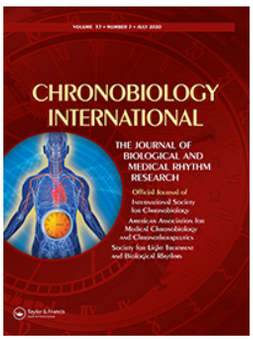

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The Journal of Biological and Medical Rhythm Research

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/icbi20

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To cite this article: S. Bagci , H. Sabir , A. Müller & R.J. Reiter (2020) Effects of altered photoperiod due to COVID-19 lockdown on pregnant women and their fetuses, Chronobiology International, 37:7, 961-973, DOI: 10.1080/07420528.2020.1772809

To link to this article: https://doi.org/10.1080/07420528.2020.1772809

Published online: 10 Jun 2020.

CHRONOBIOLOGY INTERNATIONAL
2020, VOL. 37, NO. 7, 961–973
https://doi.org/10.1080/07420528.2020.1772809

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Effects of altered photoperiod due to COVID-19 lockdown on pregnant women and their fetuses

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ABSTRACT

Maternal circadian rhythms provide highly important input into the entrainment and programming of fetal and newborn circadian rhythms. The light-dark cycle is an important regulator of the internal biological clock. Even though pregnant women spend a greater part of the day at home during the latter stages of pregnancy, natural light exposure is crucial for the fetus. The current recommended COVID-19 lockdown might dramatically alter normal environmental lighting conditions of pregnant women, resulting in exposure to extremely low levels of natural daylight and high-intensity artificial light sources during both day and night. This article summarizes the potential effects on pregnant woman and their fetuses due to prolonged exposure to altered photoperiod and as consequence altered circadian system, known as chronodisruption, that may result from the COVID-19 lockdown.

ARTICLE HISTORY
Received 3 May 2020
Revised 14 May 2020
Accepted 16 May 2020

KEYWORDS
COVID-19; lockdown; circadian disruption; melatonin; pregnant Women; fetus

Introduction

A large number of physiological and psychological functions in humans are organized as circadian rhythms. Circadian rhythms enable organisms to anticipate and respond to periodic changes in the environment and are consequently important for molecular, physiological, and psychological processes, such as gene expression, glucose availability, body temperature maintenance, heart rate regulation, and hormone production, as well as sleep, mood, and higher cognitive functions (Plano et al. 2017). Pregnancy is a normal physiological process that requires the synchronized adjustment of multiple organ systems. It is well known that several physiological processes during pregnancy, including body temperature, blood pressure, uterine contraction, blood flow, glucose availability, hormone levels, such as cortisol and estriol, and intra-amniotic fluid pressure, are regulated by the maternal suprachiasmatic nucleus (SCN) that is synchronized in the 24 h periodicity by the ambient day-night cycle (Valenzuela et al. 2015). These rhythmic activities are important for maintaining maternal and fetal homeostasis. Therefore, any prolonged alteration may have detrimental effects on fetal development and/or maternal health (Valenzuela et al. 2015).

Light is known to be the principal environmental factor regulating circadian rhythms, seasonal cycles, and neuroendocrine responses in many species, including humans (Küller 2002). The effects of light on circadian rhythms depend on the length of the day, duration of exposure to daylight, and timing of exposure to artificial light (Blume et al. 2019). Natural daylight regulates the activity of the internal biological clock. With the growing evidence that maternal circadian rhythms are highly important in the entrainment and programming fetal and newborn circadian rhythms, it is likely the COVID-19 lockdown may dramatically alter lighting conditions in pregnant women, resulting in chronodisruption – disruption of the circadian time organization – with as consequence risk comprised health and wellbeing as a result of exposure to very limited amounts of natural daylight and increased amount of artificial light sources, both day and night (Smolensky et al. 2016). In this review, we summarize the potential effects of chronodisruption during pregnancy by COVID-19 lockdown on pregnant woman and their fetuses.

Regulation of circadian rhythm in humans by light

Although both genetic background and environmental stimuli, such as temperature, sound, food, and social cues may be able to influence circadian phase control, the daily environmental light-dark cycle is the primary

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cue for circadian entrainment in humans (Golombek and Rosenstein 2010). In mammals, circadian rhythms are regulated by a circadian timing system, being synchronized to the environmental light-dark cycle by ocular light detected by the retina and neurotransmissions transferred to the SCN of the hypothalamus primarily via the retinohypothalamic neural tract. The SCN regulates the pineal gland, a central structure of the circadian timing system and major source of melatonin (Moore 1997). In adult human synthesis and secretion of melatonin increases shortly after the beginning of darkness, with maximal levels observed usually during the middle of the night, and decreases gradually to basal daytime levels during the second half of the night (Reiter 1991). This circadian fluctuation of melatonin is crucial for maintaining the normal circadian time organization. Melatonin is a small lipid and water-soluble indoleamine molecule that easily crosses membrane barriers. Thus, melatonin regulates not only circadian rhythms but many physiological processes, including, immune, antioxidative, cardiovascular, sleep, mood, reproductive, endocrine, and metabolic/thermal ones (Erren and Reiter 2015). These processes are regulated both by direct entrance of melatonin into cells, tissues, and organs and indirectly through binding to specialized melatonin and nuclear receptors (Smolensky et al. 2015).

The circadian system's response to light varies according to its level, duration, and timing of light exposure as well as the light's spectral properties (Blume et al. 2019). Therefore, the effects of light on the circadian system depend on the length of the day, duration of exposure to daylight, and timing of exposure to artificial light (Blume et al. 2019). Sufficient light in the appropriate spectrum, for a sufficient span during the appropriate time of the day is essential for the synchronization of circadian rhythms to the solar day and night. Highly specialized light-sensitive retinal photoreceptors are the primary means by which the central circadian clock is synchronized to environmental time. Chronic daylight deprivation increases retinal sensitivity to blue light, and it decreases circadian rhythm stability (Kawasaki et al. 2018). It is recognized that exposure to low illuminance morning light over several days augments circadian phase shifts induced by light exposures in the evening (Munch et al. 2016).

During the daytime, outdoor light intensities can be as great as 100,000 lux in direct sunlight and usually ~25,000 lux in full daylight, while light intensity in closed rooms with artificial lightning is considerably less, only 200 to 300 lux (Spitschan et al. 2016). Typical levels provided by artificial light sources, for example, commercially available "white" light sources (color temperature between 4500 and 6000 Kelvin, K), are in the middle of this range, between ~ 0.1 and 1000 lux. However, the color temperature of natural illumination changes during the day, i.e. from sunrise (2000 K), early morning (3000 K), late morning (4000 K), noon (6600 K), early afternoon (4000 K), late afternoon (3000 K), to sunset (2000 K) (Lin et al. 2019). Natural sunlight is the primary environmental time cue that regulates the internal circadian clock, which permits organisms to synchronize to environmental time, allowing physiological functions to occur at optimal times of the day (Wright et al. 2013). Compared to the color characteristics of natural daylight, the range of exposed color temperature in closed rooms are within a very narrow spectrum, resulting in the absence of many spectral components of natural daylight.

Thus, spending a great part of the day in dim light conditions, e.g. only indoors, might have detrimental effects. First, the architecture of many old (perhaps also new) buildings were not designed for the specific needs of healthy people during the day. Therefore, it is not expected for an individual living in such buildings to be exposed to enough illuminance and changing spectrums of daylight during the day. Second, artificial lighting systems have only been installed to meet the needs of the human visual system, not the circadian system. The human circadian system is most sensitive to shorter wavelengths (~450 nm [blue light]). Blue LED is the most efficacious light band that stimulates the human circadian system, resulting in a suppression of melatonin synthesis at night, and resetting and shifting of the circadian system. Light derived from compact fluorescent lamps, compared to 8000 K (long light wavelengths) lamps, 2700 K (short light wavelengths), requires nearly three-fold the corneal (photopic) illuminance and three-fold the electric power to produce the same circadian response of 50% melatonin suppression (Rea and Figueiro 2011). Moreover, not only the illuminance and spectrum but also the duration and time of exposure to artificial lighting must be considered to properly predict the effect of light on the circadian system. For example, 50% melatonin suppression by "white" light (5500 K) at night is achieved within 33 min of exposure to 1000 lux at eye level; however, 50% suppression is not achieved following 100 lux exposure levels for any duration. Of importance, sufficient light every morning upon awakening advances the circadian clock's timing every day in order to keep biological functions synchronized with the solar day. Based on current scientific data, a disrupted circadian system response due to changed environmental lighting conditions can be expected in pregnant women during the COVID-19 lockdown quarantine processes. Therefore, it may be important to establish a day-night light cycle

that mimics as much as possible natural conditions to limit the detrimental effects of reduced exposure to natural daylight and elevated exposure to artificial lighting systems on human circadian rhythms.

Maternal and fetal circadian rhythm

There is clear evidence supporting the role of melatonin in human pregnancy, and it appears that melatonin is essential for successful pregnancy (Tamura et al. 2008a). Moreover, preclinical and clinical data show the human fetus exhibits circadian rhythms in several physiological functions, such as gross body movements, heart rate, breathing, sleep/wake cycling, and synthesis of hormones, such as cortisol (De Vries et al. 1987; Patrick et al. 1981a, 1982; Seron-Ferre et al. 2012). The fetal pineal gland may actively secrete melatonin, however not as periodic rhythm (Muñoz-Hoyos et al. 1993). Melatonin is rapidly transferred from maternal blood to fetal circulation, and it is present in amniotic fluid (Bagci et al. 2017; Okatani et al. 1998). Therefore, melatonin permits the transmission of maternal photoperiodic information to generate day/night difference in the fetus and circadian organization during development, which is essential for the maturation of the fetal biological clock (Nakamura et al. 2001; Okatani et al. 1998). As day-night light cycles in sufficient manner and duration modify the rhythm of melatonin secretion, altered lighting conditions, such as weak daylight, absence of darkness during the night, or constant environmental lighting, dampen the environmental differences between day and night, resulting in disrupted circadian physiology not only in the pregnant woman but also in her offspring (Martinez-Nicolas et al. 2014). Our recent study demonstrated illuminance of a patient's room to which hospitalized pregnant women are exposed are greatly different from those of natural daylight. The incidence of median exposure illuminance <100 lux by hospitalized pregnant women of our cohort was 61% in the morning and 43% in the afternoon. Moreover, women restricted entirely to their hospital room were rarely exposed to >300 lux, either in the morning or afternoon, demonstrating total day light deprivation and decreased melatonin production (Bagci et al. under review, see abstract (Bagci et al. 2018; Wieduwilt et al. 2018)).

Previous studies have demonstrated the intact maternal SCN is paramount importance for optimal fetal growth, perinatal neurodevelopment, and normal metabolic functions of adulthood (Reiter et al. 2014a). Moreover, an important function of maternal circadian rhythms during perinatal development is preparation of the fetal circadian timing system for later independent life (Mirmiran et al. 1992). There is general agreement that the maternal circadian system coordinates the phasing of the fetal clock in relation to environmental lighting conditions, either via the melatonin signal and/or by other means. Therefore, it is important to acknowledge potential problems of pregnant women and their newborns caused by disrupted circadian systems responses as a consequence of sustained exposure to altered environmental lighting conditions during pregnancy (Mendez et al. 2012; Reiter et al. 2014b).

Effects of altered photoperiod during pregnancy on maternal and fetal physiology

Placental functions

The placenta is a highly specialized endocrine organ of pregnancy that plays a major role in the adaptation of maternal physiology to pregnancy and normal growth and development of the fetus (Burton and Jauniaux 2015). Moreover, it is the main unit of bidirectional communication and exchange between mother and fetus. Melatonin synthesis and its membrane receptors MT1 and MT2 have been identified in the placenta (Lanoix et al. 2008, 2012). Melatonin derived from the placenta acts at all levels of the maternal–placental–fetal system as an autocrine, paracrine, and endocrine molecule that modulates circadian endocrine rhythms and protects placental tissues via free radical scavenging, indirect antioxidant effects, and immune regulation (Lanoix et al. 2012; Reiter et al. 2014b). Changes in placental circadian rhythms with reduced melatonin production are associated with increased risk of preterm delivery, uterine growth restriction, and preeclampsia, resulting in perinatal death, preterm births, fetal growth restriction, and retardation of brain development (Chuffa et al. 2019; Reiter et al. 2014b). Importantly, deficiency of melatonin production or suppression of melatonin levels by prolonged light exposure at night is related to spontaneous abortion, as found in the absence of chromosomal anomalies or uterine malfunctions (Berbets et al. 2019; Tamura et al. 2008b). On the other hand, it has been shown that oral melatonin supplementation enhances placental perfusion, and prevents artery insufficiency, hypercoagulation, and inflammatory and oxidative damage (Chuffa et al. 2019; Sagrillo-Fagundes et al. 2014). Moreover, Lemley et al. (Lemley et al. 2012) demonstrated melatonin supplementation from mid-gestation through term restored umbilical artery blood flow and fetal growth in nutritionally restricted pregnancies. It is also possible that melatonin acts directly via its MT1/MT2 receptors and/or via its antioxidant actions to promote fetal growth and development (Richter et al. 2009).

The effects of the light-dark cycle on normal placental physiology have been known for many years. Non-human primate studies have showed placental blood flow decreases in the light period and increases in the dark period (Harbert et al. 1979). It is also known that some placental hormones, such as human chorionic gonadotropin, progesterone, estriol, and estradiol, exhibit circadian variation (Nakajima et al. 1990; Rotmensch et al. 2001; Serín-Ferré et al. 1993).

Cardiovascular functions

Growing evidence indicates there is marked 24 h variation, both in normal cardiovascular functions and pathological cardiovascular events (Anwar and White 1998; Kario et al. 2003; Muller et al. 1985). Epidemiological studies demonstrated peak incidence between 06:00 and 12:00 h of myocardial infarction, sudden cardiac death, and ischemic and hemorrhagic stroke (Anwar and White 1998; Muller et al. 1985). Blood pressure exhibits circadian variation, attaining in diurnally active persons without complicating co-morbidities of type 2 diabetes and renal disease, with elevated levels during the daytime (from 10:00 to 18:00 h), lower levels thereafter, and lowest level between 00:00 and 03:00 h (White 2001). Moreover, indices of sympathetic activity, such as heart rate, cardiac output, and peripheral resistance also show marked reductions during sleep that coincide with the fall in blood pressure (Kario et al. 2003). Serial measurements of plasma catecholamines over the 24 h indicate that fluctuations in norepinephrine and epinephrine levels correlate closely with the day-night pattern of blood pressure (Linsell et al. 1985). Another factor regulating the 24 h pattern of blood pressure is the diurnal variation in renin–angiotensin–aldosterone system activity, demonstrating a gradual decrease during the day and an increase overnight, with peak plasma renin activity and plasma angiotensin II and aldosterone level during the early hours of the morning (Gordon et al. 1966). Lesioning of the SCN suppressed these cardiovascular rhythms, indicating they are controlled by an endogenous circadian pacemaker (Sano et al. 1995; Witte et al. 1998b). Melatonin serves as an endocrine regulator of nighttime blood pressure in healthy adults by contributing to its normal decline during sleep by 10–20% from its daytime mean level (Portaluppi et al. 1996). In addition, melatonin acts as a potent radical scavenger, reducing oxidative stress caused by arterial hypertension, and it improves endothelial function by increasing nitric oxide bioavailability, which may reduce blood pressure through attenuation of peripheral arterial resistance (Portaluppi et al. 2004). Melatonin also inhibits the vasospastic effect of hydrogen peroxide on the human umbilical artery (Okatani et al. 1997). Therefore, it has been suggested that melatonin, having several pleiotropic actions, might be protective of the cardiovascular system and also against the development of hypertension and end organ damage.

An increasing number of studies suggest dysregulation of photoperiod due to long working hours and shift work during pregnancy could increase the risk for hypertensive disorders (Cai et al. 2019; Suzumori et al. 2020). Exposure of experimental animals to constant low-intensity light (5–10 lux) abolishes nighttime melatonin production and also circadian rhythm in cardiovascular parameters, including blood pressure and heart rate (Briaud et al. 2004; Witte et al. 1998a). It has also been observed that young adults gestated under chronic photoperiod shift during pregnancy had higher systolic blood pressure during the night and lowest during the daytime and had an increased heart rate variability during the rest period (Mendez et al. 2016). Reduced levels of nighttime circulating melatonin have been found in pregnant women with severe preeclampsia in comparison with women with normal pregnancy or with mild preeclampsia (Nakamura et al. 2001). It is important to point out that insufficient nocturnal decline in blood pressure puts greater burden on the cardiovascular system and increases morbidity and mortality, independent of other risk factors (Hermida et al. 2011).

Epidemiological and experimental evidence indicates the origins of adult cardiovascular disease, such as elevated blood pressure, may be traced back to chronodisruption in fetal life (Chaves et al. 2019; Galdames et al. 2014; Law and Barker 1994). Circadian variation in fetal heart rate has been reported commencing as early as 20–22 weeks through the end of pregnancy (De Vries et al. 1987; Patrick et al. 1981a). Lunshof et al. (Lunshof et al. 1998) reported significant correlation between fetal and maternal diurnal heart rate rhythms with a phase lag of −2 to +2 h. They hypothesized the fetal SCN, although not completely mature, is involved in transferring maternal diurnal rhythm information to the fetal heart (Lunshof et al. 1998). Changes in the time of day staging of both fetal activity and heart rate variables have implications on of fetal well-being. Galdames et al. (Galdames et al. 2014) demonstrated alteration of the circadian system results in dysregulation of fetal cardiac gene expression, increasing the risk of cardiovascular disorders in adult offspring. Recently, Chaves et al. (Chaves et al. 2019) showed offspring of mice exposed to repeated jet lag during pregnancy exhibit structural alterations of heart tissue, and impaired heart function. Moreover, melatonin prevents cardiac hypertrophy in hyperthyroid rats, plus reduced oxidative load, and altered expression of metabolically important genes (Ghosh et al. 2007).

Endocrine functions

Glucose intolerance and insulin resistance

Several lines of evidence suggest numerous metabolic parameters, such as blood glucose levels, and pattern of insulin secretion by pancreatic β-cells vary according to the time of the day by means of melatonin-dependent synchronization (Bruckdorfer et al. 1974). Daily blood glucose control is modulated by both the central circadian clock in the SCN and by peripheral clocks in the pancreas, liver, muscle, and white adipose tissue. The nocturnal increase in melatonin levels and consequent activation of MT1 signaling modulate insulin sensitivity on the following day (Owino et al. 2018). Absence or low levels of melatonin at night is associated with metabolic abnormalities, such as glucose intolerance and insulin resistance, while prolonged exposure of β islet cells to melatonin (mimicking a night period) increases β-cell glucose sensitivity (Lima et al. 1998; McMullan et al. 2013; Nogueira et al. 2011; Ramracheya et al. 2008). Zimmet et al. (Zimmet et al. 1974) performed oral glucose tolerance tests in the morning and afternoon of separate days on 31 people derived from a normal population sample. They found that the pancreatic β-cell response to a glucose challenge is more intense in the morning hours and declines as evening approaches.

It has been demonstrated that an altered photoperiod every 3–4 days during rat pregnancy resulted in glucose intolerance and insulin resistance in 12-month-old offspring (Varcoe et al. 2011). An in-vitro study using rat pancreatic islets revealed exposure of islet cells to continuous light was associated with disruption of the islet circadian clock function through impairment of the amplitude, phase, and interislet synchrony of clock transcriptional oscillations and diminished glucose-stimulated insulin secretion due to a decrease in insulin secretory pulse mass (Qian et al. 2013). The results of a forced desynchrony protocol performed by Sheer and coworkers (Scheer et al. 2009) indicated the combination of circadian misalignment and circadian evening impaired glucose tolerance, in part via reduced insulin sensitivity and in part via reduced beta cell function, as compared with circadian alignment in the circadian morning. When sleep was restricted to 5 h, participants sleeping mostly during the day (circadian misalignment) had 47% greater reduction in insulin sensitivity compared with 34% reduction in insulin sensitivity of participants sleeping during the night (Leproult et al. 2014). A recent study showed pregnant women with glucose metabolic disorders had a smaller circadian variation in salivary melatonin secretion, and their melatonin values were lower throughout the day than healthy pregnant women (Shimada et al. 2016). Melatonin therapy in pregnant woman with hyperglycemia is reported to be clinically efficacious (Fang et al. 2016). As all human epidemiological, genetic, and experimental studies provide substantial evidence that inverted behavioral/environmental cycles impairs β-cell function and insulin sensitivity, resulting in impaired glucose tolerance, it is important to maintain the endogenous, behavioral, and environmental rhythms for pregnant woman with risk for impaired glucose tolerance and transition to gestational diabetes.

Endocrine functions

Maternal and fetal hypothalamic-pituitary-adrenal (HPA) axis

The basal activity of the hypothalamic–pituitary–adrenal (HPA) axis clearly displays an endogenous circadian rhythm with the peak of adrenocorticotropic hormone (ACTH) and cortisol in the early morning, declining level during the daytime activity span, prolonged low level until late evening, nadir ~00:00 h, and rapid rise during the latter half of the night until again reaching highest level in the morning (Van Cauter and Refetoff 1985; Weibel et al. 1995). The HPA axis circadian variation depends on clock gene rhythms in the hypothalamus. Animal experiments demonstrate the endogenous circadian rhythm in corticosteroid level is generated by the central circadian SCN pacemaker, which is entrained by light. Moreover, meals and other external factors may also elicit transient changes in the circulating levels of these hormones (Van Cauter and Refetoff 1985).

Scheer *et al.* (Scheer and Buijs 1999) investigated the effect of light on the morning-cortisol peak in humans by exposing them to darkness (0 lux) and to light of 800 lux during a 1 h span on two subsequent mornings. Although morning awakening is consistently followed by a short-term increase in cortisol levels, light exposure resulted in significantly higher cortisol levels (±35% further increase) 20 and 40 min after waking than extended darkness. Under well controlled conditions of constant recumbent posture, constant wakefulness, constant caloric intake, and constant activity levels, Leproult et al. (Leproult et al. 2001) demonstrated time-of-day dependent effect of changes in ambient light intensity on cortisol levels. The transition from dim light to bright light, achieved by a stepwise increase from <150 lux (low indoor light intensity) to 4500 lux (outdoor light intensity on a cloudy day) induced rapid and robust 110–140 nmol/L increase in plasma cortisol level in the early morning, but not in the afternoon. This study indicates a normal natural day rhythm is important to amplify the morning acrophase of the circadian rhythm of cortisol secretion.

It is important to note activity of HPA axis promotes release of energy stores to meet high fetal demand after mid-gestation (Patrick et al. 1980). Wharfe et al. (Wharfe et al. 2016) concluded pregnancy-induced changes in the central circadian clock and HPA axis likely promote pregnancy success by driving maternal physiological adaptations to meet metabolic demands of fetal growth. Moreover, Patrick et al. (Patrick et al. 1981b) suggested maternal cortisol may act as a zeitgeber for fetal diurnal rhythms. Why is this interaction between mother and fetus important? First, it has been shown that elimination or suppression of maternal adrenal cortical rhythms inhibits diurnal rhythmicity in fetal adrenal gland, which is a key endocrine organ that orchestrates maturational processes central for the transition to extra-uterine life and thereby impairs development of the diverse physiological processes normally influenced by circadian glucocorticoid oscillations (e.g. lung maturation and metabolic, cardiovascular, immune, and neural functions) (Hassell et al. 2013; Patrick et al. 1981b). Second, diurnal rhythms in fetal body movements, fetal breathing, and fetal hearth rate is linked to intact maternal or fetal adrenal systems (Backing 1989). Therefore, suppression of maternal adrenal cortical rhythms also inhibits diurnal rhythmicity in fetal movements, fetal breathing, and heart rate variability (Arduini et al. 1986, 1987; Challis et al. 1981). Third, epidemiological evidence indicates the fetal and early postnatal environment has profound influence on endocrine function throughout life (Barker 2002). Alterations in the regulation of HPA activity in utero can lead to long-term pathologies, including cardiovascular disease, metabolic dysfunction, such as insulin resistance and dyslipidaemia, and cognitive/behavioral dysfunction in later life (Kapoor et al. 2006).

Endocrine functions

Fetal growth

Intrauterine growth retardation is one of the major causes of both pre- and postnatal mortality and morbidity (Alberry and Soothill 2007). The timing of balanced and precise daily delivery of oxygen, nutrients, hormones, and biophysical cues from mother to fetus is essential for fetal growth. The findings of several studies support the link between seasonal changes in daylight and growth patterns of normal children. Growth appears to increase during times of greatest daylight exposure – during summer – and decrease during periods of darkness – winter (Hermanussen et al. 1988; Shulman et al. 2013). Moreover, the growth response to recombinant-human growth hormone appears to be related not only to gene polymorphisms but also to daylight exposure (De Leonibus et al. 2016). Epidemiological evidence indicates altering the light-dark cycle disrupts fetal growth and elevates risk of small gestational age and intrauterine growth restriction in the offspring of women who regularly maintained a shift work schedule (Barr 1973; Croteau et al. 2006; Gozeri et al. 2008; Lemley et al. 2012; Reiter et al. 2014b; Richter et al. 2009). Gozeri et al. (Gozeri et al. 2008) reported different light manipulations all impacted negatively on fetal growth, the greatest effect was observed under conditions of constant light (24% fetal weight reduction at term). Although underlying mechanisms by which daylight could modulate growth response are yet not completely known, based on the current studies several pathways can be suggested. First, fetal growth restriction is believed to be a consequence of the combined impact of maternal stress, decreased maternal melatonin levels by an altered maternal circadian rhythm, reduced placental blood flow, and increased placental inflammation, as well as endocrine disruption (Gozeri et al. 2008; Hassell et al. 2013; Waddell et al. 2012). Placental histology is abnormal in pregnancies subjected to an altered light schedule, with increased placental edema, fibrin accumulation, and leukocyte infiltration (Gozeri et al. 2008). Therefore, maternal treatment with melatonin in complicated pregnancy might reduce placental oxidative stress and inflammation, and improve placental blood flow and nutrient delivery to the fetus, thereby diminishing risk of intrauterine growth retardation (Hassell et al. 2013; Lemley et al. 2012). Second, there is known relationship between melatonin and glucocorticoid receptor pathway and between the circadian cortisol cycle and growth rate. Therefore, it is possible modulation of glucocorticoid receptor pathway by altered photoperiod could affect growth rate (De Leonibus et al. 2016). Third, melatonin plays a role in the regulation of growth hormone secretion and growth hormone responsiveness to growth hormone-releasing hormone through the same pathway as pyridostigmine (Valcavi et al. 1993). Melatonin was also observed to act via the melatonin MT2 receptor as a key regulator of cell proliferation, differentiation, and migration (Danilova et al. 2004). Moreover, there is evidence circadian disturbances by maternal pinealectomy during gestation leads to adverse programming outcomes in offspring, resulting in desynchronization of the rhythm of drinking behavior of offspring, an effect prevented by daily maternal melatonin replacement in late gestation (Bellavia et al. 2006).

Respiratory functions

Fetal breathing movements are detectable as early as 10 weeks of gestation in the human fetus. The fetal breathing pattern shows changes that are linked to time of day and maternal factors, such as blood glucose

levels. During the daytime, fetal breathing movements are not continuous, but rather exhibits diurnal variation, being lowest in the morning and highest during the evening and night (De Vries et al. 1987; Patrick et al. 1980, 1978). McMillen et al. (McMillen et al. 1990) demonstrated in their experiment that maternal pinealectomy alters the 24 h pattern of fetal breathing activity, suggesting it is dependent on the increase in fetal plasma melatonin concentrations that occurs immediately after the lights are switched off and is dependent on the presence of the maternal pineal gland (McMillen and Nowak 1989; McMillen et al. 1990; Yellon and Longo 1988). Maternal pinealectomy abolishes the nocturnal increase in fetal breathing, although it unmasks its increase in the morning (09:00–12:00 h) (Houghton et al. 1993; McMillen et al. 1990). Moreover, it has been reported that fetal breathing increases after maternal meals of breakfast, lunch, and dinner. Postprandial elevations in fetal breathing were associated with transient increases in maternal plasma glucose concentration (Boddy et al. 1974; Patrick et al. 1978).

Constant distending pressure from the production and retention of fetal lung fluid and inhalation and exhalation of amniotic fluid due to episodic cyclic fetal breathing play an important role in lung development during fetal life (Hooper and Harding 1995). Moreover, it is possible that these circadian episodes of breathing movements result in small phasic changes in pulmonary tissue stress that facilitate growth and maturation of epithelial cells. Animal studies have clearly shown abolition or impairment of fetal breathing movements is associated with impaired fetal lung growth, while an increase in fetal breathing movements, as a result of maternal inhalation of 8% CO2, results in acceleration in structural maturation of fetal lungs (Nagai et al. 1987). Moreover, fetal breathing-elicited alterations of doppler ultrasound flow waveforms for umbilical venous system, mitral and tricuspid valves, middle cerebral artery, and descending aorta, indicating breathing movements of the human fetus modulate cardiovascular function (Hecher et al. 1995). In conclusion, although the impact on fetal lung development of short-term alterations in fetal breathing frequency and amplitude is unknown, change in the circadian system of pregnant woman can alter not only fetal breathing movements but also eating and sleeping habits, and circadian rhythm of the HPA axis, resulting in decreased fetal circulating levels of corticosteroids, which could decelerate lung maturation.

Fetal neurodevelopment

Melatonin exerts several important roles during normal fetal development (Hassell et al. 2013). Melatonin crosses the placenta and blood brain barrier and constitutes the main source of the hormone in the fetal brain is of maternal origin (Okatani et al. 1998). Fetal and neonatal brain development undergoes significant growth spurt during the last trimester of pregnancy and early neonatal period. The fetus and the newborn spend most of their time (16–18 h/day) sleeping (rapid eye movement sleep, active sleep) (Mirmiran et al. 2003). Experimentally, even short interference with these active sleep periods during pregnancy and in the neonatal period results in delayed neurogenesis, neuronal apoptosis, reduced brain development, and abnormal long-term function (Hassell et al. 2013).

As already stated, fetal brain melatonin levels are highly dependent on maternal levels. However, the fetal brain also has the ability to produce melatonin from the second trimester onwards (Jimenez-Jorge et al. 2007). Fetal melatonin synthesis seems to be necessary for early postnatal brain development, a period during which oxidative stress is elevated.

During delivery the fetus is rapidly exposed to high levels of oxygen, resulting in high physiological levels of oxidative stress. One of the main functions of fetal and early neonatal melatonin is maintaining balance between production of the antioxidant melatonin and amount of free oxygen radicals (Galano et al. 2013). Besides its main antioxidant action, melatonin has several different cellular mechanisms. These include regulation of gene transcription involved in neuronal differentiation, promotion of neuronal differentiation, regulation of neuronal apoptosis, and modulation of neuro-inflammation (Voiculescu et al. 2014).

The main sources of abnormal brain development are disturbances during early fetal and neonatal life such as ones of prematurity and neonatal encephalopathy, mainly of hypoxic-ischemic origin. Several pre-clinical studies have shown that maintaining physiological melatonin levels is neuroprotective during these phases (Cardinali 2019). Additionally, melatonin has been shown to be neuroprotective in different small and large animal models following hypoxic-ischemic brain injury (Cardinali 2019). Therefore, postnatal melatonin administration may be a very promising neuroprotective treatment, due to its different modes of action. Ongoing clinical studies are examining the neuroprotective effects of melatonin in newborns with neonatal encephalopathy.

Circadian rhythm of labor and birth

Labor is a complex multifactorial process beginning with myometrial activation in late pregnancy, followed by stimulation leading to uterine contraction, and

subsequent delivery of the infant (Smith 2007). Both the onset of labor and birth in humans, as well as many animal species, show prominent 24 h patterning (Smolensky et al. 1972). Studies in animals including rats, monkeys, and baboons pointed to a natural selection which has favored mechanisms that couple the time of birth to the most appropriate phase of the daily cycle of light and darkness (Honnebier and Nathanielsz 1994). In humans, peak hours of onset of labor and of birth are between 23:00 and 06:00 h, regardless of gestational age (Lindow et al. 2000; Serín-Ferré et al. 1993). It is also well documented that deliveries during the day have the highest risk for operative intervention and are associated with a high rate of perinatal death (Paccaud et al. 1988). Moreover, women who give birth during the night hours have a shorter labor than women that give birth during the day or evening (Backe 1991).

The effect of melatonin on rat uterine smooth muscle is well known (Hertz-Eshel and Rahamimoff 1965). Furthermore, it is known that there is a nocturnal increase in uterine contractile activity which is similar to circadian rhythm of melatonin in the pregnant rhesus monkeys (Ducsay and Yellon 1991). However, melatonin has shown to inhibit spontaneous and oxytocin-induced contractions of rat myometrium in a dose-dependent manner (Abd-Allah et al. 2003; Ayar et al. 2001). In contrast to animal studies, the results of human investigations show the human myometrium is a target for melatonin and expresses both MT1 and MT2 receptors (Schlabritz-Loutsevitch et al. 2003; Sharkey and Olcese 2007). Martensonn et al. (Martensson et al. 1996) showed melatonin potentiates norepinephrine-induced contractility in a dose-dependent manner in human myometrial strips. Recently, Skarkey et al. (Sharkey et al. 2009) demonstrated myometria from nonlaboring term pregnant women generally have low levels of both oxytocin and melatonin receptor protein, whereas myometria from laboring term pregnant women have high levels. Moreover, co-treatment with physiological concentrations of melatonin increases both basal- and oxytocin-induced contractility of myometrial cells via MT2 receptors. The authors proposed melatonin plays an in human myometrial physiology during pregnancy (Sharkey et al. 2009). Our study demonstrating significant difference for melatonin concentration between elective cesarean section deliveries and emergency cesarean section deliveries after induced labor also suggested neuroendocrine synergy between melatonin and oxytocin is possible and that melatonin plays a key role on the onset of uterine contraction (Bagci et al. 2012).

Conclusion

Several lines of evidence support the importance of maintaining the normal environmental light-dark cycle for balance of maternal and fetal homeostasis during pregnancy. Dysregulation of homeostatic controls, e.g. by chronodisruption may lead to serious problems, not only for pregnant women and fetus during pregnancy but also offspring throughout development into adults. Therefore, it is important to provide, wherever possible, a regularly cycling circadian (quantity, spectrum, spatial, distribution, and duration) light exposure to reduce the risk for and effect of chronodisruption in pregnant women and in their fetuses during the quarantine process for COVID-19. The contents of this article have focused on the effects, including circadian disruption, of COVID-19 lockdown on pregnant women and their fetuses primarily from the perspective of altered melatonin synthesis and its 24 h rhythm. However, the effects of the COVID-19 lockdown on biological processes, including their circadian disruption, due to alteration of Vitamin D synthesis and other usual and normal 24 h environmental cycles that as biological time cues and can affect the normal course of pregnancy and fetal development, should not be ignored (Smolensky et al. 2015).

Disclosure statement

The authors have no conflicts of interest to disclose.

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