactions in women, which do not exceed previous observations.

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INTRODUCTION:

The average success rate of an in vitro fertilisation (IVF) cycle is about one in three (ESHRE-EIM-Consortium, et al., 2020) and most female fertility patients know that average success rates are below 40% (Birenbaum-Carmeli and Dirnfeld, 2008, Maheshwari, et al., 2008). When it relates to their own IVF cycle, female patients, however, expect a success rate of no less than one in two, despite recalling their physician to have given them a success rate of around one in three (Boivin and Takefman, 1995, Miron-Shatz, et al., 2020). The discordance between female patient's knowledge of average IVF success rates and their high expectations from their own cycle seems driven by their desire to achieve success and their decision to continue IVF (Croyle and Cooper, 1983, Festinger, 1957, Harmon-Jones and Mills, 1999). In response to open-ended questions, female patients shared that they expect an above average performance of their fertility clinic and (family) reproductive systems (de Groot, et al., 2016, Miron-Shatz, et al., 2020). To the best of our knowledge, expectations of male patients from their own IVF cycle and the effect of partners on each other's expectations (i.e. inter-partner correlation) have yet to be studied. Insight into IVF experiences and (personality) characteristics driving patient expectations of IVF success is limited.

This study hypothesized that expectations of IVF success would be negatively associated with the number of previous unsuccessful embryo transfers and positively associated with having achieved a live birth with IVF treatment. Given female members of the general public had lower expectations than males (Adashi, et al., 2000, 79 Stoebel-Richter, et al., 2012), a negative association with expectations of IVF success was hypothesized for female gender. A negative association with expectations of IVF success was also hypothesized for female age as female patients know that average IVF success rates depend on age (Maheshwari, et al., 2008, Swift and Liu, 2014). A positive association was hypothesized between expectations of IVF success and patient and partner 'dispositional optimism', the relatively stable generalized expectation that positive outcomes will occur across important life domains (Scheier and Carver, 2018). The personality trait dispositional optimism proved to be associated with expecting therapeutic benefit in cancer patients (Jansen, et al., 2016) and with better long term health expectations in patients with acute coronary disease (Bekke-Hansen, et al., 2014).

Fertility clinic staff reported complexity in treating patients with unrealistic expectations despite being informed about average success rates (Boivin, et al., 2017, van den Boogaard, et al., 2011). University student's knowledge about average IVF success rates could be improved by providing an information brochure (Wojcieszek and Thompson, 2013) but strategies for improving patient expectations of their own cycle had yet to be developed. Patients and professionals have both advocated the value of informing patients of their IVF prognosis (i.e. chance of IVF success calculated for a specific couple)(Dancet, et al., 2011, van Loendersloot, et al., 2013). Several performant prognostic models have recently been published but their impact on clinical practice has yet to be studied (Ratna, et al., 2020). It would be interesting to explore the impact of providing a less than average IVF prognosis on expectations of IVF success in male and female patients. In addition, finding out whether receiving a less than average IVF prognosis causes psychological reactions in male and female patients would be of interest as IVF patients had higher levels of distress on days on which they received negative medical feedback (e.g. quantity or quality of oocytes or embryos) (Boivin, 2000, Boivin, 2019).

The aim of this study was to examine both male and female expectations of IVF success, its inter-partner correlation, and potential determinants (e.g. dispositional optimism). In addition, this study explored the impact of providing women and men with a less than average IVF prognosis on their expectations of IVF success and on their psychological reactions.

MATERIAL & METHODS

Design, setting

A prospective cohort study was conducted between March 2019 and September 2020 at the tertiary fertility clinic of the University hospital of Leuven (Belgium).

Ethical approval

Approval was obtained from the medical ethics committee of the Leuven University and the Leuven University Hospital (s61837).

Sample

Eligible heterosexual couples starting a 2nd - 6th IVF cycle (with or without ICSI, with own fresh gametes, without Pre-implantation Genetic testing) after at least one previous IVF cycle with the same partner at the recruiting clinic. Couples starting their first IVF cycle were not eligible as this study relied on a prognostic model taking account of whether fertilisation occurred in the previous IVF cycle (Devroe, et al., 2020). Couples initially recruited but not having an embryo transfer (i.e. due to failed fertilisation, no suitable embryo or the last-minute decision to freeze all embryos due to the risk of ovarian hyper stimulation syndrome) or completing <50% of the questionnaires were excluded. The a priori defined sample size of 70 female and 70 male partners was calculated to have more than 10 participants of each gender for each of the six factors for which we wanted to examine the association with expectations of IVF success (Kleinbaum, et al., 1988).

Recruitment, data-collection and study procedures

Table I displays the study procedures and their timing. On the day of their oocyte aspiration, eligible couples were invited to participate in the study by their reproductive medicine midwife. Interested couples were thoroughly informed by the researcher and were asked to confirm informed consent in writing. Coded paper pencil questionnaires were disseminated among women and their partners to be completed immediately following oocyte aspiration (T1) and again following fresh embryo transfer (T2). Partners were asked to complete their questionnaire separately, each taking approximately five minutes. In contrast to the mean clinic success rate of one in three given prior to IVF, gynaecologists provided participants with their IVF prognosis (i.e. chance of IVF Live birth per oocyte aspiration calculated for a specific couple) in written format and discussed it with them at the time of embryo transfer. In line with patient preference, this written individualized information included an image of the transferred embryo(s)(Bladh Blomquis, et al., 2017). In line with standard clinical practice, it also included the (mean) 1-4 star quality rating of the transferred embryo(s) (i.e. based on the number of cells, their symmetry in size and degree of fragmentation) and number of cryopreserved embryos.

(insert table I about here)

Variables

Of the cycles studied, several variables were assessed immediately after oocyte aspiration (T1) and/or immediately after embryo transfer (T2) of the studied IVF cycles, as displayed in table I.

Both partner's dispositional optimism was assessed using the reliable Live Orientation Test (LOT-R) (Scheier *et al.* 1994). This questionnaire included 10 questions to be rated on a 5-point-Likert scale and results in a score between 0 and 24 (the higher, the more optimistic, no cut-off value)(Scheier, et al., 1994).

Both partners' expectations of IVF success, i.e. the live birth rate expected per completed IVF cycle including all fresh and frozen embryo transfers from the same episode of ovarian stimulation, was assessed with a single question. This question was to be rated on a numerical rating scale, based on the 'Factors Affecting Fertility Scale' (Bunting and Boivin, 2008), which ranges from 0 to 100 (intervals of 10) and has three explanatory text balloons (Figure 1). If patients did not tick a whole number (e.g. 40 or 50), the distance was measured and registered in more detail (e.g. 43).

(insert figure 1 about here)

Each couple's IVF prognosis, i.e. the live birth rate predicted per completed IVF cycle including all fresh and frozen embryo transfers from the same episode of ovarian stimulation, was generated on the day of embryo transfer with the 'Adapted van Loendersloot model' (Devroe, et al., 2020, van Loendersloot, et al., 2013). This model includes eight clinical variables (i.e. female age, duration of infertility, previous delivery, male infertility, diminished ovarian reserve, endometriosis, basal FSH, number of failed IVF cycles) and five IVF laboratory variables of the previous IVF cycle (i.e. fertilisation) or of the studied IVF cycle (i.e. number of embryos and mean morphological score, presence of 8 cell embryos and morulae on day 3). The Adapted van Loendersloot model proved to be performant for the studied clinic with a c-statistic of 0.74 (0.71 after cross-validation) and a calibration plot practically coinciding with the diagonal (Devroe, et al., 2020).

Both partners' anxiety immediately after embryo transfer and receiving their IVF prognosis was assessed with the 'State-Anxiety Inventory (STAI-state)'. The STAI-state includes twenty questions rated on a 4-point Likert scale and results in a score between 20 and 80 (the higher the score, the more anxious; cut-off for clinical cases in female fertility patients: 50.93; in male fertility patients: 45.70)(Hashemi, et al., 2012, Spielberger and Sydeman, 1994, Zurlo, et al., 2020)

Three variables were extracted from couple's medical records: female age, live birth following IVF (yes/no) and number of unsuccessful embryo transfers.

Finally, both partners assessed the novel individualized information by indicating whether they would recommend it to family and friends having an embryo transfer on a 4-point Likert scale (i.e. definitely not, probably not, probably yes, definitely).

Analysis

Data were imported and analysed in the Statistical Package for Social Science (SPSS version 27.0). Missing data were managed with mean imputation. The clinical, IVF laboratory and other examined characteristics of the sample were described. The previously proven reliability of the LOT-R and STAI-state was re-evaluated for our sample of Belgian fertility patients with Cronbach's alpha statistics (cut-offs: >0.70 reliable; 0.60-0.70 moderately reliable) and Item Total Correlations (ITC; cut-offs: >0.40) (Sixma, et al., 1998).

- ***Expectations of IVF success and inter-partner correlations***

A scatterplot was computed to display (the ranges of) the expectations of IVF success of women and their male partner immediately after oocyte aspiration (T1) and their inter-partner correlation (i.e. Pearson correlation coefficient, r). In addition, whether expectations of IVF success (T1) depended on gender was examined with linear mixed models, taking account of clustering within couples with random intercepts.

- ***Determinants of expectations of IVF success***

Linear mixed models examined the univariable associations between the IVF success expected by participants immediately after oocyte aspiration (T1; dependent variable) and its hypothesized determinants, whilst taking account of clustering within couples with random intercepts (Hendriks, et al., 2017, Kenny, et al., 2020). More specifically, the following six hypothesized determinants were examined: gender, female age, live birth following IVF, number of previous failed embryo transfers, patient's dispositional optimism and partner's dispositional optimism. Hypotheses were only accepted if the p-value was smaller or equal to 0.007 (=0.05/7, taking account of a Bonferroni correction for multiple testing). Whether these associations were affected by gender (i.e. interaction with gender) was also assessed.

- ***IVF prognoses and reconsidering expectations of IVF success***

A linear mixed model including a random intercept for couple-ID explored the association between the appreciation of the individualized information (dependent variable) and receiving a below average IVF prognosis (yes/no) and gender and the interaction between the latter two variables.

Couple's mean IVF prognosis and participant's mean expectation of IVF success immediately after embryo transfer and being informed of their IVF prognosis (T2) were described.

A linear mixed model with expectations of IVF success (two time points) as dependent continuous variable, with the main effect of time point, gender and below average prognosis and their four potential interactions and with random intercepts for couple-ID and subject-ID was fitted. This model allowed exploring whether participants reconsidered their expectations of IVF success (i.e. main effect of time point) and which participants had higher expectations (i.e. main effect of the determinants gender and below average prognosis) and/or reconsidered their expectations (i.e. interaction effect of time point and a determinant). Backward elimination from this model, ensured that only significant main and interaction effects remained in the final model. The direction of the significant main effects on expectations of IVF success were to be appraised by describing the mean expectation of IVF success of the subgroups differing in dichotomous determinant. Significant interaction effects on expectations of IVF success were to be appraised with linear mixed models per subgroup.

- ***IVF prognoses and anxious reactions***

A linear mixed model explored whether anxiety (i.e. dependent variable) was associated with gender and with receiving a below average IVF prognosis (i.e. main effects), and whether gender (m/f) influenced the association between anxiety and the received prognosis (i.e. interaction effect), whilst including a random intercept for couple-ID. The potential interaction effect was to be appraised with linear regressions per subgroup.

RESULTS

Participants

A total of 87 of the 102 invited eligible couples agreed to participate (participation rate = 85%). Reasons for declining study participation were: not willing to participate in any study (n=9) and not interested in receiving their IVF prognosis (n=6). Thirteen couples were excluded for the following reasons: failed fertilisation (n=6), no suitable embryo for transfer (n=2), freeze all due to risk over ovarian hyper stimulation syndrome (n=1) and <50% completion of questionnaires (n=4). The following missing data was imputed (i.e. replaced by the mean) for a very small minority of couples: (i) male partner's questionnaires from the day of embryo transfer (T2; n=3) and both partner's expectations of IVF success immediately after the embryo transfer (T2; n=1). The characteristics of the 74 finally included couples are summarized in Table II.

(insert table II about here)

Regarding the clinical variables of this cohort, the mean female and male age were respectively 33.8 (±4.4) and 36.1 (±5.0) years of age. About a third of the couples had a previous delivery (31.1%). The mean duration of infertility was 3.2 (±1.6) years and participating couples previously experienced on average 1.57 (±1.0) failed IVF cycles. About half of the couples had a male infertility diagnosis (52.7%). A minority of the couples had a diagnosis of diminished ovarian reserve (4.1%) and one in five had a laparoscopic diagnosis of stage III or IV endometriosis (20.3%). The mean basal FSH (IU/ml) was 8.5 (±6.4). Regarding the IVF laboratory variables, for the vast majority fertilization had occurred in the previous cycle (94.6%). The mean number of embryos after oocyte retrieval was 5.6 (±3.0) and the mean morphological score on day three was 2.6 (on a scale of 1 to 4; the lower, the better). On day three a majority had at least one eight-cell embryo (70.3%). Having a morula on day three was very uncommon (1.4%). Regarding the additional variables for which the association with expectations of IVF success (T1) was examined, about one in five couples previously delivered an IVF child (18.9%) and the mean number of previous failed embryo transfers was 2.39 (±2.0). The mean level of dispositional optimism of women and men was, respectively: 14.52 (±4.6) and 15.3 (±3.3)(p=0.21).

Reliability of the questionnaires

The reliability of both questionnaires was confirmed in our sample of Belgian fertility patients. More specifically, the Cronbach's Alpha coefficients of the LOT-R and STAI-state questionnaires were 0.81 and 0.94 respectively and all item total correlations were larger than 0.4.

Expectations of IVF success and inter-partner correlations

The vast majority of patients (88.5%) expected their IVF success rate to be more than one in three immediately after oocyte aspiration (T1). On average, patients expected an IVF success rate of 59.1% (SD= 20.0; range= 8-100%) and this did not depend on gender (p=0.077). The scatterplot in figure 2 displays a moderate inter-partner correlation (r=0.483; p<0.001).

(insert Figure 2 about here)

Determinants of expectations of IVF success

Table III summarizes the findings of the linear mixed model analyses examining the associations between expectations of IVF success immediately after oocyte aspiration (T1) and each of its six hypothesized determinants. None of the hypothesized determinants of expectations of IVF success interacted with gender ($p \geqslant 0.50$). Only one of the six hypotheses was accepted: patient's own level of dispositional optimism was significantly associated with their expectations of IVF success immediately after oocyte aspiration (p<0.001). Participant's expectations of IVF success was not associated with their gender, female age, (un)successful IVF experiences and their partner's dispositional optimism.

(insert table III about here)

IVF prognoses and reconsideration of expectations of IVF success

The vast majority of participants (92%) would recommend the individualised information including the IVF prognosis to family and friends. The appreciation of the individualised information was not associated with gender (p=0.412), with receiving a below average IVF prognosis (p=0.063) and these two factors did not interact (p=0.879).

The mean IVF prognosis of couples was 30.9% ($\pm$16.8; range=4.8-69.2%). The mean expectation of IVF success of participants immediately after embryo transfer and receiving their IVF prognosis (T2) of 54.5% (SD= 23.6; range= 0-100%) was almost twice as high.

Gender did not appear to influence expectations of IVF success (main effect: p=0.085) nor whether participants reconsidered their expectations after receiving their IVF prognosis (i.e. interaction between gender and time point; p=0.237). 'Below average IVF prognosis' (<30.9%) affected expectations of IVF success

(p<0.001) and whether participants reconsidered their expectations after receiving their IVF prognosis (p<0.001). The full model, including all three potential determinants and their interactions, and backward elimination did not identify additional significant main or interaction effects. The final model included below average IVF prognosis (p<0.001), time point (p<0.001) and the interaction between time point and below average IVF prognosis (p<0.001). Expectations of IVF success (T1&T2) was lower in participants with a below average IVF prognosis compared to participants with at least an average IVF prognosis (50.6 vs. 63.8, on average). The subgroup of 78 participants with at least an average IVF prognosis did not reconsider their expectations of IVF success after receiving their prognosis (p=0.480) whilst those with an below average IVF prognosis (n=70) changed their expectations of IVF success (p<0.001) from a mean of 55% to a mean of 46%. Figure 3 displays the following for the participants with and without a below average IVF prognosis: expectations of IVF success immediately after oocyte aspiration, received IVF prognosis and expectations of IVF success immediately after the embryo transfer and receiving their IVF prognosis.

(insert figure 3 about here)

IVF prognoses and anxious reactions

The model included the main effects of gender (p<0.001) and of below average IVF prognoses (p=0.003) and the interaction effect between below average IVF prognoses and gender (p=0.043). More specifically, females were more anxious than males but only about 15% of both female and male participants scored above the fertility patient and gender specific clinical threshold for state anxiety (Table IV). Women who received a less than average IVF prognosis had more anxious reactions than women with at least an average IVF prognosis (45.3 vs. 37.2; p<0.001) whilst a below average IVF prognosis was not associated with anxious reactions in men (p=0.126). Of note, state anxiety (male, female) immediately after the embryo transfer and receiving individual IVF prognosis was not associated with clinical pregnancy rate (i.e. presence of fetal heart pulsation; n=15/74) from this fresh embryo transfer (p=0.443; p=0.521).

(insert table IV about here)

DISCUSSION

Female and male IVF patients both expect a live birth rate from their completed IVF cycle of around 60%, with partner expectations moderately correlated. Of six hypothesized determinants, only patient's own level of dispositional optimism determined expectations of IVF success. To our knowledge, no previous study explored a strategy to offset patient's unrealistic expectations from their own IVF cycles. This study exploring the impact of sharing personalized IVF prognoses with patients, suggests that only patients who received a less than average IVF prognosis (<31%) lowered their expectations from 55% to 46% (irrespective of gender). Receiving a less than average prognosis was associated with anxious reactions in female participants, but not in their male partners. Males and females, however, rarely scored above the clinical threshold for state-anxiety.

Reflection on the findings

Interestingly, this study shows that male patients have equally high expectations of IVF as previously shown in females (Boivin and Takefman, 1995, Miron-Shatz, et al., 2020) and that expectations of women and men depend on their dispositional optimism. Males and females do not differ either in the limited extent in which they reconsider their expectations after having received a below average IVF prognosis. Females did have higher state anxiety scores than males, as previously reported (Edelmann and Connolly, 2000, Schaller, et al., 2016, Zurlo, et al., 2020), but equally small proportions of males and females (15-16%) scored above the clinical thresholds for state anxiety in fertility patients, as these thresholds are gender specific (Zurlo, et al., 2020). The interesting observation that a below average prognosis was only associated to the anxiety of females and not of males is in line with females being mainly concerned about not achieving pregnancy whilst males are mainly concerned about the health risks for their female partners (Schaller, et al., 2016) and with the fertility specific distress dimension 'need for parenthood' being associated to the state anxiety of females but not of males (Zurlo, et al., 2020). The observed anxious reactions of women with a below average prognosis were in line with those previously reported in women in the active phase of treatment (45.3 vs 40 – 53 on average) (Gabnai-Nagy, et al., 2020, Gürhan, et al., 2009, Karlidere, et al., 2008, Turner, et al., 2013) and more implicit medical feedback (e.g. number of oocytes and embryos) also causes distress (Boivin, 2000, Boivin, 2019). Moreover, no association between anxiety immediately after the embryo transfer and IVF

success was observed in this cohort and compelling evidence on an association between (changes in) state-anxiety during treatment and actual IVF success is missing as prospective studies and meta-analyses thereof are equivocal (Boivin, 2019, Nicoloro-SantaBarbara, et al., 2018, Purewal, et al., 2018).

Strengths & limitations

This prospective cohort study has five important strengths. First, male and female participants both completed questionnaires independently as opposed to only studying female expectations of IVF success (Boivin and Takefman, 1995, Miron-Shatz, et al., 2020). Including men and studying partner-correlations is relevant as men and women have similar psychological reactions to the uncertainty of IVF procedures (Boivin, et al., 1998) and as men contribute to women's treatment decisions (Sol Olafsdottir, et al., 2013). Secondly, our sample is representative of the average fertility population, with an 85% participation rate and with an average predicted prognosis of live birth per completed IVF cycle of 31%, ranging from 5 to 69% (ESHRE-EIM-Consortium, et al., 2020). Thirdly, dispositional optimism (Scheier, et al., 1994) and state-anxiety (Spielberger and Sydeman, 1994) were assessed with reliable standardized questionnaires. In the absence of a standardized tool for assessing expectations of IVF success, we based our novel tool on the reliable Factors Affecting Fertility Scale of Bunting and Boivin (2008). Furthermore, the expectations of IVF success and the IVF prognosis were both clearly defined as the chance of live birth per completed IVF cycle and the provided IVF prognosis was generated by a prognostic model with proven performance for the recruiting clinic (c-statistic= 0.74; (Devroe, et al., 2020). Finally, the holistic scope of our study is demonstrated by the examined determinants ranging from previous IVF experiences to personality characteristics and by exploring the impact of sharing prognoses with patients on both expectations and psychological reactions. This prospective cohort study has limitations too. The restricted sample size and design were appropriate for examining the six hypothesized determinants of expectations of IVF success but only allowed exploring the impact of sharing calculated IVF prognoses with patients. A larger sample size would have allowed examining the impact of more potential determinants on expectations and reconsiderations thereof. A randomized controlled trial (RCT) design rather than a pre-test-post-test design would have disentangled the impact of providing IVF prognoses from the effect of treatment stage and implicit medical feedback on expectations and anxiety. Our complex mixed models that took account of dyadic measurements of expectations and anxiety and of repeated measurements of expectations

were valuable for exploring the impact of gender and of a below average IVF prognosis. Our complex models did not correct for a difference in state anxiety at T1, as we did not assess anxiety at T1 and as oocyte aspiration (T1) and embryo transfer (T2) might affect anxiety differently.

Implications for research

The effect of sharing IVF prognoses suggested by this longitudinal study triggers the design of a randomized controlled trial disentangling the effect of sharing IVF prognoses from the effect of treatment stage (oocyte aspiration vs. embryo transfer) and of more implicit medical feedback (e.g. number of supernumerary embryos for cryopreservation) on the expectations of IVF success and on anxious reactions (Boivin, et al., 1998, Svanberg, et al., 2001).

Another suggestion for further research is to follow up the current or preferably a larger cohort to elicit whether the dispositional optimism of females and males is associated with actual (besides expected) cumulative IVF success rates. Older small-scale studies and several large-scale epidemiological studies from other fields make a strong case that optimism translates into health outcomes, such as coronary heart disease and even mortality (Kim, et al., 2017, Rasmussen, et al., 2009, Scheier and Carver, 2018, Tindle, et al., 2009). In IVF women dispositional optimism, which seemed part of a broader personality constellation, was found to be positively associated with ovarian response (Lancastle and Boivin, 2005), and it was negatively associated with clinical depressive symptoms following IVF failure (Litt, et al., 1992). It seems important for follow-up studies to monitor IVF discontinuation as a behavioural pathway explaining the potential association between dispositional optimism and physical health (Scheier & Carver, 2018) as IVF discontinuation impacts cumulative IVF success rates (Gameiro, et al., 2013). Moreover, examining the hypothesis that receiving a below average IVF prognosis increases IVF discontinuation seems interesting. The currently observed decrease in expectations of IVF success among men and women receiving a less than average IVF prognosis might translate into an increased IVF discontinuation rate, as previous surveys showed that women's low expectations of IVF success were associated with high IVF discontinuation rates (Boivin, et al., ESHRE 2020, Callan, et al., 1988). Surprisingly though, patients shared in interviews that repeated unsuccessful embryo transfers whilst having high (rather than low) expectations led to distress and ultimately to IVF discontinuation (Peddie, et al., 2005).

Furthermore, it would also be interesting to interview couples in-depth on how they process a provided personal IVF prognosis, depending on their health literacy, mathematical skills and beliefs. Interestingly, the expectations of patients with an above average prognosis were not affected and patients with a below average prognosis only slightly reconsidered their expectations after receiving their prognosis (i.e. from 55% to 46%). A small minority of couples (6% of addressed couples) even explicitly opted for denial by choosing not to receive their personal IVF prognosis.

Finally, examining the experience of gynaecologists who communicate IVF prognoses would be interesting as professionals are known to struggle with communicating natural conception prognoses (van den Boogaard, et al., 2011) and bad news (Boivin, et al., 2017). The availability of performant prognostic models (Ratna, et al., 2020) and the written individualized information tested in this study might facilitate communicating IVF prognoses (van den Boogaard, et al., 2011). In this study, prognoses were provided at the time of embryo transfer, when patients are known to request personalized feedback (Bladh Blomquis, et al., 2017, Dancet, et al., 2010, Tuil, et al., 2006) and when the performant Adapted van Loendersloot model, taking account of laboratory variables from that IVF cycle, can be used (Devroe et al, 2020). The model of McLernon and colleagues is complementary to the currently used model and can be used prior to the start of IVF or in between cycles for providing prognoses for entire multiple cycle IVF trajectories (McLernon, et al., 2016).

Implications for clinical practice

Clinics are advised to offer patients the opportunity of receiving their personal IVF prognosis from the very first to their very last contact with patients, as it tempers the unrealistic expectations of patients with a below average prognosis. Offering patients their prognosis is patient-centred as it gives voice to patient's request for personalized information (Bladh Blomquis, et al., 2017, Dancet, et al., 2010, Tuil, et al., 2006) and as practically all currently studied patients would advise family and friends to ask for their personal IVF prognosis. The observed association between having received a below average prognosis and state anxiety should not hold clinics back from sharing IVF prognoses but importantly should encourage clinics to adopt a sensitive communication style whilst providing prognoses.

Data availability statement: The data underlying this article will be shared on reasonable request to the corresponding author.

Contributors: JD, KP, TMD, JV and EAFD contributed substantially to the conception and design of this study. JD and KP made an essential effort for the acquisition of the data. JD, AL and EAFD analysed the data and involved JB in the interpreted of the data. JD and EAFD prepared this manuscript and KP, TD, JB, AL and JV revised the intellectual content critically, approved the final manuscript and agreed to be accountable for all aspects of the work.

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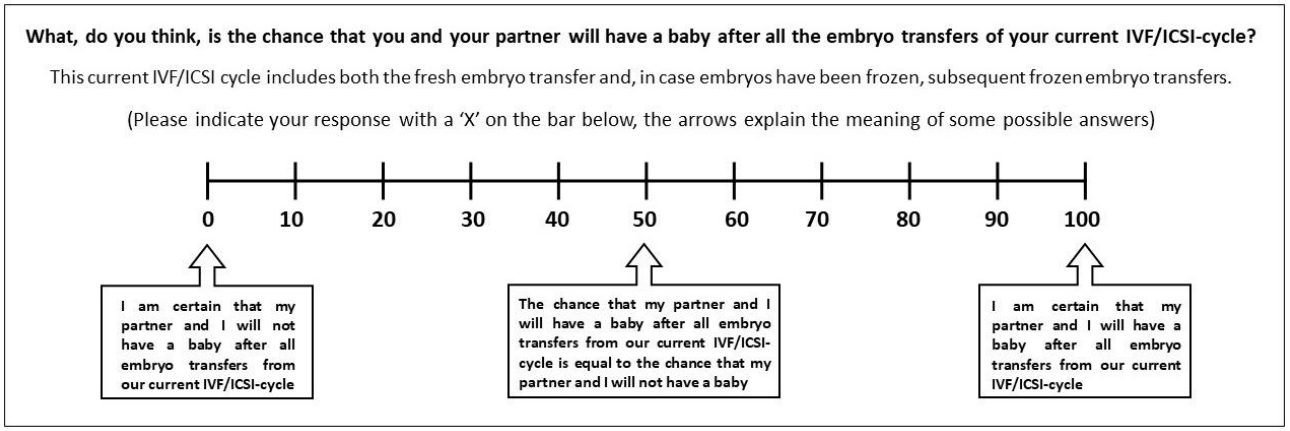
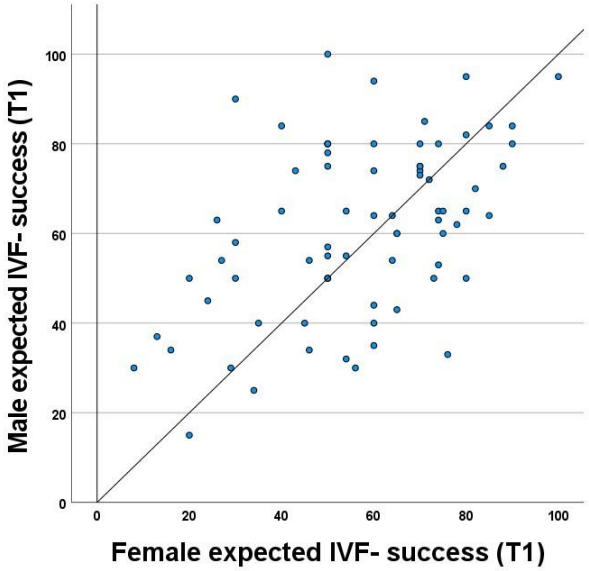


Figure 1: Question used to assess the expectations of IVF success



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414 **Figure 2: Scatterplot of female vs. male partner's expectations of IVF success (T1)**

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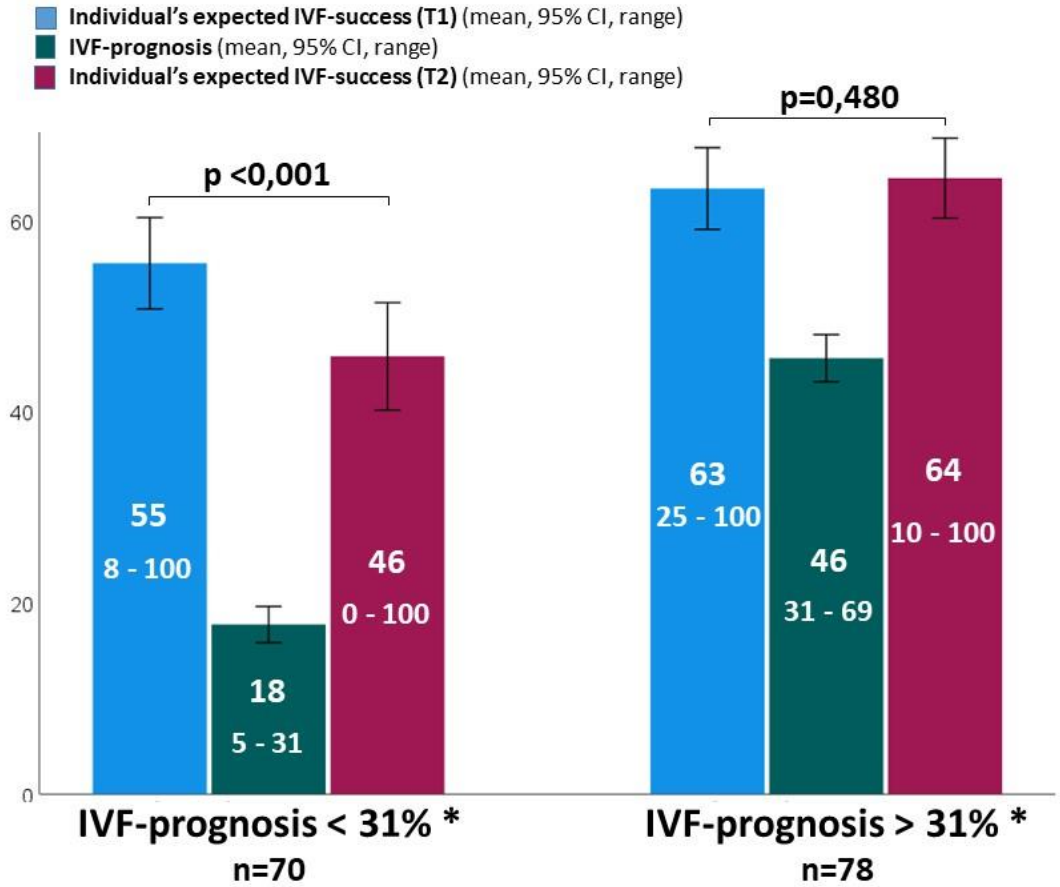

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417 **Figure 3: Individual's reconsideration of expectations of IVF success prior to and after receiving their IVF**
418 **prognosis at the time of embryo transfer**
419 Legend: *31% is the mean IVF prognosis of this cohort

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Table I: Study procedures, variables and tools according to their timing		
Immediately after oocyte aspiration **(T1)**	At the time of fresh embryo transfer	Immediately after fresh embryo transfer **(T2)**
• Study information • Each partner signs informed consent form Each partner independently fills out a questionnaire assessing: • Dispositional optimism (LOT-R) • Expectation of IVF success (numerical rating scale with three explanatory text balloons)	Gynaecologist gives couple their IVF prognosis	Each partner independently fills out a questionnaire assessing: • Expectation of IVF success (numerical rating scale with three explanatory text balloons) • Anxiety (STAI-state) • Likelihood of advising the novel feedback sheet (4-point Likert scale)

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Table II: Characteristics of the 74 participating couples	
Variables presented purely to describe the sample	
Age men (years; mean, SD)	36.1 (±5.0)
Female infertility (n/N; %)	46 (62.2%)
Clinical variables taken into account in the IVF prognosis	
Age women (years; mean, SD)	33.8 (±4.4)
Previous delivery (n/N; %)	23/74 (31.1%)
Failed IVF cycles (№; mean, SD)	1.57 (±1.0)
Duration of infertility (years; mean, SD)	3.2 (±1.6)
Male infertility (n/N; %)	39/74 (52.7%)
Diminished ovarian reserve (n/N; %)	3/74 (4.1%)
Endometriosis (n/N; %)	15/74 (20.3%)
Basal FSH (IU/ml; mean, SD)	8.5 (±6.4)
IVF Laboratory variables taken into account in the IVF prognosis	
Fertilization in previous cycle (n/N; %)	70/74 (94.6%)
Embryos in current cycle (№; mean, SD)	5.6 (±3.0)
Mean morphological score of all embryos on day 3 in the current cycle (1-4; mean, SD)	2.6 (±0.8)
Presence of 8-cell embryos on day 3 in current cycle (n/N; %)	52/74 (70.3%)
Presence of Morulae on day 3 in current cycle (n/N; %)	1/74 (1.4%)
Additional variables for which the association with expected IVF success-T1 was examined	
Previous IVF child (n/N; %)	14/74 (18.9%)
Number of previous failed ET (mean, SD)	2.39 (±2.0)
Dispositional optimism women* (mean; SD)	14.52 (±4.6)
Dispositional optimism men* (mean; SD)	15.3 (±3.3)
Legend: *Men and their female partner did not differ significantly in their level of dispositional optimism (p=0.21) Abbreviations: IVF: in vitro fertilisation LBR: live birth rate	

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Table III: Findings on the hypothesized determinants of individual's expectations of IVF success immediately after oocyte aspiration			
Hypothesized determinants	**Univariable association**		**Interaction with gender**
	Estimate (95% confidence interval)	**p-value**	**p-value**
Female gender	-4.203 (-8.875; 0.470)	0.077	Not applicable
Female age	-0.674 (-1.568; 0.221)	0.138	0.738
Having an IVF child	7.919 (-1.993; 17.837)	0.116	0.679
Number of unsuccessful ETs	0.845 (-1.105; 2.795)	0.391	0.891
Dispositional optimism	1.491 (0.778; 2.205)	<0.001*	0.500
Dispositional optimism partner	-0.298 (-1.046; 0.449)	0.431	0.858
*Significant compared to the Bonferroni corrected threshold of 0.007			

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Table IV. State-anxiety immediately after receiving their IVF prognosis at the time of embryo transfer		
	Proportion scoring higher than gender specific cut-offs* (%)	Mean anxiety (SD)
Women (entire group)	12/74 (16.2%)	41.5 (±10.6)
- Having received a below average prognosis	9/35 (25.7%)	45.3(±10.4)
- Having received at least an average prognosis	3/39 (7.7%)	37.2(±9.3)
Men (entire group)	11/74 (15.0%)	37.0 (±8.9)
- Having received a below average prognosis	7/35 (20.0%)	38.5(±10.1)
- Having received at least an average prognosis	4/39 (10.3%)	35.3(±7.0)
* Gender specific cut-off for State anxiety scores to define clinical cases in fertility patients: female 50.93; males 45.70 (Zurlo et al, 2020)		

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References

Bekke-Hansen S, Weinman J, Thastum M, Thygesen K, Zachariae R. Psycho-social factors are important for the perception of disease in patients with acute coronary disease. *Dan Med J* 2014;61: A4885.

Birenbaum-Carmeli D, Dirnfeld M. In vitro fertilisation policy in Israel and women's perspectives: the more the better? *Reproductive health matters* 2008;16: 182-191.

Bladh Blomquis A, Samir R, Engström A, Nilsson S, Lind A, Westlander G, Larsson S, Hardarson T, Hreinsson J. Patients experience of viewing time-lapse sequences: A prospective survey study. *Gynecology and Reproductive Endocrinology* 2017;1: 1-6.

Boivin J. Patient-staff communication and its effect on reactions to treatment and

treatment failure. *Proceedings of Social Science Research on Childlessness in a Global Perspectiv* 2000.

Boivin J. How does stress, depression and anxiety affect patients undergoing treatment? *Curr Opin Obstet Gynecol* 2019;31: 195-199.

Boivin J, Andersson L, Skoog-Svanberg A, Hjelmstedt A, Collins A, Bergh T. Psychological reactions during in-vitro fertilization: similar response pattern in husbands and wives. *Hum Reprod* 1998;13: 3262-3267.

Boivin J, Bunting L, Koert E, ieng U C, Verhaak C. Perceived challenges of working in a fertility clinic: a qualitative analysis of work stressors and difficulties working with patients. *Human Reproduction* 2017;32: 403-408.

Boivin J, Ockhuijsen H, Morey R, van den Hoogen A, Domar A, Macklon N. The impact of pre-treatment optimism on emotional health during and after treatment. *P-461*. ESHRE 2020.

Boivin J, Takefman JE. Stress level across stages of in vitro fertilization in subsequently pregnant and nonpregnant women*†. *Fertility and Sterility* 1995;64: 802-810.

Bunting L, Boivin J. Knowledge about infertility risk factors, fertility myths and illusory benefits of healthy habits in young people. *Human Reproduction* 2008;23: 1858-1864.

Callan VJ, Kloske B, Kashima Y, Hennessey JF. Toward understanding women's decisions to continue or stop in vitro fertilization: the role of social, psychological, and background factors. *Journal of in vitro fertilization and embryo transfer : IVF* 1988;5: 363-369.

Croyle RT, Cooper J. Dissonance arousal: Physiological evidence. *Journal of personality and social psychology* 1983;45: 782.

Dancet EA, Nelen WL, Sermeus W, De Leeuw L, Kremer JA, D'Hooghe TM. The patients' perspective on fertility care: a systematic review. *Hum Reprod Update* 2010;16: 467-487.

Dancet EA, Van Empel IW, Rober P, Nelen WL, Kremer JA, D'Hooghe TM. Patient-centred infertility care: a qualitative study to listen to the patient's voice. *Hum Reprod* 2011;26: 827-833.

de Groot M, Dancet E, Repping S, Goddijn M, Stoop D, van der Veen F, Gerrits T. Perceptions of oocyte banking from women intending to circumvent age-related fertility decline. *Acta Obstet Gynecol Scand* 2016;95: 1396-1401.

459 Devroe J, Peeraer K, Verbeke G, Spiessens C, Vriens J, Dancet E. Predicting the chance on live birth per cycle at each step
460 of the IVF journey: external validation and update of the van Loendersloot multivariable prognostic model. *BMJ Open*
461 2020;10: e037289.

462 Edelmann RJ, Connolly KJ. Gender differences in response to infertility and infertility investigations: Real or illusory. *British*
463 *Journal of Health Psychology* 2000;5: 365-375.

464 ESHRE-EIM-Consortium, Wyns C, Bergh C, Calhaz-Jorge C, De Geyter C, Kupka MS, Motrenko T, Rugescu I, Smeenk J,
465 Tandler-Schneider A *et al.* ART in Europe, 2016: results generated from European registries by ESHRE†. *Human*
466 *Reproduction Open* 2020;2020.

467 Festinger L. *A theory of cognitive dissonance*, 1957. Stanford university press.

468 Gabnai-Nagy E, Bugán A, Bodnár B, Papp G, Nagy BE. Association between Emotional State Changes in Infertile Couples
469 and Outcome of Fertility Treatment. *Geburtshilfe und Frauenheilkunde* 2020;80: 200-210.

470 Gameiro S, Verhaak CM, Kremer JA, Boivin J. Why we should talk about compliance with assisted reproductive
471 technologies (ART): a systematic review and meta-analysis of ART compliance rates. *Hum Reprod Update* 2013;19: 124-
472 135.

473 Gürhan N, Akyüz A, Atici D, Kisa S. Association of depression and anxiety with oocyte and sperm numbers and pregnancy
474 outcomes during in vitro fertilization treatment. *Psychol Rep* 2009;104: 796-806.

475 Harmon-Jones EE, Mills JE. Cognitive dissonance: Progress on a pivotal theory in social psychology *Scientific Conferences*
476 *Program, 1997, U Texas, Arlington, TX, US; This volume is based on papers presented at a 2-day conference at the*
477 *University of Texas at Arlington, winter 1997*. 1999. American Psychological Association.

478 Hashemi S, Simbar M, Ramezani-Tehrani F, Shams J, Majd HA. Anxiety and success of in vitro fertilization. *Eur J Obstet*
479 *Gynecol Reprod Biol* 2012;164: 60-64.

480 Hendriks S, Peeraer K, Bos H, Repping S, Dancet EAF. The importance of genetic parenthood for infertile men and women.
481 *Hum Reprod* 2017;32: 2076-2087.

482 Jansen LA, Mahadevan D, Appelbaum PS, Klein WM, Weinstein ND, Mori M, Daffé R, Sulmasy DP. Dispositional optimism
483 and therapeutic expectations in early-phase oncology trials. *Cancer* 2016;122: 1238-1246.

484 Karlidere T, Bozkurt A, Ozmenler KN, Ozsahin A, Kucuk T, Yetkin S. The influence of emotional distress on the outcome of
485 in-vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI) treatment among infertile Turkish women. *The*
486 *Israel journal of psychiatry and related sciences* 2008;45: 55-64.

487 Kenny DA, Kashy DA, Cook WL. *Dyadic data analysis*, 2020. Guilford press.

488 Kim ES, Hagan KA, Grodstein F, DeMeo DL, De Vivo I, Kubzansky LD. Optimism and Cause-Specific Mortality: A Prospective
489 Cohort Study. *American journal of epidemiology* 2017;185: 21-29.

490 Kleinbaum DG, Kupper LL, Muller KE. *Applied Regression Analysis and Other Multivariate Methods: Student's Partial*
491 *Solutions Manual*, 1988. PWS-Kent.

492 Lancastle D, Boivin J. Dispositional optimism, trait anxiety, and coping: unique or shared effects on biological response to
493 fertility treatment? *Health psychology : official journal of the Division of Health Psychology, American Psychological*
494 *Association* 2005;24: 171-178.

Litt MD, Tennen H, Affleck G, Klock S. Coping and cognitive factors in adaptation to in vitro fertilization failure. *Journal of behavioral medicine* 1992;15: 171-187.

Maheshwari A, Porter M, Shetty A, Bhattacharya S. Women's awareness and perceptions of delay in childbearing. *Fertil Steril* 2008;90: 1036-1042.

McLernon DJ, Steyerberg EW, Te Velde ER, Lee AJ, Bhattacharya S. Predicting the chances of a live birth after one or more complete cycles of in vitro fertilisation: population based study of linked cycle data from 113 873 women. *BMJ (Clinical research ed)* 2016;355: i5735.

Miron-Shatz T, Holzer H, Revel A, Weissman A, Tarashandegan D, Hurwitz A, Gal M, Ben-chetrit A, Weintraub A, Ravhon A *et al.* 'Luckily, I don't believe in statistics': survey of women's understanding of chance of success with futile fertility treatments. *Reproductive BioMedicine Online* 2020.

Nicoloro-SantaBarbara J, Busso C, Moyer A, Lobel M. Just relax and you'll get pregnant? Meta-analysis examining women's emotional distress and the outcome of assisted reproductive technology. *Social science & medicine (1982)* 2018;213: 54-62.

Peddie VL, van Teijlingen E, Bhattacharya S. A qualitative study of women's decision-making at the end of IVF treatment. *Hum Reprod* 2005;20: 1944-1951.

Purewal S, Chapman SCE, van den Akker OBA. Depression and state anxiety scores during assisted reproductive treatment are associated with outcome: a meta-analysis. *Reproductive BioMedicine Online* 2018;36: 646-657.

Rasmussen HN, Scheier MF, Greenhouse JB. Optimism and physical health: a meta-analytic review. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2009;37: 239-256.

Ratna MB, Bhattacharya S, Abdulrahim B, McLernon DJ. A systematic review of the quality of clinical prediction models in in vitro fertilisation. *Hum Reprod* 2020;35: 100-116.

Schaller MA, Griesinger G, Banz-Jansen C. Women show a higher level of anxiety during IVF treatment than men and hold different concerns: a cohort study. *Archives of gynecology and obstetrics* 2016;293: 1137-1145.

Scheier MF, Carver CS. Dispositional optimism and physical health: A long look back, a quick look forward. *Am Psychol* 2018;73: 1082-1094.

Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *J Pers Soc Psychol* 1994;67: 1063-1078.

Sixma HJ, Kerssens JJ, Campen Cv, Peters L. Quality of care from the patients' perspective: from theoretical concept to a new measuring instrument. *Health expectations* 1998;1: 82-95.

Sol Olafsdottir H, Wikland M, Möller A. Nordic couples' decision-making processes during assisted reproduction treatments. *Sexual & reproductive healthcare : official journal of the Swedish Association of Midwives* 2013;4: 49-55.

Spielberger C, Sydeman S. State Trait Anxiety Inventory and State-Trait Anger Expression Inventory, The Use of Psychological Tests for Treatment Planning and Outcome Assessment. *Edited by Maruish ME Hillsdale, LEA* 1994: 292-321.

Svanberg AS, Boivin J, Hjelmstedt A, Bergh LA, Collins A, Bergh T. The impact of frozen embryos on emotional reactions during in vitro fertilization. *Acta Obstet Gynecol Scand* 2001;80: 1110-1114.

Swift BE, Liu KE. The Effect of Age, Ethnicity, and Level of Education on Fertility Awareness and Duration of Infertility. *Journal of Obstetrics and Gynaecology Canada* 2014;36: 990-996.

Tindle HA, Chang YF, Kuller LH, Manson JE, Robinson JG, Rosal MC, Siegle GJ, Matthews KA. Optimism, cynical hostility, and incident coronary heart disease and mortality in the Women's Health Initiative. *Circulation* 2009;120: 656-662.

Tuil WS, ten Hoopen AJ, Braat DD, de Vries Robbé PF, Kremer JA. Patient-centred care: using online personal medical records in IVF practice. *Hum Reprod* 2006;21: 2955-2959.

Turner K, Reynolds-May MF, Zitek EM, Tisdale RL, Carlisle AB, Westphal LM. Stress and anxiety scores in first and repeat IVF cycles: a pilot study. *PLoS One* 2013;8: e63743.

van den Boogaard NM, van den Boogaard E, Bokslag A, van Zwieten MCB, Hompes PGA, Bhattacharya S, Nelen W, van der Veen F, Mol BWJ. Patients' and professionals' barriers and facilitators of tailored expectant management in subfertile couples with a good prognosis of a natural conception. *Human Reproduction* 2011;26: 2122-2128.

van Loendersloot LL, van Wely M, Repping S, Bossuyt PM, van der Veen F. Individualized decision-making in IVF: calculating the chances of pregnancy. *Hum Reprod* 2013;28: 2972-2980.

Wojcieszek AM, Thompson R. Conceiving of change: a brief intervention increases young adults' knowledge of fertility and the effectiveness of in vitro fertilization. *Fertil Steril* 2013;100: 523-529.

Zurlo MC, Cattaneo Della Volta MF, Vallone F. Re-examining the Role of Coping Strategies in the Associations Between Infertility-Related Stress Dimensions and State-Anxiety: Implications for Clinical Interventions With Infertile Couples. *Frontiers in psychology* 2020;11: 614887-614887.

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