Meditation and mindfulness reduce perceived stress in women with recurrent pregnancy loss: a randomized controlled trial

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KEY MESSAGE
This randomized controlled trial shows that a 7-week daily programme of meditation and mindfulness combined with group sessions reduced perceived stress significantly more than standard supportive care only in women with recurrent pregnancy loss (RPL). Meditation and mindfulness is a valuable treatment for the many women with RPL and high stress.

ABSTRACT
Research question: Can participating in a tailored 7-week meditation and mindfulness programme with additional standard supportive care versus standard supportive care only reduce perceived stress for women with recurrent pregnancy loss (RPL)?

Design: A two-armed randomized controlled trial (RCT) with 12-month follow-up. In total 76 patients were enrolled and randomly assigned to either standard supportive care or to a 7-week meditation and mindfulness programme led by an instructor in addition to standard supportive care.

Results: At intervention completion (after 7 weeks), perceived stress decreased significantly both in the intervention group (P = 0.001) and in the control group (P = 0.006). The decrease in perceived stress in the intervention group was significantly larger (P = 0.027) compared with the control group. At the 12-month follow-up perceived stress was still significantly decreased in both groups compared with baseline (P < 0.0001 in the intervention group and P = 0.002 in the control group).

Conclusion: This first RCT of a tailored meditation and mindfulness intervention for women with RPL documents that a 7-week daily at-home meditation and mindfulness programme combined with group sessions reduced perceived stress significantly more than a standard supportive care programme. Future studies should address the most effective format and the ‘dose’ needed for an impact on perceived stress levels.

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INTRODUCTION

Pregnancy loss is a common pregnancy complication, ending 13.5–15% of all clinically recognized pregnancies (Lidegaard et al., 2020; Magnus et al., 2019). The true incidence is probably much higher, as early monitoring of healthy women trying to conceive has revealed a pregnancy loss incidence of 31% (Wilcox et al., 1988) and among pregnant women who conceived by IVF, 27.5%–29% of all pregnancies ended in pregnancy loss (Andersen et al., 2006; Devroey et al., 2012). Recurrent pregnancy loss (RPL), here defined as three or more consecutive losses before 22 weeks of gestation, affects 1–3% of couples trying to conceive (Ford and Schust, 2009; Jau найалов, 2006). Among women referred to a tertiary RPL unit, approximately one-third will not go on to have a live birth (Lund et al., 2012). RPL is associated with considerable psychological hardship and research shows higher rates of stress, depression and anxiety in this group compared with other women trying to conceive (Bailey et al., 2019; Kolte et al., 2015; Lok and Neugebauer, 2007; Toffol et al., 2013). The current European Society of Human Reproduction and Embryology (ESHRE) guideline on RPL states that the emotional impact should be considered (Bender Atik et al., 2018). Women experiencing RPL often react with shock, hopelessness, guilt, self-blame and doubts about self-worth (Bailey et al., 2015; Bardos et al., 2015; Brier, 2008; Kluger-Bell, 2000). Research has shown that women with a history of pregnancy loss are more likely to use complementary approaches during a new pregnancy, such as prayer, yoga, massage and meditation (Huberty et al., 2018). One of the few evidence-based treatments available and offered to couples in a tertiary RPL clinic is counselling and emotional support, as well as frequent ultrasound examinations in early pregnancy. However, the evidence for this approach, also known as ‘tender loving care’, is limited (Clifford et al., 1997; Lidell et al., 1997). Other studies have explored self-help therapies, which have been shown to be effective in reducing mental health problems (Bailey et al., 2015; Cuijpers and Schuursmans, 2007; Falbe-Hansen et al., 2007; Gratzar and Khalid-Khan, 2016; Spek et al., 2007) because they allow patients to increase insight and develop coping strategies independently to use in their daily lives (Cuijpers and Schuursmans, 2007; Kabat-Zinn and Hanh, 2005; Morris, 1995). One research group from the UK has tested the feasibility and acceptability of using a self-administered cognitive coping tool in the early stages of a new pregnancy after RPL (Bailey et al., 2015, 2020). Results suggest that the intervention is beneficial to the psychological well-being of women with RPL and a future randomized controlled trial (RCT) is planned.

The practice of meditation and mindfulness as a self-help treatment is grounded in ancient Buddhist and yoga philosophies and has existed for at least 2550 years. It was introduced into Western medicine and psychology in the early 1980s by Jon Kabat-Zinn (Edenfeld and Soed, 2012; Kabat-Zinn, 1994, 2003). Kabat-Zinn has defined mindfulness as an awareness that, on purpose, comes from paying attention in the present moment and is non-judgemental (Kabat-Zinn, 2003; Kabat-Zinn and Hanh, 2005). Since then, there has been much theoretical and empirical work illustrating the impact of meditation and mindfulness on psychological health for a broad range of individuals, including fertility patients, to help them cope with their problems (Boer et al., 2012; Bazarko et al., 2013; Beattie et al., 2017; de Vibe et al., 2013; Frederiksen et al., 2015; Galhardo et al., 2013; Grossman et al., 2004; Kabat-Zinn, 1982; Shapiro et al., 2008).

Previous research has found that emotional stress is highly prevalent among patients with RPL (Koert et al., 2019; Kolte et al., 2015). Because Danish clinics treating women with RPL do not offer interventions or treatments specifically aimed towards reducing the patient's psychological distress, it was postulated that a 7-week meditation and mindfulness intervention could prove beneficial in alleviating stress in this patient group. The aim was also to give the patients a self-help tool that they could apply to the stresses in their daily life including RPL.

This study aimed to investigate whether women with RPL participating in a 7-week meditation and mindfulness intervention with additional standard supportive care perceived less stress compared to women with RPL receiving only standard supportive care.

MATERIALS AND METHODS

Study design
A two-armed RCT was designed to evaluate a 7-week meditation and mindfulness intervention with standard supportive care (intervention group) versus standard supportive care only (control group) for women experiencing RPL. Out of 163 invited, 76 participants were enrolled and randomly assigned to either standard supportive care (control group with 38 participants) or to a 7-week programme of guided meditation and mindfulness and standard supportive care (intervention group with 38 participants) (Figure 1).

Pregnancy outcomes 12 months after the intervention were obtained by the study unit’s detailed RPL database, containing information about all patients including evaluation results, pregnancies and treatment information.

Setting
A tax-financed, comprehensive health system is freely available to all citizens in Denmark, and everyone has access to equal and high-quality treatments. The RPL unit at Copenhagen University Hospitals, Rigshospitalet and Hvidovre Hospital treat approximately 250 new couples every year.

Standard supportive care in the RPL unit comprises an in-depth consultation with a specialist doctor and nurse and subsequent consultations with a nurse from the clinic. The RPL unit offer as a standard a supportive ‘tender loving care programme’ consisting of blood tests, early pregnancy ultrasound scans, supportive care and follow-up from the programme nurse including general emotional support, empathy and advice throughout pre-pregnancy and pregnancy (Figure 2).

Participants and eligibility
All newly referred patients to the RPL Unit at the Fertility Clinic at Copenhagen University Hospital, Rigshospitalet, filled out the Perceived Stress Scale (PSS) and the Major Depression Inventory (MDI) immediately before their first consultation. Between 1 November 2018 and 5 April 2019, female patients were invited to participate in the study if they had a PSS score of ≥16 and no depression on the MDI. All prospective participants were informed about the study in writing and orally by the
specialist doctor or nurse. They were also informed about the possibility of reflection time before deciding whether to participate.

Additional inclusion criteria were: (i) Danish-speaking, (ii) aged 18–46 years; (iii) three or more consecutive pregnancy losses; (iv) a male partner (irrespective of whether they were married/cohabiting/living together or apart). Patients were ineligible if they were pregnant on inclusion day or already practising any form of mindfulness or meditation. From inclusion to baseline there was a period of up to 3 months for some patients because the period from November 2018 to February 2019 was included for the first intervention group. Patients were permitted to continue in the study if they became pregnant after inclusion day. The cut-off of 16 on the PSS was chosen based on a previous study of stress and depression among women with RPL where 16 was the mean score (Kolte et al., 2015).

Randomization
Randomization was computerized in REDCap (www.projectredcap.org). The study was an RCT with two groups: an intervention group and a control group. Participants were randomized in blocks of four to ensure equal allocation despite the small sample size. The study was non-blinded. Two nurses in the RPL Unit at Rigshospitalet enrolled and randomized the participants.

Outcome measures
The primary outcome was perceived stress, and secondary outcomes were RPL-associated stress and the strength of the couple’s marriages measured at three time points (baseline pre-
intervention, 7 weeks after baseline (at intervention completion) and 12 months after baseline). Both groups simultaneously received an email with a link to three questionnaires comprising questions about perceived stress, RPL-associated stress and RPL-associated marital benefit. Baseline was 1 week prior to intervention start. During the time from inclusion to baseline, which was up to 3 months, all participants received the study centre's standard supportive care, independent of randomization group. For both groups the 12-month follow-up was by questionnaire only. The questionnaires used in the study included the Perceived Stress Scale (PSS), a validated 10-item self-reporting scale of stress symptoms (Cohen and Williamson, 1988; Cohen et al., 1983). The 5-point Likert scale ranges from 0 (no stress) to 40 (extreme stress). The scale was developed to evaluate how unpredictable, uncontrollable and overloaded respondents find their lives (Cohen et al., 1983).

RPL-associated stress was measured by the Copenhagen Multi-Centre Psychosocial Infertility research program Fertility Problem Stress Scales (COMPI-FPSS), a validated 9-item self-reporting scale of infertility-specific stress assessing the impact of infertility stress in three domains of an individual's life: personal, marital and social (Schmidt et al., 2005a; Sobral et al., 2017). For this study the word ‘childlessness’ in the items is changed to ‘pregnancy loss’ and therefore the term RPL-associated stress is used. Similarly, Kogami et al. (2012) used COMPI-FPSS in a study from Japan including couples with RPL. RPL-associated stress in the personal domain tapped into the stress the pregnancy loss has on the person’s life and on mental and physical health. Stress in the marital domain assessed the extent to which pregnancy loss is producing strain on the marital/cohabiting and sexual relationship. Stress in the social domain assessed the stress pregnancy loss is having on relationships with family and friends. The response key for the social domain and for two items for the marital and personal domain is a 4-point Likert scale from 1 (‘none at all’) to 4 (‘a great deal’). The response key for the remaining one item from the marital and the personal domain is a five-Likert scale from 1 (‘strongly disagree’) to 5 (‘strongly agree’). Higher scores indicate more stress. The rating of this scale has previously been described in detail (Sobral et al., 2017). Cronbach’s alpha on RPL-associated stress in this study was 0.51 (personal domain), 0.79 (marital domain) and 0.70 (social domain), respectively, indicating good internal consistency regarding the marital and social domain and poor regarding the personal domain.

RPL-associated ‘marital benefit’ was measured by the COMPI Marital Benefit Measurement (Schmidt et al., 2005b); a two-item measure that investigates marital benefit, e.g. whether infertility has strengthened the marriage and brought the partners closer together. For this study, the word ‘childlessness’
was changed to ‘pregnancy loss’ and the concept of RPL-associated marital benefit was used. This measurement was included as previous studies among couples undergoing medically assisted reproduction reported that infertility and its simultaneous treatment can be seen as a threat or a challenge for the couple and as a situation that can bring the partners closer together and strengthen their interpersonal relationship (Greif et al., 1988; Schmidt, 1996). This measurement was developed based on results from a qualitative interview study among couples in assisted reproduction (Schmidt, 1996) and pilot tested and used in the COMPI Infertility Cohort (n = 1169 women), showing a Pearson correlation coefficient of 0.83, indicating high correlation. Scores range from 2 (lowest score) to 10 (highest score). A maximum score of 10 is required to be categorized as having high RPL-associated marital benefit. The Pearson correlation coefficient in this study was 0.79, indicating high correlation.

Clinical outcome
Sociodemographic information and reproductive characteristics such as number of pregnancy losses prior to referral was collected at baseline, as well as number of living children prior to referral and level of education. At 12 months after the intervention, as well as data on primary and secondary aims, pregnancy outcomes (ongoing pregnancy, pregnancy loss, live birth) were extracted for the patients from the study centre's detailed database. Pregnancy outcomes were not part of the primary and secondary outcomes. Among those achieving a pregnancy in the follow-up period, the study measured whether the pregnancy was ongoing, or had ended in live birth or a pregnancy loss.

Sample size
Sample size was based on an estimate from a power calculation with an alpha value of 0.05 and a power of 80% (beta = 20%). The expected effect size in the intervention group was a 5-point decrease in the PSS score, based on previous studies on meditation and mindfulness and use of the PSS (Baer et al., 2012; Balk et al., 2010; Bazarko et al., 2013; Beattie et al., 2017; dos Santos et al., 2016; Shapiro et al., 2008; Trobbridge et al., 2017). No decrease in PSS was expected in the control group. Based on these assumptions, the targeted goal was to include 62 participants (31 in each arm). In order to compensate for participant drop-out a total of 76 participants (38 in each arm) were enrolled.

Clinical intervention
A professional meditation and mindfulness instructor educated at the Morya Federation (www.Morya-federation.com) and elsewhere taught the 7-week meditation and mindfulness programme (in total for 11 h), tailored to patients with RPL and intended to support the patient’s general resilience and well-being in their everyday life, and in their work, personal lives and marriages. The intervention group sessions were conducted from 2 February 2019 to 19 June 2019 and were split into two groups with 20 participants in the first group and 18 participants in the second group before withdrawals. Both intervention groups were offered a 2-h follow-up session 2 weeks after the last meditation and mindfulness intervention. During the 7-week programme, each participant in the intervention group had access to a daily guided audio instruction in meditation and mindfulness practice with instruction and support specifically developed for this group. The recommended home practice time was 10–20 min per day, for 7 consecutive weeks. The meditation and mindfulness interventions drew on traditional mindfulness meditation techniques, as well as guided meditation, basic mindfulness practices such as breathing exercises, body scans, conscious movement, attention to experiences through the senses, and teaching in the origins of meditation. The participants in the intervention group were encouraged to write in a diary to improve gratitude, positive focus and mindfulness in their everyday life. Both the intervention and the control groups were offered the standard supportive care programme. The RPL unit in this study offer as a situation that can bring the partners closer together and strengthen their interpersonal relationship (Greil et al., 1988) and elsewhere taught the 7-week programme, each participant in the intervention was encouraged to practice meditation and mindfulness practice within the groups for the COMPI-PFSS and to obtain results of the COMPI Marital Benefit Measurement a chi-squared method was used to measure between groups and a McNemar test was used within groups. Participants with missing data (dropouts) at 12-month follow-up were included in baseline and 7-week data but not in 12-month data.

Ethical approval
The study was approved on 17 October 2018 by the Regional Ethics Committee of Copenhagen (protocol no.: H-18038456) and the Danish Data Protection Agency (I-suites number 05409 and journal number RH-2017-97). The study is registered on ClinicalTrials.gov as NCT03905395. All patient/personal identifiers were removed or disguised so that the patient/person(s) described were not identifiable and cannot be identified through clinical details.

RESULTS
Sociodemographic information
There were no significant differences in age, number of pregnancy losses prior to referral, having a living child or level of education between the two groups, as shown in Table 1. All participants were Caucasian.

Participant drop-out and missing data
Of the 76 participants, 67 completed the study. Seven women left the intervention...
TABLE 1  SOCIODEMOGRAPHIC INFORMATION AND REPRODUCTIVE CHARACTERISTICS AT BASELINE OF STUDY PARTICIPANTS IN THE INTERVENTION GROUP, CONTROL GROUP AND AMONG DROP-OUTS

| Variable                                      | Intervention group (n = 31) | Control group (n = 36) | P-value | Drop-outs (n = 9) | P-value |
|-----------------------------------------------|-----------------------------|------------------------|---------|------------------|---------|
| Age (years)                                   | 33.9 (6.0)                  | 33.5 (4.5)             | 0.79b    | 34.4 (2.1)       | 0.67f   |
| Number of pregnancy losses, median (range)    | 4 (3, 9)                    | 4 (2, 12)              | 0.42c    | 3 (2; 11)        | 0.86d   |
| Has a living child                            | 9 (29.0)                    | 13 (36.1)              | 0.61e    | 5 (55.6)         | 0.18e   |
| Level of education                            |                             |                        |         |                  |         |
| ISCED 5: short-cycle tertiary education       | 3 (9.7)                     | 6 (16.7)               | 0.80f    | 3 (33.3)         | 0.11f   |
| ISCED 6: Bachelor’s or equivalent level       | 14 (45.2)                   | 13 (36.1)              |         | 5 (55.6)         |         |
| ISCED 7: Master’s or equivalent level         | 12 (38.7)                   | 14 (38.9)              |         | 0                |         |
| Information not available                     | 2 (6.5)                     | 3 (8.3)                |         | 1 (11.1)         |         |

Data are presented as mean (SD) or n (%), except where otherwise indicated.

* Withdraw due to allocation to control group (n = 2), withdrew from intervention group after first session (n = 7).

b Compared with rest of cohort n = 67.
c Independent-samples t-test.
d Mann-Whitney U-test.
e Fisher’s exact test.
f Chi-squared test.

It was found that perceived stress decreased significantly in the intervention group and the control group from baseline to 7 weeks later (at intervention completion) and from intervention completion to 12-month follow-up. At baseline, the mean score on the PSS was 20 (SD 6) in both the intervention group and the control group. Seven weeks later (at intervention completion), the mean score in the intervention group had decreased to 15 (SD 5, P = 0.001) and in the control group the mean score had decreased to 18 (SD 5, P = 0.006). The decrease in the intervention group was significantly larger than in the control group (P = 0.027). At the 12-month follow-up, perceived stress was still significantly decreased in both groups compared with baseline, with a mean score of 14 (SD 8, P < 0.0001) in the intervention group, and a mean score of 15 (SD 7, P = 0.002) in the control group. However, there was no significant difference in the PSS in the 12-month follow-up between the intervention and control groups; P = 0.437 (see Table 2).

RPL-associated stress
RPL-associated stress measured by the COMPI-FPSS, which measures stress in three domains (personal, marital, and social), showed a numeric decline in all three domains in the intervention group and a significant decrease in the personal domain 7 weeks later (at intervention completion); P = 0.039. At the 12-month follow-up, RPL-associated stress in all three domains had decreased numerically for both groups but only statistically significantly in the control group in the personal domain; P = 0.012 (see Table 3).

TABLE 2  PERCEIVED STRESS SCALE MEASUREMENTS AT BASELINE, 7 WEEKS AFTER BASELINE AND 12 MONTHS AFTER BASELINE IN THE INTERVENTION GROUP AND CONTROL GROUP

| Perceived Stress Scale (PSS) | Intervention group (n = 31) | Control group (n = 36) | Mean difference (SD, 95% CI) | P-value (independent-samples t-test) |
|------------------------------|-----------------------------|------------------------|------------------------------|-------------------------------------|
| PSS – baseline               | 20 (6)                      | 20 (6)                 | 0 (2, –2.92; 3.04)           | 0.968                               |
| PSS – 7 weeks after baseline | 15 (5)                      | 18 (5)                 | 3 (1, 0.33; 5.33)            | 0.027                               |
| Mean difference (SD, 95%)    | 5 (4, 3.32; 6.55)           | 2 (4, 0.67; 3.66)      |                              |                                     |
| P-value from baseline to 7 weeks after paired-samples t-test | 0.001 | 0.006 |
| PSS – 12 months after        | 14 (8)                      | 15 (7)                 | 1 (2, –2.29; 5.23)           | 0.437                               |
| P-value from baseline to 12 months after paired-samples t-test | <0.0001 | 0.002 |

Data are presented as mean (SD) or mean (SD, 95% CI), (range 0–40).

* Results 12 months after baseline for the control group only include the 33 follow-up participants.
TABLE 3 RPL–ASSOCIATED STRESS IN THE PERSONAL, MARITAL AND SOCIAL DOMAIN MEASURED AT BASELINE, 7 WEEKS AFTER BASELINE AND 12 MONTHS AFTER BASELINE IN THE INTERVENTION AND CONTROL GROUPS

| RPL-associated stress measured by COMPI-FPSS | Intervention group n = 31 | Control group n = 36 | P-value (independent-samples t-test) |
|--------------------------------------------|--------------------------|----------------------|-----------------------------------|
| Range personal domain (1–5) + (1–4)        |                          |                      |                                   |
| RPL-associated stress baseline             |                          |                      |                                   |
| Personal                                   | 10.52 (1.5)              | Personal             | 10.50 (1.9)                       | 0.918 |
| Mantal                                     | 9.23 (2.8)               | Mantal              | 9.00 (2.9)                        | 0.628 |
| Social                                     | 7.90 (2.4)               | Social              | 7.00 (2.3)                        | 0.148 |
| RPL-associated stress 7 weeks after        |                          |                      |                                   |
| Personal                                   | 9.91 (1.8)               | Personal             | 10.50 (2.0)                       | 0.218 |
| Mantal                                     | 8.55 (2.7)               | Mantal              | 9.00 (3.0)                        | 0.495 |
| Social                                     | 7.25 (2.3)               | Social              | 7.00 (2.3)                        | 0.731 |
| Mean difference between baseline and 7 weeks |                          |                      |                                   |
| Personal                                   | 0.61 (1.6)               | Personal             | 0.0 (1.8)                         | 0.925 |
| Mantal                                     | 0.68 (2.0)               | Mantal              | 0.1 (1.6)                         | 0.686 |
| Social                                     | 0.65 (2.1)               | Social              | 0.0 (1.6)                         | 1.000 |
| P-value (paired t-test)                    |                          |                      |                                   |
| Personal                                   | 0.039                    | Personal             | 0.925                             |       |
| Mantal                                     | 0.066                    | Mantal              | 0.686                             |       |
| Social                                     | 0.098                    | Social              | 1.000                             |       |
| RPL-associated stress 12 months after      |                          |                      |                                   |
| Personal                                   | 9.97 (2.0)               | Personal             | 9.58 (2.3)                        | 0.468 |
| Mantal                                     | 8.77 (2.8)               | Mantal              | 8.27 (3.0)                        | 0.497 |
| Social                                     | 7.61 (2.6)               | Social              | 6.52 (2.4)                        | 0.083 |
| Mean difference between baseline and 12 months after |          |                      |                                   |
| Personal                                   | 0.55 (2.4)               | Personal             | 0.84 (1.8)                        |       |
| Mantal                                     | 0.46 (2.6)               | Mantal              | 0.46 (1.9)                        |       |
| Social                                     | 0.29 (2.5)               | Social              | 0.42 (1.6)                        |       |
| P-value (paired t-test)                    |                          |                      |                                   |
| Personal                                   | 0.279                    | Personal             | 0.012                             |       |
| Mantal                                     | 0.349                    | Mantal              | 0.169                             |       |
| Social                                     | 0.526                    | Social              | 0.147                             |       |

Data are presented as mean (SD).

* Results 12 months after baseline only include the 33 follow-up participants. COMPI-FPSS = Copenhagen Multi-Centre Psychosocial Infertility research program Fertility Problem Stress Scales, RPL = recurrent pregnancy loss.

RPL-associated marital benefit

RPL-associated marital benefit tended to increase in the intervention group. No such tendency was seen in the control group, where more participants had a high RPL-associated marital benefit at baseline, for further results see TABLE 4.

Reproductive outcome and perceived stress

Perceived stress was significantly higher in women not achieving a pregnancy within the 12-month study period. The mean score on the PSS was 20 (SD 6) for women not achieving a pregnancy and 13 (SD 7) for women achieving a pregnancy at 12-month follow-up; \( P = 0.005 \) (see TABLE 6). A significant trend of decreasing mean scores was found on the PSS at 12-month follow-up according to the four reproductive categories (see TABLE 6).

Reproductive outcome after 12 months

Reproductive outcome was similar within the two groups 12 months after baseline. Six women in each group did not achieve a pregnancy (19.4% in the intervention group versus 18.2% in control group; \( P = 0.904 \)). Among the remaining participants in the intervention group, 32% (\( n = 8 \)) lost a pregnancy versus...

TABLE 4 RPL–ASSOCIATED MARITAL BENEFIT AT BASELINE, 7 WEEKS AFTER BASELINE AND 12 MONTHS AFTER BASELINE IN THE INTERVENTION AND CONTROL GROUPS

| RPL-associated marital benefit measured by the COMPI Marital Benefit Measurement (range 2–10) | Intervention group n = 31 | Control group n = 36 | P-value (Pearson chi-squared method) |
|---------------------------------------------|--------------------------|----------------------|-----------------------------------|
| High RPL-associated marital benefit, baseline | 5 (16.1)                 | 8 (22.2)             | 0.537                             |
| High RPL-associated marital benefit, 7 weeks after baseline | 9 (29.0)                | 10 (27.8)            | 0.911                             |
| \( P \)-value from baseline to 7 weeks after baseline (McNemar test) | 0.125                    | 0.625                |                                   |
| High RPL-associated marital benefit 12 months after baseline | 11 (35.5)               | 11 (33.3)\(^*\)     | 0.926                             |
| \( P \)-value from baseline to 12 months after baseline (McNemar test) | 0.070                    | 0.508\(^*\)          |                                   |

Data are presented as n (%).

COMPI = Copenhagen Multi-Centre Psychosocial Infertility research program; RPL = recurrent pregnancy loss.

* Results 12 months after baseline only include the 33 follow-up participants.
TABLE 5 REPRODUCTIVE OUTCOME AND PERCEIVED STRESS 12 MONTHS AFTER BASELINE WITHIN BOTH GROUPS IN TOTAL

| Pregnancy/no pregnancy 12 months after baseline | Number | PSS mean (SD) | Difference PSS | P-value (independent-samples t-test) |
|-----------------------------------------------|--------|---------------|----------------|-------------------------------------|
| Intervention and control group in total       | Both groups in total, no pregnancy | 12 | 20 (6) | -7 | 0.005 |
|                                               | Both groups in total, pregnancy    | 52 | 13 (7) |              |                                |

PSS = Perceived Stress Scale.

18.5% (n = 5) in the control group; P = 0.262.

DISCUSSION

In this first RCT of a meditation and mindfulness intervention for women with RPL, it was shown that meditation and mindfulness is an effective psychological tool to reduce perceived stress. This is in line with current literature on the impact of meditation and mindfulness on psychological health for a broad range of individuals, including fertility patients, to help them cope with their problems (Boer et al., 2012; Bazarko et al., 2013; Beattie et al., 2017; de Vibe et al., 2013; Frederiksen et al., 2015; Golardo et al., 2013; Grossman et al., 2004; Kabat-Zinn, 1982; Shapiro et al., 2008).

The primary outcome, perceived stress, decreased significantly within both groups after intervention completion (7 weeks) and this decrease remained significant at the 12-month follow-up, although the difference between the groups attenuated. It could be that although perceived stress was reduced significantly more in the intervention group compared with the control group after 7 weeks of intervention, receiving the standard supportive care from the RPL Unit reduces perceived stress as well. Repeated follow-up training or ‘booster’ sessions in meditation and mindfulness may be needed to maintain training gains from the intervention. Through this intervention, the serious psychological distress experienced by RPL patients (Koert et al., 2019; Kolte et al., 2015) is acknowledged and addressed. RPL units in Denmark have limited resources and psychological treatment is not currently offered, even though there is strong evidence that the experience of pregnancy loss has both a physical and a psychological impact. This study shows that psychological interventions can be implemented and do not require a lot of staff resources.

Regarding the secondary outcomes, it was found that the RPL-associated stress in the personal domain associated with the pregnancy loss significantly decreased after the intervention was completed. This contrasts with an intervention study of a communication and stress management programme for couples undergoing fertility treatment, where no significant changes in infertility-specific stress were reported (Schmidt et al., 2005c). It could be that an intervention with meditation and mindfulness has more potential to reduce stress than a communication and stress management intervention, where many study participants changed their infertility-specific communication with family and friends, leading in some cases to increased levels of stress. Furthermore, RPL-associated marital benefit was higher in the intervention group, although this difference was not statistically significant. In contrast, in their communication and stress management intervention, Schmidt et al. (2005c) found a significant increase in infertility-specific marital benefit among women. It could be that a training course in communication is a better tool to improve communication between partners and thereby improve marital benefit.

When Kagami et al. (2012) used this measurement scale for RPL-associated stress in their sample of 76 couples having RPL, the scale showed ‘acceptable to good’ Cronbach’s alpha scores in the personal and marital domains for both men and women and poor internal consistency regarding the social domain. This is in contrast to the internal consistency for the scale in this study, where internal consistency in the personal domain is poor and for the two other domains, acceptable. Overall, the internal consistencies for the COMPI-FPSS measure, when used in study populations of women and men seeking medically assisted reproduction, shows higher correlation than when used among study populations with RPL. This indicates that using this instrument for

TABLE 6 REPRODUCTIVE OUTCOME AND PERCEIVED STRESS 12 MONTHS AFTER BASELINE IN THE INTERVENTION AND CONTROL GROUPS

| Reproductive outcome          | Groups     | Number | PSS mean (SD) | Difference PSS | P-value |
|-------------------------------|------------|--------|---------------|----------------|---------|
| No pregnancies                | Control    | 6      | 21 (5)        | -2             | 0.586*  |
|                               | Intervention | 6      | 19 (7)        |                |         |
| Only loss                     | Control    | 5      | 15 (8)        | 3              | 0.569*  |
|                               | Intervention | 8      | 18 (7)        |                |         |
| Ongoing pregnancy             | Control    | 8      | 14 (8)        | -2             | 0.602*  |
|                               | Intervention | 5      | 12 (5)        |                |         |
| Delivery live birth           | Control    | 14     | 13 (8)        | -4             | 0.152*  |
|                               | Intervention | 12     | 9 (6)         |                |         |

Trend reproductive outcome between groups: 0.004*.

* Independent-samples t-test.

* One-way analysis of variance. PSS = Perceived Stress Scale.
measuring RPL-associated stress should be validated in further studies.

These interventions were provided in groups, and group meditation and mindfulness-based formats have several benefits and some limitations. Group intervention is usually less costly than individual therapy (Wahbeh et al., 2014), and groups can mobilize motivation and synergistic learning opportunities for the participants, as meeting other people with similar challenges can give participants a wider perspective on their own situation. The participants can also see how others handle their problems (Wahbeh et al., 2014). This study did not measure whether the social interaction itself translates into a reduction in perceived stress and so it was not possible to determine whether the treatment effect was due to the content of the intervention (meditation and mindfulness) or the format of the intervention (communal meeting setting, social interaction that normalizes their experience by meeting others who have experienced the same loss). It may be that a combination of these factors facilitates a decrease in perceived stress. As such, further investigation into the preferred and most effective intervention format is warranted.

However, sharing in public can be unpleasant for some people, especially those with sensitive diagnoses like stress and also for medical conditions that carry a some shame and taboo (Wahbeh et al., 2014). In the current study, seven women dropped out of the intervention group after the first session, and it should be kept in mind that a structured programme of workshops and daily at-home meditation and mindfulness can be overwhelming and difficult for anyone, especially for patients who are already stressed, because this practice undeniably requires motivation, time and discipline. Furthermore, 17% ($n = 28$) of those asked to participate in this study said they were not interested because it was a group-based meditation and mindfulness intervention. A previous study evaluated which format of meditation and mindfulness training participants preferred: group-based, internet-based or individual therapy (Wahbeh et al., 2014). The internet-based format was rated as the first choice for most participants, followed by individual therapy and finally, the group format (Wahbeh et al., 2014). The preferred format (internet) should be considered in a future study. In the future, implementation of internet-guided, self-administered meditation and mindfulness interventions within tertiary RPL units could make self-help psychological interventions feasible. According to the literature, self-help therapies are effective in reducing mental health problems (Cuijpers and Schuurmans, 2007; Korytkowski et al., 2018; Spek et al., 2007). A self-help psychological intervention like the one studied here can effectively help patients to self-manage and understand emotional distress and bring it under personal control, and may be beneficial in many treatment settings (Bishop, 2002), although some patients may choose not to attend for practical reasons or because of discomfort in group settings. Self-help meditation and mindfulness has the potential to overcome at least some of these challenges. Besides reducing stress, we also wanted to provide our patients with a self-help tool in order for them to become independent and more self-reliant during their next pregnancy.

This study found no indication that meditation and mindfulness had an impact on future reproductive outcomes, but it should be kept in mind that the study was not intended for this purpose, nor powered for this outcome. Not surprisingly, and in accordance with previous results (Kolte et al., 2015), stress decreased in a dose-dependent manner with the four categories of reproductive outcomes at 12-month follow-up (no pregnancy achieved, pregnancy loss, ongoing pregnancy and live birth). It is an interesting finding that perceived stress also decreased in the control group. The women in this group received the same medical work-up as in the intervention group and naturally received the RPL Unit’s standard supportive care programme in their pregnancies after referral. This study was not designed to evaluate whether the standard supportive care programme is effective, but this should be investigated in future studies, as the evidence base for this practice is limited (ESHRE Guideline Group on RPL, et al., 2018). The strength of the present study is the randomized design and the 12-month follow-up. The study also has several limitations. Stress in male partners was not addressed, although other work carried out by our group since the start of this trial has documented a significant impact on their mental well-being (Koert et al., 2019). Ways to reduce stress in male partners should be explored in future studies. The uncertainty over whether the participants who were randomized to the control group practised meditation on their own and were more mindful than they normally would be (because the study had created an awareness about meditation and mindfulness) is a limitation of this study. Also, it remains unknown whether it is the meditation and mindfulness or the fact that the patients were in the active intervention group that was the reason for the stress reduction. Other limitations relate to that fact that there was no process evaluation of the intervention or non-blinded data analysts.

Finally, we did not include biological stress markers despite other studies exploring the impact of meditation and mindfulness have found these biological markers to consolidate their findings. Future studies on the mental impact of pregnancy loss should consider, for example, measurements of salivary cortisol (Christopher et al., 2018; Turokityanakan et al., 2013). In conclusion, this is thought to be the first RCT aiming to investigate the effect of a meditation and mindfulness intervention for women experiencing RPL. This study documents that a 7-week daily at-home meditation and mindfulness programme combined with group sessions reduced perceived stress significantly more than a standard supportive care programme for women with RPL after intervention completion. Future studies should address the most effective format and the ‘dose’ needed for an impact on perceived stress levels.

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