Sleep, psychological distress, and clinical pregnancy outcome in women and their partners undergoing in vitro or intracytoplasmic sperm injection fertility treatment

Marie Tholstrup Philipsen, MD a,g,* , Ulla Breth Knudsen, PhD a,b , Robert Zachariae, DMS e , Hans Jakob Ingerslev, MD a,d , Julius Edward Miller Hvidt, MD a,c , Yoon Frederiksen, PhD c,f 

a Faculty of Health, Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark
b Horsens Fertility Clinic, Horsens Hospital, Horsens, Denmark
c Department of Psychology and Behavioural Sciences, Aarhus University, Aarhus, Denmark
d Department of Gynaecology and Obstetrics, Aarhus University Hospital, Aarhus, Denmark
e Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
f The Sexology Unit, Department of Affective Disorders, Aarhus University Hospital, Aarhus, Denmark
g Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark

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ABSTRACT

Objectives: To explore the prevalence of poor sleep quality in couples undergoing fertility treatment and study possible associations.
Participants: 163 women and 132 partners receiving in vitro (IVF) or intracytoplasmic sperm injection (ICSI) fertility treatment.
Setting: Three public Danish fertility clinics.
Design and measurements: Participants completed the Pittsburgh Sleep Quality Index (PSQI) at three time-points as part of a larger RCT. Additional data from patient records and questionnaires were included to evaluate possible associations with treatment protocol type, psychological distress, and pregnancy outcome.
Results: Mean PSQI global scores before treatment were 8.1 (standard deviation = 2.3), with 91% of participants having PSQI scores > 5, indicating poor sleep quality. Scores did not differ between women and their partners and did not change during treatment. Statistically significant associations were found between sleep quality and depressive symptoms and state anxiety (p < .001). No difference in PSQI scores was found between protocol types. While there was a trend towards higher clinical pregnancy rates among women with good sleep quality (PSQI /C20/ 5 = 72.7%, PSQI 6-10 = 52.6% and PSQI /C21/ 11 = 42.3%), the differences did not reach statistical significance (p = .10-.21).
Conclusions: Poor sleep quality is a prevalent problem among couples undergoing fertility treatment and is associated with psychological distress and possibly with pregnancy outcomes. Success rates after fertility treatment remain moderate, and poor sleep quality, a potentially modifiable factor, could be relevant to screen for and treat among couples undergoing fertility treatment. The high prevalence of poor sleep quality calls for further investigation.

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Introduction

There is growing evidence that sleep plays an important role in several medical diseases,1 yet it remains unclear whether an association between sleep and infertility exists. Sleep disturbances are presumed to be frequent in patients undergoing fertility treatment,2 and a review of the topic has recommended further studies on the prevalences and possible associations.3

To our knowledge, only two small-sample studies widely examining sleep among 21 and 100 women are available, both reporting that self-reported poor sleep quality (Pittsburgh Sleep Quality Index [PSQI] above 5) is frequent with prevalences of 57.1% and 46%, respectively, among women receiving fertility treatment with in vitro fertilisation.4,5 In contrast, studies of younger adults in the general population has found PSQI scores above 5 in only 14%-40%.5,6 One study observed self-reported sleep difficulties to be associated with modestly reduced fecundability among women attempting pregnancy.6

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*Corresponding author: Marie Tholstrup Philipsen, MD. Møllestien 50, Aarhus C DK-8000, Denmark.
E-mail address: marie_tholstrup@outlook.dk (M.T. Philipsen).

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Impaired sleep has been associated with various deleterious mental and physical health outcomes, including cardiovascular disease and glucose dysregulation,\textsuperscript{9,10} psychiatric and neurodegenerative disease,\textsuperscript{11,12} dysregulated immune function,\textsuperscript{13} and it has been argued that sleep loss may affect fertility through compromised immunity in women.\textsuperscript{14} In addition, some studies have found correlations between sleep disturbances or disrupted circadian rhythm and diminished ovarian reserve, irregular menstrual cycle, and infertility.\textsuperscript{15-17} Correspondingly, several hormones are thought to present possible endocrine pathways by which sleep disturbance could affect fertility.\textsuperscript{3,14,18} Furthermore, it has been suggested that infertility could also affect sleep, and the 2 may be reciprocally determined.\textsuperscript{3,14} Sleep could thus be affected by externally administered reproductive hormones as part of advanced infertility treatment with in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Women receiving the long gonadotropin-releasing hormone (GnRH) agonist protocol have been found to report more significant impairment of sleep quality and more depressive symptoms than women receiving the short GnRH antagonist protocol, possibly due to the longer duration of treatment and pituitary down-regulation.\textsuperscript{19,20} Recent studies also suggest a bi-directional link between sleep and mental health due to overlapping neural and endogenous regulatory pathways.\textsuperscript{11,12} Research directly exploring associations between fertility and sleep duration in specific is also lacking. Two recent studies observed a weak association between shorter sleep duration and reduced fecundability among women and men attempting pregnancy.\textsuperscript{8,21} In addition, a growing body of research has confirmed non-linear associations between sleep duration and other health outcomes, with higher prevalences of psychological and physical symptoms, as well as increased mortality, not only in those who report short sleep (eg, <5 or 6 hours), but also in those with very long sleep (eg, >9 or 10 hours).\textsuperscript{22,23}

In men, self-reported sleep disturbance, short or very long sleep duration, and late bedtimes have all been associated with poor semen quality.\textsuperscript{24-27} However, only limited evidence is available on the prevalence of poor sleep quality among men undergoing fertility treatment, with only one study reporting that 46.3% of men experienced sleep disturbances during the early stages of fertility treatment.\textsuperscript{24} Taken together, the available evidence on sleep quality during fertility treatment is limited, and our objective was therefore, to explore self-reported sleep duration and sleep quality in couples undergoing IVF or ICSI fertility treatment. In addition, we wished to explore possible associations with hormonal stimulation protocol type, psychological distress, and ultimately pregnancy outcome.

Materials and methods

The present study draws on data collected in a previously published randomized controlled trial examining the effects of expressive writing intervention (EWI) on psychological and pregnancy outcomes in couples receiving fertility treatment with IVF or ICSI.\textsuperscript{28} EWI participants participated in three 20-minute home-based writing exercises focusing on emotional disclosure concerning infertility/fertility treatment (2 sessions) and benefit finding (1 session). Controls wrote nonemotionally in three 20-minute sessions about their daily activities. The data concerning sleep quality have not previously been published. The study was registered with clinicaltrials.gov (trial no. NCT01187095, date of trial registration: August 2010) and approved by the regional scientific ethical committees and the Danish Data Protection Agency. For details, see.\textsuperscript{28}

Participants

Couples experiencing infertility and scheduled to receive IVF or ICSI treatment were recruited from three Danish fertility clinics: The Fertility Clinic at Aarhus University Hospital, Skive Fertility Clinic, and Brædstrup Fertility Clinic. Participants were included from November 2010 until July 2012 and were either beginning their first treatment with IVF/ICSI or had already undergone one or more cycles without success. More than half of the participants (n = 151) were in their first cycle, and only 22.4% had revied more than three stimulations cycles. The inclusion criteria were a) couples with an indication for IVF or ICSI treatment, b) age between 18 and 45 years, and c) ability to read and write Danish. Couples requiring preimplantation genetic testing were excluded, as they generally followed a different treatment protocol with a higher hormonal dose. Data were available for 295 participants at baseline, 240 participants after the intervention, and 216 at follow-up. For further sociodemographic information, CONSORT flow diagram, sample size calculations, and method used to generate and implement random allocation, see.\textsuperscript{28}

Procedure and study design

Couples received oral and written information about the study and were informed that participation was voluntary. If the couples provided informed consent, they individually received access to the first baseline online questionnaire (t1). All couples followed standardized treatment: the women entered either a short (n = 33, 20.5%) protocol with GnRH-agonist or a long (n = 128, 79.5%) hormonal downregulation protocol with GnRH-agonist from cycle day 21 and stimulation with either rFSH or hMG in relation to IVF or ICSI treatment. When ovarian follicles had matured appropriately according to number and size, oocytes were retrieved two days after an injection to induce ovulation. Three or five days later, a single embryo or blastocyst was transferred to the women’s uterus. Sixteen days later, a blood sample was collected to assess hCG, and five weeks after embryo transfer, a vaginal ultrasound examination was performed to confirm the pregnancy. Participants received questionnaires evaluating the PSQI and psychological distress (COMPI, BDI, and STAI) at three time-points. Baseline questionnaires (t1) were intended to be collected from all the women before any medical stimulation protocols were started. However, a minority of the women receiving a short downregulation protocol may have responded to the questionnaires during the first days of commencing ovarian stimulation. Prior to the pregnancy test, the participants received a second questionnaire (t2). The third and final follow-up questionnaire (t3) was received 9-11 weeks after the second questionnaire (t2). The three time-points were selected to evaluate potential changes in sleep quality over the different stages of treatment.

Measures

All participants were asked to complete a questionnaire regarding sociodemographic and clinical characteristics. Patient records confirmed the protocol length, the ultrasound pregnancy result, and characteristics such as age and gender.

Subjective sleep measures

Self-reported sleep quality was measured with the PSQI, a widely used questionnaire for assessing sleep quality.\textsuperscript{29,30} The PSQI yields a seven-component score, measuring subjective sleep quality, latency, efficiency, duration and disturbances, use of sleeping medication, and daytime dysfunction, summed to produce a global measure of sleep, with higher scores denoting poorer sleep quality (range = 0–21). A cut-off of 5” has been suggested to distinguish between “good” and “poor” sleepers, with a diagnostic sensitivity of 89.6% and specificity of 86.5%.\textsuperscript{29} Sleep quality was measured at all three time points (t1-t3). As done in a previous study, (7), global PSQI scores were further categorized into three groups: “good sleepers” (≤5), “poor sleepers” (>5), and “very poor sleepers” (>10). Sleep duration was also
assessed at t1, t2, and t3 using item 4 on the PSQI, which asks "During the last month, how many hours of actual sleep did you get at night?".

Psychological distress

Psychological distress was measured at all three time-points (t1-t3) and included a) self-reported infertility-related stress measured with the 14-item Copenhagen Multi-Centre Psychosocial Infertility scale (COMPI) with continuous total scores ranging between 14 and 38, b) depressive symptoms measured with the 21-item Beck Depression Inventory (BDI) with continuous scores ranging from 0 to 63, and c) state anxiety assessed with the State-Trait Anxiety Inventory (STAI) Form Y with continuous scores ranging from 20 to 80.

Clinical pregnancy

Pregnancy outcome was defined as clinical pregnancy, that is, a vaginal ultrasound examination showing at least one gestational sac with fetal heartbeat performed 5 weeks after embryo transfer. Pregnancy data were obtained from clinical records. The women participated with only one treatment cycle and one embryo transfer.

Data analysis, statistical analysis

Statistical analyses and assessments were performed using IBM SPSS statistics version 24. Mixed linear models (MLMs) were recreated in R 4.0.2 using the lmer package to facilitate assumption checking. Results are based on mixed linear models, bivariate Pearson's correlations, logistic regression, and chi-square tests.

An MLM with random intercept was selected to evaluate possible associations between sleep quality and the study parameters. Effect of time (t1, t2, t3), group randomization EW1/control, long/short protocol type, psychological distress (COMPI, STAI, BDI) and woman/partner were coded as fixed variables. The random effects were coded as a random intercept due to the dyadic nature of the data. Couples were assigned individual unique identifiers throughout the dataset prior to analysis to account for the possible interconnectedness in couples' responses. An expanded model including random slope with time as a random effect was also explored allowing each partner to vary individually over time. However, this extended model did not vary significantly from the simpler random intercept model and hence the simpler model was chosen.

The data were analyzed for the women, their partners, and both combined. The variable "protocol type" was included in the women's analyses only, as only the women received the hormonal treatment. For the separate women/partner models, a 2-level model was used, with level one being each observation and level 2 on a per subject level. In the combined model, a 3-level model was utilized, with level one being each observation, level 2 on a per subject observation, and level 3 the dyad identifier of the couple. Assumptions regarding the mixed linear models were tested with QQ normal distribution plots of the residuals. It was observed that residuals were not normally distributed when using PSQI as a dependent variable. Therefore, the data were transformed by creating a PSQI_log dependent variable in the models instead, which represented a better fit of the residuals. Residuals vs. fitted values were also compared with the logged data performing better. The resulting coefficients are reported as $10^2$ due to the results being small. All parameter $p$ values were significant in the Type III test of the fixed effects.

Bivariate Pearson's correlations were used to analyze associations between PSQI results and age, and logistic regression to explore associations between sleep quality at t1 and t2 and pregnancy outcome at t3. Differences in mean PSQI scores and sleep duration between women who obtained pregnancy and those who did not were analyzed with paired t tests.

Finally, possible nonlinear associations between self-reported sleep duration at t1 during the previous month (PSQI item 4) and pregnancy were explored by comparing percentages of pregnancies in women reporting to have slept <5 hours, 6 hours, 7 hours, 8 hours, and >9 hours, the association analyzed with a chi-square test. Study dropouts were defined as participants failing to complete questionnaires at t2 and t3.

Results

A total of 651 women and their partners were approached, and 308 (47.3%) agreed to participate in the study. Thirteen did not complete the baseline questionnaire, resulting in 295 included participants. Twenty-one women and one man participated without their partners. Two couples consisted of two females, with the woman undergoing IVF/ICSI treatment completing the female questionnaire and the other woman the partner questionnaire. A total of 79 participants (26.7%) dropped out during the study, of whom 65.8% were partners (n = 52). At t2 and t3 respectively 55 participants (women n = 22 and partners n = 33) and 24 participants (women n = 5 and partners n = 19) were lost to follow-up. Compared with participants who completed the study, dropouts did not differ on any of the observed characteristics or outcomes at baseline. Three women were excluded from the data set due to invalid answers regarding protocol type. For further details, see.

Sleep quality

As seen in Table 1, the mean PSQI global score for the total sample at baseline was 8.1 (standard deviation [SD]: 2.3), with 91.1% of the participants having a PSQI global score > 5, indicating poor sleep quality.

| Table 1 |
|---|
| **Sleep quality as PSQI global score at t1-t3.** |
| **Category** | **Global PSQI score - t1** | **Global PSQI score - t2** | **Global PSQI score - t3** |
| Women | Mean | 8.25 ± 2.41 (4-17) | 8.39 ± 2.29 (3-17) | 8.13 ± 2.29 (4-16) |
| | N | 154 | 136 | 120 |
| | PSQI > 5 | 92.2% | 94.5% | 90.0% |
| Partners | Mean | 8.02 ± 2.12 (4-17) | 7.83 ± 2.26 (4-13) | 7.85 ± 2.15 (4-14) |
| | N | 128 | 94 | 76 |
| | PSQI > 5 | 89.1% | 85.1% | 86.8% |
| Total | Mean | 8.14 ± 2.29 (4-17) | 8.16 ± 2.29 (3-17) | 8.02 ± 2.23 (4-16) |
| | N | 282 | 230 | 196 |
| | PSQI > 5 | 91.1% | 90.9% | 88.8% |
| Difference | p | .049 | .09 | .049 |

PSQI, Pittsburgh Sleep Quality Index. Data presented as mean ± SD (range) or frequency (%). Significant difference between women and partners (p < .05), calculated with t test.
The women had received either a long GnRH agonist protocol (n = 128, 79.5%) or a short GnRH antagonist protocol (n = 33, 20.5%). No association was found between fertility treatment protocol type and sleep quality (p = .35; Table 2).

Sleep quality and psychological distress data

Mean psychological distress scores for the total sample at baseline were 10.0 (SD: 8.6) for depressive symptoms, 37.3 (SD: 10.9) for state anxiety, and 16.5 (SD: 9.1) for infertility-related distress.
As seen in Table 2, Models 2, 4, and 6 examining women, partners, and both combined, PSQI global scores were statistically significantly associated with state anxiety and depressive symptoms in all three models \((p = .00-.01)\). Sleep quality was not associated with infertility-related stress, as measured with the COMPI \((p = .21-.65)\).

**Sleep quality and pregnancy**

Among women undergoing treatment, the overall pregnancy rate at t3 was 49.4% \((80/162)\). When examining the association of PSQI global scores at t1, t2, and t3 with pregnancy at t3, none of the associations reached statistical significance \((Odds ratio (OR) = 0.96, p = .55; 0.94; p = .40; 1.02, p = .76)\). To further explore the data, based on PSQI scores, the women were categorized as “good sleepers” \((PSQI \leq 5; n = 11)\), “poor sleepers” \((PSQI 6-10; n = 116)\), and “very poor sleepers” \((PSQI \geq 11; n = 26)\). When compared to “good sleepers” in a logistic regression, fewer “poor” \((OR = 0.42; p = .21)\) and “very poor sleepers” \((OR = 0.28; p = .10)\) became pregnant. The difference did, however, not reach statistical significance. Adjusting for group allocation \((controls vs intervention with EWI)\), did not change the results. The mean PSQI scores of women who became pregnant were 8.1 \((SD: 2.48)\) and 8.4 \((SD: 2.35)\) for those who did not. The PSQI scores of the two groups did not differ \((p = .52)\).

**Sleep duration and pregnancy**

Self-reported daily sleep duration within the last month \((PSQI item 4)\) of men and women is shown in Fig. 1. There was no statistical significant association between self-reported sleep duration at baseline \((t1)\) and pregnancy \((chi-square = 1.4; p = .84, effect size w = 0.093)\). Mean sleep duration was 7.54 \((SD:1.21)\) hours for the group of women who became pregnant during the study and 7.42 \((SD: 0.77)\) for the women who did not. There was no statistically significant difference between the two groups, \(p = .48\).

**Discussion**

**Subjective sleep quality**

In the present study, the majority \((91.1\%)\) of the women undergoing fertility treatment and their partners reported poor sleep quality at baseline \((t1)\), as measured by a global PSQI score above the suggested cut-off of 5, which is considerably more prevalent than the 14%-40% found in studies of younger adults in the general population \((age 15-40 years)\).\(^6^,^7\) The proportion of poor sleepers in the present study was also considerably higher than in previously published PSQI data on women receiving fertility treatment \((4, 5)\). In one study of 21 women, 57%, 43%, and 29% were poor sleepers before ovarian stimulation, during hormonal stimulation, and after embryo transfer, respectively.\(^4\) In another study with 100 participating women, 23% had poor sleep quality during oocyte retrieval and 46% at the time of embryo transfer. However, this study used a PSQI cut-off score for poor sleep quality at 6 or higher.\(^5\) Furthermore, in the present study, the proportion of poor sleepers among women did not change much over time \((t1 = 92.2%, t2 = 94.9% and t3 = 90.0\%)\). We have no clear explanation for the difference between our results and the previous findings. One possible explanation could be variations in assessment time points. Furthermore, the smaller sample sizes in the previous studies \((n = 21 and 100)\) should caution interpretations.

As fluctuations in reproductive hormones may influence sleep regulation and quality,\(^14^,^16^,^34\) a possible explanation for the poor sleep quality observed in the women in our study could be the hormone treatment received during IVF/ICSI. This explanation finds support in previous studies, where women receiving the long GnRH agonist protocol reported more impaired sleep quality than women receiving the short protocol.\(^13\) However, in the present study, treatment-induced hormonal change did not appear to affect sleep quality, as PSQI global scores did not differ between women receiving the long and short protocol, did not change over the three assessment time points, and was already elevated before treatment at baseline. Moreover, PSQI global scores did not differ between the women and their partners. Rather than being only related to hormonal changes, the high level of sleep disturbance could thus be a response to infertility itself and the treatment situation in general. Treatment with IVF/ICSI is known to be a considerable emotional burden for couples, and sleep disturbance has been claimed to be a significant source of psychological distress in women having problems with conception.\(^5\) This interpretation is supported by the correlations between PSQI scores and depressive symptoms and anxiety observed in the present sample.

To our knowledge, the present study is the first to evaluate the sleep quality of both the women and their partners during fertility treatment.
treatment with IVF/ICSI. Our results indicated that a majority of the partners also experienced considerable sleep problems (89.1% with PSQI > 5 at baseline). One other study has investigated sleep among the men in couples seeking evaluation for primary infertility and found that 46.3% reported insufficient sleep at that time point.24 The results, however, were based only on single questions regarding subjective sleep insufficiency. Taken together, the available data suggest that poor sleep quality is common among men undergoing fertility treatment, and since sleep quality might affect semen quality,24-27 this association could have public health implications and needs to be further explored.

Sleep quality and psychological distress

Generally, the psychological distress scores obtained at baseline did not indicate a high prevalence of distress in the sample. Still, the associations found between poor sleep quality and psychological distress together with the general associations found between higher levels of distress and poorer pregnancy outcomes of fertility treatment35 call for research examining the possible effects of improving psychological distress by interventions targeting poor sleep.

Sleep and pregnancy outcome

No statistically significant difference in pregnancy outcome was found between women with good (PSQI ≤ 5) and poor sleep quality (PSQI > 5). When we further explored the associations between sleep quality and pregnancy outcome by dividing the women into “good sleepers,” “poor sleepers,” and “very poor sleepers,” a visual presentation of the data suggested a “dose-response” relationship, with poor subjective sleep being associated with reduced likelihood of becoming pregnant. It should, however, be emphasized that the results did not reach statistical significance.

As a growing body of research suggests non-linear associations between sleep duration and various psychological and physical health outcomes,8,22,23 we also explored whether there were any indications of a nonlinear relationship between sleep duration and pregnancy. When visually inspecting the association, our data suggested lower chances of pregnancy not only in women with very short daily sleep (≤5 hours) but also in those with very long daily sleep (≥9 hours). However, it should be stressed that the results did not reach statistical significance. Previous research in the associations of sleep with pregnancy outcome is minimal, but the possibility of such associations has previously been suggested by findings of a trend toward an association between total sleep time and the number of oocytes retrieved,4 with the number of oocytes retrieved being a predictor of pregnancy outcome.36,37 Furthermore, trouble sleeping at night has been found associated with modestly reduced fecundability in a dose-response manner in women attempting pregnancy without fertility treatment.8

Finally, the overall pregnancy rate in the study was high (49.4%) when compared with Danish national registry data indicating pregnancy rates following IVF/ICSI to be only around 20%.38 The clinic at Aarhus University Hospital was the best in the country at the time of the study. Thereto, the high pregnancy rate might also be due to selection bias, as participants choosing to be a part of a research study, might have better compliance according to treatment. Taken together, the possible associations between pregnancy outcomes and sleep quality and sleep duration should be further explored in larger, well-powered studies.

Strengths

The present study has several strengths. First, the sample size is the largest so far compared with previously published research on sleep quality during IVF/ICSI treatment. Second, data were included on both the women and their partners during IVF/ICSI-treatment, with previous studies only having examined the women.4,5 Third, the sample was recruited from three different sites, increasing generalizability of the findings. Fourth, sleep quality was assessed with the PSQI, a widely used, reliable, and valid measure of sleep quality.30 Finally, the present study is among the first to evaluate a possible association between sleep quality and pregnancy outcome.

Limitations

Several limitations should also be noted. First, the moderate response rate may limit generalizability, as we cannot exclude that responders and nonresponders differ in their sleep quality. Second, sleep quality was evaluated with a self-report measure. While practically challenging, the inclusion of objective measurements such as actigraphy or polysomnography could have validated the PSQI outcomes and contributed with additional data on the sleep characteristics of couples undergoing fertility treatment. Although objective measurements are not routinely indicated in evaluating sleep difficulties,39 previous studies have shown weak or inconsistent associations between the PSQI or ESS and objective measures.40 However, self-reported sleep quality may still be a highly relevant outcome measure as it captures the impact on quality-of-life that objective measures do not. Third, data on previous sleep disorders/disturbances, lifestyle factors, medical or psychiatric history prior to the study were not collected. Participants’ prior circumstances could influence their actual sleep, psychological health, and fertility. Fourth, we did not obtain information on work-related issues such as shift work and working hours. Both aspects could have an impact on circadian processes, which are believed to be an integral regulatory part of the endogen profile and the reproductive system and therefore might influence the possibility of pregnancy.3,14,16,41

Conclusion

The present—and largest study to date—demonstrated that poor sleep quality as assessed with the PSQI is common among couples undergoing IVF or ICSI. The prevalence of poor sleep found in the study was considerably higher, not only than in the comparable age group in the general population but also compared with previous samples of women in treatment for infertility. Furthermore, both the women and their partners appeared to be equally affected by poor sleep. Positive and statistically significant associations were found between sleep quality and depressive symptoms and anxiety. In addition, although results did not reach statistical significance, the data suggested possible associations between sleep quality and pregnancy outcome. As many are affected by infertility and need advanced professional treatment at considerable costs, every improvement of pregnancy outcome and mental health is of value. Since sleep is a relatively easy modifiable possible effector, it would be relevant to study this aspect further. Sleep interventions for men and women undergoing fertility treatment could be beneficial. Our results add to the evidence that poor sleep quality is a prevalent concern among couples undergoing fertility treatment and emphasize the clinical relevance in addressing sleep problems in this patient group.

Declaration of conflict of interest

None of the authors have any conflicts of interest to declare.

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