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Sleep in women undergoing in vitro fertilization: a pilot study

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Abstract

Objective—Sleep disturbances are thought to be frequent in women undergoing IVF despite minimal research of this hypothesis. Our goal was to longitudinally assess sleep duration and disturbances in women undergoing IVF and assess impact of habitual sleep duration on oocytes retrieved, an important outcome in IVF.

Methods—Actigraphy and questionnaire batteries containing sleep and psychometric instruments were performed prior to and throughout 24 IVF cycles.

Results—TST <7 hours was present in 46%, 57%, 69%, and 42% of baseline, stimulation, post-oocyte retrieval, and post-embryo transfer recordings. ESS>10 was noted in 24%, 33%, and 36% of cycles during baseline, stimulation, and post-embryo transfer. PSQI>5 was noted in 57%, 43%, and 29% of cycles during baseline, stimulation, and post-embryo transfer. TST ($F=2.95$, $p=0.04$) and ESS ($F=4.36$, $p=0.02$) were the only sleep metrics in which a significant main effect of time was found by mixed models analysis. The final linear regression model chosen by stepwise selection to best explain the variability in oocytes retrieved included anti-mullerian hormone, day 3 follicle stimulating hormone, and baseline TST and explained 40% of the variance in oocytes retrieved (adjusted $R^2=0.40$, $p=0.03$). Although not statistically significant, a trend towards a linear association between baseline TST and oocytes retrieved was seen with an increase of oocytes retrieved by 1.5 for every hour increase in TST ($p=.09$).

Conclusions—This is the first study to describe, with subjective and objective measures, sleep disturbances present throughout the IVF cycle. Importantly, a trend towards a linear relationship between TST and oocytes retrieved was found in this pilot study. Sleep may be a modifiable target to improve outcomes in women undergoing IVF and further investigations are needed.

Keywords

sleep duration; actigraphy; infertility; in vitro fertilization

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INTRODUCTION

The prevalence of infertility in the United States is estimated at 15%, and 5 billion dollars are spent yearly on its evaluation and treatment.¹ Unfortunately, a commonly used assisted reproductive technology, in vitro fertilization (IVF), is costly and limited in efficacy, producing live births in <40% of cycles.² Sleep disturbances are thought to be frequent in patients undergoing IVF^{3, 4}; however, studies that assess sleep in women undergoing infertility treatment are few. One investigation identified that 34% of women attending an infertility clinic answered yes to the question “do you experience disturbed sleep.”⁵ Sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI), was found to be poor in 35% of women receiving infertility treatment with intrauterine insemination.⁶ The same study team assessed the PSQI in women undergoing IVF and found that 23% of women had poor sleep during oocyte retrieval and 46% had poor sleep at the time of embryo transfer.⁷

Increased psychological stress has been associated with failure to achieve clinical pregnancy via IVF⁸⁻¹³; however, findings have varied.^{14, 15} The inconsistencies observed in this area may result, in part, from differences in the instruments used to measure stress and variation in the time of assessment. Psychological stress and sleep disturbances are closely related.¹⁶ The relationship may be bidirectional as stressors may disturb sleep, and poor sleep may worsen psychological distress.¹⁷ Not surprisingly, women with disturbed sleep (as measured by the PSQI) were 2-3 times more likely to display psychological distress during the IVF process.⁷ Despite the vulnerability of this group to stress and resultant sleep disruption, the impact of poor quality sleep on reproductive outcomes during IVF, in conjunction with or independently from psychological stress, remains unknown.

Further, chronic sleep deprivation, ubiquitous in modern society, is a biological stressor¹⁸ that can augment activity of the hypothalamic pituitary axis¹⁹ and sympathetic nervous system,²⁰ and result in excessive oxidative stress^{21, 22}. Similar physiological profiles may exert a negative impact on IVF outcomes²³⁻²⁷.

Given the above, disturbed or insufficient sleep may be detrimental during IVF. Since sleep is a modifiable target, the prevalence of sleep disturbance in women undergoing IVF - and the impact on outcomes - merits investigation.

The goal of this longitudinal study was to evaluate the frequency of short sleep duration and sleep disturbances in women undergoing IVF and to determine the change in sleep over the course of the IVF cycle. Actigraphy was used as a validated method to collect sleep data in the ambulatory environment to provide a more precise estimate of sleep duration than self-report.^{28, 29} Additionally, we conducted an exploratory analysis to determine the impact of habitual sleep duration on the number of oocytes retrieved, an important clinical outcome in IVF and a measure associated with the ultimate goal of live birth.³⁰

MATERIALS AND METHODS

Participants and Study Design

Women planning to undergo in vitro fertilization (IVF) were recruited from the University of Michigan Center for Reproductive Medicine. Excluded were individuals under 18 years of age, those using donor oocytes, and individuals undergoing IVF for the purpose of fertility preservation without intent for embryo transfer. Individuals with BMI over 40 kg/m² were excluded as per clinical protocol at this center. The study was approved by the University of Michigan Institutional Review Board and all women provided written informed consent.

In clinical practice, women undergoing IVF may have differing clinical protocols for treatment. The final common pathway in all women undergoing IVF is ovarian stimulation with injections of follicle stimulating hormone (FSH), human menopausal gonadotropins (hMG), or both. Doses are adjusted based on ovarian response. Prior to or during ovarian stimulation, the endogenous luteinizing hormone surge (LH) is suppressed. After the ovarian follicles have matured appropriately, oocytes are retrieved. Three or five days following oocyte retrieval, embryo or blastocyst transfer takes place. Pregnancy testing occurs 9 or 11 days later, depending on the day of transfer, with serum beta hCG. In some cases, individuals will decide to undergo preimplantation genetic testing which, at this particular clinic, requires development to the blastocyst stage and cryopreservation with plans for a transfer in a later cycle when the genetic information is available for embryo selection. Less commonly, individuals in which a fresh cycle embryo transfer was originally planned may have the transfer cancelled and require freezing of all embryos to reduce the risk of severe ovarian hyperstimulation syndrome. In this case embryo transfer occurs in a subsequent cycle depending on the health of the patient.

Due to the dynamic nature of IVF and changing hormonal profile, subjective and objective sleep measures were recorded at the following times: prior to the initiation of ovarian stimulation (baseline), during controlled ovarian stimulation (stimulation), and post-embryo transfer prior to pregnancy testing with beta hCG.

Actigraphy

Objective sleep-wake cycles were estimated by rest-activity patterns measured by an actigraph worn on the non-dominant wrist (Actiwatch 2, Phillips Respironics, Bend, OR). The Actiwatch 2 actigraph uses a solid-state piezoelectric accelerometer to monitor movement with a 32Hz sampling rate. Data are summarized over one minute epochs. Both activity and illuminance are recorded. Actigraphy is a reliable method to estimate sleep and has been validated against polysomnography.²⁸ Data were downloaded from the Actiwatch 2 and analyzed with Phillips Actiware 6.0.6 software (Phillips Respironics, Bend, OR). Wake threshold values were set at 40 activity counts/minute (medium) and 10 minutes of immobility were required for sleep onset and sleep offset. The standard Respironics Actiware algorithm was used for scoring sleep and wake (Actiware 6.0.6, Phillips Respironics, Bend, OR).

Subjects kept sleep diaries when actigraphy was conducted. The rest intervals in which the sleep wake scoring algorithm was applied were determined from sleep diary data with 'time

you tried to go to sleep' marking the start of the rest interval and 'time you got out of bed for the day' marking the end of the rest interval. In three subjects automated rest intervals were used as the sleep diary data was unavailable (lost in one subject) or appeared unreliable (n=2).

Actigraphy and sleep diaries were recorded during the baseline, stimulation, post-oocyte retrieval, and post-embryo transfer time segments. The goal was to record 3-7 days during baseline, 7-10 days during stimulation, 3-5 days post-oocyte retrieval, and 10 days post-embryo transfer. Parameters extracted from actigraphy analysis were total sleep time (TST), the total hours of scored sleep within the rest interval; sleep onset latency (SOL), the number of minutes after the start of the rest interval to the onset of sleep; sleep efficiency (SE), the TST divided by the duration of the rest interval $\times 100\%$; and wake after sleep onset (WASO) the number of minutes of wakefulness within the rest interval after sleep onset.

Subjective sleep measures

Questionnaire batteries were assessed at baseline, during ovarian stimulation, and after embryo transfer (but prior to pregnancy testing).

The following instruments were assessed. The Pittsburgh Sleep Quality Index (PSQI) measures subjective sleep quality, latency, duration, efficiency, and disturbances as well as the use of sleep medication and daytime dysfunction. The global score (a sum of these 7 components) ranges from 0-21 with a score > 5 identifying poor sleepers.³¹ The Insomnia Severity Index (ISI) is a validated tool to assess the presence and severity of insomnia.³² A score below 8 indicates no insomnia, 8-14 is considered subthreshold insomnia, 15-21 denotes insomnia of moderate severity, and 22-28 reflects severe insomnia.³² The Epworth Sleepiness Scale (ESS) measures the propensity to fall asleep in different situations and is highly associated with self-rated problematic sleepiness. Scores range from 0-24, with a score greater than 10 indicating excessive daytime sleepiness.³³ The STOP questionnaire is a validated measure to identify those at high risk for obstructive sleep apnea; answering yes to two of the four questions is highly predictive of moderate to severe obstructive sleep apnea.³⁴

Stress and anxiety measures

The following psychometric instruments were collected along with the aforementioned subjective sleep measures. The Perceived Stress Scale (PSS) is a widely used questionnaire to measure stress perception.³⁵ The 10-item scale has good validity and assesses frequency of feelings related to stress over the past month. Each item can be rated on a five-point scale (0 to 4) with a sum from 0 to 40 with higher values representing a greater degree of perceived stress.³⁵ In a sample of females drawn from the general population, mean PSS score is 13.7 ± 6.6 .³⁶ The PSS has been used in multiple studies of women with infertility.³⁷⁻⁴²

The Concerns of Women Undergoing Assisted Reproductive Technologies (CART) scale is a 10-item tool to rate concern levels regarding different components of the IVF process; the average of the items ranges from 1-3 with higher scores indicating greater concern regarding

the procedural, financial, work related, and outcome aspects of assisted reproductive technology.⁴³

Clinical characteristics

The following relevant clinical metrics were extracted from the electronic medical record. The main outcome variable is the number of oocytes retrieved. This is an important clinical outcome and has a linear association with live birth up to 15 oocytes, with a plateau around 15-20 oocytes, and decline after 20 oocytes retrieved (secondary to the association with ovarian hyperstimulation syndrome).³⁰ Anti-müllerian hormone (AMH) level, a measure of ovarian reserve, is the strongest predictor of variability in the quantity of oocytes retrieved and checked routinely before the initiation of IVF.⁴⁴ Age, BMI, day 3 follicle stimulation hormone (FSH), and total gonadotropin dose were also determined from the medical record due to their relevance in IVF. Infertility diagnoses as defined by the Society for Assisted Reproductive Technology (SART) were also obtained. The SART infertility diagnoses are: male factor, diminished ovarian reserve (decreased fecundity due to reduced quality or quantity of oocytes), ovulatory dysfunction (infrequent or absent ovulation), tubal factor (tubal disease affecting the patency of the fallopian tubes), uterine factor (uterine abnormalities preventing implantation), endometriosis (disruption of reproductive anatomy by endometriosis), recurrent pregnancy loss, unexplained (no reason found for either partner), or other^{45, 46}.

Statistical analysis

Histograms and descriptive methods were used to examine demographic, clinical, and sleep data for errors and outliers. Sleep parameters obtained from actigraphy were assessed as both continuous and dichotomous variables (TST < 7 hours versus ≥ 7 hours, sleep efficiency < 85% versus ≥ 85%, wake after sleep onset > 60 minutes versus ≤ 60 minutes). Subjective sleep covariates were examined as both continuous and dichotomous based on accepted published cut-points (PSQI > 5 versus ≤ 5; ESS > 10 versus ≤ 10; ISI > 14 versus ≤ 14).³¹⁻³³ Medians or means and standard deviations are reported for non-normally and normally distributed continuous variables respectively. Categorical data are presented as frequencies (%). Spaghetti plots were constructed to evaluate individual and overall trends in sleep parameters over time.

Because this study uses repeated measures and sleep parameters are likely to be positively correlated within subjects, specialized statistical methods were required. Both subjective and objective sleep measures were unbalanced due to different number of measurements among the subjects. Therefore, mixed models were used to account for between-participant variation and within-participant correlation of repeated outcomes. The fixed effects of mixed models were used to evaluate if sleep parameters changed significantly over time. Models with both random intercept and random slope of sleep parameters, allowing for unique time trends among each individual, were considered. Time was considered as both a categorical and linear variable with and without a quadratic term. The Akaike information criterion (AIC) was used to determine best model fit.

Multiple linear regression was used to examine the association of habitual TST (TST at baseline) with oocytes retrieved. Because of the decline in association of oocytes retrieved with live birth after 20 oocytes retrieved (due to ovarian hyperstimulation syndrome), the two individuals with more than 20 oocytes retrieved were removed from this analysis. Stepwise selection was used to determine a final model drawing from the covariate of interest, TST at baseline, along with any potential clinical (age, AMH, day 3 FSH, BMI, total gonadotropin dose), sleep (baseline PSQI, ISI, ESS, STOP) and psychometric (baseline CART and PSS) variables that could confound the relationship with baseline TST and oocytes retrieved. Covariates with p-values less than 0.15 remained in the model. Residuals were visually inspected to ensure the normality assumption was met.

RESULTS

Study participant demographics and clinical characteristics

Twenty-four IVF cycles were observed in 22 women. Two women participated in the study twice in the setting of early cycle cancellation. Their data was retained as cancellation of their initial cycles was prior to oocyte retrieval; therefore, those cycles were not included for analysis of the primary outcome. Median age was 32.5 years and median BMI was 24.7 kg/m². Infertility was attributed to one or more diagnosis per cycle. Infertility diagnoses frequency, median AMH, day 3 FSH, number of oocytes retrieved, and total gonadotropin dose are reported in **Table 1**.

Nine (37.5%) IVF cycles were cancelled during the study. Timing of cycle cancellation was as follows: one prior to the start of stimulation injections, four after stimulation injections had begun but prior to oocyte retrieval, and four after oocyte retrieval but prior to embryo transfer. Ovarian cyst was responsible for cycle cancellation prior to the start of stimulation injections. Four cycles were cancelled prior to oocyte retrieval because of poor ovarian response to stimulation. Cancellations prior to embryo transfer were attributed to: ovarian hyperstimulation syndrome, arrest of embryo development, or no euploid embryo identified with preimplantation genetic screening. Three cycles were converted from planned fresh transfer to subsequent frozen transfer due to patient decision to undergo preimplantation genetic screening and in one individual at risk of ovarian hyperstimulation syndrome.

In addition to cycle cancellation, incomplete data collection resulted from the following. Two subjects did not participate in the baseline assessment (neither actigraphy recording nor subjective). One subject declined participation in the post-embryo transfer portion of the study. One subject lost all subjective measures for the entirety of her cycle. In one subject whose IVF cycle was complete, actigraphy data could not be recovered after oocyte retrieval.

Actigraphy measures

The median number of days recorded for baseline, stimulation, post-oocyte retrieval, and post-embryo transfer segments were 7 (2-15, n=22 cycles), 10 (4-16, n=23 cycles), 5 (1-18, n=16 cycles), and 9 (4-11, n=13 cycles) respectively. Mean TST, SOL, SE, and WASO are reported in **Table 2**. Percentages of short TST, increased SOL, reduced SE, and increased

WASO at each time point are also presented in **Table 2**. Of note, almost half of women had TST <7 hours at baseline.

Pattern of TST, SE, WASO, and SOL over the four time points is illustrated in **Figure 1**. Random effects modeling of TST demonstrated that use of a random intercept best fit the covariance of the data. The best model fit of the fixed effects was achieved with time as categorical variable. Type 3 measures of fixed effects showed a significant main effect of time for TST ($F=2.95$, $p=0.04$). TST was 0.3, 0.3, and 0.5 hours shorter at baseline, stimulation, and post-oocyte retrieval time points compared to post-embryo transfer ($p=.08$, $p=.04$, $p=.005$ respectively). SE, WASO, and SOL did not significantly change over time.

Sleep and psychometric questionnaire data

Mean PSQI, ISI, ESS, STOP, CART, and PSS scores are presented in **Table 3**. A PSQI score greater than 5, indicative of poor sleep quality, was present in 57% of cycles during baseline, 43% of cycles during stimulation, and 29% of cycles post embryo transfer (**Table 3**). An ISI score indicative of clinically significant insomnia was present in 4.8% of cycles during baseline, 4.8% of cycles during stimulation, and 14.3% of cycles post embryo transfer (**Table 3**). Excessive daytime sleepiness marked by an ESS>10 was noted in 24% of cycles during baseline, 33% of cycles during stimulation, and 36% of cycles post embryo transfer (**Table 3**).

Random effects modeling of ESS demonstrated that use of a random intercept best fit the covariance of the data. The best model fit of the fixed effects was achieved with time as a categorical variable. Type 3 measures of fixed effects demonstrated that ESS significantly changed over time ($F=4.36$, $p=0.02$). There was an average increase in ESS of 2 points from baseline to stimulation with a non-significant increase of ESS from baseline to after embryo transfer. **Figure 2** demonstrates change in ESS over time. The PSQI, ISI, CART, and PSS scores did not change over time.

Linear regression model

Linear regression modeling was used to explore the association of baseline TST with the number of oocytes retrieved. Stepwise selection was used to determine the model and drew from age, total gonadotropin dose, BMI, AMH, day 3 FSH, and TST at baseline. Co-variables with the potential to confound the relationship of TST at baseline with oocytes retrieved (baseline PSQI, ISI, ESS, STOP, CART, and PSS) were also considered for inclusion in the model. Covariates with p-values less than 0.15 remained in the model. The final model included AMH, day 3 FSH, and baseline TST and explained 40% of the observed variance in oocytes retrieved (adjusted $R^2=0.40$, $p=0.03$; **Table 4**). The intercept value was not statistically different from zero ($p=0.71$). The expected number of oocytes retrieved was found to increase by 1.5 for every 1-hour increase in TST (adjusting for AMH and day 3 FSH) with a trend towards statistical significance ($p=.09$).

DISCUSSION

This novel pilot study is the first investigation to characterize sleep in women undergoing IVF with validated objective and subjective measures. We demonstrated that short sleep

duration, excessive daytime sleepiness, and poor sleep quality are common in this group. Both sleep duration and excessive daytime sleepiness changed over the course of the IVF cycle. The most notable finding in this study, although not reaching statistical significance, was the trend for a linear association between baseline sleep duration and oocytes retrieved with the number of oocytes retrieved increasing by 1.5 on average for every 1-hour increase in TST. TST, AMH, and day 3 FSH together explained 40% of the variance of oocytes retrieved. This finding suggests, for the first time, that sleep duration may be a mediator of important markers of IVF success.

Prevalence and evolution of sleep disturbances during the IVF cycle

Actigraphic sleep duration

Sleep <7 hours was noted in approximately 45-70% women depending on which point in the cycle it was measured. To our knowledge, this is the first study to assess the frequency of objectively measured sleep duration in women undergoing IVF. Park and colleagues noted (in abstract form) that among women undergoing IVF, 18.3% reported short (4-6 hours) sleep; however, the exact metric used to quantify sleep duration is unclear and the time of assessment unknown.⁴⁷ Apart from Park's investigation, the frequency of short sleep duration in women undergoing infertility evaluation or treatment has not been described. Our findings are not surprising as Centers for Disease Control survey data have demonstrated that approximately 30% of women 25-44 years of age report sleep less than or equal to 6 hours in a 24 hour day and the mean sleep duration in this age group is approximately 7.1 hours.⁴⁸

Notably, insomnia was uncommon in our population; therefore, short sleep duration was likely a result of behavioral sleep restriction as opposed to the inability to fall or stay asleep despite adequate opportunity. Restricted time allocation for sleep may be seen in this group as women who utilize IVF are often employed⁴⁹ and monetarily compensated work time has the largest inverse relationship with sleep duration compared to other time use activities.⁵⁰

Sleep duration changed over the course of the IVF cycle with a significant increase in total sleep time (TST) after embryo transfer compared to TST during stimulation and after oocyte retrieval. Decreased activity after embryo transfer (bed rest is typically not recommended, but may be self-imposed) and the tendency for actigraphy to score non-moving wakefulness as sleep may be responsible for this finding. However progesterone, which is a known GABA A receptor agonist⁵¹ that increases NREM sleep,⁵² is given exogenously after oocyte retrieval through pregnancy testing and could be implicated in these findings. However, the hypnotic effect of progesterone has been demonstrated in the context of low estrogen states which differs from the hormonal profile in IVF.^{53, 54}

Apart from the increase in sleep duration after embryo transfer, sleep duration was relatively stable during the IVF cycle and no other actigraphic sleep measures were associated with a significant effect of time. Although direct comparisons are not possible, as this is the first study to assess sleep objectively in women undergoing IVF, this finding is not surprising from a hormonal standpoint based on previous studies of sleep in reproductive age women. Multiple studies in naturally cycling women have assessed sleep with either actigraphy⁵⁴ or

polysomnography⁵⁵⁻⁵⁹ and demonstrate stability of SOL, SE, and TST despite the changing hormonal profiles through the follicular and luteal stages of the menstrual cycle. Caution must be used in equating the follicular stage of the menstrual cycle with controlled ovarian stimulation during IVF. During controlled ovarian stimulation estrogen increases; however, the endogenous LH surge is pharmacologically suppressed and the rise in progesterone is advanced.⁶⁰

Subjective sleepiness

Sleepiness, as defined by an ESS score greater than 10 was seen in 20-30% of women during the IVF cycle. A main effect for time was found with a significant increase in sleepiness from the baseline to stimulation time point. Again, although direct comparison is not possible, naturally cycling reproductive age women demonstrate an increase in subjective daytime sleepiness and increased slow wave sleep during daytime naps in the luteal as compared to follicular phase of the menstrual cycle.⁶¹ Progesterone is the dominant hormone in the luteal phase and the advancement of progesterone secretion during ovarian hyperstimulation in IVF could theoretically contribute to this finding; however, other causes such as a parallel deterioration in sleep quality (although not reflected by changes in actigraphic sleep efficiency or PSQI) cannot be ruled out in this pilot study.

Subjective sleep quality

Poor sleep quality as defined by a PSQI value over 5 was seen in a large proportion of women undergoing IVF (30% to nearly 60% depending on time point). In comparison, the only other investigation that assessed the PSQI during IVF found that 23% of women had poor sleep during oocyte retrieval and 46% had poor sleep at the time of embryo transfer.⁷ However, that investigation used a PSQI total score of 6 or more to define poor quality sleep and the time points of assessment differed from our study which assessed PSQI at baseline, during stimulation (prior to oocyte retrieval), and after embryo transfer. Comparatively, in a group of healthy, non-pregnant women of childbearing age without sleep complaints, PSQI scores >5 were found in 19%.⁶²

The high prevalence of disturbed sleep in our sample was present even prior to the start of ovarian stimulation injections and remained stable over time; therefore, psychological stress⁶³ opposed to hormonal changes during IVF may be responsible for the high percentage of women with poor quality sleep. This finding is not surprising given the work of Lin and colleagues which found an association between poor quality sleep and psychological distress during IVF.⁷ Additionally, our cohort demonstrated an elevated perceived stress scale (16-17 compared to 13.7±6.6 in a general population of women) that remained stable over time which may be consistent with this hypothesis.

Although the proportion of poor sleepers appeared to decrease throughout the IVF cycle, mixed models analysis (which accounts for between-participant variation and within-participant correlation) did not demonstrate a significant decrease in PSQI scores over the IVF cycle. As cycle cancellations are not uncommon during IVF, it is feasible that those who were poor sleepers at baseline were more likely to undergo cycle cancellation. Therefore, women whose cycles were not cancelled and progressed to later stages in the IVF process

may represent a group with inherently better sleep quality. As this is a small pilot study and underpowered to detect binary outcomes, larger groups are needed to explore this hypothesis.

Total sleep time and oocytes retrieved

Perhaps the most intriguing finding of this study was the trend toward a linear association of TST with oocytes retrieved while controlling for day 3 FSH and AMH. The number of oocytes retrieved is an important clinical outcome due to its linear association with live birth.³⁰ There are multiple plausible biological pathways including excessive activity of the sympathetic nervous system and hypothalamic pituitary adrenal axis, elevated ghrelin, and increased oxidative stress that may explain this finding.

The sympathetic nervous system modifies ovarian steroidogenesis and follicular development.⁶⁴ Additionally, cortisol is thought to facilitate follicular development and oocyte maturation^{65, 66} and pathophysiological elevation of cortisol may impede follicular development and steroidogenesis in the ovary.⁶⁶ In women undergoing IVF, despite similar levels of anxiety on psychometric instruments,²³⁻²⁵ epinephrine,²⁵ norepinephrine²³⁻²⁵ and cortisol^{23, 24} levels were significantly higher in women who failed to conceive compared to those who attained clinical pregnancy.

Excessive sympathetic nervous system activity²⁰ and dysregulated activity of the HPA axis¹⁹ can be seen in the setting of insufficient sleep and could be a mechanism explaining the observed, near significant relationship between sleep duration and oocytes retrieved. However, the above studies assessed the outcome of clinical pregnancy as opposed to oocytes retrieved; therefore, other factors may be involved. Additionally, the relationship of cortisol with ovarian function is complicated with studies demonstrating that a higher ratio of cortisol to cortisone in the follicular fluid is associated with improved oocyte maturation and increased likelihood of clinical pregnancy in IVF.^{65, 67} The aforementioned studies used cortisol levels alone without assessment of this ratio.^{23, 24} Further, some studies of the association of poor sleep with increased cortisol have been inconclusive and are complicated by circadian regulation of cortisol secretion.¹⁹

Elevation of serum ghrelin, a well-known outcome of sleep restriction,⁶⁸ may also be a potential mechanism to link sleep duration with oocytes retrieved. In a study of normal weight women undergoing IVF, serum ghrelin levels were negatively associated with oocyte maturation rate, cleavage rate, and number of viable cleavage stage embryos, all factors reflective of oocyte quality.⁶⁹

Oxidative stress, another potential outcome of sleep deprivation,^{21, 22} may be detrimental to oocyte maturation, quality and fertilization^{26, 27}; however, findings regarding the role of reactive oxidative species (ROS) in IVF are contradictory and there may be an optimal physiological level of ROS in IVF and levels below or above this could negatively affect oocyte health.

Of note, the described relationship between TST and oocytes retrieved failed to meet statistical significance. This is likely due to the small size of this pilot study, which is

underpowered to reach statistical significance. Additionally, no individuals had habitually long sleep durations; therefore, a U-shaped association of sleep duration with outcome (as noted with the association of many health outcomes with sleep⁷⁰) cannot be assessed.

Strengths

This study is novel as it is the first assessment of objective and subjective sleep in women undergoing IVF. A major strength of this investigation is the use of actigraphy, which has been validated against polysomnography to estimate sleep duration.²⁸ Further, sleep duration was assessed over multiple nights throughout the IVF cycle, which allowed for more accurate evaluation than a single assessment and also allowed for investigation of change in sleep metrics over time. Although polysomnography is the gold standard for the measurement of sleep, it is not practical over this duration of time. Another strength of this study was the use of validated self-report measures to assess the subjective experience of sleep.

Limitations

Although this is the first study of its kind, this study is not without limitations. Due to the relatively small sample size, to avoid overfitting the model, there was no forced inclusion of any covariates. However, despite allowing for selection of age, total gonadotropin dose, BMI, AMH, day 3 FSH, and multiple baseline sleep and psychometric variables the model selected that best fit the data collected in this study included only TST, AMH, and day 3 FSH,

The fact that this model is not adjusted for age may decrease generalizability; however, other models predicting ovarian response have also found that inclusion of age did not benefit the prediction of ovarian response.^{44, 71} This may be due to the fact that other covariates, in this case AMH and day 3 FSH, better account for biological age of the ovaries more so than chronological age.^{71, 72}

Nonetheless, the sample size is large enough to support three covariates as use of at least two subjects per variable can provide accurate coefficient estimates in multiple linear regression.⁷³ However, the subjects per variable for logistic regression is much larger; therefore, the most relevant outcomes in IVF (attainment of pregnancy and subsequent live birth) could not be evaluated. Additionally, to avoid overfitting the model, interactions between psychometric variables of stress and anxiety with sleep metrics were not assessed and may be important in the relationship between sleep and IVF outcomes.

A final limitation was that we did not assess the impact of circadian phase or shift work on oocytes retrieved. Although the Morningness Eveningness questionnaire and work schedules were collected, 71% of our population fell into the range of 'neither type' and only one individual worked non-day shifts (rotating shift worker) (data not shown). Ample evidence in animals demonstrates rhythmic oscillation of core clock genes in peripheral reproductive organs (reviewed by Boden).⁷⁴ Further, intrinsic circadian disruption with gene mutations⁷⁵ and external circadian disruption with light dark shifts^{76, 77} impairs early stages of conception. There is a potential for circadian contributions to human reproduction as evident

by infertility in shift workers.⁷⁸⁻⁸⁰ Future, larger investigations should address the role of circadian disruption in the success of IVF.

CONCLUSIONS

This initial investigation of sleep in women undergoing IVF demonstrated that short sleep duration and poor quality sleep are common and sleep duration and sleepiness may change over time. Importantly sleep duration may have a role in ovarian response, a critical IVF outcome.

Fifteen states have laws that require insurance companies to cover infertility treatment.⁸¹ Despite the increased resources devoted to IVF, the procedure is still largely unsuccessful with over half of cycles failing to result in live birth.² Because practice guidelines recommend reduced number of embryos transferred during IVF, mechanisms to improve oocyte health and embryo quality are crucial to achieving pregnancy while reducing multiple gestations.⁸² Sleep remains modifiable target worthy of future investigation in larger studies that include the most relevant IVF outcome, live birth.

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ABBREVIATIONS

TST	total sleep time
ESS	Epworth sleepiness scale
PSQI	Pittsburgh Sleep Quality Index
IVF	in vitro fertilization
AMH	Anti-müllerian hormone
FSH	follicle stimulation hormone

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- Short sleep duration, poor sleep quality, and sleepiness are common in IVF.
- Sleep duration and sleepiness change significantly over the IVF cycle.
- Variance in oocytes retrieved was significantly predicted by TST, AMH, and FSH.
- A trend for a linear association of TST with oocytes retrieved was found

Figure 1.

Sleep parameters over time during the IVF cycle. Time point 1=baseline, time point 2=stimulation, time point 3=post-oocyte retrieval, time point 4=post-embryo transfer. Solid black line was fitted with a penalized B-spline curve. WASO=wake after sleep onset. SOL=Sleep onset latency.

Figure 2. Epworth sleepiness scale over time during the IVF cycle. Time point 1=baseline, time point 2=stimulation, time point 3=post-embryo transfer. Solid black line was fitted with a penalized B-spline curve. ESS=Epworth sleepiness scale.

Table 1

Demographics and clinical characteristics.

Age (years)	32.5 (26-42)
BMI (kg/m ²)	24.7 (19.9-37.6)
Infertility diagnosis	
Male factor	66.7%
Diminished ovarian reserve	33.3%
Ovulatory dysfunction	16.7%
Uterine factor	0%
Tubal factor	16.7%
Endometriosis	8.3%
Recurrent pregnancy loss	4.2%
Unknown	4.2%
Other	0%
AMH (ng/mL)	1.2 (0.3-7.7)
Day 3 FSH (mIU/mL)	5.7 (0.4-14.3)
Total GN dose (IU)	3675 (1350-6300)
Oocytes retrieved	9 (6-33)

Data presented as median (range) or frequencies (%). All variables for n=24 cycles with the exception of total gonadotropin dose (n=21 secondary to 3 cycle cancellations early during or prior to stimulation) and oocytes retrieved (n=19 cycles secondary to early cycle cancellation in 5 cycles). Note that more than one infertility diagnosis may be reported for each cycle.

Table 2

Actigraphy sleep characteristics

	Baseline N=22	Stimulation N=23	Post oocyte Retrieval N=16	Post embryo transfer N=13
TST (h) *	7.0±0.9 (4.3-8.3)	7.0±0.8 (5.6-8.2)	6.6±0.6 (5.3-7.5)	7.1±0.7 (6.3-8.3)
SOL (min)	10.8±11.7 (2.3-53.3)	11.5±10.9 (1.6-47.8)	17.6±20.9 (0-81.0)	9.1±7.0 (1.7-22.1)
SE (%)	85.1±4.9 (73.5-91.9)	86.0±4.8 (73.5-93.1)	84.0±7.4 (66.6-92.9)	86.6±4.3 (78.4-93.0)
WASO (min)	43.0±16.2 (21.3-89.7)	40.9±14.4 (18.3-71.7)	41.8±17.4 (12.2-85.0)	44.0±15.5 (22.1-76.0)
TST<7 hours	45.5%	56.5%	68.8%	46.2%
SOL>30 minutes	9.1%	4.4%	25.0%	0%
SE<85%	45.5%	34.8%	43.8%	38.5%
WASO>60 minutes	9.1%	13.0%	12.5%	15.4%

Data presented as means ±SD (range) or frequencies (%).

TST=total sleep time, SOL=sleep onset latency, SE=sleep efficiency, WASO=wake after sleep onset.

* Mixed models analysis (accounting for between-participant variation and within-participant correlation of repeated outcomes) demonstrated a significant ($p<.05$) effect of time.

Table 3

Sleep and psychometric questionnaire data

	Baseline N=21	Stimulation N=21	Post embryo transfer N=13-14 ^T
PSQI	6.1±2.2 (2-11)	5.7±2.6 (2-12)	5.2±1.9 (1-8)
PSQI>5	57.1%	42.9%	28.6%
ISI	7.3±4.0 (1-17)	6.7±3.5 (2-17)	8.0±5.0 (0-15)
ISI>14	4.8%	4.8%	14.3%
ESS[*]	6.4±4.2 (1-16)	7.9±4.6 (2-18)	8.4±4.9(2-17)
ESS>10	23.8%	33.3%	35.7%
STOP	0.9±0.6(0-2)	1.0±0.6 (0-2)	1.0±0.6 (0-2)
STOP>1	9.5%	14.3%	15.4%
CART	1.7±0.3 (1.2-2.4)	1.6±0.4 (1.0-2.3)	1.6±0.4 (1.0-2.3)
PSS	16.9±5.9 (5-28)	16.7±7.2 (4-30)	16.2±6.4 (4-24)

Data presented as means ±SD (range) or frequencies (%).

PSQI=Pittsburgh Sleep Quality Index, ISI=Insomnia Severity Index, ESS=Epworth Sleepiness Scale, CART= Concerns of Women Undergoing Assisted Reproductive Technologies, PSS=Perceived Stress Scale.

^T STOP questionnaire completed only in 13 subjects post embryo transfer.

* Mixed models analysis (accounting for between-participant variation and within-participant correlation of repeated outcomes) demonstrated a significant ($p<.05$) effect of time.

Table 4

Regression analysis of baseline TST impacting oocytes retrieved

Variable	β	SE β	partial R^2	p
Intercept	2.147	5.720	NA	0.714
AMH	0.685	0.391	0.2419	0.108
Day 3 FSH	-0.617	0.285	0.1410	0.054
TST at baseline	1.509	0.809	0.1483	0.089

$R^2 = 0.531$, Adjusted $R^2=0.404$, $p=0.03$, TST=total sleep time.