Sleep variability and time to achieving pregnancy: findings from a pilot cohort study of women desiring pregnancy

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Objective: To determine whether chronodisruption is associated with achieving pregnancy.

Design: Pilot prospective cohort study.

Setting: Academic Medical Center.

Subjects: One hundred eighty-three women desiring pregnancy were recruited from the local community of an academic medical center located in the Midwest and provided sleep information between February 1, 2015, and November 30, 2017.

Exposure: Sleep and activity data were obtained via actigraphy watches worn continuously for 2 weeks to assess measures of chronodisruption, including sleep period onset, offset, midtime, and duration; as well as variability in each of these measures.

Main Outcome Measures: Time to becoming pregnant over 1-year of follow-up.

Results: Of the 183 eligible women, 82 became pregnant over a median of 2.8 months of follow-up. Greater interdaily variability in time of sleep onset and variability in sleep duration were associated with a longer time to achieving pregnancy after adjusting for age, body mass index, race, education, income, and smoking status (adjusted hazard ratio [aHR], 0.60; 95% confidence interval [CI], 0.36–0.999 comparing participants with a standard deviation of \geq 1.8 hours to <1.8 hours in daily time of sleep onset; and aHR, 0.58; 95% CI, 0.36–0.98 comparing participants with a standard deviation of \geq 2.3 hours to <2.3 hours in daily sleep duration). In adjusted analyses, no statistically significant associations were observed for average time of sleep onset and offset, midsleep time, and sleep duration, or for variability in time of sleep offset and midtime.

Conclusion: Higher day-to-day variability in time of sleep onset and sleep duration—two measures of chronodisruption—were associated with a longer time to achieving pregnancy over 1 year of follow-up in women desiring pregnancy. If replicated in additional studies, these findings could point to lifestyle interventions to help women achieve a desired pregnancy. (Fertil Steril[®] 2025;124:113–20. ©2025 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key words: pregnancy success, chronodisruption, lifestyle modification, sleep

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leep duration and timing of sleep influence numerous physiologic functions and are linked to health outcomes. For example, in the general population, deviation in sleep duration has been associated with chronic diseases, including cardiometabolic diseases (1-4). Additionally, chronic misalignment between biological preferred timing for sleep and actual timing of sleep (chronodisruption) is associated with

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negative health outcomes (5). For instance, night shift work is associated with increased risks of diabetes, cardiovascular disease, and cancer (6–8).

Sleep and timing of sleep also appear to affect reproductive health. In reproductive-age women, shortened sleep has been linked with reduced fecundity and gestational diabetes, and sleep disruption has been associated with preterm delivery (9–11). Moreover, shift work is associated with abnormal menstrual cycles, infertility, and early age at menopause (12-16). One challenge in clinical studies of the health effects of sleep and chronodisruption is that they have relied on polysomnography, which is expensive and is conducted in an artificial laboratory environment. A second challenge is that large cohort studies, such as the Pregnancy Study Online, use self-reported data on sleep duration and work schedules, which lack moment-bymoment information (17). To capture sleep patterns in a natural environment, researchers can instead record movement and sleep-wake patterns via watch-like actigraphy devices, which are an accurate substitute for polysomnography (18, 19). Here, we used actigraphy to evaluate the association between sleep characteristics and the timing of achieving pregnancy for >1 year of follow-up in reproductive-age women. We hypothesized that chronodisruption would be associated with a longer time to pregnancy in women desiring pregnancy.

MATERIALS AND METHODS Study design and population

This is a secondary analysis of data from a pilot, prospective cohort study conducted between February 1, 2015, and November 30, 2017 (20, 21). The Washington University in St. Louis Human Research Protection Office approved this study. Women desiring pregnancy were recruited from the local community through health clinics, research databases, and community advertisements. Women were eligible if they were aged between 18 and 45 years, had regular menses, were trying to conceive, and were willing to participate in actigraphy data collection. Women were excluded if they were non-English speaking (to allow for informed consent), met criteria for an infertility diagnosis based on reported selfassessment (>12 months of unprotected intercourse and no pregnancy if the female partner was younger than 35 years, or >6 months of unprotected intercourse if 35 years or older), were undergoing fertility treatments, or were positive for HIV, Hepatitis B, or Hepatitis C.

Study procedures

Participants were asked at enrollment to wear a MotionWatch 8 actigraphy watch (CamNtech Ltd., Cambridge, UK) continuously for 2 weeks. This clinically validated device has a piezoelectric accelerometer with a sensitivity of > 0.05 g and collects activity data in 1-minute epochs. Participants were contacted monthly after enrollment and asked whether they had become pregnant. They were also instructed to notify research staff in the event of a positive pregnancy test. Participants ipants who did not become pregnant were followed for 1 year after enrollment.

Assessment and definition of sleep variables

Actigraphy data were downloaded and viewed with Motion Ware 2.5 (CamNtech Ltd). Data were excluded from any day with <21 hours of on-wrist collection. Participants who provided <7 days of usable actigraphy data were excluded from the analysis. For those who provided \geq 7 days of actigraphy data, all data provided were analyzed. Only night sleep was used to assess sleep time and sleep variability; daytime naps, if they occurred, were not analyzed.

We previously developed an automated, high-throughput algorithm to analyze actigraphy data and validated it against polysomnography (20, 21). Here, we used this algorithm to determine the time of onset and offset of sleep, sleep duration, and interdaily variability for each study participant. Briefly, actigraphy data for each 24-hour period from 12:00 PM to 12:00 PM were fitted into a 3-stage function based on change in activity density (with or without activity during a 1-minute epoch). The algorithm automatically divided each 24-hour period from 12:00 PM to 12:00 PM into 3 phases: "wake," "sleep," and "wake" by activity density. Sleep onset was defined as the beginning of the sleep period. Sleep offset was defined as the end of the sleep period. The sleep midpoint was defined as the time equidistant between sleep onset and sleep offset. Sleep duration was defined as the length of time between sleep onset and sleep offset. We used the average of 14 days of data collection to summarize these variables. Day-to-day variability in sleep onset, offset, midtime, and duration were defined as the standard deviation of the interdaily differences of sleep patterns from one day to the next.

Assessment and definition of pregnancy achievement

Research staff reviewed participants' medical records to confirm a viable intrauterine gestation for each reported pregnancy. They estimated the time to pregnancy as the difference between the date of enrollment and the date of the last menstrual period before a confirmed pregnancy. Infertility was not used as the outcome because the length of time study participants were attempting to become pregnant before participating in the study was not captured.

Assessment and definition of covariates

At enrollment, research staff in the Prematurity Research Center at Washington University asked participants to complete a questionnaire that included items on sociodemographic factors, health factors, menstrual cycle characteristics, and lifestyle factors. These included several factors hypothesized to be associated with both chronodisruption and pregnancy achievement but not in the pathway between these 2 variables (i.e., potential confounders): maternal age, body mass index (BMI), race, education, annual income, cigarette smoking status, drug use, alcohol intake,

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and prior pregnancy (Supplemental Fig. 1, available online) (22). All data were stored in the secure online database Research Electronic Data Capture (23, 24).

Statistical analyses

Before examining the relationship between sleep variability and pregnancy achievement, we first explored the data to investigate the potential for selection bias and confounding. Selection bias was explored by comparing the distribution of baseline covariates between included and excluded study participants by Student's t test for continuous variables and by χ^2 test for categorical variables. Confounding was explored by comparing the distribution of baseline covariates by outcome status.

Next, we used Cox proportional hazards regression to investigate unadjusted associations between chronodisruption and time to pregnancy. Time at risk was defined as the time from the date of enrollment until the date of pregnancy or the date of their last contact during the 1-year follow-up, whichever came first. Sleep variables examined included sleep onset, sleep offset, midsleep time, sleep duration, and day-today variability in each of these variables. Sleep characteristics were dichotomized at the median and then further explored in quartiles. Proportional hazards assumption for all sleep variables was explored by Schoenfeld residuals. To address the potential for selection bias, weights corresponding to the inverse of the probability of inclusion in the analysis were applied to all estimates. These were derived by logistic regression, modeling inclusion status as the dependent variable and baseline covariates that differed between included and excluded participants as the independent variables.

Cox proportional hazards regression was also used to estimate multivariable-adjusted associations between chronodisruption and time to pregnancy. Models included all variables hypothesized as potential confounders (Supplemental Fig. 1) and found to be associated with pregnancy achievement in initial exploratory analyses. Although age was not significantly different by pregnancy status in this cohort, we included it in multivariable-adjusted analyses because of its strong association with fertility (25). For missing covariate data (race, annual income, and smoking), multiple imputation was used, pooling the results of 10 random imputations. Finally, to explore the robustness of our findings to unmeasured and uncontrolled confounding, we calculated approximate e-values for hazard ratios for common outcomes (26).

For all statistical tests, a significance level of P<.05 was applied. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and R (version 4.1).

RESULTS

In total, 278 women were approached, and 252 women enrolled in the study. Sixty-nine participants had insufficient or unusable actigraphy data, leaving 183 participants in this analysis. Common reasons for unusable data were noncompliance because of discomfort with wearing the actigraphy watch and lost or broken actigraphy watches. Participants excluded from the analysis differed significantly from those included in the analysis by BMI, race, education, annual income, drug use, and prior pregnancy (Supplemental Table 1, available online). Specifically, included participants had a lower BMI, were more likely to self-identify as white, to have a college degree or higher and an annual income >\$25,000, and were less likely to report drug use and a prior pregnancy. All effect sizes were small ($0.2 \le$ Cohen's d < 0.5 for continuous variables and $0.1 \le$ Kramer's V < 0.3 for categorical variables).

Of the 183 included participants, 82 achieved pregnancy over a median of 2.8 months and a maximum of 12 months. Participants who became pregnant had a significantly lower BMI and were more likely to self-identify as white, have a college degree or higher, have a paid job, have an annual income >\$25,000, and not smoke cigarettes than those who did not become pregnant (Table 1). They were also nonsignificantly younger and less likely to report drug use.

Sleep characteristics

On average, participants went to sleep at 10:55 PM and woke at 7:23 AM, leading to a mean midsleep time of 3:08 AM and a mean sleep duration of 508 minutes (8.5 hours; Table 2). The mean day-to-day variability of these measures in the cohort was 109 minutes for sleep onset, 102 minutes for sleep offset, 82 minutes for sleep midtime, and 139 minutes for sleep duration.

Sleep characteristics and achieving pregnancy

In unadjusted analyses, later sleep offset and sleep midtime and greater variability in sleep onset, midsleep, and duration were each associated with a significantly longer time to achieving pregnancy (Table 3; Supplemental Table 2, available online). Similar but nonstatistically significant differences were observed for later sleep onset and greater variability in sleep offset. After adjusting for age, BMI, race, education, income, and cigarette smoking, all associations attenuated to nonsignificant values, except for those for variability in sleep onset and duration (sleep onset: adjusted hazard ratio aHR, 0.60; 95% CI, 0.36-0.999 comparing participants with a standard deviation of \geq 1.8 hours to <1.8 hours; and sleep duration: aHR, 0.59; 95% CI, 0.36-0.98 comparing participants with a standard deviation of \geq 2.3 hours to <2.3 hours). When we divided variability in sleep onset and duration further into quartiles, women with the greatest day-to-day variability in sleep onset (quartile 4) had the longest time to becoming pregnant (aHR, 0.33; 95% CI, 0.15-0.74 compared with those with the lowest variability), as did those with the greatest day-to-day variability in sleep duration (aHR, 0.52; 95% CI, 0.26-1.02 comparing quartiles 4 to 1). These associations persisted after adjusting for age, BMI, race, education, annual income, and smoking (Fig. 1, Supplemental Table 2). In sensitivity analyses, we estimated that an unmeasured confounder would have to be fairly strongly associated with both sleep variability and achieving pregnancy to fully explain our adjusted findings (approximate e-value = 0.28-0.45).

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TABLE 1

Demographic and health-related characteristics of study participants who did and did not become pregnant during 1-year of follow-up.

	Pregnant	Not pregnant	
Characteristic	N = 82	N = 101	<i>P</i> value ^a
Maternal age, y, mean (SD)	29.80 (3.87)	30.98 (6.32)	.141
Body mass index, kg/m ² , mean (SD)	25.47 (5.46)	32.26 (9.82)	<.001
Race, n (%)			.001
Black	16 (19.5)	43 (44.3)	
White	56 (68.3)	42 (43.3)	
Other	10 (12.2)	12 (12.4)	
Education, n (%)			<.001
Less than college degree	18 (22.0)	59 (61.5)	
College degree or higher	64 (78.0)	37 (38.5)	
Paid job, n (%)	74 (90.2)	73 (75.3)	.016
Annual income, n (%)			<.001
<\$25,000	12 (14.6)	37 (43.0)	
>\$25,000	70 (85.4)	49 (57.0)	
Cigarette smoker, n (%)	2 (2.4)	13 (13.4)	.018
Drug use, n (%)	3 (3.7)	11 (11.3)	.108
Alcohol use in pregnancy (%)	3 (4.8)	0 (0.0)	1.000
Prior pregnancy (%)	42 (51.2)	58 (59.2)	.357
SD, standard deviation. ^a P values were calculated by Student's <i>t</i> test for continuous variable	es and v^2 test for categorical variables		

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DISCUSSION

In our pilot cohort study of women desiring pregnancy, greater day-to-day variability in time of sleep onset and variability in sleep duration were associated with a longer time to achieving pregnancy over 1-year of follow-up, whereas other possible measures of chronodisruption and sleep characteristics were not associated. Our findings for variability in time of sleep onset and sleep duration persisted after accounting for potential selection bias and confounding by a number of factors often associated with sleep characteristics and/or fertility, including age, BMI, socioeconomic factors, and cigarette smoking. They were also robust to weak, unmeasured potential confounders. If replicated in future studies, these findings suggest that promoting a regular sleep schedule could help women achieve a desired pregnancy.

TABLE 2

Sleep characteristics of study participants.

Characteristic	Mean (SD)
Sleep period onset Sleep period offset Sleep period midtime Sleep period duration Daveto-davvariability in sleep	10:55 PM (80.7 mins) 7:23 AM (67.9 mins) 3:08 AM (69.6 mins) 507.9 mins (53.3 mins) 109.4 mins (52.2 mins)
period onset	109.4 111113 (92.2 111113)
Day-to-day variability in sleep period offset	101.6 mins (49.0 mins)
Day-to-day variability in sleep midtime	81.9 mins (34.0 mins)
Day-to-day variability in sleep duration	139.3 mins (63.1 mins)

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In this study, we used actigraphy and day-to-day variability in sleep characteristics to assess several different measures of chronodisruption. Broadly defined, chronodisruption is a dyssynchronization of circadian rhythms that can be caused by alterations in light/dark cycles, medications, and neuropsychiatric disease (27, 28). Chronodisruption might influence fecundability through several different mechanisms, including alterations in concentrations of melatonin, luteinizing hormone, and follicle-stimulating hormone. Melatonin is a circadian-regulated hormone that appears to affect fertility. For example, in women undergoing in vitro fertilization, administering melatonin improved pregnancy rates (29). Although the mechanism by which melatonin influences fertility has not been determined, in vitro and in vivo studies hint at possible explanations (14). As an antioxidant, melatonin may mediate the inflammatory response of ovulation and protect the oocyte from injury (30). In animal models, melatonin promotes follicular development and oocyte maturation (31, 32). Finally, exposure of human sperm to melatonin improved motility (29, 33).

Luteinizing hormone and follicle-stimulating hormone are both involved in reproduction and may be disrupted by sleep variability. For example, shift workers have altered secretion of luteinizing hormone and follicle-stimulating hormone, as well as menstrual irregularity and subfertility (14, 16). Additionally, serum concentrations of follicle-stimulating hormone were elevated in premenopausal women with reported trouble sleeping and in perimenopausal women with polysomnogramderived measures of wakefulness (34, 35).

Although our findings for day-to-day variability in sleep characteristics and time to achieving pregnancy are biologically plausible, they must be viewed in light of potential noncausal methodologic explanations. These include selection bias, residual confounding, and chance. As expected,

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TABLE 3

Unadjusted and adjusted hazard ratios for sleep characteristics and time to pregnancy over a 1	-year follow-up period.

Characteristic	Crude HR (95% CI) N = 183	Adjusted ^a HR (95%CI) N = 183
Late vs. early sleep period onset (10:55 PM) Late vs. early sleep period offset (7:16 AM) Late vs. early sleep period mid time (3:09 AM) Short vs. long sleep period duration (8.5 h) High vs. low day-to-day variability in sleep onset (1.8 h) High vs. low day-to-day variability in sleep offset (1.7 h) High vs. low day-to-day variability in mid sleep (1.4 h) High vs. low day-to-day variability in sleep duration (2.3 h)	0.73 (0.46–1.15) 0.52 (0.33–0.83) 0.57 (0.35–0.91) 0.96 (0.62–1.48) 0.46 (0.29–0.73) 0.67 (0.42–1.06) 0.53 (0.34–0.84) 0.44 (0.28–0.71)	1.14 (0.69–1.89) 0.83 (0.47–1.48) 0.89 (0.48–1.64) 1.26 (0.79–2.00) 0.60 (0.36–.999) 0.89 (0.56–1.41) 0.72 (0.45–1.15) 0.59 (0.36–0.98)
() = dichotomization cutoff values; $CI = confidence$ interval; $HR = hazard$ ratio.		

^a Adjusted for age, body mass index, race, education, income, and cigarette smoking. Multiple imputation of education, annual income, and smoking was performed. Inverse probability of selection weights were applied to account for the potential selection bias introduced by actigraphy data collection.

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participants who provided actigraphy data differed from those who did not provide data by factors associated with chronodisruption and/or achieving pregnancy. However, it is unlikely that these differences affected our findings appreciably because weighting by the inverse of the probability of selection into our analysis did not alter our results. Selection bias may have been introduced into our study by left truncation-i.e., enrollment at a later, and in our case, unknown time after beginning to attempt to achieve pregnancy (36). It is difficult to speculate on the impact of this bias, but if dayto-day variability in sleep is truly associated with time to achieving pregnancy, then left truncation may have biased our findings toward the null because we were not able to fully observe the longer time to pregnancy in those with greater day-to-day variability. Therefore, our findings may have been even stronger if we had followed participants from the start of attempting to achieve pregnancy. This approach should be used in future studies.

We attempted to address confounding by including in the analysis data on all hypothesized confounders collected in our pilot study: age, BMI, race, education, income, and cigarette smoking. Other unmeasured potential confounders include shiftwork, frequency of intercourse and, thus, conception attempts, stress, depression, and mental illness, each of which may be related to both chronodisruption and fertility ([37], Supplemental Fig. 1). Therefore, these factors may have confounded our findings and biased them away from the null, although they are unlikely to explain all of our findings because of the strong approximate e-values (0.28-0.45) calculated in sensitivity analyses. Nonetheless, future studies should collect data on these factors to examine their impact on the association between day-to-day sleep variability and achieving pregnancy. In addition to the internal validity of our sleep variability findings, they should also be viewed in light of their external validity. A lower percentage of participants in quartile 1, who had the lowest day-today variability in sleep onset, became pregnant during the 1-year follow-up than participants in other studies (11). Thus, our population may have been subfertile, potentially limiting the generalizability of our findings to women with lower fertility. In addition, it is also possible that exclusion

of women who did not provide actigraphy data constrained the distribution of day-to-day variability in sleep onset to women with lesser variability. Therefore, stronger findings might be observed in populations with greater day-to-day variability in sleep onset, including those with greater proportions of women with lower socioeconomic status and/or more shiftwork.

Besides day-to-day variability in sleep characteristics, we also examined average sleep duration in relation to achieving pregnancy. In contrast to our findings for day-to-day sleep variability, we observed no association for average sleep duration, similar to findings from at least one previous study of people desiring conception (11, 38). Previous studies of sleep duration and fecundability used self-reported sleep duration. In contrast, we used actigraphy, which is more objective than self-report and is validated against polysomnography, the gold standard for measuring sleep (20, 21). Moreover, sleep duration and variability of sleep onset are measures of distinct processes and may be associated with the potential to become pregnant in different ways.

We note several strengths of this study. We used a more objective measure of sleep onset, offset, and duration than self-report, which often poorly correlates with objective measures of sleep (39). Furthermore, sleep onset variability is potentially modifiable, such as by promoting consistent sleep-wake patterns and other sleep hygiene practices. Lastly, our study enrolled a racially and socioeconomically diverse cohort of women desiring pregnancy. As a result, we were able to examine the relation between sleep disruption and time to achieving pregnancy in a sample more representative of the US population than was examined in previous work in this area (40, 41). We also note several limitations, as described earlier. These include missing actigraphy data on 36.5% of study participants and differences in data provision by BMI, race, education, and income, as well as left truncation and lack of data on potential confounding variables, such as number of conception attempts, stress, depression, and mental illness. Lack of data on menstrual cycles also precluded investigating sleep parameters in relation to menstrual irregularities, a potential mediator of associations between sleep characteristics and fecundability. Finally, it is possible





Time to pregnancy over a 1-year follow-up period based on day-today variability in sleep onset and sleep duration quartiles. Kaplan-Meier plot shows the cumulative incidence of achieving pregnancy during the study period. Participants were divided into quartiles according to their day-to-day variability in sleep onset (A) and sleep duration (B). Data were adjusted for body mass index, age, race, income, education, and whether they smoked cigarettes. Bolded font denotes a significant difference from the reference category (1st quartile).

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that women changed their sleep and activity behaviors because they knew those behaviors were being monitored. However, because participants wore the actigraphy watches for 2 weeks, this is unlikely to have influenced our findings.

CONCLUSION

In summary, we found that study participants with high dayto-day variability in time of sleep onset and variability in sleep duration had a longer time to achieving pregnancy over the 1year study follow-up than those with low variability. Sleep duration did not appear to affect fecundability. If a larger study confirms our findings, then further work could determine whether establishing set sleeping times would benefit women who are attempting to become pregnant.

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CRediT Authorship Contribution Statement

Peinan Zhao: Writing - review & editing, Writing - original draft, Investigation, Formal analysis, Data curation. Emily S. Jungheim: Writing - review & editing, Writing - original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. Bronwyn S. Bedrick: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. Leping Wan: Writing - review & editing, Writing - original draft, Investigation, Formal analysis, Data curation. Patricia T. Jimenez: Writing - review & editing, Writing - original draft, Investigation. Ronald McCarthy: Writing - review & editing, Writing - original draft, Methodology, Investigation. Jessica Chubiz: Supervision, Resources, Project administration, Methodology, Conceptualization. Justin C. Fay: Writing - review & editing, Writing - original draft, Methodology, Funding acquisition, Conceptualization. Erik D. Herzog: Writing - review & editing, Writing - original draft, Methodology, Investigation, Funding acquisition, Conceptualization. Siobhan Sutcliffe: Writing - review & editing, Methodology, Formal analysis. Sarah K. England: Writing - review & editing, Writing - original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of Interest

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Data sharing statement

The data underlying this article will be shared on reasonable request to the corresponding author.

REFERENCES

- Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 2010;33:414–20.
- Iftikhar IH, Donley MA, Mindel J, Pleister A, Soriano S, Magalang UJ. Sleep duration and metabolic Syndrome. An updated dose-risk meta-analysis. Ann Am Thorac Soc 2015;12:1364–72.
- Sabanayagam C, Shankar A. Sleep duration and cardiovascular disease: results from the National Health Interview Survey. Sleep 2010;33:1037–42.
- Yin J, Jin X, Shan Z, Li S, Huang H, Li P, et al. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. J Am Heart Assoc 2017;6:e005947.
- Reschke L, McCarthy R, Herzog ED, Fay JC, Jungheim ES, England SK. Chronodisruption: an untimely cause of preterm birth? Best Pract Res Clin Obstet Gynaecol 2018;52:60–7.
- Gu F, Han J, Laden F, Pan A, Caporaso NE, Stampfer MJ, et al. Total and cause-specific mortality of U.S. nurses working rotating night shifts. Am J Prev Med 2015;48:241–52.
- Hansen AB, Stayner L, Hansen J, Andersen ZJ. Night shift work and incidence of diabetes in the Danish nurse cohort. Occup Environ Med 2016;73:262–8.
- Wegrzyn LR, Tamimi RM, Rosner BA, Brown SB, Stevens RG, Eliassen AH, et al. Rotating night-shift work and the risk of breast cancer in the nurses' health studies. Am J Epidemiol 2017;186:532–40.
- Facco FL, Grobman WA, Reid KJ, Parker CB, Hunter SM, Silver RM, et al. Objectively measured short sleep duration and later sleep midpoint in pregnancy are associated with a higher risk of gestational diabetes. Am J Obstet Gynecol 2017;217:447.e1–13.
- Felder JN, Baer RJ, Rand L, Jelliffe-Pawlowski LL, Prather AA. Sleep disorder diagnosis during pregnancy and risk of preterm birth. Obstet Gynecol 2017; 130:573–81.
- Willis SK, Hatch EE, Wesselink AK, Rothman KJ, Mikkelsen EM, Wise LA. Female sleep patterns, shift work, and fecundability in a North American preconception cohort study. Fertil Steril 2019;111:1201–12010.e1.
- Stocker LJ, Macklon NS, Cheong YC, Bewley SJ. Influence of shift work on early reproductive outcomes: a systematic review and meta-analysis. Obstet Gynecol 2014;124:99–110.
- Stock D, Knight JA, Raboud J, Cotterchio M, Strohmaier S, Willett W, et al. Rotating night shift work and menopausal age. Hum Reprod 2019;34:539–48.
- 14. Kloss JD, Perlis ML, Zamzow JA, Culnan EJ, Gracia CR. Sleep, sleep disturbance, and fertility in women. Sleep Med Rev 2015;22:78–87.
- Bisanti L, Olsen J, Basso O, Thonneau P, Karmaus W. Shift work and subfecundity: a European multicenter study. European Study Group on Infertility and Subfecundity. J Occup Environ Med 1996;38:352–8.
- Lawson CC, Whelan EA, Lividoti Hibert EN, Spiegelman D, Schernhammer ES, Rich-Edwards JW. Rotating shift work and menstrual cycle characteristics. Epidemiology 2011;22:305–12.
- Wise LA, Rothman KJ, Mikkelsen EM, Stanford JB, Wesselink AK, McKinnon C, et al. Design and conduct of an internet-based preconception cohort study in North America: pregnancy study online. Paediatr Perinat Epidemiol 2015;29:360–71.
- Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjec-

tive assessment of sleep parameters in sleep-disordered patients. Sleep Med 2001;2:389–96.

- Sadeh A, Acebo C. The role of actigraphy in sleep medicine. Sleep Med Rev 2002;6:113–24.
- Martin-Fairey CA, Zhao P, Wan L, Roenneberg T, Fay J, Ma X, et al. Pregnancy induces an earlier chronotype in both mice and women. J Biol Rhythms 2019;34:323–31.
- Zhao P, Bedrick BS, Brown KE, McCarthy R, Chubiz JE, Ju YS, et al. Sleep behavior and chronotype before and throughout pregnancy. Sleep Med 2022;94:54–62.
- Committee on Practice Bulletince-Obstetrics and the American Institute of Ultrasound in Medicine. Practice bulletin No. 175: Ultrasound in pregnancy. Obstet Gynecol 2016;128:e241–56.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
- Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208.
- American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee. Female age-related fertility decline. Committee opinion No. 589. Fertil Steril 2014;101:633–4.
- VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–74.
- Erren TC, Reiter RJ. Revisiting chronodisruption: when the physiological nexus between internal and external times splits in humans. Naturwissenschaften 2013;100:291–8.
- 28. Erren TC, Reiter RJ. Defining chronodisruption. J Pineal Res 2009;46: 245–7.
- Tamura H, Takasaki A, Miwa I, Taniguchi K, Maekawa R, Asada H, et al. Oxidative stress impairs oocyte quality and melatonin protects oocytes from free radical damage and improves fertilization rate. J Pineal Res 2008;44:280–7.
- Reiter RJ, Rosales-Corral SA, Manchester LC, Tan DX. Peripheral reproductive organ health and melatonin: ready for prime time. Int J Mol Sci 2013;14:7231–72.
- Tong J, Sheng S, Sun Y, Li H, Li WP, Zhang C, et al. Melatonin levels in follicular fluid as markers for IVF outcomes and predicting ovarian reserve. Reproduction 2017;153:443–51.
- Zheng M, Tong J, Li WP, Chen ZJ, Zhang C. Melatonin concentration in follicular fluid is correlated with antral follicle count (AFC) and in vitro fertilization (IVF) outcomes in women undergoing assisted reproductive technology (ART) procedures. Gynecol Endocrinol 2018;34:446–50.
- Ortiz A, Espino J, Bejarano I, Lozano GM, Monllor F, Garcia JF, et al. High endogenous melatonin concentrations enhance sperm quality and shortterm in vitro exposure to melatonin improves aspects of sperm motility. J Pineal Res 2011;50:132–9.
- Kravitz HM, Janssen I, Santoro N, Bromberger JT, Schocken M, Everson-Rose SA, et al. Relationship of day-to-day reproductive hormone levels to sleep in midlife women. Arch Intern Med 2005;165:2370–6.
- de Zambotti M, Colrain IM, Baker FC. Interaction between reproductive hormones and physiological sleep in women. J Clin Endocrinol Metab 2015;100:1426–33.
- Schisterman EF, Cole SR, Ye A, Platt RW. Accuracy loss due to selection bias in cohort studies with left truncation. Paediatr Perinat Epidemiol 2013;27:491–502.
- **37.** Rooney KL, Domar AD. The relationship between stress and infertility. Dial Clin Neurosci 2018;20:41–7.
- Wise LA, Rothman KJ, Wesselink AK, Mikkelsen EM, Sorensen HT, McKinnon CJ, et al. Male sleep duration and fecundability in a North American preconception cohort study. Fertil Steril 2018;109:453–9.
- Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? Epidemiology 2008;19:838–45.
- Evenson KR, Calhoun KC, Herring AH, Pritchard D, Wen F, Steiner AZ. Association of physical activity in the past year and immediately after in vitro fertilization on pregnancy. Fertil Steril 2014;101:1047–10454.e5.
- Steiner AZ, Pritchard D, Stanczyk FZ, Kesner JS, Meadows JW, Herring AH, et al. Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. JAMA 2017;318:1367–76.

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Variabilidad en el sueño y tiempo para lograr el embarazo: hallazgos a partir de un estudio piloto de cohortes de mujeres deseando quedarse embarazadas

Objetivo: Determinar si la cronodisrupción está asociada con la consecución del embarazo.

Diseño: Estudio piloto de cohortes prospectivo

Sujetos: Se reclutaron ciento ochenta y tres mujeres que deseaban quedarse embarazadas de la comunidad local de un centro médico académico ubicado en el Medio Oeste y que proporcionaron información sobre el sueño entre el 1 de febrero de 2015 y el 30 de nov-iembre de 2017.

Exposición: Los datos de sueño y actividad se obtuvieron a través de relojes de actigrafía usados continuamente durante 2 semanas para evaluar medidas de cronodisrupción, incluyendo el inicio, el final, la mitad y la duración del período de sueño; así como la variabilidad en cada una de estas medidas.

Principal(es) medida(s) de resultado(s): el tiempo transcurrido hasta el embarazo a lo largo de un año de seguimiento.

Resultado(s): De las 183 mujeres elegibles, 82 se embarazaron durante una mediana de 2.8 meses de seguimiento. Se asoció una mayor variabilidad interdiaria en la hora de inicio del sueño y en la duración del mismo con un mayor tiempo para lograr el embarazo tras ajustar por edad, índice de masa corporal, raza, educación, ingresos y tabaquismo (cociente de riesgos instantáneos ajustado [HRa]: 0.60; intervalo de confianza [IC] del 95 %: 0.36-0.999, comparando a las participantes con una desviación estándar de >1.8 horas a <1.8 horas en la hora diaria de inicio del sueño; y HRa: 0.58; IC del 95 %: 0.36-0.98, comparando a las participantes con una desviación estándar de >2.3 horas a <2.3 horas en la duración diaria del sueño). En los análisis ajustados, no se observaron asociaciones estadísticamente significativas para el tiempo promedio de inicio y fin del sueño, el tiempo intermedio del sueño y la duración del sueño, ni para la variabilidad en el tiempo intermedio y final del sueño.

Conclusión(es): Una mayor variabilidad diaria en la hora de inicio y la duración del sueño (dos medidas de cronodisrupción) se asoció con un mayor tiempo para lograr el embarazo durante un año de seguimiento en mujeres que deseaban concebir. Si se replican en estudios adicionales, estos hallazgos podrían indicar intervenciones en el estilo de vida para ayudar a las mujeres a lograr el embarazo deseado.