Chronodisruption: effects on reproduction, transgenerational health of offspring and epigenome

Leyla Sati

Department of Histology and Embryology, Akdeniz University School of Medicine, Antalya, Turkey

Correspondence should be addressed to L Sati; Email: leylasati@yahoo.com

Abstract

The circadian system regulates the daily temporal organization in behavior and physiology, including neuroendocrine rhythms and reproduction. Modern life, however, increasingly impacts this complex biological system. Due to limitations of working with human subjects exposed to shift work schedules, most chronoregulation research has used rodent models. Recent publications in these model systems have emphasized the negative effects of circadian rhythm disruption on both female and male reproductive systems and fertility. Additionally, there is growing concern about the long-term effects of circadian rhythm disruptions during pregnancy on human offspring and their descendants as circadian regulation during pregnancy can also alter epigenetic programming in offspring. However, to truly know if such concerns apply to humans will require retrospective and prospective human studies. Therefore, this review will highlight the latest available evidence regarding potential effects of chronodisruption on both female and male reproductive systems. Additionally, it presents a comprehensive summary of transgenerational and epigenetic effects on adult offspring that result from maternal chronodisruption.

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Introduction

Circadian rhythms align the biological processes of an organism to 24-h environmental cycles. The internal timing system, or circadian clock, coordinates the rhythmic regulation of physiological and behavioral processes in mammals and includes food intake, nutrient processing, sleep/awakening, body temperature, hormone secretion, tissue repair and many others. A discordance between the ambient environment and the circadian rhythm is defined as chronodisruption. However, modern lifestyle factors such as shift work, night eating syndrome and sleep disorders can disrupt the inner rhythm and impair synchronization between the internal clock and the metabolic rhythm. Therefore, there are several reports indicating a link between shift work and obesity, diabetes, heart disease, and other metabolic conditions such as energy metabolism, adverse pregnancy outcomes and psychosocial mental disorders such as depression and anxiety and even with some types of cancers including breast cancer (Sun *et al.* 2018, Cai *et al.* 2019, Nikpour *et al.* 2019, Rosa *et al.* 2019, Rivera *et al.* 2020). A recent study also reported an association between rotating night shift work and earlier menopause among women particularly under the age of 45 years (Stock *et al.* 2019). In humans, even 2 h of ‘social jetlag’ (disruptions to the typical sleep wake cycle) is associated with an adverse endocrine, behavioral and cardiovascular risk profile in apparently healthy participants, further illustrating the

significance of the circadian regulation on the biological and behavioral rhythms (Rutters *et al.* 2014). One of the limitations in this area of research is that the most studied laboratory animal models and species are nocturnal as compared to diurnal circadian process in humans.

Pregnancy also seems to induce circadian changes in daily rhythms in both mice and women, altering both time of onset and amount of physical activity at different stages of the pregnancy (Martin-Fairey *et al.* 2019). Furthermore, maternal circadian rhythm changes in these processes may potentially affect epigenetic programming in offspring. In this concept, circadian regulatory pathways might play an important role in the formation of circadian epigenomes and rhythmic epigenetic changes. However, the discovery of links between circadian rhythm, genetic determinants and related potential phenotypes are needed. Therefore, this review mainly focuses on the role of chronodisruption on both female and male reproduction. Moreover, the potential effects of maternal circadian regulation during pregnancy and lactation periods on the transgenerational health of the offspring and its epigenome are discussed.

Molecular machinery of the mammalian circadian clock

In mammals, circadian rhythms are driven by a master pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus (Welsh *et al.* 2010). The current evidence

suggests that there is not much difference for either the activity cycle or the efferent projections of SCNs of nocturnal versus diurnal species (Novak *et al.* 2000) and this is also conserved in humans. Photosensitive retinal ganglion cells project axons to the SCN creating the retinohypothalamic tract that the SCN uses to coordinate circadian rhythms. An oscillation process initiates and distributes this information over the whole organism by means of hormonal and autonomic signals to instruct cells that are not directly exposed to light. Even though the SCN acts as a central pacemaker atop this hierarchy, a surprising number of mammalian peripheral tissues appear to contain the molecular machinery necessary for circadian oscillation and on occasion, might exhibit dampened circadian oscillations even in the absence of the SCN. Both SCN and peripheral oscillators require regular periodic input from environmental stimuli called zeitgebers (German, time-giver) or *synchronizers*. Zeitgebers synchronize the internal clock network with external time. The most potent zeitgeber of the mammalian circadian system is the 24 h light:24 h darkness cycle. In other words, Zeitgeber Time (ZT) refers to time relative to the onset of light, defined as ZT0 (lights on)-ZT12 (lights off), while the dark phase

is defined as ZT12-ZT24. On the other hand, circadian time (CT) is a standard unit of time based on the endogenous free-running period of a rhythm. However, how the signals generated in the SCN reach oscillators in the brain or other parts of the organism have not been fully elucidated and the function of genes in the circadian machinery in peripheral tissues generally is unclear.

Circadian rhythms are driven by transcription-translation feedback loops (TTFLs) involving a number of central (core) clock genes, that is, Aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL) or brain and muscle ARNT-like 1 protein (BMAL1), circadian locomotor output cycles kaput (Clock), cryptochrome 1 and 2 (Cry1, Cry2) and period 1, 2, 3 (Per1, Per2, Per3) (Fig. 1). Even though the molecular circadian clock acts like a widespread cellular mechanism, alterations for different rhythmic functions exist from bacteria to animals. For instance, orthologous *Drosophila* clock genes are variably characterized in disparate species such as birds, rodents and humans, and genome-wide sequencing is emerging as a powerful tool in comparative genetics of circadian machinery in these different species.

Figure 1 Molecular circadian core machinery in mammals. The transcriptional–translational feedback loops (TTFLs) are presented. The core clock genes as well as other clock-controlled genes (CCGs) are regulated through binding of different protein regulators to E-boxes, D-boxes or ROREs. Factors such as light, polyunsaturated fatty acids (PUFAs), carbon monoxide (CO) and nitric oxide (NO) can reset the circadian TTFL. Circadian locomotor output cycles kaput, CLOCK; Neuronal PAS domain protein 2, NPAS2; Muscle ARNT-Like 1 protein, BMAL1; Period 1, 2, 3, Per1, Per2, Per3; Cryptochrome 1 and 2, Cry1, Cry2; casein kinases, CK1 δ and CK1 ϵ ; Retinoic acid-related orphan receptors, ROR $\alpha/\beta/\gamma$; Reverse erythroblastosis virus α/β , Rev-erb α/β (Nr1d1/2); Retinoic acid-related orphan receptor response element, RREs or ROREs; Ubiquitin, Ub.

CLOCK and NPAS2 (Neuronal PAS domain protein 2) are the transcriptional factors that play central and overlapping roles in the TTFLs and can both form heterodimers with BMAL1. To run the molecular clock, the CLOCK (or NPAS2) and BMAL1 heterodimer enters the nucleus and binds to the enhancer sequence E-box regulatory element in promoter region (CACGTG) of PER, CRY and other clock-controlled genes (CCGs). On the other hand, the accumulation of PER:CRY dimers in the nucleus inhibit the activity of the CLOCK:BMAL1 heterodimer and also control its transcriptional regulation. Casein kinases I epsilon (CKI ϵ) and delta (CKI δ) regulate the degradation of PER:CRY dimers. Casein kinase δ/ϵ phosphorylation of PER leads to destabilization of the PER1 complex resulting in its degradation.

Retinoic acid-related orphan receptors (ROR $\alpha/\beta/\gamma$) and reverse erythroblastosis virus α/β (Rev-erb α/β , Nr1d1/2) recognize the retinoic acid-related orphan receptor response element (RREs or ROREs) in the BMAL1 promoter with a competition in secondary TTFL. They act in a way to stabilize the TTFLs that RORs activate while, on the contrary, REV-ERBs inhibit BMAL1 transcription. On the other hand, regulation of destruction (D)-boxes in the promoters of several clock genes preserves a different feedback mechanism for molecular circadian machinery (Jolley *et al.* 2014). D-box-dependent transactivation is repressed by Nuclear factor interleukin 3 regulated protein (NFIL3, E4BP4) although Albumin D-site-Binding Protein (DBP) rhythmically activates transcription of various genes through a D-box. Therefore, the components of circadian machinery are regulated by different ways of binding to E-boxes, D-boxes and ROREs (Fig. 1). The TTFL can be reset by PER gene transcription through light stimulation in the SCN. In addition to light stimulation, polyunsaturated fatty acids (PUFAs), carbon monoxide and nitric oxide can also downregulate circadian clock function (Lavialle *et al.* 2008, Minegishi *et al.* 2018). PUFAs activate peroxisome proliferator-activated receptors (PPARs) that regulate the transcription of some clock genes such as BMAL1, PER2 and REV-ERB α (Chen & Yang 2014). These transcriptional feedback cycles take 24 h to complete and form the basis for the circadian rhythms. However, local physiological demands for cell-specific organization of circadian clocks such as extracellular matrix involvement with implications for acquisition of diseases have also been described (Streuli & Meng 2019). Thus, circadian clock arrest in mammals may be due to defective TTFLs by different states of circadian system components. The emergence of the circadian machinery during mammalian development and its maintenance throughout life is not well-understood. In addition, it is known that nocturnal and diurnal species display opposite phases for several biological process including sleep/wake cycles, hormonal and metabolic rhythms (Kumar Jha *et al.* 2015). Thus, it is of note that even though SCN projections seem similar between nocturnal and diurnal species, the response of the peripheral target areas might

alter the interpretation of signals from the SCN (e.g. opposite effects of SCN-derived vasopressin within the area of the paraventricular nucleus in the hypothalamus on the release of corticosterone) (Kalsbeek *et al.* 2008). Additionally, the circadian regulation between nocturnal and diurnal species remains unclear. In seasonal breeders, such as short-day (e.g. sheep and goats) and long-day (e.g. horses) breeders, regulation of the molecular clock between these different species is yet unidentified in detail even though differences in the 24 h rhythmicity of plasma melatonin among these species was very recently demonstrated (Giannetto *et al.* 2020).

In a recent study, the genome-wide RNA transcriptome from peripheral blood mononuclear cells (PBMCs) between hospital nurses working day shift versus night shift, compared on a day off, indicated distinct gene expression patterns (Resuehr *et al.* 2019). This study analyzed the 24 h circadian transcriptome to allow proper alignment of circadian gene expression of PBMCs. However, only a relatively small sample size was studied and males were excluded. Also, this study did not restrict the use of agents such as oral contraceptives and caffeine which might influence the transcriptome. Another study reported alterations in the expression of genes such as Per3 and nuclear receptor subfamily 1 group D member 2 (Nr1d2) in the molecular machinery for night shift workers depending on an individual's shift work type such as one night shift work versus consecutive night shift work versus daytime only, using hair follicle samples (Hattamaru *et al.* 2019). As in the previous study, only a small sample size for only one 24 h period was analyzed and, in this instance, female workers were excluded. Ideally, gender specific alterations should be considered over multiple 24 h circadian cycles. Molecular circadian dysregulation was also addressed in both central and peripheral clocks for police officers performing night shift work (Koshy *et al.* 2019). The study assessed urinary 6-sulfatoxymelatonin and salivary cortisol as central clock markers and clock gene expressions in oral mucosa cells and PBMCs as two different peripheral clocks in 11 police officers. It should be noted that all of these studies reported substantial differences between individuals, even within the same group. Since transcriptome alterations might depend on multiple factors, for example, the number of non-working days, the sleep/wake pattern during off-days, the work and off-work environments, and the health of the participants need to be considered when designing experiments and drawing conclusions. The tissue sampled and the conditions of sampling, such as ambient lighting, should also be considered.

The role of circadian system in female reproductive biology

The SCN has a well-defined role in the physiology of female reproduction. Initial evidence of circadian

control of ovulation was found more than 50 years ago in rodent models. SCN peptides such as vasoactive intestinal polypeptide (VIP) and vasopressin were found to possibly act in concert to precisely coordinate the timing and generation of the luteinizing hormone (LH) surge and ovulation (Evans & Anderson 2018). Ovarian theca cells are reported to play an important role in the timing of ovulation by modulating phasic sensitivity to LH (Mereness *et al.* 2016). After puberty the ovary shows a rhythmicity in circadian clock gene expression in large preantral, small antral and Graafian follicles and in corpora lutea (Sellix 2015). In particular, mice lacking *Bmal1* reveal severe infertility with implications in ovarian luteinization (Alvarez *et al.* 2008). The LH surge is also reported to induce continuous expression of BMAL1 in the mouse ovary (Kobayashi *et al.* 2018). In addition to ovulation timing, the circadian clock in the ovary is important for steroidogenesis and follicular maturation (Chen *et al.* 2016). Furthermore, decreased expression of *PER1* and *CLOCK* in older women (age 39–45 years) has been described (Brzezinski *et al.* 2018). Therefore, this may partially explain the decreased fertility and steroidogenesis in reproductive aging (Brzezinski *et al.* 2018).

Polycystic ovary syndrome (PCOS)-like changes in Sprague–Dawley rats are observed when the rats are kept under continuous light exposure for four consecutive weeks (Chu *et al.* 2019). Peripheral contributions may also mediate the circadian timing of ovulation, steroid production in follicular granulosa and theca cells, and oocyte development (Sellix 2015). Presently, the physiological importance of rhythmicity in clock gene expression in these cells is poorly defined. Unfertilized mouse oocytes express mRNAs of the six canonical clock genes (*Per 1 and 2*, *Cry1 and 2*, *Clock* and *Bmal1*) (Johnson *et al.* 2002). Expression of these mRNAs decreases between the 2-cell and 16-cell stages but reappear at the blastocyst stage (Johnson *et al.* 2002). *Clock* mutant females show irregular estrous cycles (Miller *et al.* 2004). Lower number of oocytes, litter size, higher cell apoptosis and increased miscarriage risk are reported when female mice are injected with *CLOCK*-shRNA (Li *et al.* 2015). Similarly, irregular estrous cycles and impaired ovulation are detected in mice without a functional *Bmal1* gene (Boden *et al.* 2010) and repetitive reversal of light–dark cycles seems to trigger irregular estrous cycles in mice (Yoshinaka *et al.* 2017).

Recently, researchers questioned whether Rev-erb α is involved in the balance between pro-inflammation and anti-inflammation in human endometrial stroma cells (hESCs) and whether it plays a potential role in maintaining the menstrual cycle and embryo implantation (Zhao *et al.* 2019). The results suggested that pharmacological activation of Rev-erb α attenuated the lipopolysaccharide (LPS)-induced inflammatory response of hESCs by suppressing TLR4-regulated NF- κ B activation providing a potential strategy for the treatment

of inflammation-related endometrial dysfunction and infertility or recurrent implantation failure.

Studies of reproductive function in shift workers are of great interest. These workers experience sleep disturbances and exposure to light at night which could increase their risk for altered circadian physiology. Thus, a number of studies report negative effects of chronodisruption in shift workers. Particularly, the importance of circadian rhythm release of LH for ovulation in female shift workers have been investigated by several groups. A systematic review reported that 13 of 20 studies investigated pregnancy, 3 addressed fertility and 4 the menstrual cycle (Chau *et al.* 2014). Only one prospective investigation of the association of night work and age at natural menopause exists (Stock *et al.* 2019). Irregular and longer menstrual period and mood disturbances are found to be associated with shift work (Labyak *et al.* 2002, Lawson *et al.* 2011, Boden *et al.* 2013, Wang *et al.* 2016). Deterioration of the menstrual cycle increases as the duration of chronodisruption increases (Lawson *et al.* 2011). Similarly, social jet lag, equivalent to traveling across multiple time zones, and severe menstrual symptoms for female university students has been reported (Komada *et al.* 2019). Interestingly, some investigators even suggested that the changes in menstrual regularity may be a marker of shift work intolerance (Labyak *et al.* 2002). Irrespective of whether this is true, most of the studies point to problems in reproductive physiology with night shift exposure. However, overall, there is no clear evidence to restrict women from working night shifts (Stock & Schernhammer 2019). The animal and human studies relevant to circadian regulation important for female reproductive biology are summarized in Table 1.

The role of circadian system in male reproductive biology

Expression of *Clock*, *Bmal1*, *Per1*, *Per2*, *Cry1* and *Npas2* genes were constant at all times when total RNA was extracted from mouse testes at various times of day (Alvarez *et al.* 2003). However, whether there is weak or no rhythmicity in testes is controversial (Li *et al.* 2020b). Thus, circadian clock genes have been suggested to play alternative roles aside from creating rhythmicity. *CLOCK* expression is restricted to round spermatids, specifically within the developing acrosome (Alvarez *et al.* 2003). Alterations in *PER1* protein expression in spermatogonia and the condensing spermatids have been reported during sperm maturation (Alvarez *et al.* 2003). Furthermore, some circadian clock genes are associated only with certain stages of sperm development so that, for example, *Per1* mRNA expression is limited to stages 7–10 of the cycle in mice seminiferous epithelium (Alvarez *et al.* 2003, Morse *et al.* 2003). Therefore, current data supports the idea that genes in the circadian machinery may have

Table 1 Summary of main animal and human studies mentioned in this review for circadian regulation of female reproductive biology.

Reference	Species or subjects	Major implications
Animal studies		
Boden <i>et al.</i> (2010)	Homozygous <i>Bmal1</i> null mice	Ovulation timing and problems (LH-surge)
Mereness <i>et al.</i> (2016)	<i>Bmal1</i> knockout in ovarian granulosa cells or theca cells	Ovulation timing and problems (LH-surge)
Kobayashi <i>et al.</i> (2018)	Mice administered with human chorionic gonadotropin	Ovulation timing and problems (LH-surge)
Evans & Anderson 2018 (review)		Ovulation timing and problems (LH-surge)
Miller <i>et al.</i> (2004)	Clock mutant mice	Irregular estrous cycles
Boden <i>et al.</i> (2010)	Homozygous <i>Bmal1</i> null mice	
Yoshinaka <i>et al.</i> (2017)	C57BL6 mice with repetitive reversal of light–dark cycles	
Li <i>et al.</i> (2015)	Mice injected with CLOCK-shRNA	Lower number of oocytes, litter size and higher cell apoptosis, increased miscarriage risk
Alvarez <i>et al.</i> (2008)	<i>Bmal1</i> knockout mice	Infertility on females (and also males)
Chu <i>et al.</i> (2019)	Sprague–Dawley rats kept under continuous light exposure	Polycystic ovary syndrome (PCOS)-like changes
Human studies		
Chen <i>et al.</i> (2016)	Human luteinized granulosa cells (after testosterone treatment)	Potential relationship between the circadian clock, steroidogenesis and follicular maturation in the human ovary
Brzezinski <i>et al.</i> (2018)	Human luteinized granulosa cells from young and older patients	Decreased expression of some circadian genes in older women, a potential implication for reproductive aging
Zhao <i>et al.</i> (2019)	Human endometrial stroma cells with pharmacological activation of Rev-erb α	Rev-erb α association with inflammation-related endometrial dysfunction, infertility or recurrent implantation failure
Labyak <i>et al.</i> (2002)	68 nurses <40 years old	Menstrual cycle irregularity
Lawson <i>et al.</i> (2011)	71,077 nurses aged 28–45 years	Menstrual cycle irregularity
Wang <i>et al.</i> (2016)	Shift ($n = 334$) and non-shift workers ($n = 139$)	Menstrual cycle irregularity
Komada <i>et al.</i> (2019)	150 university students/social jet lag association	Menstrual cycle irregularity
Stock <i>et al.</i> (2019)	Rotating night shift workers/nurses	Moderate risk for earlier menopause

non-circadian roles in spermatogenesis. A physiological role for testis clock-associated genes is also supported by the finding that exposure to short day length induces more rhythmic *Bmal1* mRNA expression with gonadal regression in hamsters (Tong *et al.* 2004). An interesting hypothesis suggested that the timing of expression of all clock and CCGs may depend on the relative presence of E-box, RORE, and DBP-binding elements (DBPE).

Low serum testosterone levels with low StAR protein expression in *Bmal1* knockout (KO), *Per2* KO and *Per1/Per2* double KO mice has also been shown (Alvarez *et al.* 2008). The *Clock* gene is suggested to regulate acrosin activity in sperm, further implicating circadian genes in male reproduction (Cheng *et al.* 2016). The effects of androgens on *PER2::luciferase* expression in a direct and tissue-dependent process has been reported in female mice (Mereness *et al.* 2015). Also, relatively short-term (11 days) exposure to inhibitory photoperiods has been shown to induce local and location-specific changes in androgen receptor expression. An inverse relationship between melatonin synthesis and testosterone levels has also been reported in mouse Leydig cells and involves melatonin receptors regulating hCG-induced testosterone synthesis (Gao *et al.* 2019). This information could be important in explaining how day length modifies gonadal steroid hormones and an interaction between testosterone and photoperiod can

add to our understanding of environmental regulation of neuroendocrine function.

Daily changes in clock gene expression and protein abundance of *PER1* and *BMAL1*, and various effector genes such as vacuolar-type H⁺-ATPase (V-ATPase) and carbonic anhydrase (CA-II), important for ion homeostasis in the male mammalian reproductive tract, exist in the epididymis (Bebas *et al.* 2009). Therefore, these genes may maintain an optimum environment in the epididymal lumen for maturation and stability of sperm. Temporal changes in *Per1* and *Bmal1* gene expression in vas deferens, seminal vesicles and prostate have also been shown (Bebas *et al.* 2009). However, the significance of these changes is still unclear.

Sperm production is strictly regulated but the functional significance of the circadian rhythm in human testicular function is not fully understood. A study of 12,245 semen samples from 7068 males showed that semen quality (total sperm count, sperm motility or normal morphology) varied according to both circadian and circannual rhythms in humans (Xie *et al.* 2018). Increased length of daylight positively correlated with progressive sperm motility as well (Mao *et al.* 2017). Genetic epidemiological studies have also shown that circadian clock gene polymorphisms are linked to semen parameters and risk for infertility. A case-control

study investigated polymorphisms in the CLOCK and ARNTL genes in 961 Slovenian and Serbian Caucasian men and showed that genetic variability in CLOCK might be associated with male infertility suggesting a non-circadian function of CLOCK (Hodžić *et al.* 2013). In a study of CLOCK knockdown in mice with small hairpin RNA, a significant reduction in offspring from these males was observed (Liang *et al.* 2013). In addition, *Cry1* KO mice have perturbed spermatogenesis with increased number of degenerate and apoptotic germ cells in the testis and lower epididymal sperm counts (Li *et al.* 2018). Bioinformatic analysis reveals that the differentially expressed genes are involved in important biological processes including cell-cell communication, metabolism, chromatin reorganization, spermatogenesis, and the immune response, indicating that *Cry1* is important for normal testicular function (Li *et al.* 2018).

Just like with female shift workers, male shift workers have also been studied. A study compared seminal parameters and urinary 5-HIAA levels (an indirect measure of serotonin) in night shift workers between recent fathers and infertile men, all of whom performed night shift work (Ortiz *et al.* 2010). The study revealed that high urinary 5-HIAA levels, and therefore high serotonin, may impair sperm quality and thus cause male infertility in night shift workers (Ortiz *et al.* 2010). However, caution is needed for the use of serotonin in infertility treatment or male contraception and further studies are definitely required. In addition, Ni and colleagues recently reported interesting data from 11,382 semen samples from two populations and *in*

vivo animal experiments demonstrating that sperm DNA fragmentation index (DFI) may undergo diurnal variation (Ni *et al.* 2019). These data are important since the existence of a circadian rhythm in DFI can explain the conflicting results observed in different studies related to sperm DFI since the 'timing' of the sample collection is not always considered. On the other hand, it may also underscore altered management for couples who need better semen quality for IVF treatments. Unfortunately, direct investigation of shift work on sperm quality is difficult due to difficulties to ensure environmental standardization for individuals in human studies. Thus, currently, shift work is not convincingly associated with either semen parameters or testosterone levels so far (Peterlin *et al.* 2019) and comprehensive epidemiological studies with large groups of men with appropriate controls for relevant confounders are needed. As with the circadian regulation of female reproductive biology, a summary of the animal and human studies for male reproductive biology are presented in Table 2.

Circadian rhythm and pregnancy: does chronodisruption negatively affect pregnancy?

Growing evidence suggests that early embryo development, uterine implantation, placentation and delivery may all be influenced by molecular machinery in the circadian system in rodents and other mammals. When mice are exposed to phase delays or advances in the light–dark cycle after copulation, reduced proportion of pregnancies carried to term is observed (Summa *et al.*

Table 2 Summary of main animal and human studies mentioned in this review for circadian regulation of male reproductive biology.

Authors	Animals or subjects	Major implications
Animal studies		
Alvarez <i>et al.</i> (2003)	C57BL/6 mice	Non-circadian roles in spermatogenesis
Morse <i>et al.</i> (2003)	<i>Clock^{ec}</i> mutant mice, <i>Per^{-/-}</i> mice, <i>CREM^{-/-}</i> mice	Non-circadian roles in spermatogenesis
Liang <i>et al.</i> (2013)	CLOCK knockdown in testis/mice	<i>Cry1</i> required for normal testicular function
Li <i>et al.</i> (2018)	<i>Cry1</i> knockout mice	Circadian regulation important for sperm maturation and stability
Alvarez <i>et al.</i> (2003)	C57BL/6 mice	
Bebas <i>et al.</i> (2009)	C57BL/6 mice	
Alvarez <i>et al.</i> (2008)	<i>Bmal1</i> knockout mice	<i>Bmal1</i> involvement in testosterone production and fertility
Mereness <i>et al.</i> (2015)	PER2::LUC transgenic mice	Association with androgen and circadian gene expression
Liang <i>et al.</i> (2013)	CLOCK knockdown in testis/mice	Reduced fertility
Cheng <i>et al.</i> (2016)	CLOCK knockdown in testis/mice	Reduced fertility
Human studies		
Ortiz <i>et al.</i> (2010)	Men attending infertility counseling rotating shift workers (<i>n</i> = 40)	Risk for infertility
Hodžić <i>et al.</i> (2013)	Patients with idiopathic infertility (<i>n</i> = 517) and fertile men (<i>n</i> = 444)	Genetic variability in CLOCK associated with male infertility
Mao <i>et al.</i> (2017)	Cases for routine semen analysis (<i>n</i> = 8168), morphology (<i>n</i> = 5819) and anti-sperm antibodies analysis (<i>n</i> = 5544)	Positive correlation between increased length of daylight and progressive sperm motility
Xie <i>et al.</i> (2018)	12,245 semen samples (<i>n</i> = 7068 men)	Circadian and circannual variations on semen quality
Ni <i>et al.</i> (2019)	Human semen samples (<i>n</i> = 10,752)	Diurnal variations on sperm DNA fragmentation

2012). Clock mutation also disrupts the ability to complete pregnancy (Miller *et al.* 2004). Circadian clock genes such as *Per1* and *Per2* are expressed rhythmically in the rat uterus during non-pregnancy and pregnancy (Akiyama *et al.* 2010). The conditional deletion of *Bmal1* in the mouse ovary results in complete failure of implantation (Liu *et al.* 2014). Systemic deletion significantly reduces oocyte fertilization, early embryo development as detected by blastocyst number, and implantation in *Bmal1*^{-/-} mice compared with that of *Bmal1*^{+/+} mice after superovulation and *in vivo* or *in vitro* fertilization (Xu *et al.* 2016). *Bmal1*^{-/-} mice have increased intracellular reactive oxygen species (ROS) levels in the ovary on proestrus day and in the oviduct on metestrus day when compared to *Bmal1*^{+/+} mice suggesting that excess ROS levels in ovary and oviduct negatively impact early reproductive events. This study, however, is limited by a relatively small sample size and more research will be needed to confirm these observations. More work will also be needed to better understand other ways circadian rhythm gene expression influences fertility and early embryo development.

Long photoperiodic exposure (18 h light:6 h darkness) significantly reduces the number of implantation sites in mice compared to controls (Zhang *et al.* 2017). Goldstein and colleagues exposed mice to repetitive phase advances of the photoperiod (advance of lights on and lights off by 6 h every 4 days) and used them as recipients for embryo transfer using embryos from normal light–dark cycle mice (Goldstein *et al.* 2018). Thus, this investigation studied the effects of maternal chronodisruption on early gestation and uterine receptivity. The results are interesting since the pup and placental weights were found to be similar between groups, and uterine receptivity and maintenance of early gestation was preserved despite recurrent phase advances in the photoperiod (Goldstein *et al.* 2018). This study suggests that the negative effects of chronodisruption are mediated by reproductive processes upstream of implantation. Therefore, factors contributing to embryo quality and/or early embryo development may be the reproductive mechanisms most sensitive to the negative effects of chronodisruption.

On the other hand, it is reported that chronic phase shift (CPS) throughout gestation in rodents alters circadian rhythms of maternal corticosterone, glucose, insulin, leptin, free fatty acids, triglycerides and cholesterol and disrupts the timing of food intake and the hepatic clock and metabolic gene expression (Varcoe *et al.* 2013). There is no data to show that the variations in the timing of insemination in humans play a critical role in embryo viability. Thus, it remains possible that the low fertility rate observed in humans compared with other species could be partly due to inappropriate timing of uterine clock gene expression critical for implantation and embryo viability. Gatford and colleagues demonstrated that shift work during pregnancy can influence maternal circadian

rhythms and metabolism, with differential effects on pregnancy outcomes in singleton and twin pregnancies with an increased length of gestation in twin pregnancies (Gatford *et al.* 2019). On the other hand, shift/night working conditions have been reported to increase the risk of endometriosis (Marino *et al.* 2008), miscarriage (Grajewski *et al.* 2015, Begtrup *et al.* 2019) and early, but not late, preterm birth (Lawson *et al.* 2012) in women. An abnormal expression of CLOCK is also detected in human fetuses from spontaneous miscarriage (Li *et al.* 2015). Several epidemiological studies have also suggested a relationship between shift work or repeated travel across time zones and decreased fertility as well as negative pregnancy outcomes such as increased incidence of low birth weight, preterm birth or miscarriage (Reschke *et al.* 2018, Mills & Kuohung 2019, Suzumori *et al.* 2020). Researchers have begun to explore options to alter circadian rhythms to control the timing of birth to prevent poor pregnancy outcomes such as preeclampsia and preterm birth (McCarthy *et al.* 2019). In fact, a recent study reported that the Clock gene is involved in the hypoxic process of preeclampsia (Li *et al.* 2020a). In line with these studies, a hypothesis was presented that light at night due to shift work suppresses melatonin synthesis and potentially leads to metabolic disorders in the offspring (Nehme *et al.* 2019). However, it is difficult to conclude whether these adverse outcomes are caused by circadian dysregulation or some other lifestyle factors (for instance poor sleep quality) associated with shift work. In addition, later sleep timing and circadian phase position during pregnancy is found to be associated with greater risk of increased psychiatric and psychologic symptoms across several cognitive, behavioral, and regulatory domains (Obeysekare *et al.* 2020). In contrast, a recent paper reported no relationship between shift work and fecundability in a North American preconception cohort study (Willis *et al.* 2019). The overall implications of the circadian regulation on pregnancy outcomes are summarized in Table 3.

The role of melatonin in oocyte quality, ovarian and luteal function, fertilization, embryo implantation, pregnancy and parturition in women undergoing assisted reproductive treatment and in patients with PCOS undergoing intrauterine insemination and incidence of endometriosis and preeclampsia have also been reported (Chuffa *et al.* 2019, Scarinci *et al.* 2019). For instance, melatonin treatment resulted in beneficial effects in pregnant mice, especially those subjected to long photoperiodic exposure by enhanced embryo implantation, increased E2 levels during pregnancy and up-regulated p53 expression by activating melatonin receptors MT1/2 in the uterus (Zhang *et al.* 2017). What functional importance the circadian clock genes play in uterine preparation for early development and implantation will likely be important areas of future research.

Table 3 Summary of main animal and human studies mentioned in this review for circadian system and chronodisruption in pregnancy.

Authors	Animals or subjects	Major implications
Animal studies		
Miller <i>et al.</i> (2004)	Clock mutant mice	Disruption of maintenance of pregnancy
Summa <i>et al.</i> (2012)	C57BL/6J (B6) mice	
Liu <i>et al.</i> (2014)	<i>Bmal1</i> knockout in ovarian steroidogenic cells	Failure of implantation
Xu <i>et al.</i> (2016)	<i>Bmal1</i> ^{-/-} mice	Reduced oocyte fertilization, early embryo development and implantation; Increased intracellular ovarian ROS
Zhang <i>et al.</i> (2017)	Kun Ming (KM) mice; Long photoperiodic exposure (18 h light:6 h darkness)	Reduced number of implantation sites
Goldstein <i>et al.</i> (2018)	C57BL/6J X DBA/2J mice; Repeated light–dark shifts	Preserved uterine receptivity and maintenance of early gestation
Gatford <i>et al.</i> (2019)	Simulated shift work in sheep	Differential effects on pregnancy outcomes
Human studies		
Grajewski <i>et al.</i> (2015)	Flight attendants (<i>n</i> = 673) and teachers (<i>n</i> = 91)	Miscarriage
Begtrup <i>et al.</i> (2019)	Women registered (<i>n</i> = 10,047) and non-registered (<i>n</i> = 12,697) night shift during pregnancy week 3–21	
Lawson <i>et al.</i> (2012)	US nurses (<i>n</i> = 7482 eligible for analysis)	Increased risk of early but not late preterm birth
Li <i>et al.</i> (2015)	Fetuses from spontaneous miscarriage (<i>n</i> = 58)	Abnormal CLOCK expression association with spontaneous miscarriage
Ohhashi <i>et al.</i> (2017)	Placental abruptions (<i>n</i> = 115)	Association between circadian variations and pathogenesis of placental abruption
Suzumori <i>et al.</i> (2020)	Women with singleton pregnancies (<i>n</i> = 99,744)	Chronodisruption associated with decreased fertility, negative pregnancy outcomes such as increased incidence of low birth weight, preterm birth or miscarriage
Reschke <i>et al.</i> (2018)		
Mills & Kuohung (2019)		
Bates & Herzog (2020)		
Marino <i>et al.</i> (2008)	Women with endometriotic disease (<i>n</i> = 235) and controls (<i>n</i> = 545)/Night shift work	Increased risk of endometriosis
Li <i>et al.</i> (2020b)	Patients with preeclampsia (<i>n</i> = 20 placenta) and human cytotrophoblastic cell line HTR-8/SVne	Clock gene involvement in the hypoxic process of preeclampsia
Willis <i>et al.</i> (2019)	Women aged 21–45 years attempting pregnancy	No association between shift work and fecundability

Effects of maternal circadian chronodisruption on fetal and postnatal development into adulthood

Circadian rhythms emerge gradually in humans but develop rapidly in the postnatal period (Umemura & Yagita 2020). Thus, it is important to examine the development of the fetal circadian system and how the maternal rhythm influences fetal oscillations. The fetal pineal gland does not secrete melatonin in human, sheep or rats and the circadian rhythm in the fetus is primarily controlled by the maternal system. Lipophilic melatonin passes freely through the placenta unchanged and provides light-to-dark information to the fetus although details of how that information is transferred is still not clear. Therefore, there is a growing concern about the long-term effects of maternal circadian rhythm disruptions on human offspring (and their descendants) through lifestyle and shift work during pregnancy (Hsu & Tain 2020).

In a study in which pregnant rats were exposed to a CPS protocol that completely reversed the photoperiod every 3–4 days throughout gestation and the first week after birth, increased whole body insulin resistance in the adult offspring leading to a number of metabolic disruptions including obesity, hyperleptinemia, age

and sex-related increases in glucose metabolism and metabolic syndrome were observed (Varcoe *et al.* 2011). Therefore, disruption in the developing circadian clock may play a causal role in the onset of metabolic syndrome. However, there is always a possibility that these alterations in the adult offspring might be a consequence of the reduced glucose tolerance and insulin sensitivity of the CPS exposed mothers. Moreover, this experimental design, does not identify if a specific period of gestation or postnatal development is more crucial for the development of metabolic syndrome. Maternal, but not paternal, circadian preference was found to be associated with infants' circadian rhythm development in early childhood (Morales-Munoz *et al.* 2019). Recent studies also suggest that chronodisruption during the neonatal period, when synchronization of the infant's circadian rhythms occur, might have long and short-term health consequences, potentially causing chronic stress-associated disorders (Astiz & Oster 2018, McKenna & Reiss 2018). However, demonstration of more detailed circadian effects on adverse neonatal outcomes in different subgroups will require more data.

In addition, gestational chronodisruption has been shown to alter both fetal and adult adrenal function and change the fetal adrenal transcriptome (Salazar *et al.*

2018). These alterations are likely to have long-term adverse effects on the developing fetus and adult offspring (Varcoe *et al.* 2018). In contrast, a study reported that night shift work before and during pregnancy does not increase the risk of children developing atopic dermatitis, asthma or hay fever (Rada *et al.* 2020). Although, the study included detailed information of mothers and offspring with analysis of multiple potential confounding variables, it had limited power for the assessment of paternal information. Incidence of atopic disease was solely self-reported, and neither validation of diseases nor age at diagnosis was included. Whether different biological systems might be affected differently from maternal chronodisruption and whether the disruption of TTFLs during pregnancy results in long-term changes in adult offspring, needs further investigation. On the other hand, maternal-fetal circadian communication and how signals during pregnancy can synchronize daily rhythms between the mother and the fetus is also critical for clinical problems such as preterm birth (Bates & Herzog 2020). Recently, a protocol of a prospective cohort study to determine the role of circadian rhythm in pregnant women and to identify pregnancy indices such as gestational weight gain with birth and infant outcomes was described (Kaur *et al.* 2020). These results will provide much needed information on the effects of the circadian rhythm during pregnancy and its consequences on the fetal and the first year of life of the infant's growth.

In addition, several studies in chicken, rat or sheep embryos report that a functional molecular circadian clock is important for the developmental processes including tissue homeostasis, histogenesis during early chondrogenesis (Alagha *et al.* 2020) and the release of reproductive hormones into the fetal bloodstream (Gao *et al.* 2016). Disruptions of any or all of these processes could influence fetal organ development in utero, as well as long-term health. In contrast, a melatonin producing mutant Clock gene mouse strain, Clock Δ 19+MEL, did not show any negative alterations on pregnancy outcomes such as mating, gestation length, litter size, or postnatal growth, and had minimal effects on growth or metabolic homeostasis of heterozygous offspring through adulthood (Varcoe *et al.* 2016).

Several studies observed both short- and long-term behavioral outcomes such as anxiety-like behavior in adult offspring when the maternal circadian system was disrupted during pregnancy (Voiculescu *et al.* 2016, Chaves *et al.* 2019). In a gestational hypomelatoninemia model, it has been shown that absence of maternal melatonin delays physical characteristics, neurodevelopmental and cognitive functions in rat male offspring (sex-dependent) and leads to deficits in hippocampal-dependent spatial learning and memory in adults (Motta-Teixeira *et al.* 2018). Again, with this experimental setup, it is difficult to distinguish whether these alterations are a direct result of melatonin restriction

on pup development or an indirect response from impaired maternal behavior and physiology. However, the current literature favors early life experiences, such as constant light, or dim light at night, changing specific behaviors and brain functions in adult offspring which could possibly lead to multigenerational psychological and cognitive problems (Roman & Karlsson 2013, Cisse *et al.* 2017, Salazar *et al.* 2018). However, it should also be noted that Strohmaier and colleagues reported no overall association of maternal history of rotating night shift work before pregnancy or shift work exposure during pregnancy with depression or anxiety in adolescent and young adult offspring (Strohmaier *et al.* 2019). The same limitations mentioned above for the study for Rada *et al.* (2020) apply here as both studies analyzed the same database. The overall implications on transgenerational health effects of maternal chronodisruption during pregnancy on offspring are summarized in Table 4.

Only a limited number of studies have used mutant/knockout models of circadian rhythm genes or have dysregulated the circadian rhythm through environmental manipulations to determine possible effects on the placenta. Placental clock gene rhythms are reported for the human placenta (Perez *et al.* 2015) but the extent to which these expressions are rhythmic *in vivo* remains unclear. However, disruption of the clock machinery could affect placental function and local melatonin production. In this context, melatonin synthesis might reduce apoptosis in the villous cytotrophoblasts but enhance the survival of syncytiotrophoblast cells (Reiter *et al.* 2014). Recently, it was demonstrated that maternal melatonin pretreatment in lipopolysaccharide (LPS)-treated mice resulted in reduced levels of pro-inflammatory mediators such as NF- κ B1 and IL-1 β 6 h after exposure to LPS with melatonin in the placenta (Lee *et al.* 2019b). Unfortunately, the study investigated only a single IP injection of melatonin and did not include any dose-dependent experiments which would strengthen the association of the melatonin response. Additionally, melatonin seems to enhance placental perfusion and prevent arterial insufficiency, hypercoagulation, inflammatory and oxidative damage (Lee *et al.* 2019a), and also protect from hypoxia/reoxygenation-induced damage in placental trophoblasts by regulating autophagy and apoptosis (Sagrillo-Fagundes *et al.* 2018). Thus, even though the exact mechanisms are not known, the current data indicates the likely importance of maternal circadian signals such as melatonin, in driving rhythmic placental function (Chuffa *et al.* 2019). In addition, the raised triglyceride levels observed in human placentas from pregnancies with large-for-gestational age infants are found to be associated with upregulated expression of the clock gene BMAL1 (Papacleovoulou *et al.* 2017). Ohhashi and colleagues investigated 115 cases of placental abruption retrospectively and reported that abdominal pain and adverse perinatal outcomes

Table 4 Summary of current literature from both animal and human studies on transgenerational health effects of maternal chronodisruption during pregnancy on offspring.

Authors	Species or subjects	Major implications
Animal studies		
Varcoe et al. (2011)	Albino Wistar female rats; chronic phase shifts (CPS) in every 3–4 days	Short-term and long-term gender and age dependent metabolic alterations and metabolic syndrome (e.g. increased adiposity, hyperleptinemia and alterations to glucose metabolism)
Varcoe et al. (2016)	Clock Δ 19+MEL mice	No negative effects on pregnancy outcomes, growth or metabolic homeostasis in heterozygous offspring through to adulthood
Gao et al. (2016)	Pregnant ewes; dark deprivation	Effects on the release of reproductive hormones into the fetal bloodstream
Salazar et al. (2018) Chaves et al. (2019)	Sprague–Dawley rats; CPS in every 3–4 days Mice; gestational jet lag protocol	Alterations on fetal adrenal function and transcriptome Pathological phenotype (e.g. altered heart structure and function, altered bone thickness and strength) and impairment in postnatal growth and effects on circadian behavior
Voiculescu et al. (2016)	Wistar rats; prenatal continuous light exposure	Short-term memory impairment in adult offspring with a relationship between serotonin-melatonin axis
Motta-Teixeira et al. (2018)	Wistar rats, gestational hypomelatoninemia model	Long-term effects on neurogenesis, cognitive problems and deficits in hippocampal-dependent spatial learning and memory
Roman & Karlsson (2013)	Wistar rats; maternal constant light exposure	Multigenerational chronic stress-associated disorders, neurodevelopmental and behavioral outcomes (depressive-like; anxiety-like behaviors etc.)
Voiculescu et al. (2016) Cisse et al. (2017)	Wistar rats; prenatal continuous light exposure Siberian hamsters; chronic exposure to light at night	
Salazar et al. (2018)	Sprague–Dawley rats; CPS in every 3–4 days	
Human studies		
Strohmaier et al. (2019)	Female nurses with history of rotating night shift work ($n = 4044$) and their children ($n = 4813$)	No associations between night shift work before or during pregnancy and risk of depression, anxiety or atopic dermatitis, asthma or hay fever in the offspring
Rada et al. (2020)		

including perinatal death showed significant circadian variation ([Ohhashi et al. 2017](#)). These results suggest an association between circadian variations and placental pathology. It should be pointed out that the data was collected from interviews on or after admission which could be potentially biased. However, the authors did not report any causal relationship of circadian rhythms between risk factors for placental abruption and disease onset for every 6 h period in a day with a small study population.

Circadian rhythm and lactation

Changes in the circadian clock can also affect lactation. Lactation is controlled by the temporal organization of prolactin secretion. Thus, light conditions during lactation might affect the function of the circadian pacemaker. In rats, a study revealed that constant light during lactation induces increased weight gain and disrupts daily levels of glucose and triglycerides in offspring ([Madahi et al. 2018](#)). However, exposure to a light–dark cycle until postnatal day 90 did not restore either the normal metabolic state or the daily rhythm of AVP, VIP and PER1 in the SCN of adult rats indicating a permanent impairment to the SCN during lactation ([Madahi et al. 2018](#)). In addition, exposure to chronic light–dark phase shifts during the prepartum period was

associated with increased milk fat and milk yield in the postpartum period despite decreased blood glucose pre- and postpartum ([Suarez-Trujillo et al. 2020](#)). Thus, less variation in central circadian rhythms provides a more constant milieu to support the onset of lactogenesis. More detailed studies will determine more possible effects of altered circadian rhythms on lactation and health of the offspring.

Circadian rhythm, epigenetic programming and transgenerational epigenetics

Epigenetic modifications provide plasticity in gene expression and cellular biology in multicellular organisms and can affect many physiological processes, including growth, aging and metabolism. Epigenetic modification is also a crucial regulator during development due to the depth and breadth of the epigenetic code. Epigenetic changes in the germ line may be temporary or permanent. In the case of the latter, these changes can be transmitted to subsequent generations ([Boskovic & Rando 2018](#)). When fetal circadian rhythm programming occurs, its effects can be considered long-lasting and possibly transgenerational. Therefore, transgenerational epigenetics refers to the transmission of epigenetic information from mother to offspring and even to later generations.

During the last decade, evidence increasingly demonstrates that conditions during pregnancy may have lifelong effects on offspring in both humans and animal models. Factors such as maternal malnutrition, prenatal stress, and exposure to medical and social drugs have all been shown to have adverse health consequences for adult offspring. Regulation of the circadian clock is also subject to epigenetic influence (Reszka & Zienolddiny 2018, Oh *et al.* 2019, Singh *et al.* 2019). Since significant number of genes in peripheral tissues show circadian expression, replication-independent mechanisms must be crucial for this rhythmicity restoring appropriate epigenetic patterns at a given time of the day. For instance, diurnal epigenetic alteration of CpG methylation is observed in the mouse brain. In a paternal ~150 kb *Snord116* deletion mouse, a model for human Prader Willi syndrome (PWS), diurnal regulation of the circadian genes *Per2*, *Cry1* and *Clock* lose their epigenetic diurnal rhythmicity (Powell *et al.* 2013). 4,355 differentially methylated CpG regions (DMR) in mouse cortex have been identified and in paternal *Snord116* deleted mice, 97% of these DMRs lose their diurnal epigenetic rhythmicity (Coulson *et al.* 2018). Importantly, more than 50% of the mouse DMRs identified in mouse cortex are retained in humans (Coulson *et al.* 2018). Deletion of human paternal chromosome 15q11.1, which includes *SNORD116*, results in altered metabolism, increased appetite with resultant obesity and sleep disturbances, all features of diurnal rhythms in humans.

On the other hand, potential effects of light/dark cycles during pregnancy could influence health of offspring during development or into adulthood. Epigenetic mechanisms are dynamic biological processes that have potential to mediate genetic and environmental effects on circadian processes. In recent years, there has been an increasing number of studies emphasizing the role of DNA methylation in the regulation of circadian systems in humans and other mammals (Adams *et al.* 2017, Bukowska-Damska *et al.* 2017, Ramos-Lopez *et al.* 2018). For instance, offspring from dams exposed to stress during pregnancy by a combination of restraint and 24 h constant light exhibit altered expression of epigenetic-related biomarkers such as DNMT1, HDAC1, HDAC2 and AcH3K14 in the hippocampus as compared to offspring from non-stressed dams (Zheng *et al.* 2016). Epigenetic chromatin remodeling can, therefore, influence TTFL dynamics and the regulation of clock genes which are vital to the circadian system.

Shift work is associated with altered gene-specific DNA methylation of genes such as *DLX5*, *IGF2AS*, *TP73*, *BACH2*, *JRK*, *RPS6KA2* that are linked to cancer and type-2 diabetes (e.g. *KCNQ1*) (Jacobs *et al.* 2013, Bhatti *et al.* 2015, Adams *et al.* 2017). In addition, of eight circadian clock genes investigated, promoter hypomethylation of three, *PER1*, *PER2* and *BMAL1* was

seen in rotating-shift workers (Reszka *et al.* 2018). In fact, in a previous comprehensive study, 65% of the 473,800 loci tested were found to be hypomethylated in blood among night shift workers when compared to day shift workers (Bhatti *et al.* 2015). If these methylation changes in blood are representative of other tissues, the observed epigenetic alterations with a general systemic loss of methylation may cause increased genomic instability and possible carcinogenic potential of shift work. In line with this, also in 2015, another study reported that long-term shift work may increase the risk of breast cancer via aberrant methylation of the *miR-34b* promoter which plays a key role in the p53 tumor suppressor network by decreasing the efficacy of an immunomediated tumor-suppressive response (Liu *et al.* 2015). Epigenetic regulation of the *BMAL1*, *CLOCK* and *CRY1* genes may also contribute to increased breast cancer risk in shift workers (Samulin Erdem *et al.* 2017). A strength of this study is that it compared breast cancer cases and healthy subjects with well-matched and characterized night shift work exposure patterns. However, larger patient cohorts will be needed to confirm these initial observations. In a recent study, gestational jet lag in mice was used as a model for circadian rhythm disturbance during early development (Chaves *et al.* 2019). Pregnant mice were subjected to a regular light–dark cycle or to a repeated delayed or advanced jet lag protocol, with an 8 h delayed or advanced light–dark cycle repeated every 3 days (Chaves *et al.* 2019). In the experimental group, hypermethylation of the *miR17-92* cluster, required for heart and bone development, was demonstrated in liver DNA (Chaves *et al.* 2019). This study provided mechanistic evidence that ‘gestational circadian rhythm disturbance’ is a Developmental Origins of Health and Disease hypothesis (DOHaD)-related risk factor that affects the epigenetic landscape and predisposes to later life adverse health effects, such as cardiovascular disease and skeletal defects. In addition, this study also demonstrated differential gene expression for the clock genes *Bmal1*, *Clock* and *Cry2* indicating a disturbance in the circadian oscillator.

The hypothesis that shift work is also associated with genome-wide DNA methylation changes and epigenetic age acceleration was evaluated in an epigenome-wide association study with extracted DNA from whole blood samples in non-Hispanic white women (White *et al.* 2019). Again, the results revealed that shift work is associated with differentially methylated CpG regions in the epigenome (e.g. *ZFHX3*), consistent with possible long-term adverse health effects such as risk of breast cancer since *ZFHX3* has been implicated to act as a tumor suppressor by inhibiting estrogen receptor function. Therefore, special care was taken to confirm that the women were breast cancer free at the time of blood sampling. Not surprisingly, the association is strongest at ≥10 years of night shift work. It will be interesting to investigate whether the effects of these

epigenetic changes persist into the next generation. In addition, recent data highlights a remarkable plasticity on chromatin states and dynamics in the genome during the circadian cycle. Epigenetic transitions seem to be crucial for the transcriptional reprogramming triggered by environmental cues (Pacheco-Bernal *et al.* 2019). Also, changes in the epigenetic signature of key placental circadian rhythm genes might affect placental function and impact fetal development and health later in life of the offspring. It will be of interest to determine if rhythmicity is in response to rhythmic maternal secretions of hormones, or by a local clock mechanism within the placenta or both. It will be interesting to determine if maternal chronodisruption results in altered epigenetic changes and epiphenotypes during pregnancy.

Conclusion

The recent discoveries of circadian regulation in reproductive tissues of both females and males suggests that it plays a crucial role in several aspects of fertility. The increasing numbers of shift workers in society, many of which are pregnant and lactating women, experience a series of circadian rhythm perturbations including altered sleep and activity patterns, melatonin release, body temperature and timing of food intake. These alterations may affect the developing fetus and effects may persist into adulthood. Understanding these potential risks is important for determining the safety and efficacy of chronotherapeutic approaches such as light or melatonin treatments. However, it is not possible to eliminate these concerns only with epidemiological studies. There is evidence that shift work during pregnancy increases the risk for poor pregnancy outcomes such as small offspring, miscarriage and preterm birth, but there are also reports demonstrating the suggested risk associated with shift work is small. However, currently, there is not sufficient evidence to restrict women from night shift work. Most of the studies in this research area investigating maternal shift work and its long-term health consequences suffer from small sample size, and non-standardized type and timing of night shift work. In addition, recent studies underline obvious individual differences even within the same group. To overcome the difficulties inherent in human studies, the use of animal models provides a reasonable alternative for investigating maternal chronodisruption and reproductive, neural, hormonal and behavioral system alterations. However, translational relevance of animal studies for humans has limitations and animal studies are not directly applicable to humans in many cases. Thus, caution for overextrapolating data from rodents to humans is also necessary. The 2017 Nobel Prize in Medicine award for discoveries of the molecular mechanisms controlling circadian rhythm genes reveals the great importance of this field for understanding basic biological systems and human health.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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