

Predictors for the Early Termination of a Psychological Intervention During Treatment with Assisted Reproductive Technologies

Prädiktoren für das vorzeitige Beenden einer psychologischen Intervention während einer reproduktionsmedizinischen Behandlung



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psychosocial intervention, ART, drop-out predictors, APIM model, risk score for early drop out

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ABSTRACT

Introduction Assisted reproductive technologies are typically perceived by couples as being an emotional burden. The objective of the study “Positive Ausrichtung bei unerfülltem Kinderwunsch” [Positive adjustment in infertility] (PACI) is to examine the efficacy and acceptance of a smartphone-supported psychosocial intervention during infertility treatment. In this investigation, the early drop-out of study subjects from the study is of primary interest. The objective of the investigation was to find predictors for ending a psychological intervention prematurely.

Materials and Methods There are data available from an eight-month randomised, controlled study in which 141 patients and their partners participated. Sociodemographic and fertility-related data were collected at the start of the study. The couples received the ScreenIVF questionnaire at two points in time. As part of a post-evaluation, a survey was conducted on the efficacy of the psychological online intervention. To analyse the data, a dyadic data structure was used in order to determine connections within the study subject couples between the selected stress indicators and the drop-out. In addition, a “risk score” as a possible predictor for the drop-out was tested.

Results The descriptive observation of the sample indicates in this interim assessment that the study subjects recruited are less stressed patient couples. Actor–partner interdependence models indicate statistically significant connections between the stress indicators of anxiety, little social support and helplessness and an early drop-out.

Conclusions The statistically significant effects found in this study with regard to the stress indicators in connection with drop-outs from psychosocial intervention studies indicate that it is advisable to continue to seek measures for people undergoing stressful medical treatments in order to motivate and support them and thus optimally utilise the opportunities of a medical treatment. The number of patients who endure their ART treatment may also increase as a result, which could lead in turn to increased patient satisfaction over the long term (and thus possibly to higher pregnancy rates).

ZUSAMMENFASSUNG

Einleitung Reproduktionsmedizinische Maßnahmen werden von Paaren typischerweise als emotionale Belastung empfunden. Ziel der Studie „Positive Ausrichtung bei unerfülltem Kinderwunsch“ (PAKI) ist es, die Wirksamkeit und Akzeptanz einer Smartphone-gestützten psychosozialen Intervention während einer Kinderwunschbehandlung zu prüfen. In der vorliegenden Untersuchung ist das frühzeitige Ausscheiden der ProbandInnen aus der Studie von primärem Interesse. Ziel der Untersuchung war das Finden von Prädiktoren für das vorzeitige Beenden einer psychologischen Intervention.

Material und Methoden Es liegen Daten einer 8-monatigen randomisierten kontrollierten Studie vor, an der 141 Patientinnen und ihre Partner teilnahmen. Zu Beginn der Studie wurden soziodemografische und fertilitätsbezogene Daten erfasst. Die Paare erhielten zu 2 Zeitpunkten den ScreenIVF-Fragebogen. Im Rahmen einer Post-Evaluation fand eine Befragung zur Wirksamkeit der psychologischen Online-Intervention statt. Zur Analyse der Daten wurde eine dyadische Datenstruktur verwendet, um Zusammenhänge innerhalb der Probandenpaare zwischen den ausgewählten Belastungsindikatoren und dem Drop-out zu ermitteln. Zudem wurde

ein „Risiko-Score“ als möglicher Prädiktor für den Drop-out geprüft.

Ergebnisse Die deskriptive Betrachtung der Stichprobe lässt in dieser Zwischenauswertung erkennen, dass es sich bei den rekrutierten ProbandInnen um wenig belastete Patientenpaare handelt. Actor-Partner-Interdependenz-Modelle weisen auf statistisch signifikante Zusammenhänge zwischen den Belastungsindikatoren Ängstlichkeit, wenig soziale Unterstützung und Hilflosigkeit und einem vorzeitigen Drop-out hin.

Schlussfolgerungen Die in dieser Studie gefundenen statistisch signifikante Effekte bezüglich der Belastungsindikatoren im Zusammenhang zum Drop-out aus psychosozialen Interventionsstudien deuten darauf hin, dass es empfehlenswert ist, weiterhin nach Maßnahmen für Menschen in belastenden medizinischen Behandlungen zu suchen, um sie zu motivieren, zu unterstützen und so die Chancen einer medizinischen Behandlung optimal auszuschöpfen. So kann auch die Zahl der PatientInnen steigen, die ihre ART-Behandlung durchstehen, was langfristig wiederum zu erhöhter PatientInnenzufriedenheit führen könnte (und damit eventuell zu höheren Schwangerschaftsraten).

Introduction

Assisted reproductive technologies (ART) often represent the method of choice for couples struggling with infertility but also often represent a significant emotional burden [1]. Above all, patients generally experience the 14-day waiting time between the embryo transfer and the subsequent pregnancy test (PT) to be particularly emotionally burdensome [2,3]. This is reflected in particular in somewhat increased depression and anxiety values as well as more frequently occurring somatic symptoms, as Wischmann et al. [4] discovered in comparison to the norm sample.

Until recently, it was assumed that IVF patients – at least those whose health insurance companies covered 100% of the costs – continue their treatment until a pregnancy is achieved or they are advised to end the treatment due to an unfavourable medical prognosis (so-called “active censoring”) [5]. According to a current review, however, discontinuing assisted reproductive treatment is triggered primarily through factors relating to the psychological burden (especially personal problems and relationship conflicts) [6]. Nearly 30% of couples drop out of treatment early, primarily for psychological reasons [7–10], although there is a good prognosis for a pregnancy as well as cost assumption by the health insurance company [11].

Studies throughout Europe found rates of between 17 and 70% for drop-outs from assisted reproductive treatment [7,8,12–15]. Early discontinuation of the treatment is associated with 15% lower pregnancy rates [11]. Various studies indicate that a reduction in stress for patients during treatment is useful for increasing adherence to the treatment and thus the prospects of IVF treatment [16,17].

In addition to support for patients to help them achieve their goal of parenthood, an optimized treatment programme also in-

creases the financial benefits for the clinic providing the treatment. This is reflected in increased patient compliance (i.e. patient retention) or increased rates of successful pregnancies [5]. If stressed patients are offered psychosocial support early on, this could lead to increased health-related behaviour during the treatment, along with lower drop-out rates [18]. According to one study [5], preventing early termination of the treatment should therefore be a priority for the entire clinic staff.

Psychological stress during the treatment can be buffered by “positive reappraisal coping intervention” (PRCI) in which the situation is redefined and thus seen in a more positive light [5]. This short-term coping strategy was specially developed for the waiting time following embryo transfer prior to the pregnancy test during infertility treatment [2]. Folkman and Lazarus [19] assumed that positive emotions take on an important role for motivating people to face stressful situations and be able to better cope with stress. With the aid of a psychosocial intervention, it may be possible for a reproductive medicine treatment to be continued, despite the ups and downs, and ideally be successfully completed. In an ideal case, patient satisfaction increases, but so do the chances of a pregnancy.

The PRCI has proven itself so far to be acceptable and practicable for women undergoing infertility treatment [2]. In one study [3], women who read a PRCI card with a positive message twice per day perceived this to be supportive for their coping process in this stressful situation. The patients also considered the positive messages to be helpful in viewing the stressful situation from a more optimistic viewpoint [20]. The effect of PRCI on couples was not examined to date and is currently being investigated within the scope of the PAKI study (“Positive Ausrichtung bei unerfülltem Kinderwunsch” [Positive adjustment in infertility]).

For some samples, including the sample of this PACI study, there are to some extent significantly high rates of study subjects dropping out of psychosocial interventions. In an investigation by de Klerk [21], patients who left a psychosocial intervention study early were compared with those who completed the study. This investigation found no differences between the two groups with regard to the depression and anxiety values which were measured before the IVF treatment. However, it is possible that the women who dropped out early experienced greater stress during the IVF treatment and thus they discontinued the study early.

Another study found significant differences between the various study groups with regard to their drop-out rates [22]. While the intervention group with cognitive-behavioural support had a drop-out rate of 16%, 26% dropped out early from the standardised support in the second intervention group. There was a significantly higher drop-out rate of 60% in the control group treated under routine conditions.

Following on this, it should be clarified which mental stressors increase the probability of early drop-outs and how these can be counteracted. With regard to the drop-out rates, we therefore examined the question: "Can psychological predictors for the early termination of a psychological intervention during assisted reproductive treatment be found?" The objective of the study was *not* to identify predictors for drop-outs from assisted reproductive treatment.

Material and Methods

Sample

The present data from the prospective randomised-controlled pre-post PACI intervention study (RCT) date from the period from August 2017 up to and including April 2018 (interim assessment).

Patient couples who underwent an IVF or ICSI treatment during the above time period in the outpatient infertility unit at the Heidelberg University Hospital of Gynaecology and Obstetrics were invited to take part in the study by the attending physicians.

The inclusion criteria for the sample were consent to participate in the study from IVF and ICSI patients during the above time period, owning a smartphone, and provision of the mobile telephone number. If the partner did not wish to participate, there was an option to be included as an individual person. Exclusion criteria were refusal to participate and/or a lack of German skills and/or lack of a smartphone.

After informed consent was given, computerised randomisation was performed immediately, in pairs, into the intervention group (IG) or the control group (CG). The study participants are pseudonymised by code numbers. The study has two arms and is not blinded for the patients.

Psychological assessment

The validated ScreenIVF questionnaire was selected as an evaluation instrument [18]. This questionnaire is based on a prospective Dutch study [23] whose objective was to document the emotional risk profile of patients during an assisted reproductive technology measure. In this PACI study, the ScreenIVF was used to identify

drop-out predictors and also as a measurement of the effects of the intervention (pre-post effects).

The developers of the ScreenIVF [1,23] postulated five "risk factors": Anxiety, depression, limited social support, helplessness and a lack of acceptance of the situation. The questionnaire has a multiple-choice format with four-point Likert scales. It documents the patients' anxiety with ten items which are based on the Spielberger "State and Trait Anxiety Inventory" [25]. The seven items on depression come from the Becks Depression Inventory [26]. With the Illness Cognition Questionnaire for IVF patients, helplessness is documented with six items and acceptance with six items with regard to fertility [1,27]. The perception of social support is documented using five items from the Inventory for Social Integration [28].

Course of the study

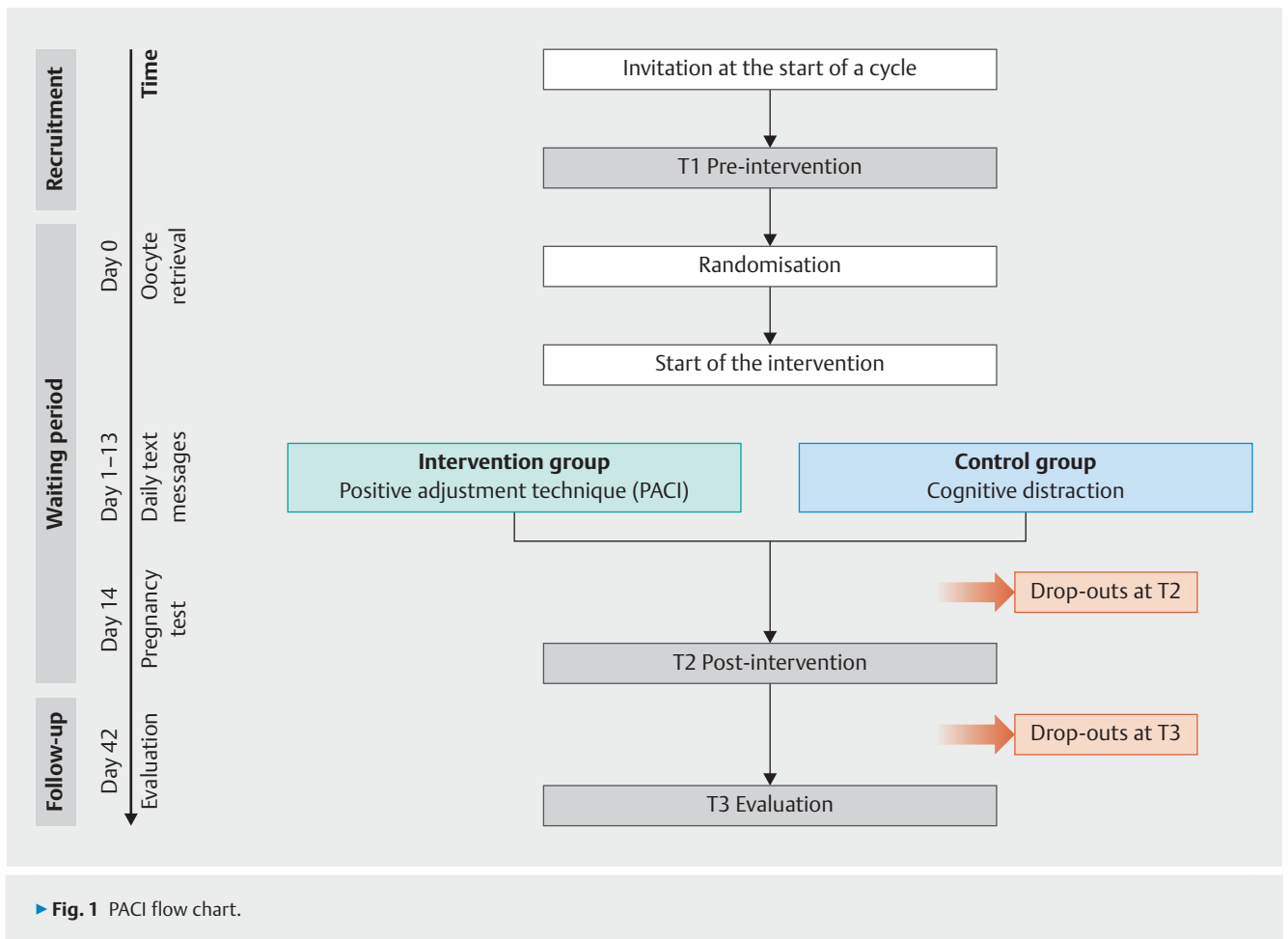
Study subject couples who wished to take part (opt-in method) received information material on the study and a brief introduction to the techniques. During this introduction, the methods (creative distraction for the CG and positive re-evaluation for the IG; see below) were briefly explained. In addition, the participants (both partners) received an informed consent form to be signed. The course of the study comprised three measurement time points (see ► Fig. 1).

At measurement time point 1 (T1: pre-intervention) a paper-and-pencil questionnaire was used to document sociodemographic data (age, sex, education level, occupation, duration of the couple's relationship) and fertility-related data (duration of infertility, number of previous children, duration of the ART treatment, suspected cause of the infertility). The ScreenIVF was filled out at T1 using the paper-and-pencil method and at T2 (post-intervention) online by the participants. At T3 (evaluation), four weeks after the pregnancy test, the study subjects were sent a link to the Unipark online survey platform via SMS. Here, they were asked about the efficacy and practicability of the online intervention (see ► Fig. 1).

If there was no online participation at T2 and T3, the study subjects received a text message with a reminder about the online participation after seven and then after fourteen days in each case. All online data were saved on the Unipark server in pseudonymised form; otherwise data were stored in encrypted form via the Heidelberg University Hospital. The data were evaluated by the Institute of Medical Psychology Heidelberg.

Intervention

After the couples were randomised and the assisted reproductive technology treatment cycle had started, the computer-aided thirteen-day SMS messaging began in parallel. The IG received the "positive adjustment technique" (PACI) described above [2,29]. Starting at the time of the oocyte retrieval, these study subjects received a sentence on their smartphone every midday which was intended to generate a positive attitude, for example "Today I'm doing something good for me" or "I am trying to think about the positive things in life more." By contrast, the CG couples received mental exercises for "creative distraction" on their smartphone every day. For example, one mental exercise involved completing a sequence of numbers.



The study was reviewed and approved by the Ethics Committee of the Medical Faculty of Heidelberg (study S-074/2017). All study details can be viewed at clinicaltrials.org under NCT03118219 and in [29].

Data analysis and statistical evaluation

The sociodemographic and fertility-related data as well as the five scales of the ScreenIVF were initially descriptively analysed in this interim assessment.

An early drop-out is defined as not answering the questionnaire at the second and/or the third measurement time point. It was checked whether specific stress indicators (or the cumulative risk score; see below) could be used as possible predictors for a premature drop-out.

Using the Actor–Partner Interdependence Model (APIM) [30] it was investigated whether there are connections within a dyad between possible predictors and the drop-out (also taking the influence of the partner on the actor into account). In each case, an APIM was calculated at T1 and T2 for the selected stress indicators. Since this involved distinct dyads, a separate equation was included in the path analytic approach for each part of the dyad and an actor effect (a) and a partner effect (p) was calculated in each case [31].

The determination of a risk score as a possible predictor for an early drop-out is derived from [21]: Patients are classified as at-risk if they demonstrate clinically relevant values above the respective cut-off level on the five scales of the ScreenIVF and thus have a greater risk of relevant emotional stress [18]. The score ranges from 0–5 points, whereby 0 means that there is no risk factor, while 5 means that the cut-offs of all five scales are exceeded (see also [24]).

The analysis was performed with the statistics software R, version 3.5.0 [32] and with the lavaan package, version 0.6.1 [33].

Results

Sociodemographic and fertility-related data

In the sample at measurement time point T1 in this interim assessment, there were $n = 141$ subjects, 60 of whom were men (42.55%) and 81 of whom were women (57.45%) (see ► **Table 1**). The age range was between 27 and 51 years ($M = 37.21$; $S = 4.79$).

On average, infertility had lasted for 4.88 years and the medical treatment lasted from 2 months to 9 years ($M = 2.6$ years, $SD = 1.96$) (see ► **Table 1**).

► **Table 1** Sociodemographic data.

	Frequency		Age distribution			
	n	%	M	SD	Min	Max
Sex distribution at T1						
▪ Women	81	57.45	36.62	4.01	27	44
▪ Men	60	42.55	38.04	5.62	28	51
▪ Total	141	100	37.21	4.79	27	51
Fertility-related data in years at T1	n		M	SD	Min	Max
▪ Duration of infertility	138		4.88	3.09	1.00	18
▪ Length of time as a couple	138		9.46	4.83	2.00	19
▪ Duration of fertility treatment	136		2.60	1.96	0.16	9
Does the couple already have children?	n	%				
▪ No	97	70.80				
▪ Yes	40	29.20				

Despite reminders, some patients in the PACI investigation did not respond to the questionnaire link sent via SMS and were thus counted among the drop-outs defined here. At T2, there were still 104 study subjects in the study, which corresponds to a drop-out rate of 26.24% (see ► **Table 2**). At the time of the evaluation (T3), 90 patients were still in the study, which indicates a drop-out rate of 13.46% and this corresponds to a total drop-out of 36.17% from T1 to T3 (see ► **Table 2**).

It was investigated whether there is a difference between men and women with regard to the likelihood of early drop-out. The probability of dropping out at T2 was significantly higher for men than for women ($b = 1.50$, $SE = 0.57$, $z = -2.63$, $p = 0.008$), the odds ratio was 4.50. At T3, a significant difference between women and men was also seen with regard to the probability of a drop-out ($b = 1.21$, $SE = 0.56$, $z = -2.15$, $p = 0.032$): For men, the probability was once again significantly higher and the odds ratio was 3.35.

Descriptive statistics of the stress indicators

Overall, the study subjects did not reach the cut-offs of the scales or the clinically abnormal values, on average, in the case of the selected stress indicators. Thus the mean value of the female study subjects for depression at T1 was $M = 2.23$ ($SD = 2.44$) and in the case of the male study subjects, it was $M = 1.10$ ($SD = 1.74$) (see ► **Table 3**). The cut-off of the short form of the BDI is at four points [26]; a score at or above this value corresponds to a mild depressive syndrome.

For the anxiety score as well (cut-off ≥ 24), the patients were, on average, below the cut-off value at T1 and T2: For women, the mean value at T1 was $M = 20.97$ ($SD = 5.64$) and for men, it was $M = 18.44$ ($SD = 4.63$). For the other stress indicators, the sample also demonstrates unremarkable values, on average (see ► **Table 3**). The study subjects achieved a risk score on average between 0.78 and 1.87 points.

► **Table 2** Sex distribution and drop-out values at T2 and T3.

Drop-out at T2	Frequency		Age distribution				Drop-out			
	n	%	M	SD	Min	Max	Number of drop-out persons T1 to T2	Drop-out in %		
▪ Women	67	64.42	36.19	3.85	27	44	14	17.28		
▪ Men	37	35.58	38.14	5.61	29	51	23	38.33		
▪ Total	104	100	36.89	4.63	27	51	37	26.24		
Drop-out at T3	n	%	M	SD	Min	Max	Number of drop-out persons T1 to T3	Drop-out in %	Number of drop-out persons T2 to T3	Drop-out in %
▪ Women	57	63.33	36.31	3.74	28	44	24	29.63	10	14.93
▪ Men	33	36.67	38.55	5.60	29	51	27	45.00	4	10.81
▪ Total	90	100	37.16	4.63	28	51	51	36.17	14	13.46

► **Table 3** Stress indicators of the study subjects over time, in a gender comparison.

Stress indicator	Sex	Measurement time point	n	M	SD	Min	Max
Depression	f	1	77	2.23	2.44	0	11
		2	67	3.06	3.56	0	14
	m	1	58	1.10	1.74	0	7
		2	37	1.16	1.72	0	7
Anxiety	f	1	75	20.97	5.64	10	33
		2	67	21.91	6.43	11	37
	m	1	57	18.44	4.63	10	30
		2	37	17.78	5.74	10	32
Social support	f	1	78	17.04	3.28	7	20
		2	67	16.78	3.28	9	20
	m	1	60	17.33	3.32	8	20
		2	37	17.73	2.71	11	20
Helplessness	f	1	77	11.58	4.38	6	24
		2	67	12.24	4.33	6	24
	m	1	59	10.00	3.09	6	17
		2	37	9.73	2.95	6	16
Acceptance	f	1	74	14.04	4.05	6	24
		2	67	13.00	4.34	6	24
	m	1	59	16.00	3.35	10	24
		2	37	16.00	4.38	7	24
Risk score	f	1	71	1.38	1.46	0	5
		2	67	1.87	1.67	0	5
	m	1	54	0.81	1.10	0	5
		2	37	0.78	1.42	0	5

Stress indicators within the scope of the actor–partner interdependence model (APIM)

In our interim assessment, a significant actor effect at T1 with regard to anxiety could be found: The higher a man's anxiety level was, the more likely he also was to drop out early ($\beta = 0.41$, $p = 0.032$). In addition, a significant connection between the drop-out of men and women is seen ($\beta = 0.43$, $p = 0.020$) (see ► **Fig. 2**). At T2, significant partner effects could be found: The higher a man's anxiety level was, the greater the likelihood of the woman dropping out early ($\beta = 0.54$, $p = 0.001$). The higher a woman's anxiety level was, the lower the likelihood of a drop-out for the man ($\beta = -0.38$, $p = 0.014$). Here as well, there is a significant connection between the drop-out of men and women overall ($\beta = 0.61$, $p = 0.061$).

A significant connection was seen between the social support experienced by men and the drop-out of the women at T1: The more social support the man perceived, the less likely his partner was to drop out early ($\beta = -0.44$, $p = 0.016$) (see ► **Fig. 3**).

A significant partner effect of the men on the women could be found for the stress indicator of helplessness at T1 ($\beta = -0.57$, $p = 0.036$): If the man indicates increased helplessness, the probability of the woman dropping out early was significantly lower (see ► **Fig. 4**).

No significant actor and partner effects were able to be determined for the cumulative risk score, which is why, for the present sample, it is not suitable as a predictor for an early drop-out.

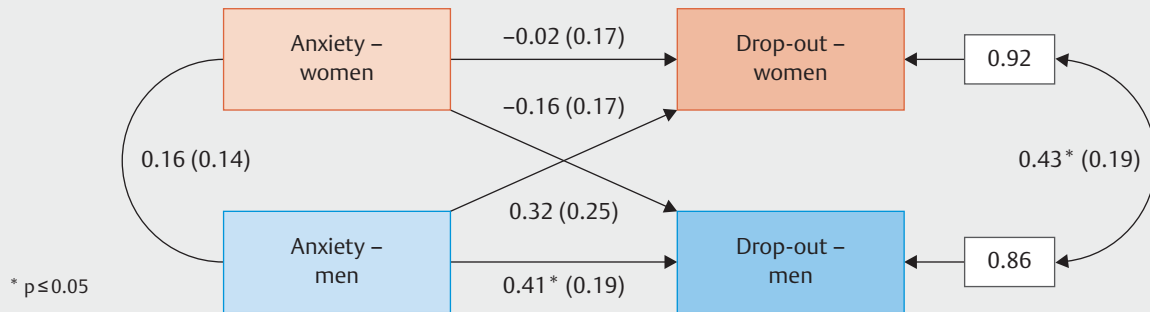
Discussion

The drop-out rate of a total of 36.17% between the first and last measurement time point shows the need to focus on patients' compliance within psychological interventions in clinical studies.

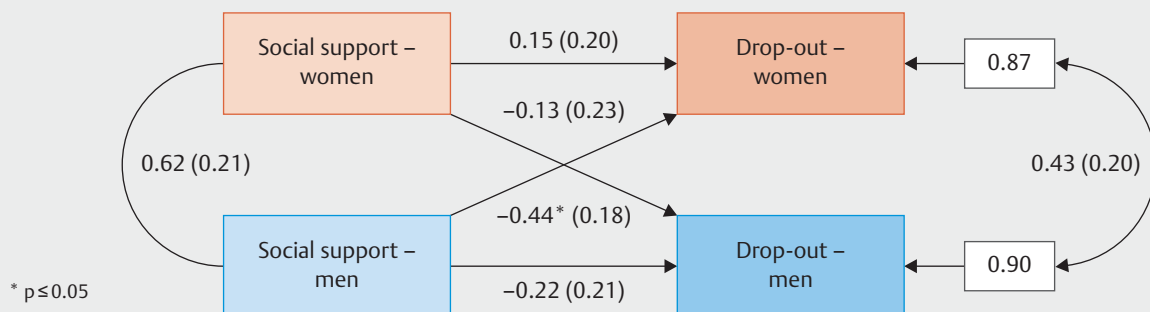
Domar et al. [22] found significantly higher drop-out values in a control group under routine conditions in comparison to a group with cognitive-behavioural interventions. This result allows us to conclude that adherence in studies can be promoted through targeted psychological interventions.

Why do drop-outs take place in the study? Is it primarily the stresses of medical treatment or a lack of efficacy of the psychosocial intervention which the subjects experience? Or is it possibly a combination of the two?

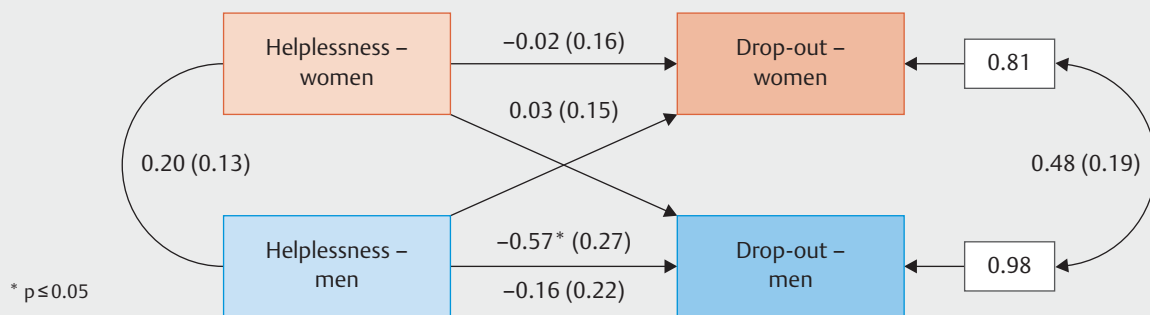
The descriptive observation of these data shows that the sample is, on average, rather non-stressed: In our interim assessment, the study subjects on average do not demonstrate any unusual values with regard to stress indicators. By contrast, other studies were able to show that emotional stressors are the main reasons



► Fig. 2 Actor-partner interdependence model for predictor of anxiety at T1.



► Fig. 3 Actor-partner interdependence model for predictor of social support at T1.



► Fig. 4 Actor-partner interdependence model for predictor of helplessness at T1.

for female study subjects to drop out early from assisted reproductive treatments [7, 14]. The most frequent reasons which were given during an investigation of female patients were “I had enough” (66%), “emotional costs” (64%) and “I could not cope with more treatment” (42%) [10].

Verhaak et al. [18] found no differences in women who dropped out of their study in comparison to those who completed the study. For this, the authors [18] had recorded the result of the pregnancy test as well as the depression and anxiety scores of the

female study subjects. In our investigation, we did not obtain any information about the reason why study subjects drop out earlier. In the future, the reason for an early drop-out should be documented; this would undoubtedly add value to further drop-out analyses.

Certain coping strategies (such as meaningful coping) make it possible for women and men to better endure stress during a treatment [20, 24], while other strategies (such as active-avoidant coping) conversely increase the risk of stress. It is worth investi-

gating whether the positive effects of PACI which were found do not demonstrate an effect just in clinical studies (so-called “efficacy”) but also when patients use the method in “everyday life” without any clinical guidance (so-called “effectiveness”).

The results of our study indicate a significant influence of the partner on a drop-out: Men who indicated more anxiety showed a higher drop-out probability. At T2, we found significant partner effects regarding anxiety: The higher the anxiety values, the greater the likelihood for the partner to drop out of the intervention early. The higher the man’s social support was, the less likely it was that his partner ended the study. By contrast, increased helplessness of the man led to a decreased drop-out risk of the woman. To motivate couples to continue participation in a psychological intervention despite significant emotional stress, fears and needs of the male partner should accordingly be explicitly and actively addressed.

Limitations

In our interim assessment of the PACI study, it was difficult to define a drop-out of the study subjects and differentiate it from a drop-out from the ART treatment (e.g. due to treatment complications, fertilisation failure or non-occurrence of a pregnancy, financial or emotional stress due to ART, switch to a different infertility centre): Documentation as to whether study subjects dropped out only from the clinical intervention study or whether the ART treatment was discontinued at the same time is not available for this investigation.

A portion of the PACI study subjects could not be included after the start of the study. One criterion in this case was embryo transfer that did not take place (e.g. due to “embryonic arrest”). For technical reasons, the telephone number of the study participants could be registered only once and thus participation in the PACI study in a subsequent ART cycle was not possible. The second exclusion criterion was the delayed submission of the informed consent (following egg cell retrieval) which would have allowed participation in the PACI study.

In the PACI study, the recommended “opt-in method” was used for study subject recruitment. By contrast, in an “opt-out method”, all eligible persons are included in the study unless they explicitly state that they do not wish to participate. Junghans et al. [34] discovered that study subjects in the opt-in method have a lower risk (44%) of various medical illnesses than study subjects in the opt-out method (60%). Various study findings show that opt-in study subjects performed better overall with regard to clinical indicators. It is suspected that opt-in study subjects can endure the additional demands of a study better [34, 35]. Overall, the rejection rate of patients with regard to the PACI study can be classified as rather low, according to our interim assessment. However, it may be that, in particular, patients who were less stressed overall registered for the study.

Since the study subject recruitment took place only in one hospital, it remains unclear if the findings can be transferred to couples throughout Germany and Europe and also worldwide. It also remains questionable whether the findings apply to other infertile couples who do not undergo medical treatment at all. Only a certain percentage of couples in Germany undergo diagnostic testing to investigate the reasons for infertility. According to the study by

Wippermann [36], approx. 63% of couples do not undergo any infertility treatment, although they have received a diagnosis for reduced fertility and frequently are fundamentally ready to use ART. Other estimates [37–39] assume that up to 30% of couples do not start ART, despite having an indication and despite (proportional) cost coverage by the health insurance company.

Strengths

The innovative intervention via the smartphone can be considered to be a strength of the PACI study. PRCI was previously sent via positive phrases on paper cards [2] or as a digital file (via e-mail) [5]. The smartphone, which has become an indispensable part of people’s everyday lives nowadays, is a useful medium for receiving a positive message every day and being able to access it at any time, as needed.

Men frequently react in other ways to the diagnosis of infertility than women and the emotional stress can manifest differently [40]. Numerous studies have found that men are also psychologically affected by the diagnosis of infertility (e.g. [41, 42]). However, many studies to date have neglected the emotional influences of fertility problems on men [1, 23]. Many psychological support measures also focus exclusively on women. If the drop-out values for men and women are compared, men in this study have a significantly higher likelihood of dropping out of the psychosocial intervention early. At T2, the men had a risk of ending the study early which was four and a half times as great as that of women, according to the odds ratio. At T3, men still have a nearly three times greater likelihood of a drop-out. Male infertility patients more frequently indicate that they believe they could manage their feelings very well alone [43]. For this reason, men are generally not addressed as the main target group for infertility counselling, although infertility represents a problem for the couple. This phenomenon could be an expression of the fact that, in an ART treatment, men tend to see themselves as an observer (or as the “female patient’s companion”) and women see themselves more as the patient and as the focus of the treatment [43]. The inclusion of the man is therefore a perspective of this investigation which should be assessed positively, because it could also lead to men being able to play a more active part in the reproductive medicine treatment.

Implications for research

Theory and research imply that PACI can have positive effects on the fertility-related quality of life, especially during the phases in which patients experience increased stress and uncertainty (e.g. [44–47]). The PACI program of our study is a “custom-made” intervention for the patients undergoing ART treatment in which all study subjects receive the same support. In the future, it would be of interest to test “tailor-made” interventions, that is, interventions which are individually tailored to study subjects. Many couples presumably feel that text messages are helpful while others prefer optional telephone or chat messages, and yet others do not want to utilise any additional aid at all. There may be a lower drop-out rate during a psychological intervention in the case of couples who receive a tailored intervention than in the case of couples during a general intervention. The different effects of psychosocial face-to-face therapy as compared to online interven-

tions should also be further investigated. Likewise, future research questions should further focus on the different needs and the possibly different effect of PACI (or other psychosocial interventions) on men in comparison to women. From our point of view, the interim assessment of the PACI study shown here clearly indicates that future research in this area should always take the role of the male partner in reproductive medicine into account.

Implications for clinical practice

Certain coping strategies can increase the risk of depression and anxiety [24]. Psychological counselling could be helpful for patients to use supportive coping strategies and not use unfavourable strategies (such as active avoidance strategies, for example). The influence of partner effects on the psychological condition, as proven, for example, by APIM [24] and which, to some extent – particularly for the male partner – was also found in this interim assessment is a reason for orienting the psychosocial fertility counselling in a targeted manner to the couple (*human reproduction takes more than one person*) and offering individual counselling as an exception or only upon an explicit request. Overall, the results of our study indicate that couples receiving reproductive medicine treatment are, from a psychological viewpoint, a less vulnerable group, on average (see also [48]).

Conclusion

The objective of the study was to identify predictors for the early drop-out of study subjects from psychosocial intervention during ART treatment. In this interim assessment, only individual significant effects with regard to the stress indicators in connection with a drop-out were found. Additional psychological interventions for couples undergoing reproductive medicine treatment should be offered in order to support them and thus optimally utilise the opportunities for medical therapy. Over the long term, this can lead to increased patient satisfaction – and possibly also to higher cumulative pregnancy rates through better compliance with regard to the medical treatment [49]. The suggestions for improvement from patients queried in the study by Domar et al. [10] refer to this: An offer of psychological support in written form as well as the presence of specialist psychosocial counsellors were the two most frequently mentioned wishes regarding reproductive medicine, from the retrospective viewpoint of drop-outs. The predominant lack of such a psychosocial offering – also and explicitly to the male partner – may represent an important reason why nearly half of all couples in Germany already leave medical treatment after the second treatment cycle as drop-outs, without achieving a pregnancy, although the health insurance companies generally pay for three cycles (proportionally) [49]. Overall, the role of the male partner in the reproductive medicine treatment should explicitly be taken into more account [36].

Comment

MB, MS, SR, AG, TS, MM, SB, BD and TW have contributed to the design of the study. MS and TW were responsible for obtaining the ethical approval. MS, SR, AG, BD and TW were involved in adapting and compiling the interventions. SR, AG and TS were responsi-

ble for maintaining the recruitment process. MM and SB were responsible for maintaining the technical processes of the intervention. MB was responsible for drafting the manuscript. MS planned the statistical analysis. All authors have read, revised, and approved the final manuscript. This study is financed by intramural funding from the Institute of Medical Psychology and the Department of Gynecological Endocrinology and Fertility Disorders, University Women's Hospital Heidelberg.

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Conflict of Interest

The persons involved in the PACI study do not report any conflicts of interest. The authors alone are responsible for the content and writing of the article.

References

- [1] Verhaak CM, Smeenk JM, van Minnen A et al. A longitudinal, prospective study on emotional adjustment before, during and after consecutive fertility treatment cycles. *Hum Reprod* 2005; 20: 2253–2260
- [2] Lancaster D, Boivin J. A feasibility study of a brief coping intervention (PRCI) for the waiting period before a pregnancy test during fertility treatment. *Hum Reprod* 2008; 23: 2299–2307
- [3] Boivin J, Lancaster D. Medical waiting periods: imminence, emotions and coping. *Womens Health (Lond)* 2010; 6: 59–69
- [4] Wischmann T, Stammer H, Scherg H et al. Psychosocial characteristics of infertile couples: a study by the 'Heidelberg Fertility Consultation Service'. *Hum Reprod* 2001; 16: 1753–1761
- [5] Domar AD, Gross J, Rooney K et al. Exploratory randomized trial on the effect of a brief psychological intervention on emotions, quality of life, discontinuation, and pregnancy rates in in vitro fertilization patients. *Fertil Steril* 2015; 104: 440–451
- [6] Gameiro S, Boivin J, Peronace L et al. Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment. *Hum Reprod Update* 2012; 18: 652–669
- [7] Olivius C, Friden B, Borg G et al. Why do couples discontinue in vitro fertilization treatment? A cohort study. *Fertil Steril* 2004; 81: 258–261
- [8] Rajkhowa M, Mcconnell A, Thomas GE. Reasons for discontinuation of IVF treatment: a questionnaire study. *Hum Reprod* 2006; 21: 358–363
- [9] Brandes M, van der Steen JO, Bokdam SB et al. When and why do subfertile couples discontinue their fertility care? A longitudinal cohort study in a secondary care subfertility population. *Hum Reprod* 2009; 24: 3127–3135
- [10] Domar AD, Smith K, Conboy L et al. A prospective investigation into the reason why insured United States patients drop out of in vitro fertilization treatment. *Fertil Steril* 2010; 94: 1457–1459
- [11] Gameiro S, Verhaak CM, Kremer J et al. Why we should talk about compliance with assisted reproductive technologies (ART): a systematic review and meta-analysis of ART compliance rates. *Hum Reprod Update* 2013; 19: 124–135
- [12] Olivius C, Friden B, Borg G et al. Psychological aspects of discontinuation of in vitro fertilization treatment. *Fertil Steril* 2004; 81: 276
- [13] Schröder AK, Katalinic A, Diedrich K et al. Cumulative pregnancy rates and drop-out rates in a German IVF programme: 4102 cycles in 2130 patients. *RBM Online* 2004; 8: 600–606

- [14] Verberg MFG, Eijkemans MJC, Heijnen EMEQ et al. Why do couples drop-out from IVF treatment? A prospective cohort study. *Hum Reprod* 2008; 23: 2050–2055
- [15] Verhagen TEM, Dumoulin JCM, Evers JLH et al. What is the most accurate estimate of pregnancy rates in IVF drop outs? *Hum Reprod* 2008; 23: 1793–1799
- [16] Boivin J, Domar A, Shapiro D et al. Tackling burden in ART: an integrated approach for medical staff. *Hum Reprod* 2012; 27: 941–950
- [17] Gameiro S, Boivin J, Domar A. Optimal IVF in 2020 should reduce treatment burden and enhance care delivery for patients and staff. *Fertil Steril* 2013; 100: 302–394
- [18] Verhaak CM, Lintsen AME, Evers AWM et al. Who is at risk of emotional problems and how do you know? Screening of women going for IVF treatment. *Hum Reprod* 2010; 25: 1234–1240
- [19] Folkman S, Lazarus RS. The relationship between coping and emotion: implications for theory and research. *Soc Sci Med* 1988; 26: 309–317
- [20] Ockhuijsen HDL, van den Hoogen A, Eijkemans MJC et al. Clarifying the benefits of the positive reappraisal coping intervention for women waiting for the outcome of IVF. *Human Reprod* 2014; 29: 2712–2718
- [21] De Klerk C, Hunfeld JAM, Duivenvoorden HJ et al. Effectiveness of a psychosocial counselling intervention for first-time IVF couples: a randomized controlled trial. *Hum Reprod* 2005; 20: 1333–1338
- [22] Domar AD, Clapp D, Slawby EA et al. Impact of group psychological interventions on pregnancy rates in infertile women. *Fertil Steril* 2000; 73: 805–811
- [23] Verhaak CM, Smeenk JM, Evers AW et al. Predicting emotional response to unsuccessful fertility treatment: a prospective study. *J Behav Med* 2005; 28: 181–190
- [24] Volmer L, Rösner S, Toth B et al. Infertile partners' coping strategies are interrelated – Implications for targeted psychological counseling. *Geburtsh Frauenheilk* 2017; 77: 52–58
- [25] Spielberger CD. Manual for the State-trait Anxiety Scale. Palo Alto: Consulting Psychologists Press; 1983
- [26] Beck AT, Guth D, Steer RA et al. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for primary care. *Behav Res Ther* 1997; 35: 785–791
- [27] Evers AW, Kraaijmaat FW, van Lankveld W et al. Beyond unfavorable thinking: The illness cognition questionnaire for chronic diseases. *J Consult. Clin Psychol* 2001; 69: 1026–1036
- [28] Van Dam-Baggen R, Kraaijmaat FW. The Inventarisation inventory to measure sociale integration: a self report inventory to assess social support. *Gedragstherapie* 1992; 25: 27–45
- [29] Schick M, Roesner S, Germeyer A et al. Smartphone-supported Positive Adjustment Coping Intervention (PACI) for couples undergoing fertility treatment: a randomised controlled trial protocol. *BMJ Open* 2019; 0: e025288
- [30] Kenny DA, Judd CM. A general procedure for the estimation of interdependence. *Psychol Bull* 1996; 119: 138–148
- [31] Kenny DA, Kashy DA, Cook WL. *Dyadic Data Analysis*. New York, NY: The Guilford Press; 2006
- [32] R Core Team. R: A language and environment for statistical computing. Wien: R Foundation for Statistical Computing; 2018. Online: <http://www.R-project.org/>; last access: 15.08.2018
- [33] Rosseel Y. lavaan: An R Package for Structural Equation Modeling. *J Stat Softw* 2012. doi:10.18637/jss.v048.i02
- [34] Junghans C, Feder G, Hemingway H et al. Recruiting patients to medical research: double blind randomised trial of “opt-in” versus “opt-out” strategies. *BMJ* 2005; 331: 940
- [35] Treweek S, Pitkethly M, Cook J et al. Strategies to improve recruitment to randomised controlled trials. *Cochrane Database Syst Rev* 2010; (4): MR000013
- [36] Wippermann C. *Kinderlose Frauen und Männer: Ungewollte oder gewollte Kinderlosigkeit im Lebenslauf und Nutzung von Unterstützungsangeboten*. Berlin: Bundesministerium für Familie, Senioren, Frauen und Jugend; 2014
- [37] Datta J, Palmer MJ, Tanton C et al. Prevalence of infertility and help seeking among 15 000 women and men. *Hum Reprod* 2016; 31: 2108–2118
- [38] Berlin-Institut für Bevölkerung und Entwicklung. Ungewollt kinderlos. Was kann die moderne Medizin gegen den Kindermangel in Deutschland tun? (Juni 2007). Online: https://www.berlin-institut.org/fileadmin/user_upload/Studien/Ungewollt_kinderlos_Webversion.pdf; last access: 13.09.2018
- [39] Terävä AN, Gissler M, Hemminki E et al. Infertility and the use of infertility treatments in Finland: prevalence and socio-demographic determinants 1992–2004. *Eur J Obstet Gynecol Reprod Biol* 2008; 136: 61–66
- [40] Wischmann T. ‘Your count is zero’–counselling the infertile man. *Hum Fertil (Camb)* 2013; 16: 35–39
- [41] Wright J, Duchesne C, Sabourin S et al. Psychological distress and infertility: men and women respond differently. *Fertil Steril* 1991; 55: 100–108
- [42] Carmeli YS, Birbaum-Carmeli D. The predicament of masculinity: towards understanding the male experience of infertility treatments. *Sex Roles* 1994; 30: 663–677
- [43] O'Donnell E. Making room for men in infertility counseling. *Sexuality, Reproduction and Menopause* 2007; 5: 28–32
- [44] Folkman S, Moskowitz JT. Positive affect and the other side of coping. *Am Psychol* 2000; 55: 647–654
- [45] Folkman S. Positive psychological states and coping with severe stress. *Soc Sci Med* 1997; 45: 1207–1221
- [46] Park CL, Folkman S. The role of meaning in the context of stress and coping. *Gen Rev Psychol* 1997; 2: 115–144
- [47] Folkman S, Greer S. Promoting psychological well-being in the face of serious illness: when theory, research and practice inform each other. *Psychooncology* 2000; 9: 11–19
- [48] Kantenich H, Brähler E, Kowalcek I, Strauß B, Thorn P, Weblus AJ, Wischmann T, Stöbel-Richter Y, Hrsg. *Leitlinie psychosomatisch orientierte Diagnostik und Therapie bei Fertilitätsstörungen*. Gießen: Psycho-sozial-Verlag; 2014
- [49] Kreuzer VK, Kimmel M, Schiffner J et al. Mögliche Gründe für einen Therapieabbruch: eine Analyse von 571 071 Behandlungszyklen aus dem Deutschen IVF-Register. *Geburtsh Frauenheilk* 2018; 78: 984–990