Women trying to have babies face different clock problem

May 23 2012

A new Northwestern University study shows that the biological clock is not the only clock women trying to conceive should consider. The circadian clock needs attention, too.

Epidemiological studies have shown female shift workers, such as nurses, and female flight attendants who work on long-distance east-west routes (i.e., those with constant jet lag) have fertility and menstrual issues. They are habitually out of sync with the external light cycle. But the role circadian rhythm disruption may play in their reproductive problems is a poorly studied area.

Research led by Northwestern circadian rhythm expert Fred W. Turek now draws a clear line between disrupted circadian rhythms and reproductive physiology. Turek and his colleagues are the first to show that if you disrupt the circadian clock environmentally in mice, with repeated changes in their light-dark cycles, there are problems with pregnancy outcomes.

And the effect can be dramatic. The researchers found evidence suggesting the severity of circadian disruption may be linked to the severity of pregnancy disruption: mice subjected to advances of the light-dark cycle had greater circadian clock disruption and lower reproductive success. This group's pregnancy success rate was only 22 percent.

The study will be published May 23 by the journal PLoS ONE.

"Our results have important implications for the reproductive health of female shift workers, women with circadian rhythm sleep disorders and/or women with disturbed circadian rhythms for other reasons," Turek said.

He is the Charles E. and Emma H. Morrison Professor of Biology in the Weinberg College of Arts and Sciences and director of Northwestern's Center for Sleep and Circadian Biology.

"If you disrupt your internal rhythms, there will be negative consequences -- that is very clear," said Keith Summa, first author of the paper and an M.D./Ph.D. candidate working in Turek's lab. "Our results suggest people should consider their biological rhythms for optimal health."

The repeated shifting of the light-dark cycle shifts the biological clock throughout the body. This environmental disturbance is more relevant to shift workers and those frequently flying across time zones, the researchers note, than genetic disruption of the circadian clock, which also negatively influences reproductive function.

Turek, Summa and their colleague and co-author Martha H. Vitaterna studied three sets of normal laboratory female mice, all who had recently mated. The study was conducted over the course of 21 days, the duration of a typical pregnancy.

One set was a control group of 12 mice that experienced normal days of 12 hours of light, followed by 12 hours of darkness. The two other groups, of 18 mice each, also experienced days of 12 hours of light and 12 hours of darkness. But the phase-advanced group had its 12 hours of light start six hours earlier every five days. The phase-delayed group had its light start six hours later every five days. (There were a total of four phase shifts over the duration of the study.)

The researchers monitored the mice throughout the gestation period to count the number of full-term pregnancies. The results surprised them.

In the control mice, 90 percent of the matings led to full-term pregnancies. But in the phase-delay group, the pregnancy success rate was 50 percent, while in the phase-advanced group, it was only 22 percent.

"We were surprised at how dramatic the effect of manipulating the light-dark cycle was, especially in the phase-advanced group," Summa said. "We expected a negative effect from the circadian clock disruption, but not this much."

They next looked at a separate group of females in the phase-delay and phase-advance protocol to see how the animals responded to the repeated phase shifts. The researchers found the phase-advanced animals required one to two days longer, on average, to return to normal rhythms. This suggests the magnitude of circadian disruption is associated with the severity of pregnancy loss.

The next steps, the researchers say, are to identify specifically the stage at which pregnancy is affected and to understand exactly how circadian disruption results in the observed adverse effects.

"We've made an interesting observation, but what's causing the reduced fertility?" Summa said. "We would like to determine where exactly the phase shifts and internal rhythm disruptions are having an effect."

More information: The title of the paper is "Environmental Perturbation of the Circadian Clock Disrupts Pregnancy in the Mouse." The paper is available at http://dx.plos.org/10.1371/journal.pone.0037668.

Provided by Northwestern University