Protocol Title: Creating Affiliations, Learning, and Mindfulness for In Vitro Fertilization patients
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Précis:

Objective: To determine if patients undergoing in vitro fertilization (IVF) have improved quality of life (assessed using the Fertility Quality of Life (FertiQoL) Questionnaire) with participation in a psychoeducational group model.
Study population: patients starting their first IVF cycle.
Design: Cluster randomized controlled trial.
Outcomes measures: Change in FertiQoL score.

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List of Abbreviations

IVF: in vitro fertilization
FertiQoL: Fertility Quality of Life Questionnaire
GAD-7: Generalized Anxiety Disorder 7-item scale
PHQ-9: Patient Health Questionnaire-9

1. Introduction and Background

Pregnancy and childrearing are evolutionarily and psychosocially fundamental components of human life. Parenthood has been celebrated throughout history through religion, mythology, art, and literature; in modern times, parenting is celebrated with baby showers, gender reveals, and diaper parties. Those who cannot conceive often experience feelings of isolation and inadequacy (1). Patients undergoing fertility treatment often suffer from depression and anxiety (2, 3). They are significantly more likely to have depression and anxiety in comparison to women who are fertile (3-5). In fact, patients undergoing treatment for infertility have been shown to have anxiety and depression scores similar to patients diagnosed with cancer (6). Emotional distress has been shown to worsen throughout the IVF treatment cycle (7, 8). Psychological burden is among the most common reasons patients report discontinuing infertility treatment, regardless of where they are in the treatment process (9, 10).

There has been a more holistic approach to patient care in medicine as the impact of stress and lack of health literacy on treatment initiation, adherence, and continuation has been increasingly understood in multiple disciplines (9-12). Ways to support patients with life-changing diagnoses have included support groups for cancer patients and group prenatal care for pregnant women. Cancer support groups have been shown to provide information, create a sense of belonging and community, and improve psychosocial well-being (13-15). Participants in cancer support groups also report enhanced feelings of empowerment and control over their lives (13). Group prenatal care has been shown to increase maternal satisfaction with care, increase knowledge of pregnancy, increase vaginal delivery, decrease cesarean delivery, increase rate of breastfeeding, and lead to shorter hospital stays (16, 17). Group prenatal care has also been shown to positively impact weight gain in pregnancy and weight loss postpartum for obese women, as well as to decrease the effects of depression on weight gain in the same cohort (18). Additionally, group prenatal care has led to decreased patient wait times and has been used successfully as a marketing platform (16).

Interventions for improved quality of life and reduced stress have been studied for patients preparing for or undergoing IVF. A six-week Hatha yoga plus fertility-themed discussion intervention yielded significantly improved quality of life scores, and significantly decreased anxiety and depression scores (19). Another study revealed improved psychological status in women who participated in a self-administered cognitive coping and relaxation intervention when preparing to begin their first IVF cycle (20). One small study even

demonstrated improved pregnancy rates after a mindfulness-based intervention during a first IVF cycle, in addition to improved quality of life scores and decreased emotional regulation difficulty scores (21). A 2015 meta-analysis suggested psychosocial interventions for couples undergoing infertility treatment reduce psychological distress and improve clinical pregnancy rates (22).

Our proposal in the current study is to design a psychoeducational group curriculum specifically for new IVF patients (both male and female) to improve their treatment knowledge and offer a support network to provide tools to help reduce participant stress and anxiety during the treatment process, thus allowing them to engage more in their care and improving their satisfaction with the process and their overall quality of life.

2. Study Objectives

a. Primary objective

To determine if the quality of life of female patients undergoing in vitro fertilization for fertility treatment is improved by participation in a psychoeducational group model, assessed using the Fertility Quality of Life Questionnaire (FertiQoL).

b. Secondary objectives

1. To determine if the male partner's quality of life is improved using a psychoeducational group model, assessed using the Fertility Quality of Life Questionnaire (FertiQoL).

2. To determine if scores for depression are improved with use of a psychoeducational group adjunct to IVF treatment, assessed by using the PHQ-9.

3. To determine if scores for anxiety are improved with use of a psychoeducational group adjunct to in vitro fertilization treatment, assessed by using the GAD-7.

4. To determine if patient knowledge about the assisted reproductive process has improved with use of a psychoeducational group adjunct to in vitro fertilization treatment, assessed with a knowledge survey.

5. To determine if patients are more resilient after participating in a psychoeducational group model, determined using the Connor-Davidson Resilience Scale.

6. To determine if patients are more likely to pursue further treatment after an unsuccessful IVF cycle if psychoeducational group support was used in the first IVF cycle.

3. Subjects

a. Description of study populations

Participants will be patients undergoing their first IVF cycle at our institution, both female and male. Our target number of female group participants is 48, with an additional 24 control subjects. We plan to recruit a total of 86 females and their partners to account for dropout.

b. Inclusion criteria

Participants must be 18 years of age and older and starting their first IVF cycle as a heterosexual couple at the University of Iowa Hospitals and Clinics.

c. Exclusion criteria

Exclusion criteria includes prior IVF treatment at any institution, non-English speakers, treatment for fertility preservation, treatment requiring donor oocytes, embryos, or sperm, and the use of psychotropic medications for depression or anxiety with dosing adjustment within 3 months of study enrollment. Insufficient number of enrolled couples with similar projected oocyte retrieval time to form a group.

4. Study Design and Methods

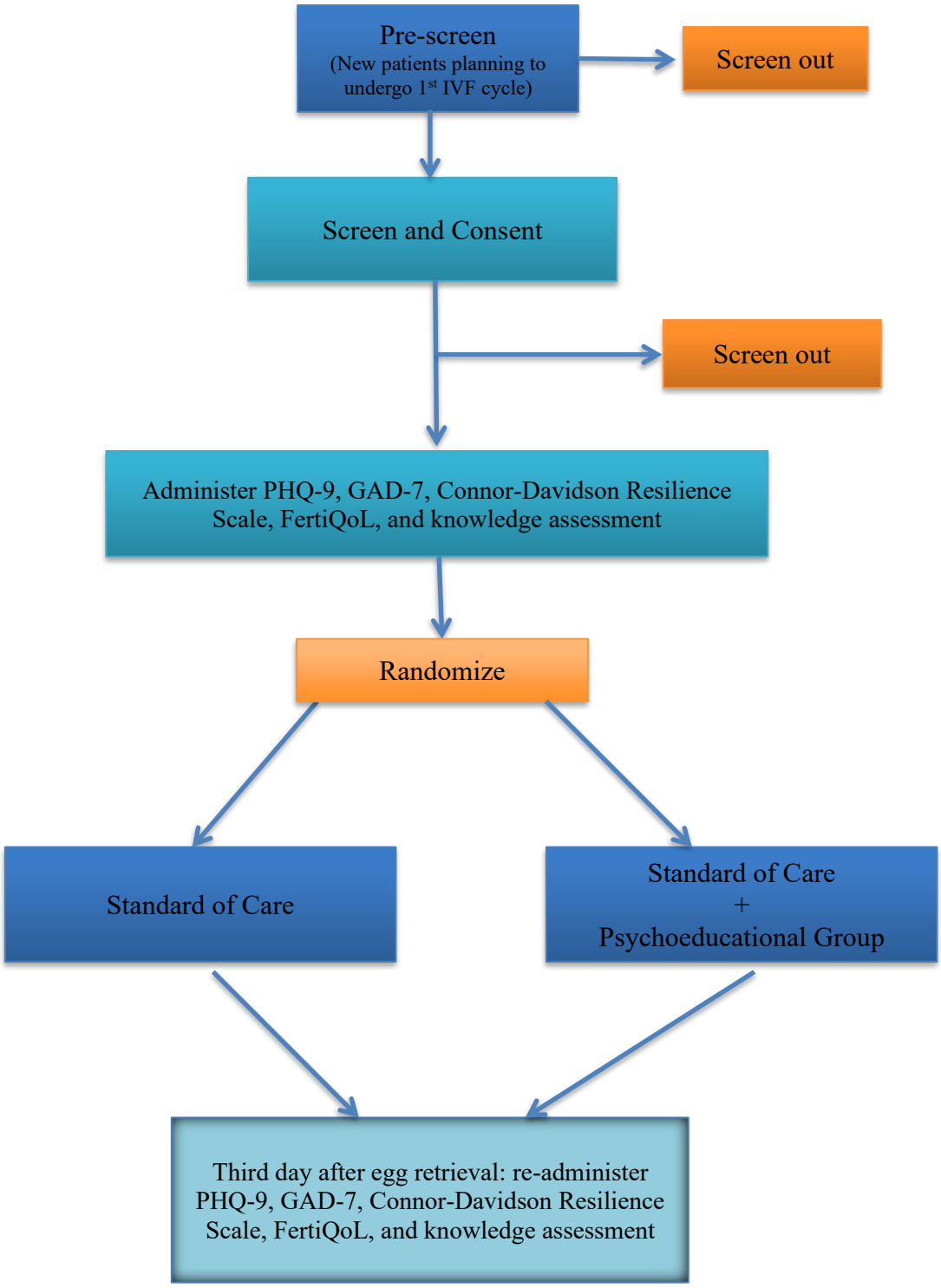
a. Study overview

This will be a single center, cluster randomized controlled trial. Subjects will be asked to answer five online REDCap surveys within 24 hours of their initial IVF visit. These surveys are the FertiQol, the Connor-Davidson Resilience Scale, the PHQ-9, the GAD-7, and a knowledge assessment. The subjects will then undergo their IVF treatment cycle using the protocol chosen by their treating physician at this institution. Based on their estimated date of egg (oocyte) retrieval, they will be placed in a group consisting of other subjects going through their first IVF cycle at approximately the same time. Once there are 5-8 women (plus or minus partners) in a group, the group will be randomized to either intervention or standard of care with $25 drawing (control group). In the event that a randomized group size falls below 3 couples, due to withdraw post randomization; enrolled couples whose groups have not been randomized due to insufficient group size with similar projected retrieval date ranges will be offered the opportunity to join the randomized group to allow the group to meet as planned. Couples added to the group through this replacement strategy will be added only to allow the group to continue to happen, and will not be included in statistical analysis for the project as their assignment was not randomized. In the event that no additional couples are available to join the group, groups of insufficient size will be canceled.

The intervention groups will meet for 1-1.5 hours on three different evenings throughout their IVF treatment cycle. The meetings will include an interactive educational component addressing common patient questions

and concerns, such as reviewing IVF myths and receiving additional information about treatment and technologies. Each session will also provide recommendations for coping strategies during challenging times such as awaiting the pregnancy test, and how to cope with insensitive remarks from friends and family. Relaxation exercises, such as progressive muscle relaxation and deep breathing techniques, will be taught and modeled. These group meetings will take place at the UIHC North Dodge clinic location.

Subjects in the intervention and in the control groups will be asked to repeat the five online surveys on the third day after their oocyte retrieval or cycle cancelation.


Pre-screen
(New patients planning to undergo 1st IVF cycle)
Screen out
Screen and Consent
Screen out
Administer PHQ-9, GAD-7, Connor-Davidson Resilience Scale, FertiQoL, and knowledge assessment
Randomize
Standard of Care
Standard of Care
+
Psychoeducational Group
Third day after egg retrieval: re-administer PHQ-9, GAD-7, Connor-Davidson Resilience Scale, FertiQoL, and knowledge assessment

b. Recruitment

Subjects will be recruited from the University of Iowa Hospitals and Clinics IVF clinic. Heterosexual partnered patients scheduled for “new IVF” patient appointments in the near future will be pre-screened by the research team and mailed recruitment materials at least one week before their scheduled appointment. A member of the research team will discuss the study with the subject in-person on the day of this scheduled “new IVF visit”. Posters announcing the study and including the research team’s contact information will be placed in consultation rooms and displayed throughout the clinic. We plan to recruit approximately ten couples per month.

c. Screening

Potential participants will be asked about previous IVF treatments at other clinics, and whether they plan to use donor egg, sperm, or embryos in their upcoming IVF cycle. Subjects will be asked whether they are planning an IVF cycle for fertility preservation purposes or for a pregnancy attempt in the near future. The subject will also be asked whether they take any medications for depression or anxiety, and if so, when the dose was last changed by the prescribing provider.

d. Study procedures

At the initial IVF visit, patients interested in participating in the study will meet with a member of the research team to review what the study entails and the study consent form.

If the subject meets eligibility criteria and consents to participate in the study, the subject (and if willing, the male partner) will be asked to answer five online REDCap surveys within 24 hours of the initial IVF visit. These surveys include the FertiQol, the Connor-Davidson Resilience Scale, the PHQ-9, the GAD-7, and a knowledge assessment.

The participant (and partner) will undergo the standard of IVF care provided at the University of Iowa Hospitals and Clinics. They will also be placed into a group that is assigned based upon their estimated oocyte retrieval day, so that they might be participating in a group consisting of other subjects going through their initial IVF cycle at the same time. Once there are enough women (and possibly partners) assigned to a group (five to eight women with or without their partners), the group will be randomized to intervention or control. The subjects will then be notified of their assignment.

The intervention groups will meet for 1-1.5 hours on three different evenings throughout the IVF treatment cycle. The meetings will include an interactive educational component addressing common patient questions and concerns, such as reviewing IVF myths and receiving

additional information about treatment and technologies. Each session will also provide recommendations for coping strategies, such as awaiting the pregnancy test and how to cope with insensitive remarks from friends and family, as well as relaxation exercises, such as progressive muscle relaxation and deep breathing techniques. Participants from both the intervention and control groups will be asked to repeat the FertiQol, the Connor-Davidson Resilience Scale, the PHQ-9, the GAD-7, and a knowledge assessment online through REDCap. Their active participation in the study will then be complete.

In the event of a negative pregnancy test, we will follow the participants through chart review for three months to see if they return for additional treatment.

e. End of participation

Active study participation will end with answering the five online REDCap surveys two to four days after oocyte retrieval or cycle cancelation. We will follow the participants for three months via chart review after a negative pregnancy test to see if they return for additional treatment. Under certain circumstances, the research team may discontinue a subject's participation in the study. These circumstances would include pregnancy prior to oocyte retrieval, if the subject discontinues their IVF cycle for any reason, if there are not a sufficient number of couples to form a group for randomization, if the subject is unable to attend the group sessions, or if the facilitators collectively agree that a subject's behavior is disruptive or hostile to the group.

5. Management of Data and Samples

a. Storage

Study data, including participant demographic and responses to assessment tools, will be kept confidential. Paper copies of consent and HIPPA forms will be stored in a locked file cabinet in the study team offices. REDCap will be used to store other project data. REDCap is password-protected and is part of University of Iowa secure server. Personal identifying information will be stored on a secure server and on a password-protected computer in a password-protected file. The server is behind the UIHC security firewalls. Only research team members will have access to the data.

b. Data sharing plan

Data will not be shared with other institutions.

6. Risks and Discomforts

Risks are minimal, but may include emotional distress or discomfort due to answering questions about feelings and infertility issues in the surveys or from speaking about infertility issues in the intervention sessions. During group

meetings, facilitators will make it clear that participants are welcome to share as much or as little about their personal journey as they wish. Participants in the group meetings will come to know the other participants in the session who are also undergoing treatment. Although participants will be expected to respect the privacy of the others, there remains a risk of identity disclosure due to the group setting. To help protect confidentiality, subjects will be required to fill out HIPPA forms at time of study consent. Participants will also be educated regarding the importance of respecting the confidentiality of other group members who may share personal information during meetings. Participants will be provided contact information for the University of Iowa Women's Wellness and Counseling Service should they experience any emotional/psychological reaction requiring further attention.

7. Subject Safety Monitoring

This study involves minimal risk. However, although the intervention was designed to be beneficial, any intervention carries some risk for participants. Answering questions or speaking about infertility issues in the intervention sessions may incur some emotional or psychological risks. Answering questionnaire items may also incur some emotional and psychological risk, although that is not the researchers' intention. Additionally, subjects are informed that they do not have to respond to any question they do not wish to.

Participants will be filling out screening questionnaires for depression and anxiety. If a participant screens positive and the participant has opted for disclosure of this information, the participant will be informed of the positive screening result and will be referred to the University of Iowa Women's Wellness and Counseling Service.

8. Outcome Measures

a. Primary outcome measures

Fertility patient quality of life will be assessed using the Fertility Quality of Life Questionnaire (FertiQoL).

b. Secondary outcome measures

The fertility patient's partner's quality of life will be assessed using the Fertility Quality of Life Questionnaire (FertiQoL).

The fertility patient and partner's depression scores will be assessed using the PHQ-9.

The fertility patient and partner's anxiety scores will be assessed using the GAD-7.

The fertility patient and partner's knowledge regarding IVF treatment will be assessed with a knowledge survey.

The fertility patient and partner's likelihood to pursue additional treatment in the instance of a negative pregnancy test in the first in vitro fertilization cycle will be assessed by tracking patient follow up after negative pregnancy test. We will follow patients for three months via chart review after a negative pregnancy test to determine follow up at our institution.

The fertility patient and partner's resilience scores will be assessed using the Connor-Davidson Resilience Scale.

9. Statistical Analysis

a. Analysis of data/ study outcomes

As this is a study with a low number of subjects, we do not plan to have an interim analysis. Change in scale scores from pre-to post will be calculated and compared between intervention and control groups using generalized linear models to control for effects of group. An alpha of 0.05 will be considered significant.

b. Power analysis

Our power analysis determined that 48 intervention cases and 24 control cases would be sufficient to detect a previously published difference of 8 points in the FertiQol score (21), using a T-test with 81% power and α=0.05. To account for potential withdrawals, we plan to recruit a total of 86 women. Due to the nature of the groups, the study will utilize randomization without replacement.

10. Human Subjects Protection

a. Subject selection

All patients meeting eligibility criteria will be considered for the study without attention to race, color, religion, national origin, and veteran or disability status.

b. Qualifications of investigators

The Principal Investigators have verified that all individuals working on this protocol who are required to take Certifications in Human Subjects Protections (CITI) training have completed this required training.

11. Anticipated Benefit

The subjects in the intervention group will spend additional time with providers outside of the regularly scheduled visits and therefore will have additional time to have questions and concerns addressed. The subjects will also receive additional education regarding their medical treatment as well as coping and

stress reduction strategies that they can utilize in all aspects of their lives. The subjects will also meet people in a situation similar to their own and form bonds that likely would not have had the opportunity to form otherwise. The subjects may also gain satisfaction from the prospect that they may be helping future fertility patients. The control group participants may benefit from anxiety and depression screening, as they will be referred to the Women's Wellness and Counseling Service should they screen positive.

12. Classification of Risk (for the study as a whole)

a. For adults

- Minimal risk.

b. Overall risk and benefit consideration

- The risks are reasonable in relation to anticipated benefit.

13. Consent Documents and Process

a. Designation of those obtaining consent

Any of the study investigators may obtain informed consent.

b. Consent procedures

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing.

c. Consent documents

The consent document can be found in the appendices of this research protocol.

14. Confidentiality

a. For research data and investigator medical records

Paper copies of consent and HIPPA forms will be stored in a locked file cabinet in the study team offices. REDCap will be used to store project data. REDCap is password-protected and is part of University of Iowa secure server. All data will be stored on a secure server and on a password-protected computer in a password-protected file. The server is behind the UIHC security firewalls.

b. Special precautions

Participants are taking part in a psychoeducational group, where they may opt to share as much or as little about themselves and their medical treatment as they choose. Participants will be required to fill out HIPPA forms at time of study consent, and will be educated regarding the

keeping of personal information confidential that may be shared by others during the group. Information given by the participants in questionnaires will be kept confidential as well as information from their medical files for demographic purposes.

15. Conflict of Interest

a. Conflict of interest

There are no conflicts of interest to report.

16. Research and Travel Compensation

There is no compensation for staff as part of this research study. Participants in the control groups will be entered in a drawing for $25 when they complete both the pre- and post-intervention surveys.

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