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Skipping breakfast seems to decline the fecundity of mice and even humans.

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#### OBJECTIVE:

It is known that mistimed food intake perturbs the circadian rhythms of tissues, leading to a misalignment with the central circadian clock in the suprachiasmatic nucleus. Previous studies have demonstrated that disruption of the circadian rhythm adversely affects reproductive function. Influence of skipping breakfast habit on female reproductive function has not been fully evaluated yet. The objective of this study was to investigate whether initiation of their meals from the onset or midpoint of their active phase would affect female reproduction in mice and humans.

#### MATERIALS AND METHODS:

Six-week-old female mice were fed a normal diet (29.9% protein, 11.6% fat, and 58.5% carbohydrates) at two distinct time frames: from ZT12:00 to ZT20:00 (breakfast-supplied) or from ZT16:00 to ZT24:00 (breakfast-skipping model) for five weeks. The length of estrous cycle was evaluated by vaginal smear (n=62). Diurnal variations of LH levels during proestrus were evaluated to assess the LH surge. Furthermore, diurnal oscillations of clock gene expression (*Bmal1* and *Reverb-α*) in the hypothalamus were assessed. Two cohorts were mated with male counterparts for 40 days, and the outcomes of delivery were assessed (n=34). In addition, 149 human infertile women underwent a nutritional assessment questionnaire where they were asked about their eating habits and menstrual abnormalities.

#### RESULTS:

The duration of the estrous cycle in the breakfast-skipping cohort was significantly longer than in the

breakfast-supplied cohort ( $9.4 \pm 3.0$  vs.  $7.2 \pm 1.8$ ). In the breakfast-supplied cohort, a physiological fluctuation in LH was observed, culminating at the onset of the active phase, on the other hand in the breakfast-skipping cohort, no surge in LH was observed. The peak expression of clock gene in the breakfast-skipping cohort delayed 4-8 hours relative to the breakfast-supplied cohort. The live birth rate post-mating in the breakfast-skipping cohort was significantly lower than in the breakfast-supplied cohort (17.6% vs. 82.4%). A significantly higher incidence of oligomenorrhea was observed among women who habitually skip breakfast compared to those who consistently have breakfast (33.3% vs. 10.9%).

#### CONCLUSIONS:

The breakfast-skipping regimen engendered a prolonged estrous cycle and a disruption in the LH surge that typically occurs in the proestrus stage, resulting in declined fertility in mice. This regimen also induced alterations in the oscillation pattern of clock genes in hypothalamus that controls the LH surge via estrogen's feedback. Additionally, prolongation of the menstrual cycle was observed in humans who skip breakfast. The present study suggests that the breakfast-skipping regimen leads to infertility due to the disruption in the endocrine milieu and estrous cycle, and this may be attributed to the disrupted clock gene expression caused by delayed initiation of the meal.

#### IMPACT STATEMENT:

The scheduling of meal consumption holds great significance in reproduction. Eating habits could potentially influence the hormonal milieu, the estrous cycle, and consequently, the processes of gestation.