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Review

The Circadian Clock, Nutritional Signals and Reproduction: A Close Relationship

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Abstract: The circadian rhythm, which is necessary for reproduction, is controlled by clock genes. In the mouse uterus, the oscillation of the circadian clock gene has been observed. The transcription of the core clock gene period (*Per*) and cryptochrome (*Cry*) is activated by the heterodimer of the transcription factor circadian locomotor output cycles kaput (*Clock*) and brain and muscle Arnt-like protein-1 (*Bmal1*). By binding to E-box sequences in the promoters of *Per1/2* and *Cry1/2* genes, the CLOCK-BMAL1 heterodimer promotes the transcription of these genes. Per1/2 and Cry1/2 form a complex with the Clock/Bmal1 heterodimer and inactivate its transcriptional activities. Endometrial BMAL1 expression levels are lower in human recurrent-miscarriage sufferers. Additionally, it was shown that the presence of BMAL1-depleted decidual cells prevents trophoblast invasion, highlighting the importance of the endometrial clock throughout pregnancy. It is widely known that hormone synthesis is disturbed and sterility develops in Bmal1-deficient mice. Recently, we discovered that animals with uterus-specific Bmal1 loss also had poor placental development, and these mice also had intrauterine fetal death. Furthermore, it was shown that time-restricted feeding controlled the uterine clock's circadian rhythm. The uterine clock system may be a possibility for pregnancy complications, according to these results. We summarize the most recent research on the close connection between the circadian clock and reproduction in this review.

Keywords: BMAL1; circadian rhythm; clock gene; miscarriage; pregnancy; reproduction

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1. Introduction

In all mammalian species, including humans, circadian timing is essential for successful female reproduction. For instance, women who have irregular sleep or work schedules have lower fertility and higher chances of miscarriage [1]. Similar to humans, rats exhibit substantial anomalies in ovulation, fertility, and sexual drive as a result of changes to circadian rhythm [2,3]. Infertility/reproductive disorders are one of the main physiological features of animals with clock mutations. Arnt-like protein-1 (*Bmal1*) knockout in arginine vasopressin (AVP) neurons, kisspeptin neurons, GnRH neurons, or the whole body disrupts the timing and pattern of LH secretion, suggesting that the circadian clock system may

integrate the HPG axis [4,5]. Circadian rhythms have been reported for the HPG axis in mice, rats, and humans [3,6–8]. In this context, clock genes are also expressed within the reproductive organs [9,10], and the rhythmic expression of *Bmal1*, circadian locomotor output cycles kaput (*Clock*), period (*Per*), and cryptochrome (*Cry*) within the uterus during pregnancy has been reported [11]. Moreover, mutations that alter the clock function can cause infertility in female mice [3,7,8]. Previous studies demonstrated that clock genes play important roles in regulating fertility [12–14], and those endocrine factors affect these clock genes [15–17]. Compared with the large amount of rodent data available, there have, however, been few studies on the relationship between fertility and clock disturbances in humans. Circadian clock dysfunction causes abnormalities in sleep, appetite, and emotional control [18–22]. Similarly, disturbances in circadian rhythms due to jet lag and night shift work are related to an increased frequency in menstrual cycle abnormalities, altered serum gonadotropin levels, and decreased fertility [23,24]. Meta-analyses have revealed associations between night shift work and an increased frequency of miscarriages [25,26]. Similar findings were noted in a study examining the miscarriage rate of pregnant flight attendants who worked during overnight hours [27]. Moreover, long-time workers whose schedules include night shifts during pregnancy have an increased risk of preterm delivery and low birth weight [28,29]. Given this, pregnant workers are no longer required to work at night when medically indicated in Europe and Japan.

The CLOCK-BMAL1 heterodimer induces transcription of Per1/2 and Cry1/2 genes by binding to E-box (CACGTG/T) regions in their promoters. Together with the Clock/Bmal1 heterodimer, Per1/2 and Cry1/2 form a complex that inhibits the transcriptional activity of CLOCK-BMAL1 [30,31]. Significant alterations in the circadian behavioral rhythms have been seen in *Bmal1*-knockout mice, Clock mutant mice, and *Per*- and *Cry*-deficient animals [32–35]. The suprachiasmatic nucleus (SCN) integrates information from the external light–dark cycle of the sun to entrain the cellular clocks of organs with the external environment [36–38]. The SCN is divided into two major parts: the core and the shell SCN. The core SCN contains the cell bodies of vasoactive intestinal polypeptide (VIP) neurons and the shell SCN contains the cell bodies of arginine vasopressin (AVP) neurons [39]. VIP neurons input onto gonadotropin-releasing hormone (GnRH) neurons in the preoptic area (POA), and AVP neurons input onto kisspeptin neurons in the anterior ventral periventricular (AVPV) nucleus [40]. It has been noted that the circadian rhythms of AVPV Kiss1 expression in Kiss1 neurons peaked coincident with LH, suggesting the interactions between the SCN and the reproductive neurons in the female hypothalamic–pituitary–gonad (HPG) axis [41]. The primary subject of this review is how circadian clock disorders cause these abnormalities in reproduction.

2. Effects of the Circadian Clock on the Hypothalamic–Pituitary–Gonadal (HPG) Axis and Reproduction

Female reproduction is under circadian control and temporal information is relayed through the HPG axis [13,42–44]. The 24 h rotation of the Earth produces regular patterns of environmental modifications, consisting of adjustments in light–dark, changes in temperature, risks of predation, and food availability [45]. The impact of molecular clocks on the HPG axis in relation to female reproduction is well known (Figure 1). The SCN regulates the circadian rhythm of *Kiss1* expression in the AVPV [46]. Importantly, *Bmal1* and other clock genes have also been identified in kisspeptin neurons [47].

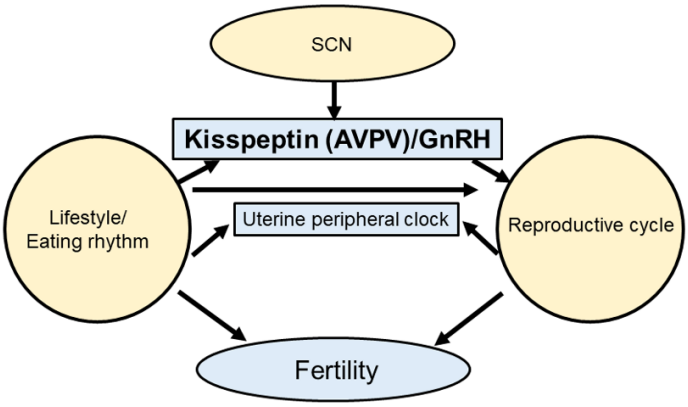

Figure 1. Synchrony of the circadian clock and reproduction. The central clock controls kisspeptin secretion. Feeding rhythms also control hormone secretion. Moreover, circadian clocks and reproductive cycles affect fertility.

2.1. Circadian Clock Regulation of the HPG Axis

Kisspeptin regulates the secretion of sex steroids such as estrogen through the HPG axis [48]. Kisspeptin signaling is necessary for the timing of reproductive activity, including the pulsatile and estrous cycle of GnRH [40,49]. It is known that GnRH secretion is regulated by circulating hormones, kisspeptin, and neurotransmitters [50–54]. Daily changes in GnRH cell responsiveness to kisspeptin have also been reported [55]. The sensitivity of the GnRH system to kisspeptin stimulation fluctuates significantly during the day, peaking in the afternoon [56]. Kisspeptin neurons are found in the AVPV and ARC nuclei of the hypothalamus, and the SCN controls the AVPV nucleus. AVPV kisspeptin neurons, whose activity is regulated by SCN signals in an E_2-dependent manner, are responsible for controlling LH surge [41]. Although kisspeptin neurons in the ARC are more influenced by E_2 and leptin than SCN signals [57,58], the effects of circadian dysregulation (e.g., skipping breakfast, shift work, and transmeridian travel) as a factor affecting infertility cannot be overlooked [59–61] (Figure 2). For the GPR54 receptor, kisspeptin serves as the endogenous agonist. It was determined that GPR54 expression can become rhythmic when E2 levels are raised, a behavior that appears to be controlled by intracellular ERβ receptors [62].

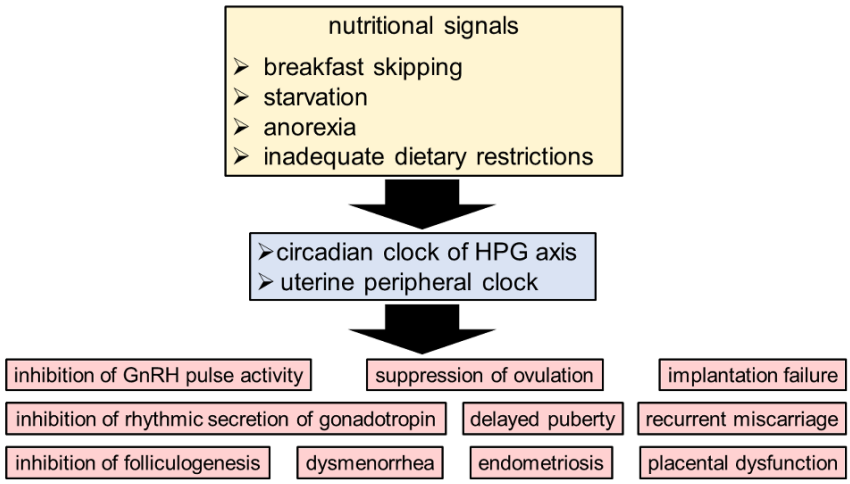

Figure 2. The circadian clock system as a relationship between reproductive health and nutritional signals. The circadian rhythm in the HPG axis and uterus is negatively impacted by nutritional signals such as skipping breakfast, starvation, anorexia, and inadequate dietary restrictions.

2.2. Ovarian Circadian Clock

In the rat ovary, clock genes associated with the ovulation cycle have been identified. The day of proestrus sees a considerable increase in BMAL1 expression following the LH surge [15]. In follicular development, *Per1* and *Per2* mRNA are localized to steroidogenic cells in preantral, antral, and preovulatory follicles, corpora lutea, and interstitial glandular tissue by in situ hybridization histochemistry [63]. Furthermore, *Per1* and *Per2* mRNA and proteins oscillate in a circadian manner in follicles, granulosa cells, and theca cells. In contrast, LH promotes *Per1* as well as *Bmal1* expression in the ovary [15]. These clock genes display different amplitudes at different stages of the estrus cycle, suggesting endocrine control of the circadian clock [16]. Importantly, gonadotropins also control the ovarian clock, which is supported by experiments indicating that the administration of gonadotropins can synchronize isolated ovaries [64]. Using a *Per1*-luciferase reporter assay, circadian rhythms were noted in the ovaries, and clock gene phasing was observed in response to LH and FSH [64]. In addition, the ovaries of a mouse model of polycystic ovarian syndrome (PCOS) were shown to have an anomaly for the time of *Per2* rhythm [65].

2.3. Endometrial Circadian Clock

An analysis of the relationship between the decidual circadian rhythm and recurrent miscarriage showed that *BMAL1* expression in the human decidua during early pregnancy was decreased in patients that experienced recurrent miscarriage [66]. In particular, knockdown may impair the regulation of trophoblast invasion by decidual cells, disrupting proper placenta formation. Polymorphisms in the circadian clock genes are also associated with a higher risk of miscarriage, and gene variants were found in *BMAL1* and *NPAS2* [67]. Furthermore, progesterone is known to affect the peripheral endometrial clock rhythm in humans. When progesterone acts on the endometrium and decidualization occurs, the level of *PER1* in the endometrium increases [68]. The microenvironment of the uterus responds to circadian rhythms and adapts to physiological functions. During pregnancy, the fetus is continuously exposed to hormonal and nutritional signals in the maternal endometrium [69,70]. These results suggest that the circadian rhythms play significant roles in reproduction.

2.4. Animal Studies on the Circadian Clock and Reproductive Function

Consistent with its expression pattern, global *Bmal1* knockout mice were found to have significantly reduced ovulation compared with control mice [8]. Global *Bmal1* knockout mice were also known to be infertile [5,8,71] (Table 1). Global *Bmal1* knockout mice also showed delayed puberty and abnormal estrous cycles [5,72], and the deletion of *Bmal1* was shown to reduce progesterone levels [5,73]. Later, the failure of embryo implantation in steroidogenic factor-1 (SF-1) expression-dependent *Bmal1*-deleted female mice ($Bmal1^{SF1d/d}$) was shown to be rescued by P_4 supplementation or normal ovarian transplantation, demonstrating that insufficient ovarian P_4 production is one of the primary causes of infertility in *Bmal1* knockout female mice [73]. Additional studies were carried out involving the conditional knockout of *Bmal1* in ovarian granulosa cells or theca cells [7] (Table 1). Theca cells are the pacemakers that regulate ovulation timing and transient sensitivity to LH [14]. In these conditional knockout mice, transient susceptibility to LH was found in littermate controls and granulosa cell-specific *Bmal1* knockout mice, but not in theca cell-specific *Bmal1* knockouts [7,74]. This indicated that follicle development and ovulation are affected by circadian rhythm disfunction in theca cells (Table 1).

Recently, we generated mice with a conditional deletion (cKO) of uterine *Bmal1* to examine the pathogenic functions of the uterine clock genes during pregnancy [75]. We found that cKO mice could achieve embryo implantation but could not maintain pregnancy. A histological analysis of their placentas showed that the maternal vascular spaces failed to form properly. In contrast to WT mice, cKO mice expressed scarce levels of the immunosuppressive NK marker CD161 in the spongiotrophoblast layer where maternal

uNK cells are in close contact with the fetal trophoblast. These data suggest that *Bmal1* plays a significant role in the reproductive organs (Table 1).

Table 1. Distinct reproductive characteristics of *Bmal1* mutant mice.

Mutant Mice	Phenotypes of Reproduction	References
Conventional *Bmal1* KO	Delayed puberty; females have longer estrous cycles; infertile	[5,76]
Gonadotrope *Bmal1* KO	Irregular estrous cycle; fertile	[7,77]
Granulosa cell *Bmal1* KO (GCKO)	Normal ovarian morphology and a typical estrous cycle; fertile	[7]
Ovarian steroidogenic cells *Bmal1* KO	Typical puberty; early pregnancy loss; infertile	[73]
Theca cell *Bmal1* KO	Fewer offsprings and increased mating failure; regular estrous cycle; subfertile	[7]
Uterine *Bmal1* KO	Reducing placental vascularization and causing fetal mortality within the uterus; subfertile	[75]

Similarly, *Per1* and *Per2* knockout mice experienced reduced reproductive rates because of estrous cycle irregularities [78,79]. Moreover, in *Per1-Per2* double knockout mice, the follicular reserve was depleted, resulting in infertility [80]. Mice with a dominant negative mutation in *Clock* (*Clock* Δ19/Δ19 mice) were generated to investigate the molecular mechanisms governing circadian clocks [81]. These mice are capable of producing the BMAL1-CLOCK dimer, but possess a defective form of the CLOCK protein that is unable to regulate *Per* and *Cry* expression, resulting in the loss of the feedback loop for circadian clock genes [81]. *Clock* Δ19/Δ19 mice are also overweight and develop symptoms of metabolic syndrome under high-fat diet (HFD) conditions [82]. This obesity-induced phenotype is associated with feeding during rest time. Untimely feeding is associated with obesity and excess body weight in mice and humans [83,84]. Fasting is also involved in circadian rhythm accommodation or dysregulation. Time-restricted feeding (TRF) in which food access is restricted to the dark phase has been reported to protect mice from obesity, fatty liver, hyperinsulinemia, and inflammation when they are fed an HFD [85–87]. Rodents fed an HFD ad libitum showed changes in circadian rhythms compared with rodents fed an HFD with TRF [85,88]. This suggests that feeding affects the circadian clock. In addition to the loss of a circadian rhythm, these mice were also reported to have increased risks of stillbirth and neonatal death compared with controls [89].

The pars tuberalis is situated between the anterior lobe of the pituitary gland and the median eminence. It has been demonstrated that melatonin acts as a photoperiodic signal, synchronizing an endogenous oscillator in the pars tuberalis to the photoperiod [90]. Thyroid-stimulating hormone beta (TSH) cells are found in the pars tuberalis, which also trigger the secretion of TSH. TSH promotes triiodothyronine synthesis, which helps gonadotropin-releasing hormone-I release, luteinizing hormone and follicle, stimulating hormone release [91]. Recent research has shown that pars tuberalis controls seasonal reproduction with its TSH secretion [92,93].

In diurnal primates, labor is often initiated at night, consistent with the increased sensitivity to oxytocin that causes pregnancy-related uterine contractions [94,95]. This suggests that circadian rhythms alter uterine sensitivity to oxytocin [96]. Furthermore, studies in rodents have shown that the uterus has a functional peripheral circadian clock [17,97,98]. It has also been suggested that embryo implantation and delivery are controlled by a peripheral circadian clock in the uterus [99,100]. Maternal myometrium and the bladder-specific deletion of *Bmal1* cause the mistiming of labor onset [101]. While control mice gave birth early in the morning [29], maternal myometrium- and bladder-specific *Bmal1* knockout mice had 28% more daytime births than control mice, demonstrating that the peripheral circadian clock is involved in the timing of labor [29]. These data suggest the importance of circadian clocks in reproduction.

3. The Circadian Clock System as a Link between Nutritional Signals and Reproduction

Reproduction is critical for species survival. Nevertheless, under certain environmental conditions, reproductive activity is suppressed. Many organisms, together with humans, adaptively reduce reproductive activity during periods of starvation and/or anorexia [102,103]. Inadequate dietary restrictions are known to adversely affect the rhythmic secretion of luteinizing hormone (LH) [4], ovarian development [5], and decreased human gonadotropin levels [104–106]. Food restriction inhibits both GnRH pulse activity and gonadotropin secretion, resulting in insufficient gonadotropin for folliculogenesis [107,108]. This ultimately results in delayed puberty and the suppression of ovulation when the food supply is insufficient [109].

Feeding rhythms are important for animals because food-entrainable oscillators are located within peripheral tissues, and these peripheral oscillators are independent of the SCN [110–112]. We found that time-restricted feeding regulates the circadian rhythm of the uterine clock that is synchronized throughout the uterine body [113]. Furthermore, we postulated that breakfast skipping impairs reproductive function by disrupting the circadian clock [114,115]. In modern society, breakfast skipping is a common habit. Previously, we discovered that skipping breakfast is related to dysmenorrhea [116], and later studies have also revealed a similar correlation between skipping breakfast and dysmenorrhea [117–120]. Experiments in mice were conducted in which feeding was limited to two meals per day at specified intervals (16 and 8 h). These studies found that the circadian clock was reset by a longer interval (16 h fast) than a shorter interval (8 h fast) between meals [88,121]. In general, breakfast corresponds to the start of one's daily activities, and skipping breakfast interferes with circadian clocks [116,122–124]. This suggests that breakfast has the greatest impact on the chronobiology of the daily diet in humans, and skipping breakfast has been proposed to affect the reproductive system [120,125,126].

4. The Circadian Clock and Puberty

Proper timing of sexual maturation is necessary for reproduction [127–129]. Circadian regulation of the reproductive organs is associated with the timing of GnRH release and gonadotropin secretion, and these processes affect sexual maturation [77,130]. Moreover, human and animal puberty relies on complex endocrine regulation [131]. In European sea bass, a prolonged photoperiod delays or prevents puberty and the release of the hormones associated with reproduction [132,133]. One variable in female puberty is the age at menarche, and the timing of menarche is impacted by light. In women who are blind with loss of light perception, menarche occurs earlier than in women with normal light perception [134]. In addition, women are more likely to experience precocious puberty than men [135,136]. From a disease perspective, the associations between the timing of puberty and the risk of developing endometrial or breast cancer in women and prostate cancer in men have been described [137]. Thus, focusing on circadian rhythms may provide clues to preventing and/or treating these diseases.

Other factors affecting sexual maturation are endocrine-disrupting chemicals (EDCs). EDCs are substances that can mimic hormones in the body and are found in common household products. EDCs bind to hormone receptors and cause activation or suppression of natural hormones or alter the breakdown of natural hormones, thereby causing changes in normal hormonal signaling. Puberty is a complex developmental stage in which physical changes promote sexual maturation, and this process is sensitive to hormonal disruptions. EDCs have been reported to be involved in pubertal-onset variability [138] and can enter the body through drinking, eating, breathing, or direct contact [139]. Exposure to EDCs with estrogenic and/or anti-androgenic effects can disrupt the reproductive tract and sexual maturation [140]. Over the last 200 years, the timing of pubertal onset has changed. The age of menarche has been reduced from 17 in the early 19th century to 13 in the 1950s [141]. The liver of adult male Wistar rats treated with 4-hydroxy-2,3,3′,4′,5-pentachlorobiphenyl showed altered expression of the clock genes including BMAL1 [142]. Moreover, various

studies have demonstrated changes in circadian clock-gene expression and the endocrine system after exposure to EDCs, and the importance of this is now clear [143–145].

5. Conclusions

In conclusion, elucidating the factors that modify circadian clocks in reproductive organs will provide clues to treating reproductive dysfunction. Moreover, it may suggest strategies for optimizing existing therapeutic interventions. We expect that the appropriate re-establishment of the networks governing circadian rhythms and the reproductive cycle in early life will help prevent future obstetric and gynecological diseases. The influence of circadian rhythms governing protein translation on the regenerative capacity of tissues must be considered in future studies of regeneration.

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Abbreviations

ADHOGD	adolescent dietary habit-induced obstetric and gynecologic disease
Bmal1	brain and muscle Arnt-like protein-1
Clock	circadian locomotor output cycles kaput
Cry1	cryptochrome circadian regulator 1
Cry2	cryptochrome circadian regulator 2
Dbp	albumin D-binding protein
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDP	hypertensive disorders of pregnancy
HPG	hypothalamic–pituitary–gonadal
LH	luteinizing hormone
PCOS	polycystic ovary syndrome
Per1	period circadian regulator 1
Per2	period circadian regulator 2
Per3	period circadian regulator 3
NR1D1	nuclear receptor subfamily 1, group D, member 1

References

1. Mahoney, M.M. Shift work, jet lag and female reproduction. *Int. J. Endocrinol.* **2010**, *2010*, 813764. [CrossRef] [PubMed]
2. Summa, K.C.; Vitaterna, M.H.; Turek, F.W. Environmental perturbation of the circadian clock disrupts pregnancy in the mouse. *PLoS ONE* **2012**, *7*, e37668. [CrossRef] [PubMed]
3. Miller, B.H.; Olson, S.L.; Turek, F.W.; Levine, J.E.; Horton, T.H.; Takahashi, J.S. Circadian clock mutation disrupts estrous cyclicity and maintenance of pregnancy. *Curr. Biol.* **2004**, *14*, 1367–1373. [CrossRef] [PubMed]
4. Bittman, E.L. Circadian Function in Multiple Cell Types Is Necessary for Proper Timing of the Preovulatory LH Surge. *J. Biol. Rhythm.* **2019**, *34*, 622–633. [CrossRef] [PubMed]
5. Boden, M.J.; Varcoe, T.J.; Voultsios, A.; Kennaway, D.J. Reproductive biology of female Bmal1 null mice. *Reproduction* **2010**, *139*, 1077–1090. [CrossRef] [PubMed]
6. Sellix, M.T. Clocks underneath: The role of peripheral clocks in the timing of female reproductive physiology. *Front. Endocrinol.* **2013**, *4*, 91. [CrossRef]
7. Mereness, A.L.; Murphy, Z.C.; Forrestel, A.C.; Butler, S.; Ko, C.; Richards, J.S.; Sellix, M.T. Conditional Deletion of Bmal1 in Ovarian Theca Cells Disrupts Ovulation in Female Mice. *Endocrinology* **2016**, *157*, 913–927. [CrossRef]

8. Xu, J.; Li, Y.; Wang, Y.; Xu, Y.; Zhou, C. Loss of Bmal1 decreases oocyte fertilization, early embryo development and implantation potential in female mice. *Zygote* **2016**, *24*, 760–767. [CrossRef]
9. Perez, S.; Murias, L.; Fernandez-Plaza, C.; Diaz, I.; Gonzalez, C.; Otero, J.; Diaz, E. Evidence for clock genes circadian rhythms in human full-term placenta. *Syst. Biol. Reprod. Med.* **2015**, *61*, 360–366. [CrossRef]
10. Muter, J.; Lucas, E.S.; Chan, Y.W.; Brighton, P.J.; Moore, J.D.; Lacey, L.; Quenby, S.; Lam, E.W.; Brosens, J.J. The clock protein period 2 synchronizes mitotic expansion and decidual transformation of human endometrial stromal cells. *FASEB J.* **2015**, *29*, 1603–1614. [CrossRef]
11. Ratajczak, C.K.; Herzog, E.D.; Muglia, L.J. Clock gene expression in gravid uterus and extra-embryonic tissues during late gestation in the mouse. *Reprod. Fertil. Dev.* **2010**, *22*, 743–750. [CrossRef]
12. Kennaway, D.J.; Boden, M.J.; Varcoe, T.J. Circadian rhythms and fertility. *Mol. Cell. Endocrinol.* **2012**, *349*, 56–61. [CrossRef]
13. Sen, A.; Hoffmann, H.M. Role of core circadian clock genes in hormone release and target tissue sensitivity in the reproductive axis. *Mol. Cell. Endocrinol.* **2020**, *501*, 110655. [CrossRef]
14. Pan, X.; Taylor, M.J.; Cohen, E.; Hanna, N.; Mota, S. Circadian Clock, Time-Restricted Feeding and Reproduction. *Int. J. Mol. Sci.* **2020**, *21*, 831. [CrossRef]
15. Karman, B.N.; Tischkau, S.A. Circadian clock gene expression in the ovary: Effects of luteinizing hormone. *Biol. Reprod.* **2006**, *75*, 624–632. [CrossRef]
16. Nakamura, T.J.; Sellix, M.T.; Kudo, T.; Nakao, N.; Yoshimura, T.; Ebihara, S.; Colwell, C.S.; Block, G.D. Influence of the estrous cycle on clock gene expression in reproductive tissues: Effects of fluctuating ovarian steroid hormone levels. *Steroids* **2010**, *75*, 203–212. [CrossRef]
17. Yaw, A.M.; Duong, T.V.; Nguyen, D.; Hoffmann, H.M. Circadian rhythms in the mouse reproductive axis during the estrous cycle and pregnancy. *J. Neurosci. Res.* **2021**, *99*, 294–308. [CrossRef]
18. Mieda, M.; Okamoto, H.; Sakurai, T. Manipulating the Cellular Circadian Period of Arginine Vasopressin Neurons Alters the Behavioral Circadian Period. *Curr. Biol.* **2016**, *26*, 2535–2542. [CrossRef]
19. Sun, W.; Li, S.X.; Wang, G.; Dong, S.; Jiang, Y.; Spruyt, K.; Ling, J.; Zhu, Q.; Lee, T.M.; Jiang, F. Association of Sleep and Circadian Activity Rhythm with Emotional Face Processing among 12-month-old Infants. *Sci. Rep.* **2018**, *8*, 3200. [CrossRef]
20. Ikeda, Y.; Kumagai, H.; Skach, A.; Sato, M.; Yanagisawa, M. Modulation of circadian glucocorticoid oscillation via adrenal opioid-CXCR7 signaling alters emotional behavior. *Cell* **2013**, *155*, 1323–1336. [CrossRef]
21. Page, A.J.; Christie, S.; Symonds, E.; Li, H. Circadian regulation of appetite and time restricted feeding. *Physiol. Behav.* **2020**, *220*, 112873. [CrossRef] [PubMed]
22. Scheer, F.A.; Morris, C.J.; Shea, S.A. The internal circadian clock increases hunger and appetite in the evening independent of food intake and other behaviors. *Obesity* **2013**, *21*, 421–423. [CrossRef] [PubMed]
23. Baker, F.C.; Driver, H.S. Circadian rhythms, sleep, and the menstrual cycle. *Sleep Med.* **2007**, *8*, 613–622. [CrossRef] [PubMed]
24. Lawson, C.C.; Whelan, E.A.; Lividoti Hibert, E.N.; Spiegelman, D.; Schernhammer, E.S.; Rich-Edwards, J.W. Rotating shift work and menstrual cycle characteristics. *Epidemiology* **2011**, *22*, 305–312. [CrossRef] [PubMed]
25. Stocker, L.J.; Macklon, N.S.; Cheong, Y.C.; Bewley, S.J. Influence of shift work on early reproductive outcomes: A systematic review and meta-analysis. *Obstet. Gynecol.* **2014**, *124*, 99–110. [CrossRef] [PubMed]
26. Bonde, J.P.; Jorgensen, K.T.; Bonzini, M.; Palmer, K.T. Miscarriage and occupational activity: A systematic review and meta-analysis regarding shift work, working hours, lifting, standing, and physical workload. *Scand. J. Work Environ. Health* **2013**, *39*, 325–334. [CrossRef]
27. Grajewski, B.; Whelan, E.A.; Lawson, C.C.; Hein, M.J.; Waters, M.A.; Anderson, J.L.; MacDonald, L.A.; Mertens, C.J.; Tseng, C.Y.; Cassinelli, R.T., II; et al. Miscarriage among flight attendants. *Epidemiology* **2015**, *26*, 192–203. [CrossRef]
28. Suzumori, N.; Ebara, T.; Matsuki, T.; Yamada, Y.; Kato, S.; Omori, T.; Saitoh, S.; Kamijima, M.; Sugiura-Ogasawara, M.; Japan Environment & Children's Study Group. Effects of long working hours and shift work during pregnancy on obstetric and perinatal outcomes: A large prospective cohort study-Japan Environment and Children's Study. *Birth* **2020**, *47*, 67–79. [CrossRef]
29. Patil, D.; Enquobahrie, D.A.; Peckham, T.; Seixas, N.; Hajat, A. Retrospective cohort study of the association between maternal employment precarity and infant low birth weight in women in the USA. *BMJ Open* **2020**, *10*, e029584. [CrossRef]
30. Xie, Y.; Tang, Q.; Chen, G.; Xie, M.; Yu, S.; Zhao, J.; Chen, L. New Insights into the Circadian Rhythm and Its Related Diseases. *Front. Physiol.* **2019**, *10*, 682. [CrossRef]
31. Rijo-Ferreira, F.; Takahashi, J.S. Genomics of circadian rhythms in health and disease. *Genome Med.* **2019**, *11*, 82. [CrossRef]
32. Abbas, S.; Ahmed, I.; Kudo, T.; Iqbal, M.; Lee, Y.J.; Fujiwara, T.; Ohkuma, M. A heavy metal tolerant novel bacterium, *Bacillus malikii* sp. nov., isolated from tannery effluent wastewater. *Antonie Leeuwenhoek* **2015**, *108*, 1319–1330. [CrossRef]
33. Miller, B.H.; Olson, S.L.; Levine, J.E.; Turek, F.W.; Horton, T.H.; Takahashi, J.S. Vasopressin regulation of the proestrous luteinizing hormone surge in wild-type and Clock mutant mice. *Biol. Reprod.* **2006**, *75*, 778–784. [CrossRef]
34. Pendergast, J.S.; Oda, G.A.; Niswender, K.D.; Yamazaki, S. Period determination in the food-entrainable and methamphetamine-sensitive circadian oscillator(s). *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 14218–14223. [CrossRef]
35. De Bundel, D.; Gangarossa, G.; Biever, A.; Bonnefont, X.; Valjent, E. Cognitive dysfunction, elevated anxiety, and reduced cocaine response in circadian clock-deficient cryptochrome knockout mice. *Front. Behav. Neurosci.* **2013**, *7*, 152. [CrossRef]
36. Mohawk, J.A.; Green, C.B.; Takahashi, J.S. Central and peripheral circadian clocks in mammals. *Annu. Rev. Neurosci.* **2012**, *35*, 445–462. [CrossRef]

37. Whitmore, D.; Foulkes, N.S.; Sassone-Corsi, P. Light acts directly on organs and cells in culture to set the vertebrate circadian clock. *Nature* **2000**, *404*, 87–91. [CrossRef]
38. Bass, J. Circadian topology of metabolism. *Nature* **2012**, *491*, 348–356. [CrossRef]
39. Moore, R.Y.; Speh, J.C.; Leak, R.K. Suprachiasmatic nucleus organization. *Cell Tissue Res.* **2002**, *309*, 89–98. [CrossRef]
40. Putteeraj, M.; Soga, T.; Ubuka, T.; Parhar, I.S. A "Timed" Kiss Is Essential for Reproduction: Lessons from Mammalian Studies. *Front. Endocrinol.* **2016**, *7*, 121. [CrossRef]
41. Robertson, J.L.; Clifton, D.K.; de la Iglesia, H.O.; Steiner, R.A.; Kauffman, A.S. Circadian regulation of Kiss1 neurons: Implications for timing the preovulatory gonadotropin-releasing hormone/luteinizing hormone surge. *Endocrinology* **2009**, *150*, 3664–3671. [CrossRef] [PubMed]
42. Christian, C.A.; Moenter, S.M. The neurobiology of preovulatory and estradiol-induced gonadotropin-releasing hormone surges. *Endocr. Rev.* **2010**, *31*, 544–577. [CrossRef] [PubMed]
43. Neumann, A.M.; Schmidt, C.X.; Brockmann, R.M.; Oster, H. Circadian regulation of endocrine systems. *Auton. Neurosci.* **2019**, *216*, 1–8. [CrossRef] [PubMed]
44. Sen, A.; Sellix, M.T. The Circadian Timing System and Environmental Circadian Disruption: From Follicles to Fertility. *Endocrinology* **2016**, *157*, 3366–3373. [CrossRef] [PubMed]
45. Van der Vinne, V.; Tachinardi, P.; Riede, S.J.; Akkerman, J.; Scheepe, J.; Daan, S.; Hut, R.A. Maximising survival by shifting the daily timing of activity. *Ecol. Lett.* **2019**, *22*, 2097–2102. [CrossRef]
46. Smarr, B.L.; Morris, E.; de la Iglesia, H.O. The dorsomedial suprachiasmatic nucleus times circadian expression of Kiss1 and the luteinizing hormone surge. *Endocrinology* **2012**, *153*, 2839–2850. [CrossRef]
47. Chassard, D.; Bur, I.; Poirel, V.J.; Mendoza, J.; Simonneaux, V. Evidence for a Putative Circadian Kiss-Clock in the Hypothalamic AVPV in Female Mice. *Endocrinology* **2015**, *156*, 2999–3011. [CrossRef]
48. Comninos, A.N.; Wall, M.B.; Demetriou, L.; Shah, A.J.; Clarke, S.A.; Narayanaswamy, S.; Nesbitt, A.; Izzi-Engbeaya, C.; Prague, J.K.; Abbara, A.; et al. Kisspeptin modulates sexual and emotional brain processing in humans. *J. Clin. Investig.* **2017**, *127*, 709–719. [CrossRef]
49. Dror, T.; Franks, J.; Kauffman, A.S. Analysis of multiple positive feedback paradigms demonstrates a complete absence of LH surges and GnRH activation in mice lacking kisspeptin signaling. *Biol. Reprod.* **2013**, *88*, 146. [CrossRef]
50. Saedi, S.; Khoradmehr, A.; Mohammad Reza, J.S.; Tamadon, A. The role of neuropeptides and neurotransmitters on kisspeptin/kiss1r-signaling in female reproduction. *J. Chem. Neuroanat.* **2018**, *92*, 71–82. [CrossRef]
51. Kunimura, Y.; Iwata, K.; Ishigami, A.; Ozawa, H. Age-related alterations in hypothalamic kisspeptin, neurokinin B, and dynorphin neurons and in pulsatile LH release in female and male rats. *Neurobiol. Aging.* **2017**, *50*, 30–38. [CrossRef]
52. Garcia, J.P.; Guerriero, K.A.; Keen, K.L.; Kenealy, B.P.; Seminara, S.B.; Terasawa, E. Kisspeptin and Neurokinin B Signaling Network Underlies the Pubertal Increase in GnRH Release in Female Rhesus Monkeys. *Endocrinology* **2017**, *158*, 3269–3280. [CrossRef]
53. Qiu, J.; Nestor, C.C.; Zhang, C.; Padilla, S.L.; Palmiter, R.D.; Kelly, M.J.; Ronnekleiv, O.K. High-frequency stimulation-induced peptide release synchronizes arcuate kisspeptin neurons and excites GnRH neurons. *eLife* **2016**, *5*, e16246. [CrossRef]
54. Kalil, B.; Ribeiro, A.B.; Leite, C.M.; Uchoa, E.T.; Carolino, R.O.; Cardoso, T.S.; Elias, L.L.; Rodrigues, J.A.; Plant, T.M.; Poletini, M.O.; et al. The Increase in Signaling by Kisspeptin Neurons in the Preoptic Area and Associated Changes in Clock Gene Expression That Trigger the LH Surge in Female Rats Are Dependent on the Facilitatory Action of a Noradrenaline Input. *Endocrinology* **2016**, *157*, 323–335. [CrossRef]
55. Adams, C.; Stroberg, W.; DeFazio, R.A.; Schnell, S.; Moenter, S.M. Gonadotropin-Releasing Hormone (GnRH) Neuron Excitability Is Regulated by Estradiol Feedback and Kisspeptin. *J. Neurosci.* **2018**, *38*, 1249–1263. [CrossRef]
56. Williams, W.P., III; Jarjisian, S.G.; Mikkelsen, J.D.; Kriegsfeld, L.J. Circadian control of kisspeptin and a gated GnRH response mediate the preovulatory luteinizing hormone surge. *Endocrinology* **2011**, *152*, 595–606. [CrossRef]
57. Smith, J.T.; Acohido, B.V.; Clifton, D.K.; Steiner, R.A. KiSS-1 neurones are direct targets for leptin in the *ob/ob* mouse. *J. Neuroendocrinol.* **2006**, *18*, 298–303. [CrossRef]
58. Navarro, V.M.; Castellano, J.M.; McConkey, S.M.; Pineda, R.; Ruiz-Pino, F.; Pinilla, L.; Clifton, D.K.; Tena-Sempere, M.; Steiner, R.A. Interactions between kisspeptin and neurokinin B in the control of GnRH secretion in the female rat. *Am. J. Physiol. Endocrinol. Metab.* **2011**, *300*, E202–E210. [CrossRef]
59. Laposky, A.D.; Bradley, M.A.; Williams, D.L.; Bass, J.; Turek, F.W. Sleep-wake regulation is altered in leptin-resistant (*db/db*) genetically obese and diabetic mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2008**, *295*, R2059–R2066. [CrossRef]
60. Sutton, G.M.; Centanni, A.V.; Butler, A.A. Protein malnutrition during pregnancy in C57BL/6J mice results in offspring with altered circadian physiology before obesity. *Endocrinology* **2010**, *151*, 1570–1580. [CrossRef]
61. Ando, H.; Kumazaki, M.; Motosugi, Y.; Ushijima, K.; Maekawa, T.; Ishikawa, E.; Fujimura, A. Impairment of peripheral circadian clocks precedes metabolic abnormalities in ob/ob mice. *Endocrinology* **2011**, *152*, 1347–1354. [CrossRef] [PubMed]
62. Tonsfeldt, K.J.; Goodall, C.P.; Latham, K.L.; Chappell, P.E. Oestrogen induces rhythmic expression of the Kisspeptin-1 receptor GPR54 in hypothalamic gonadotrophin-releasing hormone-secreting GT1-7 cells. *J. Neuroendocrinol.* **2011**, *23*, 823–830. [CrossRef] [PubMed]
63. Fahrenkrug, J.; Georg, B.; Hannibal, J.; Hindersson, P.; Gras, S. Diurnal rhythmicity of the clock genes Per1 and Per2 in the rat ovary. *Endocrinology* **2006**, *147*, 3769–3776. [CrossRef] [PubMed]

64. Yoshikawa, T.; Sellix, M.; Pezuk, P.; Menaker, M. Timing of the ovarian circadian clock is regulated by gonadotropins. *Endocrinology* **2009**, *150*, 4338–4347. [CrossRef] [PubMed]
65. Mereness, A.L.; Murphy, Z.C.; Sellix, M.T. Developmental programming by androgen affects the circadian timing system in female mice. *Biol. Reprod.* **2015**, *92*, 88. [CrossRef]
66. Lv, S.; Wang, N.; Ma, J.; Li, W.P.; Chen, Z.J.; Zhang, C. Impaired decidualization caused by downregulation of circadian clock gene BMAL1 contributes to human recurrent miscarriage dagger. *Biol. Reprod.* **2019**, *101*, 138–147. [CrossRef]
67. Kovanen, L.; Saarikoski, S.T.; Aromaa, A.; Lonnqvist, J.; Partonen, T. ARNTL (BMAL1) and NPAS2 gene variants contribute to fertility and seasonality. *PLoS ONE* **2010**, *5*, e10007. [CrossRef]
68. Zhang, Y.; Meng, N.; Bao, H.; Jiang, Y.; Yang, N.; Wu, K.; Wu, J.; Wang, H.; Kong, S.; Zhang, Y. Circadian gene *PER1* senses progesterone signal during human endometrial decidualization. *J. Endocrinol.* **2019**, *243*, 229–242. [CrossRef]
69. Seron-Ferre, M.; Valenzuela, G.J.; Torres-Farfan, C. Circadian clocks during embryonic and fetal development. *Birth Defects Res. C Embryo Today* **2007**, *81*, 204–214. [CrossRef]
70. Akiyama, S.; Ohta, H.; Watanabe, S.; Moriya, T.; Hariu, A.; Nakahata, N.; Chisaka, H.; Matsuda, T.; Kimura, Y.; Tsuchiya, S.; et al. The uterus sustains stable biological clock during pregnancy. *Tohoku J. Exp. Med.* **2010**, *221*, 287–298. [CrossRef]
71. Papacleovoulou, G.; Nikolova, V.; Oduwole, O.; Chambers, J.; Vazquez-Lopez, M.; Jansen, E.; Nicolaides, K.; Parker, M.; Williamson, C. Gestational disruptions in metabolic rhythmicity of the liver, muscle, and placenta affect fetal size. *FASEB J.* **2017**, *31*, 1698–1708. [CrossRef]
72. Alvarez, J.D.; Hansen, A.; Ord, T.; Bebas, P.; Chappell, P.E.; Giebultowicz, J.M.; Williams, C.; Moss, S.; Sehgal, A. The circadian clock protein BMAL1 is necessary for fertility and proper testosterone production in mice. *J. Biol. Rhythm.* **2008**, *23*, 26–36. [CrossRef]
73. Liu, Y.; Johnson, B.P.; Shen, A.L.; Wallisser, J.A.; Krentz, K.J.; Moran, S.M.; Sullivan, R.; Glover, E.; Parlow, A.F.; Drinkwater, N.R.; et al. Loss of BMAL1 in ovarian steroidogenic cells results in implantation failure in female mice. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 14295–14300. [CrossRef]
74. Jiang, Y.; Li, S.; Xu, W.; Ying, J.; Qu, Y.; Jiang, X.; Zhang, A.; Yue, Y.; Zhou, R.; Ruan, T.; et al. Critical Roles of the Circadian Transcription Factor BMAL1 in Reproductive Endocrinology and Fertility. *Front. Endocrinol.* **2022**, *13*, 818272. [CrossRef]
75. Ono, M.; Toyoda, N.; Kagami, K.; Hosono, T.; Matsumoto, T.; Horike, S.I.; Yamazaki, R.; Nakamura, M.; Mizumoto, Y.; Fujiwara, T.; et al. Uterine Deletion of Bmal1 Impairs Placental Vascularization and Induces Intrauterine Fetal Death in Mice. *Int. J. Mol. Sci.* **2022**, *23*, 7637. [CrossRef]
76. Ratajczak, C.K.; Boehle, K.L.; Muglia, L.J. Impaired steroidogenesis and implantation failure in *Bmal1*$^{-/-}$ mice. *Endocrinology* **2009**, *150*, 1879–1885. [CrossRef]
77. Chu, A.; Zhu, L.; Blum, I.D.; Mai, O.; Leliavski, A.; Fahrenkrug, J.; Oster, H.; Boehm, U.; Storch, K.F. Global but not gonadotrope-specific disruption of Bmal1 abolishes the luteinizing hormone surge without affecting ovulation. *Endocrinology* **2013**, *154*, 2924–2935. [CrossRef]
78. Pilorz, V.; Steinlechner, S. Low reproductive success in Per1 and Per2 mutant mouse females due to accelerated ageing? *Reproduction* **2008**, *135*, 559–568. [CrossRef]
79. Zheng, B.; Albrecht, U.; Kaasik, K.; Sage, M.; Lu, W.; Vaishnav, S.; Li, Q.; Sun, Z.S.; Eichele, G.; Bradley, A.; et al. Nonredundant roles of the mPer1 and mPer2 genes in the mammalian circadian clock. *Cell* **2001**, *105*, 683–694. [CrossRef]
80. Zheng, Y.; Liu, C.; Li, Y.; Jiang, H.; Yang, P.; Tang, J.; Xu, Y.; Wang, H.; He, Y. Loss-of-function mutations with circadian rhythm regulator Per1/Per2 lead to premature ovarian insufficiency dagger. *Biol. Reprod.* **2019**, *100*, 1066–1072. [CrossRef]
81. Vitaterna, M.H.; King, D.P.; Chang, A.M.; Kornhauser, J.M.; Lowrey, P.L.; McDonald, J.D.; Dove, W.F.; Pinto, L.H.; Turek, F.W.; Takahashi, J.S. Mutagenesis and mapping of a mouse gene, Clock, essential for circadian behavior. *Science* **1994**, *264*, 719–725. [CrossRef] [PubMed]
82. Turek, F.W.; Joshu, C.; Kohsaka, A.; Lin, E.; Ivanova, G.; McDearmon, E.; Laposky, A.; Losee-Olson, S.; Easton, A.; Jensen, D.R.; et al. Obesity and metabolic syndrome in circadian Clock mutant mice. *Science* **2005**, *308*, 1043–1045. [CrossRef]
83. Lamia, K.A.; Storch, K.F.; Weitz, C.J. Physiological significance of a peripheral tissue circadian clock. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 15172–15177. [CrossRef] [PubMed]
84. Barclay, J.L.; Shostak, A.; Leliavski, A.; Tsang, A.H.; Johren, O.; Muller-Fielitz, H.; Landgraf, D.; Naujokat, N.; van der Horst, G.T.; Oster, H. High-fat diet-induced hyperinsulinemia and tissue-specific insulin resistance in Cry-deficient mice. *Am. J. Physiol. Endocrinol. Metab.* **2013**, *304*, E1053–E1063. [CrossRef]
85. Hatori, M.; Vollmers, C.; Zarrinpar, A.; DiTacchio, L.; Bushong, E.A.; Gill, S.; Leblanc, M.; Chaix, A.; Joens, M.; Fitzpatrick, J.A.; et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. *Cell Metab.* **2012**, *15*, 848–860. [CrossRef] [PubMed]
86. Sherman, H.; Genzer, Y.; Cohen, R.; Chapnik, N.; Madar, Z.; Froy, O. Timed high-fat diet resets circadian metabolism and prevents obesity. *FASEB J.* **2012**, *26*, 3493–3502. [CrossRef]
87. Chaix, A.; Lin, T.; Le, H.D.; Chang, M.W.; Panda, S. Time-Restricted Feeding Prevents Obesity and Metabolic Syndrome in Mice Lacking a Circadian Clock. *Cell Metab.* **2019**, *29*, 303–319.e4. [CrossRef]
88. Arble, D.M.; Bass, J.; Laposky, A.D.; Vitaterna, M.H.; Turek, F.W. Circadian timing of food intake contributes to weight gain. *Obesity* **2009**, *17*, 2100–2102. [CrossRef]

89. Dolatshad, H.; Campbell, E.A.; O'Hara, L.; Maywood, E.S.; Hastings, M.H.; Johnson, M.H. Developmental and reproductive performance in circadian mutant mice. *Hum. Reprod.* **2006**, *21*, 68–79. [CrossRef]
90. Wagner, G.C.; Johnston, J.D.; Tournier, B.B.; Ebling, F.J.; Hazlerigg, D.G. Melatonin induces gene-specific effects on rhythmic mRNA expression in the pars tuberalis of the Siberian hamster (*Phodopus sungorus*). *Eur. J. Neurosci.* **2007**, *25*, 485–490. [CrossRef]
91. Kosonsiriluk, S.; Mauro, L.J.; Chaiworakul, V.; Chaiseha, Y.; El Halawani, M.E. Photoreceptive oscillators within neurons of the premammillary nucleus (PMM) and seasonal reproduction in temperate zone birds. *Gen. Comp. Endocrinol.* **2013**, *190*, 149–155. [CrossRef]
92. Yoshimura, T.; Yasuo, S.; Watanabe, M.; Iigo, M.; Yamamura, T.; Hirunagi, K.; Ebihara, S. Light-induced hormone conversion of T4 to T3 regulates photoperiodic response of gonads in birds. *Nature* **2003**, *426*, 178–181. [CrossRef]
93. Nakao, N.; Ono, H.; Yamamura, T.; Anraku, T.; Takagi, T.; Higashi, K.; Yasuo, S.; Katou, Y.; Kageyama, S.; Uno, Y.; et al. Thyrotrophin in the pars tuberalis triggers photoperiodic response. *Nature* **2008**, *452*, 317–322. [CrossRef]
94. Olcese, J.; Lozier, S.; Paradise, C. Melatonin and the circadian timing of human parturition. *Reprod. Sci.* **2013**, *20*, 168–174. [CrossRef]
95. Olcese, J. Circadian clocks and pregnancy. *Front. Endocrinol.* **2014**, *5*, 123. [CrossRef]
96. Sharkey, J.T.; Puttaramu, R.; Word, R.A.; Olcese, J. Melatonin synergizes with oxytocin to enhance contractility of human myometrial smooth muscle cells. *J. Clin. Endocrinol. Metab.* **2009**, *94*, 421–427. [CrossRef]
97. Nakamura, T.J.; Sellix, M.T.; Menaker, M.; Block, G.D. Estrogen directly modulates circadian rhythms of PER2 expression in the uterus. *Am. J. Physiol. Endocrinol. Metab.* **2008**, *295*, E1025–E1031. [CrossRef]
98. Loh, D.H.; Kuljis, D.A.; Azuma, L.; Wu, Y.; Truong, D.; Wang, H.B.; Colwell, C.S. Disrupted reproduction, estrous cycle, and circadian rhythms in female mice deficient in vasoactive intestinal peptide. *J. Biol. Rhythm.* **2014**, *29*, 355–369. [CrossRef]
99. Gamble, K.L.; Resuehr, D.; Johnson, C.H. Shift work and circadian dysregulation of reproduction. *Front. Endocrinol.* **2013**, *4*, 92. [CrossRef]
100. Miller, B.H.; Takahashi, J.S. Central circadian control of female reproductive function. *Front. Endocrinol.* **2013**, *4*, 195. [CrossRef]
101. Ratajczak, C.K.; Asada, M.; Allen, G.C.; McMahon, D.G.; Muglia, L.M.; Smith, D.; Bhattacharyya, S.; Muglia, L.J. Generation of myometrium-specific Bmal1 knockout mice for parturition analysis. *Reprod. Fertil. Dev.* **2012**, *24*, 759–767. [CrossRef] [PubMed]
102. Andrisani, A.; Sabbadin, C.; Minardi, S.; Favaro, A.; Dona, G.; Bordin, L.; Ambrosini, G.; Armanini, D. Persistent amenorrhea and decreased DHEAS to cortisol ratio after recovery from anorexia nervosa. *Gynecol. Endocrinol.* **2017**, *33*, 311–314. [CrossRef] [PubMed]
103. Luisi, S.; Ciani, V.; Podfigurna-Stopa, A.; Lazzeri, L.; De Pascalis, F.; Meczekalski, B.; Petraglia, F. Serum anti-Mullerian hormone, inhibin B, and total inhibin levels in women with hypothalamic amenorrhea and anorexia nervosa. *Gynecol. Endocrinol.* **2012**, *28*, 34–38. [CrossRef] [PubMed]
104. Booth, P.J.; Cosgrove, J.R.; Foxcroft, G.R. Endocrine and metabolic responses to realimentation in feed-restricted prepubertal gilts: Associations among gonadotropins, metabolic hormones, glucose and uteroovarian development. *J. Anim. Sci.* **1996**, *74*, 840–848. [CrossRef] [PubMed]
105. Quesnel, H.; Pasquier, A.; Mounier, A.M.; Prunier, A. Influence of feed restriction during lactation on gonadotropic hormones and ovarian development in primiparous sows. *J. Anim. Sci.* **1998**, *76*, 856–863. [CrossRef]
106. Veldhuis, J.D.; Iranmanesh, A.; Evans, W.S.; Lizarralde, G.; Thorner, M.O.; Vance, M.L. Amplitude suppression of the pulsatile mode of immunoradiometric luteinizing hormone release in fasting-induced hypoandrogenemia in normal men. *J. Clin. Endocrinol. Metab.* **1993**, *76*, 587–593.
107. Brito, L.F.; Barth, A.D.; Rawlings, N.C.; Wilde, R.E.; Crews, D.H.J.; Boisclair, Y.R.; Ehrhardt, R.A.; Kastelic, J.P. Effect of feed restriction during calfhood on serum concentrations of metabolic hormones, gonadotropins, testosterone, and on sexual development in bulls. *Reproduction* **2007**, *134*, 171–181. [CrossRef]
108. Brito, L.F.; Barth, A.D.; Rawlings, N.C.; Wilde, R.E.; Crews, D.H.J.; Mir, P.S.; Kastelic, J.P. Effect of nutrition during calfhood and peripubertal period on serum metabolic hormones, gonadotropins and testosterone concentrations, and on sexual development in bulls. *Domest. Anim. Endocrinol.* **2007**, *33*, 1–18. [CrossRef]
109. Tropp, J.; Markus, E.J. Effects of mild food deprivation on the estrous cycle of rats. *Physiol. Behav.* **2001**, *73*, 553–559. [CrossRef]
110. Stephan, F.K. Phase shifts of circadian rhythms in activity entrained to food access. *Physiol. Behav.* **1984**, *32*, 663–671. [CrossRef]
111. Mistlberger, R.E. Circadian food-anticipatory activity: Formal models and physiological mechanisms. *Neurosci. Biobehav. Rev.* **1994**, *18*, 171–195. [CrossRef]
112. Vollmers, C.; Gill, S.; DiTacchio, L.; Pulivarthy, S.R.; Le, H.D.; Panda, S. Time of feeding and the intrinsic circadian clock drive rhythms in hepatic gene expression. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 21453–21458. [CrossRef]
113. Hosono, T.; Ono, M.; Daikoku, T.; Mieda, M.; Nomura, S.; Kagami, K.; Iizuka, T.; Nakata, R.; Fujiwara, T.; Fujiwara, H.; et al. Time-Restricted Feeding Regulates Circadian Rhythm of Murine Uterine Clock. *Curr. Dev. Nutr.* **2021**, *5*, nzab064. [CrossRef]
114. Fujiwara, T.; Nakata, R. Skipping breakfast is associated with reproductive dysfunction in post-adolescent female college students. *Appetite* **2010**, *55*, 714–717. [CrossRef]
115. Fujiwara, T.; Ono, M.; Mieda, M.; Yoshikawa, H.; Nakata, R.; Daikoku, T.; Sekizuka-Kagami, N.; Maida, Y.; Ando, H.; Fujiwara, H. Adolescent Dietary Habit-induced Obstetric and Gynecologic Disease (ADHOGD) as a New Hypothesis-Possible Involvement of Clock System. *Nutrients* **2020**, *12*, 1294. [CrossRef]

116. Fujiwara, T. Skipping breakfast is associated with dysmenorrhea in young women in Japan. *Int. J. Food Sci. Nutr.* **2003**, *54*, 505–509. [CrossRef]
117. Angelin, P.; Dileep, D.; Manju, T.; Veena, M.; Pradeep, D.; Amreen, K.; Soumitra, S. Effect of Skipping Breakfast on Young Girls' Menstruation. *Ind. J. Youth Adol. Health* **2017**, *4*, 17–20.
118. Abu Helwa, H.A.; Mitaeb, A.A.; Al-Hamshri, S.; Sweileh, W.M. Prevalence of dysmenorrhea and predictors of its pain intensity among Palestinian female university students. *BMC Women's Health* **2018**, *18*, 18. [CrossRef]
119. Hu, Z.; Tang, L.; Chen, L.; Kaminga, A.C.; Xu, H. Prevalence and Risk Factors Associated with Primary Dysmenorrhea among Chinese Female University Students: A Cross-sectional Study. *J. Pediatr. Adolesc. Gynecol.* **2020**, *33*, 15–22. [CrossRef]
120. Fujiwara, T.; Ono, M.; Iizuka, T.; Sekizuka-Kagami, N.; Maida, Y.; Adachi, Y.; Fujiwara, H.; Yoshikawa, H. Breakfast Skipping in Female College Students Is a Potential and Preventable Predictor of Gynecologic Disorders at Health Service Centers. *Diagnostics* **2020**, *10*, 476. [CrossRef]
121. Shibata, S.; Tahara, Y.; Hirao, A. The adjustment and manipulation of biological rhythms by light, nutrition and abused drugs. *Adv. Drug Deliv. Rev.* **2010**, *62*, 918–927. [CrossRef] [PubMed]
122. Bajalan, Z.; Alimoradi, Z.; Moafi, F. Nutrition as a Potential Factor of Primary Dysmenorrhea: A Systematic Review of Observational Studies. *Gynecol. Obstet. Investig.* **2019**, *84*, 209–224. [CrossRef] [PubMed]
123. Dashti, H.S.; Merino, J.; Lane, J.M.; Song, Y.; Smith, C.E.; Tanaka, T.; McKeown, N.M.; Tucker, C.; Sun, D.; Bartz, T.M.; et al. Genome-wide association study of breakfast skipping links clock regulation with food timing. *Am. J. Clin. Nutr.* **2019**, *110*, 473–484. [CrossRef] [PubMed]
124. Shimizu, H.; Hanzawa, F.; Kim, D.; Sun, S.; Laurent, T.; Umeki, M.; Ikeda, S.; Mochizuki, S.; Oda, H. Delayed first active-phase meal, a breakfast-skipping model, led to increased body weight and shifted the circadian oscillation of the hepatic clock and lipid metabolism-related genes in rats fed a high-fat diet. *PLoS ONE* **2018**, *13*, e0206669. [CrossRef] [PubMed]
125. Fujiwara, T.; Nakata, R.; Ono, M.; Mieda, M.; Ando, H.; Daikoku, T.; Fujiwara, H. Time Restriction of Food Intake During the Circadian Cycle Is a Possible Regulator of Reproductive Function in Postadolescent Female Rats. *Curr. Dev. Nutr.* **2019**, *3*, nzy093. [CrossRef]
126. Fujiwara, T.; Nakata, R. Current problems of food intake in young women in Japan: Their influence on female reproductive function. *Reprod. Med. Biol.* **2004**, *3*, 107–114. [CrossRef]
127. Simonneaux, V.; Bahougne, T.; Angelopoulou, E. Daily rhythms count for female fertility. *Best Pract. Res. Clin. Endocrinol. Metab.* **2017**, *31*, 505–519. [CrossRef]
128. Sellix, M.T.; Murphy, Z.C.; Menaker, M. Excess androgen during puberty disrupts circadian organization in female rats. *Endocrinology* **2013**, *154*, 1636–1647. [CrossRef]
129. Huhtaniemi, I. Mutations along the pituitary-gonadal axis affecting sexual maturation: Novel information from transgenic and knockout mice. *Mol. Cell. Endocrinol.* **2006**, *254–255*, 84–90. [CrossRef]
130. Resuehr, H.E.; Resuehr, D.; Olcese, J. Induction of mPer1 expression by GnRH in pituitary gonadotrope cells involves EGR-1. *Mol. Cell. Endocrinol.* **2009**, *311*, 120–125. [CrossRef]
131. Perry, J.R.; Day, F.; Elks, C.E.; Sulem, P.; Thompson, D.J.; Ferreira, T.; He, C.; Chasman, D.I.; Esko, T.; Thorleifsson, G.; et al. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. *Nature* **2014**, *514*, 92–97. [CrossRef]
132. Bayarri, M.J.; Rodriguez, L.; Zanuy, S.; Madrid, J.A.; Sanchez-Vazquez, F.J.; Kagawa, H.; Okuzawa, K.; Carrillo, M. Effect of photoperiod manipulation on the daily rhythms of melatonin and reproductive hormones in caged European sea bass (*Dicentrarchus labrax*). *Gen. Comp. Endocrinol.* **2004**, *136*, 72–81. [CrossRef]
133. Bayarri, M.J.; Zanuy, S.; Yilmaz, O.; Carrillo, M. Effects of continuous light on the reproductive system of European sea bass gauged by alterations of circadian variations during their first reproductive cycle. *Chronobiol. Int.* **2009**, *26*, 184–199. [CrossRef]
134. Flynn-Evans, E.E.; Stevens, R.G.; Tabandeh, H.; Schernhammer, E.S.; Lockley, S.W. Effect of light perception on menarche in blind women. *Ophthalmic Epidemiol.* **2009**, *16*, 243–248. [CrossRef]
135. De Vries, L.; Kauschansky, A.; Shohat, M.; Phillip, M. Familial central precocious puberty suggests autosomal dominant inheritance. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 1794–1800. [CrossRef]
136. Wehkalampi, K.; Widen, E.; Laine, T.; Palotie, A.; Dunkel, L. Patterns of inheritance of constitutional delay of growth and puberty in families of adolescent girls and boys referred to specialist pediatric care. *J. Clin. Endocrinol. Metab.* **2008**, *93*, 723–728. [CrossRef]
137. Day, F.R.; Thompson, D.J.; Helgason, H.; Chasman, D.I.; Finucane, H.; Sulem, P.; Ruth, K.S.; Whalen, S.; Sarkar, A.K.; Albrecht, E.; et al. Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk. *Nat. Genet.* **2017**, *49*, 834–841. [CrossRef]
138. Livadas, S.; Chrousos, G.P. Molecular and Environmental Mechanisms Regulating Puberty Initiation: An Integrated Approach. *Front. Endocrinol.* **2019**, *10*, 828. [CrossRef] [PubMed]
139. Beszterda, M.; Franski, R. Endocrine disruptor compounds in environment: As a danger for children health. *Pediatr. Endocrinol. Diabetes Metab.* **2018**, *24*, 88–95. [CrossRef]
140. Fudvoye, J.; Lopez-Rodriguez, D.; Franssen, D.; Parent, A.S. Endocrine disrupters and possible contribution to pubertal changes. *Best Pract. Res. Clin. Endocrinol. Metab.* **2019**, *33*, 101300. [CrossRef]
141. Sorensen, K.; Mouritsen, A.; Aksglaede, L.; Hagen, C.P.; Mogensen, S.S.; Juul, A. Recent secular trends in pubertal timing: Implications for evaluation and diagnosis of precocious puberty. *Horm. Res. Paediatr.* **2012**, *77*, 137–145. [CrossRef] [PubMed]

142. Ochiai, M.; Iida, M.; Agusa, T.; Takaguchi, K.; Fujii, S.; Nomiyama, K.; Iwata, H. Effects of 4-Hydroxy-2,3,3′,4′,5-Pentachlorobiphenyl (4-OH-CB107) on Liver Transcriptome in Rats: Implication in the Disruption of Circadian Rhythm and Fatty Acid Metabolism. *Toxicol. Sci.* **2018**, *165*, 118–130. [CrossRef] [PubMed]
143. Zucchi, S.; Mirbahai, L.; Castiglioni, S.; Fent, K. Transcriptional and physiological responses induced by binary mixtures of drospirenone and progesterone in zebrafish (*Danio rerio*). *Environ. Sci. Technol.* **2014**, *48*, 3523–3531. [CrossRef]
144. Zhao, Y.; Castiglioni, S.; Fent, K. Synthetic progestins medroxyprogesterone acetate and dydrogesterone and their binary mixtures adversely affect reproduction and lead to histological and transcriptional alterations in zebrafish (*Danio rerio*). *Environ. Sci. Technol.* **2015**, *49*, 4636–4645. [CrossRef]
145. Wang, J.; Wang, X.; Xiong, C.; Liu, J.; Hu, B.; Zheng, L. Chronic bisphenol A exposure alters behaviors of zebrafish (*Danio rerio*). *Environ. Pollut.* **2015**, *206*, 275–281. [CrossRef]