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# THE EFFECT OF CIRCADIAN RHYTHM ON FEMALE REPRODUCTIVE HEALTH IN HUMANS: A REVIEW

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**ABSTRACT** Circadian clocks are built-in, self-maintaining timekeeping systems that allow organisms to predict changes in their environment and adjust their behaviour and physiology accordingly (Morse and Sassone-Corsi, 2002). Losing circadian clocks is bad for organisms because it makes them less likely to reproduce and live longer in controlled lab settings and less likely to survive in the wild (Vaze et al 2014). Disruptions in the circadian system can throw biological and behavioural cycles out of sync, which can have severe consequences for human health (Bedrosian and Nelson, 2017). This paper offers an in-depth review of the concept of circadian rhythm, the effect of disruption on human systems and diseases linked to such disruption, such as cancer, immunodeficiency, sleep disorders, metabolic and cardiovascular system disorders, mental and health problems. It specifically focuses on the adverse impact of disruption in circadian rhythm on the female reproductive system in the form of infertility, ovulatory disturbances, frequent miscarriages, birth defects and breast carcinoma. It also discusses some interventions that can be used to mitigate disruptions in circadian rhythm, based on the existing research. This paper adds to the existing literature on impact of circadian rhythm, especially on issues related to female reproductive health and is a useful resource for students, researchers and medical practitioners.

**KEYWORDS :** circadian rhythm, disruption, human health, female reproductive system, review

## INTRODUCTION

Circadian clocks are endogenic and self-sustaining time-tracking systems that allow organisms to anticipate changes in the environment, and adjust their behavior and physiology to the proper time of day (Morse and Sassone-Corsi, 2002). This affords organisms an pre-emptive adaptive mechanism that can help cope with the day-to-day unavoidable variations in their environment related to temperature, light, and social communication, and assists in synchronizing various biochemical, molecular, behavioral and physiological processes (Rana and Mahmood, 2010).

Disruption of circadian rhythms can cause cancerous cells to undergo abnormal cell division (Farhud and Aryan, 2018). Research shows an association between changes in circadian clock and tumorigenesis in adenocarcinoma and some cancers (Thirlaway and Upton, 2009). Disruptions in circadian rhythm has also been found to have a connection with cardiovascular diseases and its risk factors, such as obesity and diabetes. There is a connection between mood disorders and circadian rhythms that goes both ways. Mood disorders are often linked to problems with how the circadian clock controls things like sleep and cortisol release. Jet lag, working night shifts, or being exposed to artificial light at night-time can cause or make mood disorders worse in people who are already at risk. Strong links have been found between mental health and circadian rhythms and recently some studies have also explored the effect of the circadian system on mood (Walker II, Walton, DeVries and Nelson, 2020).

Studies on women who work in shifts have shown that they have a greater chance of losing a pregnancy early and having an abnormally long menstrual cycle, which could be a sign of problems with ovulation. It is known that short sleep duration, obstructive sleep apnea (OSA) and disruption of the circadian rhythm all cause glucose intolerance and insulin resistance, which may also be linked to infertility (Goldstein et al., 2016). Being exposed to light at night can change the circadian phase and stop the pineal gland from making more melatonin at night (Mirick and Davis, 2008). In turn, melatonin's ability to slow down tumour metabolism is stopped, and the risk of cancer grows (Lagiou, 2016). There was a strong link between working the night shift and PCOS. PCOS-model rats had different changes in corticotropin-releasing hormone, adrenocorticotropic hormone, and prolactin levels throughout the day, and their thyrotropic hormone levels were 4 hours behind schedule. Analysis from the Kyoto Encyclopedia of Genes and Genomes brought up more problems with metabolism, such as with carbohydrate and amino acid metabolism and the tricarboxylic acid cycle (Wang et al., 2021).

About 40% of the world's workforce worldwide is made up by women, particularly in agriculture, manufacturing, and service sector (ILO, 2015). Over time, global fertility patterns have changed and there have been observed falls in total fertility rates (TFRs) in most countries (de Silva & Tenreyro, 2020). Various studies show the effect of circadian rhythm disruption on infertility and other female reproductive health issues such as ovulatory disruptions, frequent miscarriages, birth defects and breast cancer (Akerstedt, Perski and Kecklund, 2017). However, to the best of the researcher's knowledge, there is very little collation of research on these diverse, yet related areas. Therefore, this study aims to review the effect of CR disruption on female reproductive health.

The study examines the following research questions in detail:
RQ1: What is the impact of circadian rhythm on the various anatomical processes and human systems?
RQ2: What is the impact of disruption in circadian rhythm on female reproductive system functions such as ovulation, conception and pregnancy?
RQ3: What effect does circadian rhythm and its disruption have on fertility, cancers of the reproductive system organs and disorders such as PCOS?
RQ4: What are the interventions that can help minimize or mitigate these effects?

The paper is organized as follows. The next section deals with an in-depth literature review about circadian rhythm and its effect on various human systems and processes. The next section discusses the effect of disruptions in circadian rhythm on female reproductive systems, followed by some interventions that can help mitigate these effects. Finally, the discussion section mentions the practical implications of the study, limitations and further scope for research.

### Circadian Rhythm

Circadian clocks are built-in, self-maintaining timekeeping systems that allow organisms to predict changes in their environment and adjust their behaviour and physiology accordingly (Morse and Sassone-Corsi, 2002). The circadian timing system makes sure that the body's functions are in sync with 24-hour cycles set by the environment or by the organism itself (Hastings, Reddy and Maywood, 2003). This helps to synchronise various molecular, biochemical, physiological, and behavioural activities and provides organisms with a mechanism for anticipatory adaptation to day-to-day fluctuations in their environment, such as temperature, light, and social communication. Genetics influence the clock's period, but its phase is deeply affected by environmental zeitgebers (e.g. light) (Rana and Mahmood, 2010).

The fact that there are 24 hours of day and night on Earth caused circadian rhythms to develop in the cells of the body. These tell us when to rest, eat, look out for danger or predation, and when to stay away from it. This biological equilibrium helps keeps everything in the body in check, from blood sugar to circadian rhythms (Farhud and Aryan, 2018).

The fundamental architecture of the circadian clock in all organisms is a cell-autonomous autoregulatory feedback loop (Johnson, Zhao, Xu and Mori, 2017). Numerous species, including nitrogen-fixing cyanobacteria and humans, demonstrate circadian rhythms.

From an ecological point of view, if biological processes happen at the

right time, the organism is more likely to survive (by avoiding harsh conditions), find more mates, and find food, among other things. Conspecific activity schedules can be synchronised to increase the likelihood of successful mating, and activity can be scheduled when predators are sleeping to reduce the risk of predation. Thus, it is believed that circadian clocks provide organisms with a fitness advantage by coordinating a variety of important biological processes at times of day that are best for them, depending on extrinsic environmental conditions (Vaze et al., 2014).

Numerous biological variables, including sleep/wake cycles, hormone concentrations, immune response, and metabolic enzymes, exhibit circadian rhythms in humans (Dunlap et al., 2004). People think that these rhythms are controlled by a network of oscillators that are linked together, and that the stable time relationship (fixed time difference) between them is functionally important. Circadian rhythmicity is a property of biological processes like sleep and metabolic processes that involve the oxidation of food. The first one happens at night and the second one happens during the day. During sleep, our body temperature drops to its lowest point, our blood pressure drops, and our metabolism slows down. If these cycles happened at the same time or in sync, it would be bad for the body's health because it wouldn't be able to metabolise food well. So, keeping internal rhythms in sync is an important part of physiology, and circadian rhythms help living things by putting time in order (Vaze et al., 2014).

Circadian clocks are most helpful to the people who use them when they are synchronised with natural cycles whose cycles match the clock's period. "Circadian resonance" is another name for this idea (Dunlap et al., 2004).

Losing circadian clocks is bad for organisms because it makes them less likely to reproduce and live longer in controlled lab settings and less likely to survive in wild environments (Vaze et al 2014).

**Effect of Circadian Rhythm on Human Systems**

The circadian system is disrupted when a person is exposed to light during the night because light is the main attuning cue that the body uses to differentiate between night and day. Inappropriate or near-constant exposure to light can throw biological and behavioural cycles out of sync, which can have severe consequences for human health (Bedrosian and Nelson, 2017; Walker II, Walton, DeVries and Nelson, 2020).

Without external stimuli, the molecular clock would keep on creating 24-hour or circadian rhythms. People who do not have access to light or temperature cues, such as those who live in bunkers, will retain their circadian cycles of sleeping-waking, but will start moving to a pattern that is somewhat longer than 24 hours (Aschoff, 1965).

The suprachiasmatic nucleus (SCN) transmits information regarding the time of day to the pineal gland in order to regulate the production and secretion of melatonin (Hardeland, Madrid, Tan and Reiter, 2012). Melatonin-exposed peripheral cells display "night mode" behaviour, while melatonin-unexposed peripheral cells display "daymode" behaviour. Light exerts a powerful effect on melatonin production (Gooley et al., 2011).

**Cancer**

Multiple studies show that cancer in mice and humans is a circadian disorder (Sahar and Sassone-Corsi, 2009).

Circadian rhythms are governed by a core of eight genes, which also regulate important cell-cycle checkpoint and apoptosis genes (Fu and Lee, 2003). Incorrect artificial lighting and a lack of sunlight can interfere with these rhythms. According to the circadian disruption hypothesis, environmental factors (such as nighttime light) that disturb the body's natural circadian rhythm and stop melatonin from being made at night raise the risk of breast cancer (Stevens, 2001).

Exposure to light during the night can change the circadian clock as well as inhibit the pineal gland's secretion of melatonin (Mirick and Davis, 2008). As a result, the suppression of tumour metabolism induced by melatonin is impeded, increasing the risk of cancer. In addition, low melatonin levels are associated with oestrogen signalling, which promotes the growth of cancer cells (Blask, Dauchy, Xiang, Yuan, Duplessis, Mao, Dauchy, and Sauer, 2011).

Circadian proteins influence an organism's circadian control and thereby its response to DNA damage. These proteins are important for cell proliferation and response control to genotoxic stress at the cellular and organismal levels (Antoch and Kondratov, 2010). Damage to the DNA activates cellular stress response pathways, and these may result in apoptosis, arrest, or DNA repair of cell cycle checkpoint (Rana et al., 2010).

Thirlaway and Upton (2009) discovered a correlation between alterations in circadian rhythms and tumorigenesis in certain cancers and adenocarcinoma.

Several researchers predict that women who work evening or overnight shifts will have a higher risk of developing cancer (Stevens, Davis, Thomas, Anderson, and Wilson, 1992), whereas women who are profoundly blind will have a lower risk (Stevens, Davis, Thomas, Anderson, and Wilson, 1992).

Ablation of the SCN or being exposed to experimental chronic jetlag (CJL) induce changes in the circadian rhythm and enhance tumour growth substantially. Filipski and Levi (2009) found that CJL inhibited or modified the rhythmic expression of clock and cell cycle genes in mice. However, the impact of CJL on the growth of a tumour is offset by the constant availability of food throughout the day because the timing of meals disallowed the disruption of circadian rhythm that was caused by CJL and reduced the speed of development of tumours.

The genetic or functional disruption of the molecular circadian clock may result in genomic instability and accelerated cellular proliferation, two precancerous conditions (Hanahan and Weinberg, 2000). Thus, abnormal representation of circadian clock genes may have significant effects on the regulation of the cell cycle and the cells' apoptosis capacity, thereby possibly supporting carcinogenesis (Rana et al., 2010).

Disruption of the sleep cycle due to abnormal working times may have a greater impact on the pathophysiology of cancer than a single mutation. Depending on the circumstances, abnormal working hours desynchronize the endogenous clock and the external environment which can influence the clock-controlled bodily processes, resulting in incomplete or complete shifts in phases between behaviour and physiology.

The autonomic nervous system, that is controlled by circadian rhythms, is a key part of how bone marrow works (Lucas, Scheiermann, Chow, Kunisaki, Bruns, Barrick, Tessarollo, Frenette, 2013). Multiple stromal cells that are present in the bone marrow send sympathetic signals to help hematopoietic progenitors leave the bone marrow in a natural or forced way (Hanoun et al., 2015). In addition, circadian-dependent hormones glucocorticoids and melatonin play a role in the regulation of bone marrow hematopoiesis (Li, Kwok, Chan, Wang and Tse, 2018).

The circadian system and sleep are intricately intertwined. Most of the time, both work together to help the body adapt to the shifting needs of the day and distinct functions that would otherwise interfere with each other. Consequently, the regular sleep–wake cycle is associated with substantial alterations not only in physical and mental activity, cardiovascular function, and temperature regulation, but also in immune parameters such as leukocyte numbers, function, proliferation, and cytokine production (Besedovsky, Lange and Born, 2012).

Several experiments demonstrate a consistent and interesting array of rhythms of endocrine and immune systems that show an "inflammatory peak" during night-time sleep and mostly anti-inflammatory activity during wakefulness (Besedovsky et al., 2012)

**Immunodeficiency**

Chronic sleep deprivation is associated with both an increase in inflammatory markers and immunodeficiency. Spiegel, Sheridan, and Van Cauter found in 2002 that after six nights of not getting enough sleep, the immune response to a flu shot was lessened. There is also evidence that poor sleep efficiency increases susceptibility to the common cold (Cohen, Doyle, Alper, Janicki-Deverts and Turner, 2009). Even though lack of sleep for a long time led to an increase in inflammation and a general activation of the immune system, the immune system wasn't strong enough to fight off bacteria and toxins, and the rats died of bacteremia (Everson, 2005).

**Sleep Disorders**

Shift work disorder (SWD) is a circadian rhythm sleep disorder caused by working outside of the typical 8:00 a.m. to 5:00 p.m. shifts (Lee, Myung, Cho, Jung, Yoon, Kim, 2017). People who having this disorder experience difficulty falling asleep, insomnia, and too much sleepiness when alertness and productivity are essential (Sack et al, 2007). SWD is characterised by irritability, depression, and trouble in preserving interpersonal relationships. It is also associated with persistent sleep debt and chronic sleep deprivation (National Sleep Foundation, 2019). This chronic lack of sleep has severe effects on health, productivity, and safety. Jet travel across time zones is another modern convenience that can disrupt circadian rhythms. Jet lag, also known as jet lag disorder, is a temporary sleep disorder that occurs when a person crosses multiple time zones (Choy and Salbu, 2011).

**Metabolic and Cardiovascular System Disorders**

Circadian rhythm has been linked on multiple levels to cardiovascular disease and risk factors such as diabetes and obesity (Farhud and Aryan, 2018).

Several risk factors for metabolic and heart diseases, such as high glucose, insulin, and triacylglycerol levels and high white blood cell counts, are made worse by shift work, according to many studies (Manodpitipong et al, 2017; Wirth et al, 2017). A link between shift work and impaired glucose tolerance, obesity, and weight gain has also been demonstrated by longitudinal studies (Proper, van de Langenberg, Rodenburg, Vermeulen, van der Beek, van Steeg, and van Kerkhof, 2016). Sex appears to affect these associations, and some studies demonstrate that women who work shifts are more likely than men to get metabolic syndrome and diabetes mellitus (Gao et al, 2020; Wang et al, 2021).

**Mental Health**

The circadian system controls how much glucocorticoid is released from the adrenal glands. In diurnal animals, like humans, the levels of glucocorticoid tend to be highest just before waking up and go down during the day (Nelson and Kriegsfeld, 2017). Due to its important role in glucose homeostasis, glucocorticoid concentrations are functionally important when they are higher during the active period and lower during sleep. Glucocorticoids are important for a number of physiological and behavioural responses to stress. In fact, glucocorticoid secretion that isn't under control is linked to a number of painful diseases, such as major depressive disorder (Dedovic and Ngiam, 2015). Being exposed to light at night may upset the way the HPA axis works, making cortisol-related mood disorders more common (Dijk, Duffy, Silva, Shanahan, Boivin and Czeisler, 2012).

Mood disorders are more common where circadian rhythms are disrupted (Bedrosian et al., 2017). Numerous research studies show that mood changes, particularly dysphoria, are a significant facet of jet lag (Sack, 2010). Circadian rhythms control all emotional neural systems like monoamine neurotransmitters, the limbic brain, and the hypothalamic–pituitary–adrenal axis (Li et al, 2013).

Major depressive disorder (MDD) is characterised by mood changes, increased sadness and/or irritability, along with one or more of the following: changes in sleep, appetite or sexual desire; inability to experience pleasure; crying; slowing of speech or actions; and suicidal thoughts (Belmaker and Agam, 2008). Clinical data from people show that MDD and circadian processes interact in a strong way. Depression symptoms change throughout the day; people usually feel worse in the morning or evening (Rusting and Larsen, 1998). Changes in the rhythms of sleeping/waking, social activities, hormonal levels and body temperature are seen in people with major depressive disorder (Vadnie and McClung, 2017). Existing research shows that the degree of seriousness of MDD is directly related to how much the circadian rhythm is out of sync (Emens, Lewy, Kinzie, Arntz and Rough, 2009).

Bipolar disorder (BD) is characterised by manic and depressive episodes that alternate with periods of normal affect. Dysregulation or specific polymorphisms in the genes that control the circadian molecular clock can make it more likely that someone will get BD. They can also change the circadian phenotypes that can cause relapses (Bellivier et al., 2015). Travellers who travel by air across multiple time zones and experience jet lag may have bipolar episodes. Travellers with BD who are moving from east to west suffer a phase delay in circadian rhythms and are more likely to get depressed when they arrive at their destination, while those who are moving from west to east undergo a phase advance which causes them to get manic (Katz, Knobler, Laibel, Strauss and Durst, 2002). Social jet lag and other disturbances of circadian social rhythms may also trigger bipolar episodes.

Schizophrenia (SZ) symptoms include delusions, hallucinations, problems with how you think, and problems with how you move. Negative symptoms include less social activity, flat affect, alogia, anhedonia, and avolition which leads to diminished executive function, deficits in attention span and decreased working memory. Researchers have found a link between the severity of SZ symptoms and how much sleep disturbance or disruption of the body's natural clock there is (Benson, 2015). A number of parts of the melatonin rhythm are altered in SZ patients who are not currently taking medication, including reduced nighttime melatonin concentrations (Vigan et al, 2001). In fact, due to the disruption of the normal association between the rhythm of melatonin and the cycle of sleeping/waking, many studies have posited that the sleep-inducing characteristics of endogenic melatonin are reduced in SZ (Afonso, Figueira and Paiva, 2011). Other studies have found that social withdrawal caused due to SZ may cause disturbance in the circadian rhythm by restricting exposure to zeitgebers which are crucial for maintaining the body's 24-hour clock (Bromundt et al., 2011).

A recent study that looked at digital login information from almost 15,000 students found that disturbances in circadian rhythm hurts learning outcomes (Smarr and Schirmer, 2018).

**Effect of Circadian Rhythm on Female Reproductive Health**

Infertility

Infertility is defined as the inability to conceive after 12 months of regular, unprotected sexual activity in women under the age of 35 or 6 months in women over the age of 35. Critical to reproductive success is the ovulatory cycle. The hypothalamic-pituitary-gonadal (HPG) axis controls the ovulatory cycle, which lasts about 28 days. (Reed and Carr, 2018). The ovulatory cycle is controlled by the hypothalamus, which releases gonadotropin-releasing hormone (GnRH). This hormone tells the pituitary gland to make the follicle stimulating hormone (FSH) and luteinizing hormone (LH) (Reed et al., 2018).

Seasonally reproducing animals were the first to reveal the importance of melatonin for reproduction. The duration of melatonin secretion informs the reproductive axis about the length of the day (Reiter, Tamura, Tan and Xu, 2014). Therefore, reproductive functions are optimised so that mating and having babies happen at the right time so that births happen when conditions are best for offspring to survive (Reiter et al., 2014).

Melatonin levels are especially elevated in human ovarian follicular fluid, which comes from both the pineal gland and the ovaries. Melatonin may protect the egg from oxidative stress in the ovary, especially during ovulation. Studies have shown that infertile women with lower levels of follicular melatonin had more reactive oxidative species in their bodies and poorer quality oocytes (Tamura et al, 2008). Studies show that sleep alters reproductive hormone levels. FSH, which encourages the growing of ovarian follicles, is a key regulator of reproductive function. In a study of 160 women of reproductive age with normal menstrual cycles, a positive correlation between FSH and sleep duration persisted after adjusting for age and body mass index (Touzet, Rabilloud, Boehringer, Barranco and Ecochard, 2002). Prolactin is also a hormone involved in the reproductive system that has been found to rise during sleep (Van Cauter and Tasali, 2017).

Psychological stress could hurt fertility by making the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system work harder (Campagne, 2006). Stress has the same physical effects as not getting enough sleep (Akerstedt, Perski and Kecklund, 2017). So, not getting enough sleep may affect fertility through these ways, or it may change the link between psychological stress and infertility, since sleep problems often go hand in hand with stress.

Studies show that women who work shifts are more likely to have menstrual cycles that aren't normal in length, which may be a sign of problems with the process of ovulation. Due to the fact that sex steroids and gonadotropins have circadian rhythms and be changed by changes in sleep patterns, shorter duration of sleep or disturbances in circadian rhythms may be bad for their normal secretion and lead to inadequate primary reproductive outcomes.

Infertility may also be linked to short sleep duration, obstructive sleep apnea and disruption of the circadian rhythm, all of which are known to

cause glucose intolerance and insulin resistance. The way clock genes move around in the uterus may be a sign that the body's 24-hour clock helps with embryo implantation and early pregnancy. It has been thought that increased activation of the hypothalamic-pituitary axis (HPA), increased activity of the sympathetic nervous system (SNS), and too much oxidative stress are bad for several steps that are important for getting pregnant. All of these things could be changed by sleep (Goldstein et al., 2016).

**Frequent Miscarriages**

Implanting the embryo within the human uterus needs a responsive endometrium, a healthy embryo, and the right way for the two to work together (Simon and Laufer, 2012). Muter et al. (2015) think that the way the uterus's peripheral clock works may have something to do with these important reproductive events. More important to fertility are recent findings that Per2 is also expressed in a rhythmic way in the endometrial stromal cells of the human uterus. The level of its expression goes down during the process of decidualization. Premature downregulation results in a disorganised decidual response. Midluteal endometrial biopsies from women who had a lot of miscarriages showed that the number of failed pregnancies was inversely related to the amount of Per2 transcript (Muter et al., 2015). These results suggest that a normal 24-hour cycle of reproductive events after ovulation may be needed for a pregnancy to complete term (Goldstein et al., 2016).

Too much oxidative stress, which can be caused by not getting enough sleep, is thought to be bad for early reproductive outcomes like embryo implantation, ovarian function and maintenance of early-stage pregnancy (Ruder, Hartman, Blumberg and Goldman, 2008).

**Birth Defects**

Melatonin is rapidly transferred from maternal to foetal circulation (Okatani, Okamoto, Hayashi, Wakatsuki, Tamura, and Sagara, 1998; Schenker, Yang, Perez, Acuff, Papas, Henderson, and Lee, 1998), and foetal melatonin levels and rhythms are comparable to those of the mother (Tamura et al, 2014). Since it is not known if foetuses make melatonin, any melatonin in the foetal bloodstream must come from the placenta.

It is apparent that the foetus depends on information from the mother for the rhythmic and regular expression of its SCN. Obviously, the melatonin cycle is a reliable way for the mother to send a message to the foetus. This rhythm may have an important effect on how the foetal SCN develops and what it does (Novakova et al., 2010).

Researchers like Novakova, Paclt, Ptacek, Kuzelova, Hajek, and Sumova (2011) and Damiani, Sweet, and Sohoni (2014) thought about the possibility that the rise in attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) may be linked to a prenatal disruption of the mother's circadian rhythm, since these children do not have a normal melatonin rhythm. The results indicate that variations in the rhythm of melatonin in the mother may slow down the maturation of the foetal SCN circadian clock.

**Breast Carcinoma**

When women are exposed to tirile light at night-time, it may modify the circadian phase and stop the pineal gland from making more melatonin at night (Mirick and Davis, 2008). In turn, the suppression of tumour metastasis induced by melatonin is repressed, and the risk of cancer increases. In addition, it has been reported that low melatonin levels produce oestrogen signalling, which releases cancer cells from growth inhibition (Lagiou, 2016).

**Interventions**

Most of the issues described above can be mitigated by interventions that attempt to regularize the circadian rhythm, as shown by various studies.

**Mental Health**

Bright light therapy, wake therapy, social rhythm therapy, and antidepressants (SSRIs, SNRIs, and agomelatine) that directly affect circadian rhythms have all been found to help treat MDD (Germain and Kupfer, 2008). Antidepressants such as SNIRs, SSRIs, and agomelatine also lead circadian rhythms (body temperature, activity, melatonin, and cortisol) to move ahead by one phase (Leproult et al, 2005).

Normalizing and stabilising circadian rhythms has been shown to help treat bipolar disorder. This can be done with lithium or other drugs (Gold and Kinrys, 2019). Clinical trials have also shown that restoring normal circadian rhythms with bright light therapy in the middle of the day can end depressive episodes in people with bipolar disorder (Sit et al, 2018).

**Ovulatory Disruptions**

In an interesting twist, bright light therapy may also change the way a woman's period works. Bright light given to women at different circadian times during a 90-minute protocol increased the secretion of LH compared to the starting point (Kripke, Elliott, Youngstedt, Parry, Hauger and Rex, 2010). In the same study that used a different method, bright light in the morning and evening led to enhanced secretion of LH in the follicular and luteal phases of the menstruation cycle (Kripke et al., 2010). In another study, women who were in the follicular phase of their menstrual cycle and were exposed to a 45-minute light pulse a short while after waking up had higher levels of the reproductive hormones prolactin, FSH, and LH (Danilenko and Samoilova, 2007). Also, the size of ovarian follicles and the number of ovulatory cycles went up (Danilenko et al., 2007).

**Infertility**

Knowing that melatonin can reduce ovarian oxidative stress has led to research on the use of exogenic melatonin as a protective agent during in vitro fertilisation (IVF) (Reiter et al., 2014). Melatonin supplements of 3 mg for 2 to 3 months have been shown to improve IVF outcomes, such as the number of oocytes retrieved, how well they mature, and how healthy they are (Eryilmaz et al., 2011; Unfer et al., 2011). Melatonin supplements have also been linked to better results with IVF in women with polycystic ovary syndrome (PCOS) (Pacchiarotti, Carlomagno, Antonini and Pacchiarotti, 2016).

Tamura et al. (200) found that giving 3 mg of melatonin orally every day to women with low fertilisation rates in previous IVF cycles doubled the fertilisation and pregnancy success rate by reducing damage caused by free radicals. Tamura et al (2009) found that 3 mg melatonin administered orally daily to women with a low fertilisation rate in a previous IVF cycle doubled the fertilisation and pregnancy success rate by reducing free radical–mediated damage.

**Conclusion**

This paper offers an in-depth review of the concept of circadian rhythm, the effect of disruption on human systems and diseases linked to such disruption, such as cancer, immunodeficiency, sleep disorders, metabolic and cardiovascular system disorders, mental and health problems. It specifically focuses on the adverse impact of disruption in circadian rhythm on the female reproductive system in the form of infertility, ovulatory disturbances, frequent miscarriages, birth defects and breast carcinoma.

Circadian clocks are built-in and self-sustaining timekeeping systems that allow organisms to predict changes in their environment and adjust their behaviour and physiology accordingly. (Morse and Sassone-Corsi, 2002). This gives organisms a way to adapt to fluctuations in their external environment, like temperature, light, and social communication, that happen every day and can be predicted. It also helps keep multiple biochemical, molecular, behavioural and physiological processes in sync (Rana and Mahmood, 2010). It makes sure that the body's functions are in sync with 24-hour cycles set by the environment or by the organism itself (Hastings, Reddy and Maywood, 2003).

Exposure to light at night can disrupt the circadian system because light is the body's main way to tell the difference between day and night. Inappropriate or near-constant exposure to light can throw biological and behavioural cycles out of sync, which can have severe consequences for human health (Bedrosian and Nelson, 2017).

Researchers have found that disruption of circadian rhythms causes cancerous cells to undergo abnormal cell division and that essentially cancer is a circadian disorder. Studies have also shown that Women who work at night or in the evening are more likely to get cancer (Stevens, Davis, Thomas, Anderson, and Wilson, 1992)

Chronic sleep deprivation due to disruption of circadian rhythm is found to be linked with both an increase in inflammatory markers and immunodeficiency, and also has severe effects on health, productivity, and safety.

Circadian rhythm has been linked on multiple levels to cardiovascular

disease (Farhud and Aryan, 2018). There are many risk factors, such as high levels of glucose, insulin, and triacylglycerol and a high number of white blood cells that have been shown to be negatively affected by disruptions in circadian rhythm (Sookoian et al, 2007).

In terms of mental health, disturbances in circadian rhythms contribute to mood disorders, MDD and may also increase susceptibility to bipolar disorder. Some researchers have also found that the disruption of the normal association between the melatonin rhythm and the sleep-wake cycle leads to diminished sleep-inducing properties of endogenous melatonin in schizophrenic patients (Afonso, Figueira and Paiva, 2011).

The circadian rhythm is very important for a woman's ability to have children. In nature, reproductive functions are set up so that mating and conception happen at the right time so that births happen when conditions are best for offspring to survive (Reiter et al., 2014). When the circadian rhythm is off, there is less melatonin in the follicles. This leads to more reactive oxidative species and lower quality oocytes, which may be one of the causes of infertility.

Existing studies demonstrate that sleep can alter the levels of reproductive hormone such as FSH, which promotes the growth of ovarian follicles and prolactin, an additional hormone involved in reproductive physiology. Both these are linked to sleep, and hence affected by disruption in circadian rhythm. Psychological stress negatively affects fertility by increasing hypothalamic-pituitary-adrenal (HPA) axis activation and sympathetic nervous system activity. Thus, sleep deprivation and disruptions in circadian rhythm affect fertility through these mechanisms, or, by modifying the association between psychological stress and infertility. Infertility may also be linked to short sleep duration, obstructive sleep apnea and circadian disruption, all of which can cause glucose intolerance and insulin resistance.

Circadian rhythm also affects miscarriages as undamaged circadian timing of certain reproductive events after the ovulation may be necessary for productive conception. Also, the foetus is not known to make melatonin, so the foetus gets its melatonin cycle from the mother. Disruptions in the mother's melatonin cycle may slow down the development of the foetal SCN's circadian clock. Some studies have suggested that the rising number of children with attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) may be linked to a prenatal disruption of the mother's circadian rhythm as these children do not have a normal melatonin rhythm.

All these findings suggest a strong link between circadian rhythm and female reproductive health.

Existing research posits various interventions that may be used to stabilize circadian rhthms. Some examples are wake therapy, bright light therapy, social rhythm therapy, and antidepressants such as SSRIs, SNRIs, and agomelatine which impact circadian rhythms (Germain and Kupfer, 2008), interventions that attempt to normalize circadian rhythms via lithium or other means. Administering melatonin orally has also been found to reduce oxidative stress in the ovary, improve IVF outcomes and double the fertilisation and pregnancy success rate.

This paper adds to the existing literature on impact of circadian rhythm, especially on issues related to female reproductive health and is a useful resource for students, researchers and medical practitioners. Future studies can study the effect of circadian rhythm of specific diseases or disroders, or can focus on the challenges that are yet to be resolved in the attempt to stabilize disrupted circadian rhythms.

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