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Basic Medicine COMMENTARY

The Innovation Medicine

The impact of maternal circadian rhythm disruption on offspring

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Received: September 19, 2025; Accepted: January 9, 2026; Published Online: January 10, 2026; https://doi.org/10.59717/j.xinn-med.2026.100192

Citation: Lin Y., Cheng W., Weng H., et al. (2026). The impact of maternal circadian rhythm disruption on offspring. *The Innovation Medicine* **4**:100192.

The circadian rhythm is a self-sustaining oscillation and adaptive mechanism that sustains a 24-hour cycle while synchronizing with environmental signals and influencing nearly all physiological activities. This biological clock is regulated by TTFL (transcription-translation feedback loop), comprising the core feedback loop and secondary regulatory networks.[1] The primary feedback loop comprises the transcription activators (BMAL1 and CLOCK) and the inhibitory feedback repressors (PER and CRY protein families). In the initial stage of the circadian cycle, BMAL1 and CLOCK heterodimer triggers the gene expression of PER and CRY by attaching to their E-box response sequence. In the subsequent stage, PER-CRY dimers move from cytoplasm into nucleus to suppress the transcription activity of CLOCK-BMAL1. In the terminal stage, PER/CRY proteins are broken down and reactivate CLOCK-BMAL1 gene transcription. The auxiliary regulatory network entails the synchronized operation of ROR/REV-ERB response elements, a particular DNA sequence in the promoter area of target genes such as Bmal1. CLOCK-BMAL1 controls the production of the nuclear receptors REV-ERBα/β or RORα/β/γ, which compete to bind to the REV-ERB and ROR response element in Bmal1 promoter, consequently inhibiting or enhancing Bmal1 gene transcription, respectively. Thus, the primary feedback loop and auxiliary regulatory networks offer a basic model for controlling the activity of clock-controlled genes.

Since the industrial revolution and the use of artificial light, people increasingly suffer from circadian rhythm disorders triggered by overwork, stress, transcontinental travel, and irregular eating patterns, especially by the expansion of shift work and the 24/7 economy. Recent epidemiological data and model organism studies have demonstrated that circadian disruption critically impacts metabolic diseases (such as obesity), mental illnesses (such as insomnia), cardiovascular diseases (such as hypertension), endocrine disorders, immune system dysfunctions, and more. Rodent model assays have demonstrated the impact of circadian disruption on female reproduction and/or offspring using different disruption paradigm, such as constant lightning, chronic jet lag,[2] or genetic mutation of clock genes. Moreover, some epidemiological studies also show the negative impact of shift work on reproduction and offspring health. Nonetheless, the effects of circadian disruption on offspring health should be further investigated. Several studies have demonstrated that maternal circadian disruption exerts a critical impact on offspring health, including growth, neonatal immune system development, and metabolic function.[3-5] There is an urgent need for more research to explore the effects of circadian rhythm disruption on female reproductive function and offspring health, to address the research void and establish a scientific foundation for preventing and treating associated reproductive disorders.

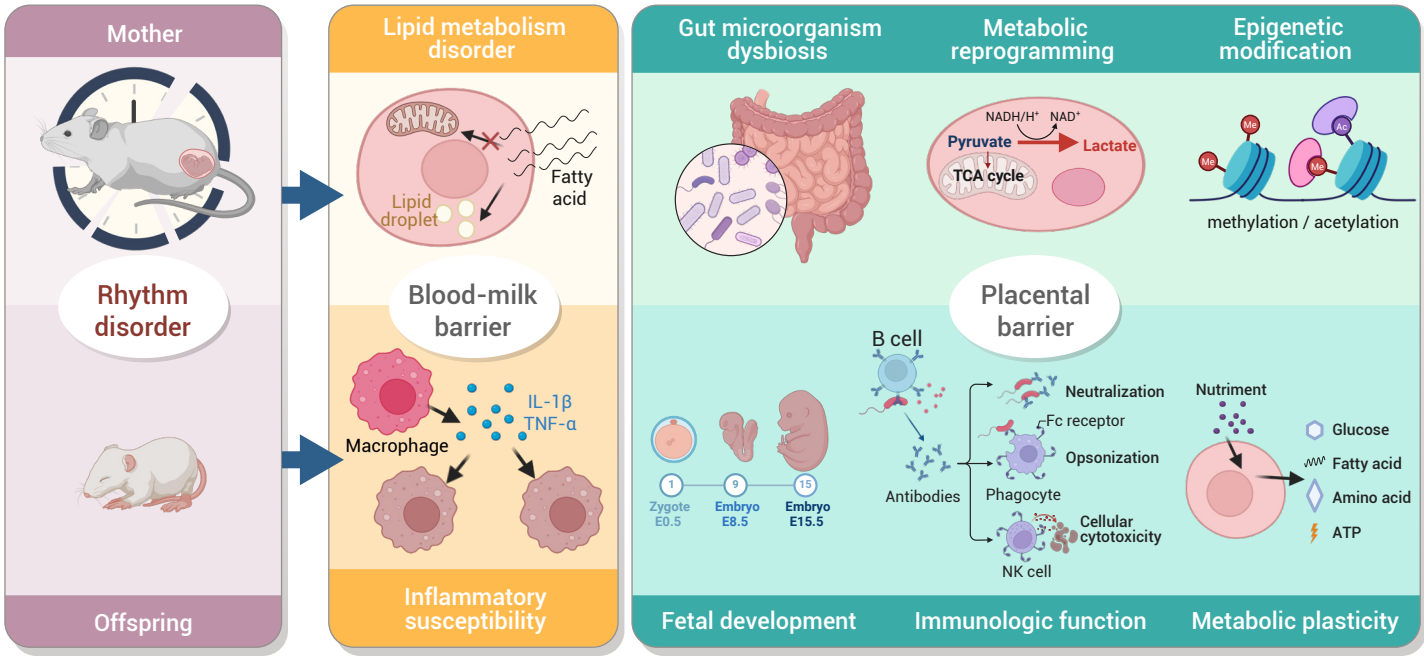

Figure 1. The overview of maternal circadian rhythms during pregnancy in shaping offspring health, including multifaceted impacts on developmental processes, metabolic homeostasis, and immune functions.

Maternal pregnancy status is closely related to the growth and development of offspring. Niu et al. found that the imposed maternal inactive phase feeding, a method known to alter peripheral circadian clocks, induces circadian rhythm genes abnormal expression in pregnant rats, increasing intestinal permeability and pro-inflammatory factors.[3] The imposed maternal inactive phase feeding, acting as a potent environmental zeitgeber, primarily

disrupts the intestinal circadian clock, which dysregulates the core clock genes such as *Bmal1*. The reduction of *Bmal1* directly impairs the intestinal barrier and alters the gut microbiota composition, elevating LPS (lipopolysaccharide) production and promoting its translocation. Subsequently, the translocated LPS activates *Tlr4* (Toll-like receptor 4, a pattern recognition receptor and pivotal component of the Toll-like receptor family), inducing a strong inflammatory response both locally within the maternal gut and systemically. This maternal inflammation and circulating LPS then cross the compromised placental barrier to the fetus, stimulating the fetal intestinal *Tlr4* pathway and resulting in ileal inflammation in offspring. Thus, this rat model indicates that pregnant women adhering to an appropriate eating schedule during pregnancy could effectively prevent gut dysbiosis arising from dietary habits that may harm both maternal and fetal development.[3]

Meanwhile, another mouse model shows that circadian rhythm breakdown in mothers affects immune suppression of myeloid-derived suppressor cells (MDSCs) in offspring, exacerbating neonatal inflammatory diseases.[4] However, supplement with docosahexaenoic acid (DHA), a metabolite in breast milk, can reverse this occurrence. Mechanistically, the maternal liver transforms α-linolenic acid into DHA via the fatty acid elongation enzymes *Elovl2* and *Elovl5*; and DHA is subsequently conveyed to fetus by placental-specific transport proteins. This process is controlled by mother's circadian rhythm. During the postpartum period, DHA moves into breast milk through lipid release mechanisms in mammary epithelial cells. DHA concentration in breast milk exhibits circadian rhythm fluctuations, which are tightly linked with the expression levels of *Bmal1*, a circadian rhythm gene in maternal liver. Disruption of circadian rhythms impairs the *Bmal1*-regulated lipid metabolism pathway in mammary glands, leading to a 30-40% reduction in breast milk DHA levels. Afterward, DHA enhances MDSC immune function in neonatal mice through PPARγ-regulated fatty acid uptake and mitochondrial ATP production. Crucially, administering MDSCs or supplementing DHA during perinatal periods mitigates the inflammatory impacts on neonates caused by maternal circadian rhythm disruption. This mouse model displays new roles of maternal circadian rhythms in regulating neonatal inflammation via myeloid cell metabolic reprogramming.[4]

Moreover, tissue-intrinsic clocks also induce tissue-level oscillations, accompanied by network-dependent signals that stem from distal organs and organismal behavior. Itoh et al. demonstrate using a mouse model that circadian disruption during pregnancy decreases placental and neonatal weight yet retains transcriptional and structural maturation.[5] Notably, diet-induced obesity worsens alongside arrhythmic feeding, hypothalamic leptin resistance, and reprogrammed liver clocks in offspring from mothers with disrupted circadian rhythms. During development, this maternal circadian misalignment alters the mother-fetus phase relationship and reduces placental efficiency. While restricting feeding times in offspring only partially prevents obesity, aligning caloric restriction with the start of their active phase significantly improves the condition. Therefore, maternal circadian rhythms during pregnancy program metabolic adaptations in offspring, offering insights into the developmental origins of health and disease.

Therefore, these findings highlight the critical regulatory roles of maternal circadian rhythms during pregnancy in shaping maternal and offspring health, encompassing multifaceted impacts on developmental processes, metabolic homeostasis, and immune functions. Beyond influencing fetal development through the gut microbiota-immune signaling axis, maternal factors also affect immune system development via placental blood exchange and breastfeeding. Furthermore, maternal circadian rhythm disorders can alter the expression pattern of placental genes through epigenetic regulation. This expression change may further alter metabolic system in offspring to ultimately affect placental functions (Figure 1). Further investigation is still urgently needed to determine whether the disruptions observed in animal models could be translated to clinical practice. There is also a need for in-depth research into more aspects of the female reproductive systems, including the effects of circadian rhythm disruption on ovaries, embryos, and endocrine systems, to fully assess its potential risks to women's reproductive health. High-quality intervention studies are also needed. For instance, enhancing sleep during pregnancy and after childbirth could be highly effective in preventing or delaying the onset of metabolic diseases among a significant portion of the population. Moreover, aside from variability in sleep timing during pregnancy, there are limited data on circadian disruption during pregnancy in humans. Understanding how circadian regulation alters healthy pregnancy status and induces other reproductive diseases is an emerging area in current research.

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FUNDING AND ACKNOWLEDGMENTS

The authors acknowledge financial support from the Natural Science Foundation of China (NSFC No. 82373602), Guangdong Basic and Applied Basic Research Foundation (2023B1515120054), Shenzhen Medical Research Fund (No. B2303002), Shenzhen Science and Technology Program (No. JCYJ20241202152800001, JCYJ20220530144403008, JCYJ20220818103607015, and JCYJ20230807111401002), Futian Healthcare Research Project (No. FTWS011 and FTWS2022002), and Health Commission of Guangdong Province (A2024281). We also acknowledge the facility supports by Medical Research Center at the Eighth Affiliated Hospital, Sun Yat-sen University and Fujian medical university. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.