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Review

Melatonin and pregnancy in the human

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ABSTRACT

The purpose of this systematic review is to access the current state of knowledge concerning the role for melatonin in human pregnancy. Melatonin is a neuroendocrine hormone secreted nightly by pineal gland and regulates biological rhythms. The nighttime serum concentration of melatonin shows an incremental change toward the end of pregnancy. This small lipophilic indoleamine crosses the placenta freely without being altered. Maternal melatonin enters the fetal circulation with ease providing photoperiodic information to the fetus. Melatonin works in a variety of ways as a circadian rhythm modulator, endocrine modulator, immunomodulator, direct free radical scavenger and indirect antioxidant and cytoprotective agent in human pregnancy, and it appears to be essential for successful pregnancy. It also seems to be involved in correcting the pathophysiology of complications during pregnancy including those due to abortion, pre-eclampsia and fetal brain damage. The scientific evidence supporting a role for melatonin in human pregnancy is summarized.

Contents

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is a small lipophilic indoleamine generated primarily in pineal gland and secreted in a circadian manner with high levels occurring in all species at night. In mammals including the human, the melatonin rhythm is generated by an endogenous circadian clock in the suprachiasmatic nuclei (SCN) of the hypothalamus; via a multisynaptic pathway, efferent fibers in these nuclei direct sympathetic neural activity to the pineal gland thereby stimulating melatonin synthesis. The period of melatonin secretion is proportional to the duration of darkness, and it thus acts as a neuroendocrine transducer of photoperiodic information [1]. The initial precursor of melatonin biosynthesis is an amino acid, tryptophan. Pinealocytes take up tryptophan from the blood and convert it to serotonin through hydroxylation and decarboxylation; serotonin is then converted to *N*-acetyl-serotonin by the enzyme arylalkylamine *N*-acetyltransferase (NAT); *N*-acetyl-serotonin is methylated to form melatonin by the enzyme hydroxyindole-*O*-methyltransferase (HIOMT).

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Melatonin plays a key role in a variety of important physiological functions, including regulation of circadian rhythms, as well as visual, reproductive, cerebrovascular, neuroendocrine, and neuroimmunological actions [2]. Melatonin also has a critical role in the seasonal timing of reproductive activities in a number of mammalian species, including the sheep, mink, ferret, skunk, horse, hamster and feral mice [1,3]. When transferred from long photoperiod (14L:10D) to short photoperiod (8L:16D), female Syrian hamsters exhibit depressions in follicle stimulating hormone (FSH) and follicular development and they become anestrus [4]. Likewise, males transferred from long (16L:8D) to short photoperiod (8L:16D) causes testicular atrophy and a reduction in the associated hormones. Pinealectomy blocks the reproductive inhibitory effect of short photoperiod in both genders while exogenously administered melatonin retards testicular development in pinealectomized hamsters [5]. The duration of the daily melatonin signal conveys photoperiodic information which modulates reproductive activity. Circadian melatonin secretion has not been definitively established as having a role in human reproduction. However, herein we offer the hypothesis as to melatonin's involvement.

Some actions of melatonin are mediated via specific membrane receptors and nuclear binding sites; the latter correspond to orphan members of the nuclear receptor RZR/ROR superfamily [6]. Three subtypes of mammalian membrane melatonin receptors have been proposed, and three proteins have been cloned. Two of these receptors, MT1 and MT2, are members of the 7-transmembrane G protein-coupled receptor family [7–9]. The third receptor, MT3, is an enzyme identified as quinone reductase 2 which possesses, in some animals, features of a melatonin receptor [10]. Less is known of the nuclear melatonin-binding sites. The signal transduction system associated with the activation of MT1 or MT2 in target cells results in the inhibition of adenylate cyclase activity [9]. Activation of these receptors inhibits forskolin-induced cAMP formation with a subsequent reduction in activated protein kinase A [11]. This is a general rule in the biochemical pathways for MT1 and MT2 receptors; however, it is not the only signal transduction mechanism that they can trigger. Depending on the tissue, organ and species, melatonin can activate different second messenger cascades by interacting with the same receptor subtype. In the brain, the MT1 receptor is commonly found in the SCN, hippocampus, cerebellum and pars tuberalis of the pituitary [12]. The MT2 receptor is most strongly expressed in the retina, and at considerably lower levels in the SCN, hippocampus and cerebellum [13]. Melatonin receptor expression in peripheral human tissues is also well documented [9]. The mRNA and/or protein expression of melatonin receptors (MT1, MT2) has been identified in human reproductive tissues, including the breast epithelium [14], uterine myometrium [15], and ovarian granulosa and luteal cells [16,17].

The physiologic levels of melatonin in maternal circulation during pregnancy have been reported in sheep [18,19] and rats [20]. These reports noted that serum melatonin levels in maternal circulation exhibit a diurnal rhythm that provides an important signal for the fetus to entrain the light–dark rhythm of newborns after delivery. The changes in serum melatonin concentrations and their roles in pregnancy are not clearly understood in humans. The purpose of this review is to summarize recent developments in the field of melatonin research as they relate to the human reproduction, focusing on how melatonin influences human pregnancy.

2. Melatonin and human reproduction

While humans are generally considered to reproduce continually, virtually all human populations exhibit some seasonality in terms of birth, owing primarily to seasonal fluctuations in conception [21]. Seasonal variability in fertilization rates and embryo quality [22], and the sperm concentration and chromatin condensation in men show seasonal variation with peaks during late winter and early spring [23]. On the basis of the inverse correlation between seasonally high melatonin [24] and seasonally low ovarian activity in high latitude populations [25], it is often assumed that the changes in melatonin may be the cause of these alterations in seasonal fertility [26].

In women, an influence of melatonin on reproductive function can be inferred from the studies indicating high melatonin levels in both primary and secondary hypothalamic amenorrhea [27,28]; these findings generally support a casual relationship between high melatonin concentrations and hypothalamic–pituitary–gonadal hypofunction [29]. Normal melatonin rhythms are closely related to those of the reproductive hormones during infancy and they reciprocally correlated during puberty. The elevated melatonin levels during the prepubertal period may help to maintain the hypothalamic–pituitary–gonadal axis in a quiescence state; however, nighttime blood melatonin levels are reported to drop between Tanner stages 1 and 5 [30]. Pineal tumors, possibly depending on their cell of origin, may either promote or delay sexual development [31]. It has been assumed that the advancement of puberty which is associated with reduced melatonin levels is a consequence of a tumor that destroys the pineal gland, i.e., it effectively causes a pinealectomy. Conversely, delayed puberty may result from a tumor of pinealocyte origin and it secretes increased amounts of melatonin. While both these suggestions have been made, neither is proven. Both totally and partially blind patients have melatonin levels higher than sighted controls [32]. Consistently, blind boys had significantly lower basal and peak plasma luteinizing hormone (LH), FSH, and testosterone levels compared with those in the normally sighted boys [33].

In many species the pineal gland influences the hypothalamus–pituitary–gonadal axis by means of the secretory product, melatonin; in these species the indoleamine is involved in the regulation of gonadotropin and prolactin secretion in the response to environmental photoperiods [34,35]. The pulsatile secretion of gonadotropin-releasing hormone (GnRH), from a small number of neurons in the hypothalamus, controls LH and FSH secretion which, in turn, regulate the functional activity of the gonads [36,37]. Melatonin (10 nM) has been shown to down-regulate GnRH gene expression in a cyclical manner over a 24-h period in a cell line of GnRH-secreting neurons [38].

Melatonin has been shown to have a direct effect on the female reproductive tract, where it regulates sex steroid secretion in hamster [39] and human [16,40]. High levels of melatonin, which may undergo seasonal variations [41], are found in human preovulatory follicular fluid in concentrations which are almost threefold higher than serum levels [42,43]. We recently showed that melatonin reduces oxidative stress in ovarian follicles and protects oocytes from free radical damage [44,45].

3. Melatonin in maternal–fetal circulation

Prenatally, information about day length and circadian phase, presumably mediated by the maternal melatonin rhythm, is transferred to the fetus. Thus, photoperiodic information perceived by the mother plays a role in synchronizing fetal physiology [46]. When pregnant ewes were maintained in constant light from 133 to 138 days (term pregnancy is 146 days), the day–night difference in cellular Fos, a marker of cellular activity, immunoreactivity in the fetal SCN is abolished [47], suggesting that the diurnal activity of the fetal SCN is maintained by a signal related to the external lighting regime. A 24-h rhythm of plasma prolactin is present in the fetal sheep under a 14L:10D cycle in the late pregnancy, however, fetuses under constant light exhibit individual 24-h

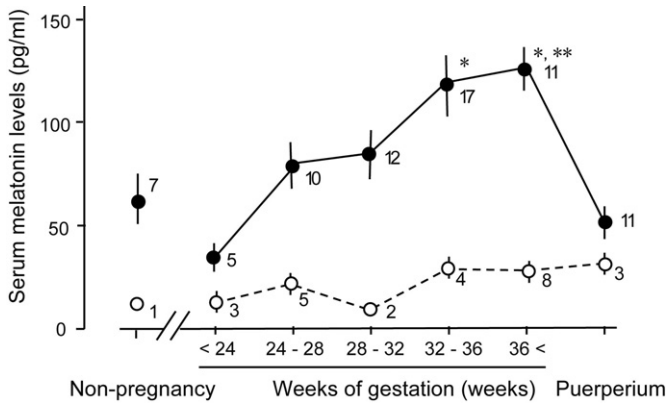

Fig. 1. Levels of maternal serum melatonin during the night (solid line) and day (dotted line) in normal singleton pregnancy. Values are means ± S.E.M. for the number of patients indicated beside each point. Daytime levels below the lower limit (5.6 pg/ml) of the assay were excluded from the analysis. *$P < 0.01$ compared with the non-pregnancy values, <24-week values, or puerperium values. **$P < 0.05$ compared with the 24–28-week value. From Nakamura et al. [53].

prolactin rhythms whose peaks and troughs are distributed around the clock [48]. In the late pregnant ewes (between 120 and 138 days) exposed to a normal regime of 12L:12D with lights off at 19:00 h, the incidence of fetal breathing movements were highest at 16:00–21:00 h with a minimum at 05:00–06:00 h. In contrast, animals maintained under an altered lighting regime of 12L:12D with lights off at 11:00 h, the incidence of fetal breathing movements was lowest at 19:00–20:00 h and reached a maximum at 11:00–12:00 h [49]. Moreover, pinealectomy of pregnant ewes changed the daily pattern of fetal breathing movements [50]; this evidence suggests that photoperiodic information, via maternal melatonin, provides the fetus with time of day information.

The circadian variations of melatonin in the maternal circulation during pregnancy have been reported in sheep [18,51] and rat [20]. In these species, the diurnal maternal rhythm serves as an important signal for the fetus to entrain the light–dark rhythms in the newborns after delivery. In the human, serum melatonin levels during pregnancy and labor are reportedly significantly higher than they are postpartum [52]. We previously measured daytime (14:00 h) and nighttime (02:00 h) serum melatonin concentrations in normal women during pregnancy [53]. The daytime serum melatonin levels showed an incremental change toward the end of pregnancy but the rise was not significant in normal singleton patients; however, nighttime serum melatonin levels were significantly higher than daytime values throughout pregnancy, gradually increasing after 24 weeks of gestation, and exhibiting significantly higher levels after 32 weeks of gestation. Thereafter, they declined to non-pregnant levels on the 2nd day of puerperium in normal singleton pregnancies (Fig. 1). These data are consistent with previous report that a clear diurnal rhythm in serum melatonin concentrations was found both in early and in late pregnancy, and serum melatonin levels during the third trimester of pregnancy were significantly higher than those during the first and the second trimester and those of non-pregnant control women [54].

We also recently measured maternal serum melatonin levels throughout pregnancy in normal pregnant (more than 10 conceptuses) rats and in 1-conceptus rats (the number of conceptuses had been experimentally reduced to one on day 7 of pregnancy) [55]. Maternal nighttime (00:00–01:00 h) melatonin levels increased toward day 21 of pregnancy and rapidly dropped to the non-pregnancy levels after parturition in rats with normal pregnancy. Although there was no significant difference in the daytime (12:00–13:00 h) melatonin levels in 10- and 1-conceptus animals, nighttime serum melatonin levels were significantly higher in normal pregnancy than those in 1-conceptus rats on day 21 of pregnancy. When the fetuses were removed by fetectomy (all fetuses but not the placentae) on day 12 of pregnancy, nighttime serum melatonin concentrations on day 21 of pregnancy were not lower than normal. To examine the effect of placental hormones on maternal melatonin production, a conditioned medium, which was produced by incubating placenta of day 20 of pregnancy with medium, was injected into the 1-conceptus dams from day 17 to day 20 of pregnancy. The conditioned medium significantly increased serum melatonin concentrations. To identified the source of circulating maternal melatonin, NAT mRNA expression was examined in the placenta and fetal pineal. NAT mRNA was negligible in the placenta and the pineal gland of the fetus compared with these parameters in the maternal pineal gland [55]. The implication of the finding is that maternal circulating melatonin is likely of maternal pineal gland origin which is increased via the action of a yet unidentified placental hormone (Fig. 2).

We also showed that nighttime melatonin levels were significantly higher in twin pregnancies after 28 weeks of gestation as compared to normal singleton pregnancies [53]. There was no significant difference between melatonin levels in the umbilical vein and artery at delivery, which were lower than melatonin levels in the maternal circulation. In sheep, plasma melatonin concentrations exhibit a 24-h rhythm as early as day 120 of gestation [51], while maternal pinealectomy reduces fetal plasma melatonin concentrations and abolishes the fetal melatonin rhythm [19]. These findings suggest that the major source of increased melatonin in both the maternal and fetal circulation during pregnancy is of maternal pineal origin. Interestingly, melatonin concentrations in human umbilical arteries are generally higher than those in the corresponding veins at normal vaginal delivery [53], indicating that the fetus may produce melatonin, but that the mechanism seems to be immature. A recent report presented data to show that fetal rat brain does synthesize melatonin [56]. Although the SCN and the pineal gland appear to mature in early fetal life [57], the neurological circuitry linking these structures is not complete [58]. Due to its ability to diffuse through the placenta, maternal melatonin readily passes to all fetal tissues [59]. After birth, the full-term neonate does not produce melatonin for 2–4 months, leading to a transient absence of melatonin [56,60].

Previous studies confirm a circadian rhythm in the level of melatonin in the umbilical circulation of term fetuses [61]. It has also been suggested that melatonin is transferred from the maternal to the fetal circulation, generating a day–night difference in the melatonin concentration in the umbilical circulation [62]. Okatani et al. [59] evaluated the maternal–fetal transfer of melatonin in humans by measuring the concentration of melatonin in the fetal circulation after its administration to near-term pregnant women. They showed that the oral administration of 3 mg of melatonin led to marked increases in the serum levels with maximum values being observed 2 h (21.84 ± 2.09 ng/ml) after drug administration; they also found that serum levels of melatonin in the umbilical vein were closely correlated with those in the maternal vein. These findings support the idea that, in humans, melatonin is transferred from the maternal to the fetal circulation both easily and rapidly.

4. Melatonin, fetal circadian rhythms and fetal development

The origins of circadian rhythm development are found during the fetal period [57]. A fetal biological clock responsive to maternal entraining signals is already oscillating by the last trimester of gestation in primates [63]. A clear day–night rhythm of fetal heart rate synchronized with maternal rest-activity, heart rate, cortisol,

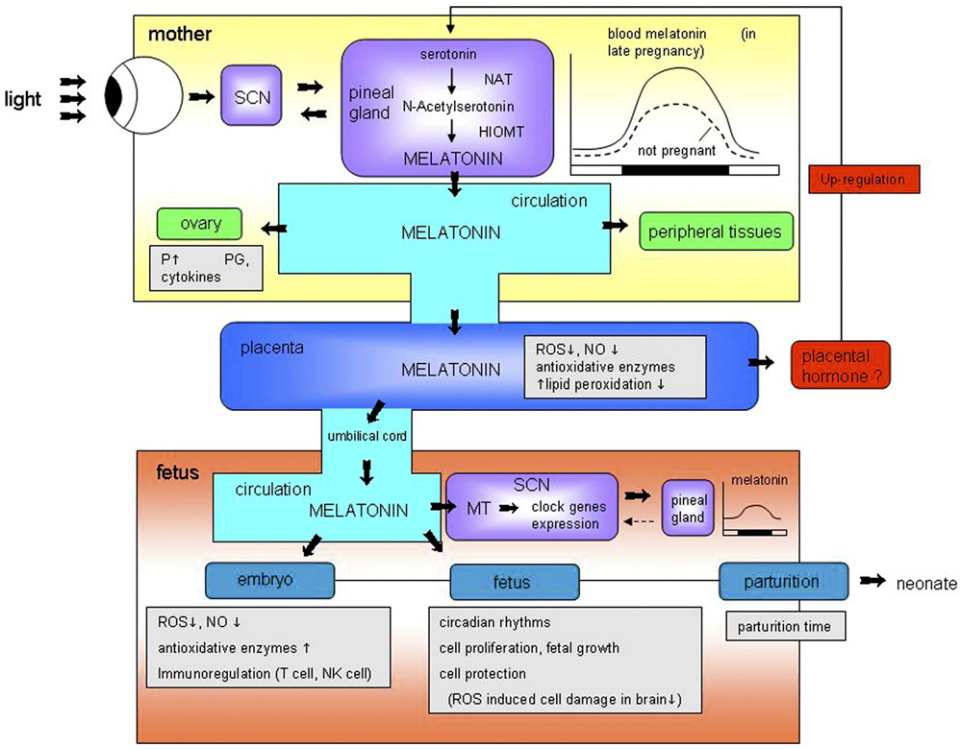

Fig. 2. Schematic representation of the proposed entrainment pathway and role of melatonin in maternal–placental–fetal system. Photoperiod information detected by the eyes of the mother is conveyed to the circadian pacemaker in the SCN. Neural signal from SCN is transferred to pineal gland to regulate the circadian rhythm of melatonin secretion. In the pinealocyte, serotonin is converted to melatonin by two enzyme, HIOMT and NAT. In pregnant women, a placental hormone seems to up-regulate the melatonin synthesis in the mother's pineal gland. Melatonin is secreted into mother's circulation and is available to peripheral tissues and the placenta. Melatonin easily crosses the placenta without being altered and enters the fetal circulation. Melatonin works in a variety of ways as a circadian rhythm modulator, endocrine modulator, immunomodulator, direct free radical scavenger and indirect antioxidant and cytoprotective agent at all levels in the mother–placenta–fetal system. SCN: suprachiasmatic nucleus; NAT: *N*-acetyltrasferase; HIOMT: hydroxyindole-*O*-methyltrasferase; P: progesterone; PG: prostaglandin; PRL: prolactin; ROS: reactive oxygen species; NO: nitric oxide; MT: melatonin receptor.

melatonin, and body temperature rhythms has been reported [64], and human fetuses exhibit circadian rhythms in hormones, behavior, heart rate, and sleep [65,66]. A 24-h rhythm in cord plasma cortisol concentrations at term has been documented with the peak, twofold over the nadir, occurring in the day between 12:00 and 14:00 h [67]. A 24-h rhythm of vasopressin is found in the CSF of sheep fetuses whose mothers were maintained in natural light/dark environment; maximal concentrations of vasopressin were observed in the daytime (14:00 h). However, this rhythm was disrupted when the mothers were placed in a continuous light environment in late gestation. Near term human fetuses have a peak in limb and body movements at nighttime between 21:00 and 01:00 h [68]. Since maternal adrenocorticotropic hormone (ACTH) does not cross the placenta [69] while the majority of maternal cortisol is metabolized and reaches the fetus in an inactive form [70], these molecules likely have little to do with stimulating circadian rhythms in the fetus.

An obvious candidate signal is melatonin, however, since it is one of the few maternal hormones that crosses the placenta without being altered. Maternal melatonin crosses the placenta freely and enters the fetal circulation with ease providing photoperiodic information to the fetus. Fetal plasma melatonin is very low after maternal pinealectomy, and the rhythm of fetal melatonin is absent in sheep during late gestation [19]. In sheep, maternal melatonin may be required for the rhythm in fetal breathing movements, as fetuses of pinealectomized ewes show no rhythm, whereas maternal infusion of melatonin which mimics the nighttime pattern of this hormone re-establishes the rhythm. In addition, maternal melatonin may entrain the fetal breathing movement rhythm, since shifting of the time of the melatonin infusion results in a shift of the fetal respiratory rhythm [71].

Melatonin receptors are present in the human fetal SCN [72,73] and in several areas of the fetal human brain [73,74]. Maternal pinealectomy increases melatonin receptors in the fetal and newborn SCN in rats [75]. Melatonin binds to SCN neurons by day 18 of gestation in the rat fetus [76] and the fetal SCN exhibit rhythms of metabolic and electric activity [77]. Melatonin infusion (0.01–10 nM, 10 min) significantly influences the basal rhythm in protein kinase C activity in rat SCN cells [78]. At the cellular level, circadian rhythms are driven by the self-regulatory interaction of a set of genes including brain and muscle ARNT-like protein 1 (Bmal-1), Period (Per1–3), Crytochrome (Cry1–2), and Clock, named clock genes, and their protein products (BMAL1, PER, CRY, CLOCK) [79]. The generation and maintenance of circadian clock function depends on clock genes and their protein products in autoregulatory transcriptional feedback loops, consisting of both positive and negative elements [80]. The positive arm of the clock depends on the protein products of the Clock and Bmal1 genes. Clock is expressed constitutively in the SCN, while Bmal-1 expression cycles with a circadian period. CLOCK and BMAL1 are basic helix–loop–helix factors that form heterodimers capable of activating the transcription of the Per1-3 and Cry1-2 genes [80,81]. In negative feedback, the cyclic translation of Per and Cry mRNA leads to cyclic levels of PER and CRY proteins. These proteins form complexes and accumulate in the nucleus where they inhibit expression of their genes by acting on CLOCK/BMAL1 heterodimers [81]. During murine development as early as at the embryonic day 19, all clock genes (Per-1, Per-2, Cry-1, Bmal-l, Clock) are expressed in SCN

of the fetal rat [82]. In the SCN and adrenal, the peaks of Bmal-1 and Per-2 expression are in antiphase, Bmal-1 peaking at the beginning of the night and Per-2 peaking about 10 h later, at the end of the night. When pregnant capuchin monkeys were maintained in constant light, the absence of maternal melatonin changed the expression of Bmal-1 and Per-2 in the fetal SCN. The expression of Bmal-1 was low at 08:00 h and increased at 14:00 h in contrast to the two low values observed in the SCN of fetuses whose mothers were maintained under normal lightning (14L:10D). Conversely, two low values were observed for Per-2 expression during this time interval, instead of the peak at 08:00 h and the low value at 14:00 h as observed in the SCN under normal lightning (14L:10D) [83]. The expression of melatonin receptor (MT1) in fetal capuchin SCN has been documented and it exhibits clock time changes [83]. Maternal melatonin suppression or its replacement had effects on expression of not only clock genes but also the MT1 gene [83], suggesting that maternal melatonin may modulate fetal clock gene function via MT1 in the fetal SCN.

During the last trimester of pregnancy and in the neonatal period, the human brain exhibits the most rapid development. Fetuses and newborns sleep 16–18 h/day and exhibit the rapid eye movement (REM) state during most of their sleep period [65]. Interruption of REM sleep in developing animals results in diminished brain growth since neuronal activation occurs mainly during this sleep period [84]. Mendelson and Bergmann [85] demonstrated that pinealectomy increases non-REM sleep in rats. In human, both REM and non-REM sleep are distinguishable after 30 weeks of gestation. [65]. Administration of 5 mg melatonin to healthy young men increases REM sleep [86]. Maternal melatonin may be a one of the factors that regulates the fetal REM and non-REM sleep cycle.

Maternal melatonin may be involved in a wider array of fetal functions given the presence of melatonin receptors in human peripheral tissues [87]. Several reports showed that fetal cell proliferation was under the control of a daily rise and fall of melatonin levels in human tissues. Proliferation in human epithelial cells is higher at night and lower during afternoon [88], and the proliferative activity of bone marrow cells, myeloid and erythroid cells exhibit a circadian rhythm [89]. Melatonin (50–100 μM) increases proliferation in human bone cells and osteoblastic cells [90]. The lack of a circadian melatonin rhythm suppresses neurogenesis in rats [91]. Torres-Farfan et al. [92] reported that maternal melatonin inhibits cortisol production in the primate fetal and newborn adrenal gland. Recent findings document that maternal melatonin stimulates the growth of the fetal adrenal gland in the capuchin monkey [93].

Gonadal growth of fetuses and newborns is influenced by photoperiodic information received in utero from the mother. The rhythm of maternal pineal melatonin secretion provides the fetus with information about daylength [94], and maternal melatonin has an essential role in prenatal gonadal growth in the hamster fetus [95] and postnatal reproductive development [96]. Male hamsters born to pinealectomized mothers that had received 10-h melatonin infusions exhibited faster testicular growth postnatally than did the males born to mothers that had been given 5-h melatonin infusions [94]. Also, male hamsters whose mothers had been exposed to 10 or 12 h of light daily during gestation showed more rapid testicular growth when raised postnatally in 14 h of light daily, as compared with males born to mothers exposed to 16 h of light each day during gestation and reared postnatally in a 14:10 light:dark cycle [97].

5. Melatonin and abortion

Spontaneous abortion, i.e., termination of pregnancy before 20 complete gestational weeks from the last menstrual period or a fetal weight of less than 500 g (World Health Organization, WHO), is estimated to occur in 15–20% of identified pregnancies; the frequency of spontaneous abortions increases with age from 15% in women younger than 25 years to 35% in women older than 38 years [98]. The causes of spontaneous abortion can be divided into two main categories: those arising from chromosomal anomalies and those arising from abnormalities in the intrauterine environment. Some studies implicate systemic and placental oxidative stress in the pathophysiology of abortion and recurrent pregnancy loss [99,100]. A deficiency in antioxidant defenses is associated with recurrent pregnancy loss [101]. Biochemical markers of reactive oxygen species (ROS)-induced membrane damage with lipid peroxidation products reach high levels immediately before abortion [102].

We propose that a deficient pineal melatonin production in early pregnancy may be causally related to the development of spontaneous abortions in cases where chromosomal anomalies or structural abnormalities of the uterus have been excluded. This hypothesis is based on the findings that: (a) melatonin is known as a powerful free-radical scavenger and antioxidant; (b) plasma melatonin levels normally increase during pregnancy; (c) pinealectomy increases the frequency of spontaneous abortions in pregnant rats; (d) melatonin has immunomodulatory effects; (e) melatonin stimulates the secretion of progesterone, which reduces uterine contractility and prevents immunological rejection of the trophoblast; and (f) melatonin inhibits the synthesis of prostaglandins, which are potent inducers of uterine contractility and labor.

Elevated generation of the superoxide free radical ($O_2^{\bullet -}$) by placental mitochondria [103] and polymorphonuclear leukocytes [104] from pregnant women in their first trimester of pregnancy has been reported. Moreover, it has been proposed that an oxidant/antioxidant imbalance is associated with pregnancy loss [105]. In normal pregnant women, melatonin levels increase with gestation [53,54], which would aid in reducing oxidative stress. Pinealectomy, which lowers circulating melatonin levels, leads to abortion in pregnant rats [106].

Melatonin works in a variety of ways to reduce the levels of oxidative stress. It is a powerful direct free radical scavenger [107]. It has been shown that melatonin has the capability of quenching reactive oxygen as well as reactive nitrogen species including the $O_2^{\bullet -}$, the hydroxyl radical ($^{\bullet}OH$), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), nitric oxide ($NO^{\bullet}$) and the peroxynitrite anion ($ONOO^-$) [108–111]. Not only is melatonin itself a direct free radical scavenger, but also metabolites that are formed during these interactions, i.e., cyclic 3-hydroxmelatonin, *N*1-acetyl-*N*2-formyl-5-methoxykynuramine (AFMK) and *N*1-acetyl-5-methoxykynuramine (AMK) are likewise excellent scavengers of reactive species [109,112–115]. Melatonin also stimulates a number of enzymes that are either involved in metabolizing potentially reactive species to harmless molecules or inducing the synthesis of other endogenously produced antioxidants. Thus, melatonin increases the activity of superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GRd) [116,117]. This is consistent with melatonin's ability to elevate antioxidant enzyme (SOD, GPx) gene expression [118]. Furthermore, melatonin stimulates the rate-limiting enzyme in glutathione production [119]; glutathione is an important intracellular antioxidant. Elevated levels of melatonin in pregnant women may have an essential role as an antioxidant to reduce oxidative stress which is a consequence of placenta metabolism and polymorphonuclear leukocytes.

Tolerance mechanisms are responsible for the survival of the fetus within the maternal uterus to prevent it from being attacked by the cells of the maternal immune system despite their direct contact. In recent years, the focus of this debate has moved away from the concept of specific immune rejection, or tolerance of the

genetically dissimilar fetus, toward a wider appreciation of how the maternal immune system recognizes and even nurtures the developing trophoblast. Pineal ablation, or any other experimental procedure that reduces melatonin synthesis and secretion, such as exposure to constant illumination or pineal denervation, depresses both cellular and humoral immunity which is counteracted partly by exogenous melatonin [120,121]. The immunostimulatory and antiapoptotic role of melatonin is exerted mainly through its action on T-helper lymphocytes (Th). However, it has become increasingly clear that melatonin also acts on T-lymphocyte precursors and affects both natural killer (NK) cell and monocyte function. The direct effect of melatonin on the human immune system is supported by the existence of specific melatonin-binding sites on lymphocytes [122], monocytes [123] and granulocytes [124].

Th1/Th2 cytokine balance with Th2 predominance has been seen as an important mechanism determining the survival of the fetus in the maternal uterus [125]. Physiologically, the melatonin rhythm correlates with rhythmicity in the Th1/Th2 ratio [126], and melatonin stimulates Th2 immune activity [127]. Recently, regulatory T cells (Treg) were claimed to be important players in the tolerance towards the fetus bearing alloantigens. CD4+/CD25+ regulatory T cells (Treg) are a unique subpopulation of T cells [128]. They were confirmed to play a major role in preventing autoimmunity and tolerating allogeneic organ grafts [129]. The acceptance of paternally derived tumor cells supports the involvement of systemic regulatory processes in pregnancy [130]. It has been reported that melatonin increases the number of Th (CD4+) lymphocytes [131] and T-lymphocyte proliferation [132]. However, the relation between melatonin and Treg production and function is obscure. Further studies will be necessary to clarify these relationships, clarifying that association could help in understanding the regulation of successful pregnancy.

NK cells are the predominant immune cells present in the endometrium in the luteal phase and in early pregnancy [133]. There are two types of natural killer cells currently recognized, defined by their expression of the surface antigen CD56. More than 90% of peripheral blood NK cells are $CD56^{dim}$. There have been numerous studies of peripheral blood natural killer cells in women with recurrent miscarriage [134–136]. Over 90% of uterine NK cells are $CD56^{bright}$ cells, which have low 'killing ability', do not lyse the trophoblast in vitro and produce numerous cytokines that promote trophoblast growth and proliferation [137]. It may be hypothesized that, rather than the numbers of NK cells present, the ratio of cytotoxic $CD56^{dim}$ cells to cytokine-producing $CD56^{bright}$ cells may be significant. Indeed, a flow cytometric study has shown that women with recurrent miscarriage have more $CD56^{dim}$ cells and fewer $CD56^{bright}$ cells [134]. As a potential regulator of the immune system, the influence of melatonin on NK cells is of particular interest. It has been reported that melatonin increases NK cell levels and NK cell activity [138]. However, it remains undetermined whether melatonin regulates the ratio of $CD56^{dim}$ cells to $CD56^{bright}$ cells; further studies will be necessary to answer this question.

Progesterone is essential for the maintenance of pregnancy in most animal species and humans. It is necessary to maintain progesterone production for successful pregnancy; this is achieved when the corpus luteum is rescued by pregnancy. The sources of progesterone and estradiol in the first trimester are the corpus luteum and the placenta. The shift of progesterone production from the corpus luteum to the placenta occurs around 8 or 9 weeks of gestation. The importance of the corpus luteum in early pregnancy has been clinically demonstrated by the fact that its removal before 7 or 8 weeks of gestation causes a reduction in serum progesterone leading to abortion [139]. There is evidence to suggest that melatonin acts at the level of the ovary to modify its function. In the human, melatonin-binding sites have been detected in granulosa-luteal cells [16,17], and melatonin can have a direct effect on ovarian steroidogenesis [40,140]. Melatonin directly stimulates the secretion of progesterone by human granulosa and/or luteal cells [16,140]. There are reports of increased melatonin levels in the luteal phase compared with the follicular phase of the menstrual cycle [141,142]. Recently, Dair et al. [143] documented the essential effects of melatonin on endometrial morphology and embryo implantation. They demonstrated that the implantation rates and serum progesterone levels were decreased in pinealectomized rats. Elevated melatonin in the luteal phase and early pregnancy may induce progesterone production by luteal cells which is necessary for successful pregnancy.

Much information exists relative to various biochemical and endocrine factors that impact progesterone production by luteal cells. Human chorionic gonadotropin (hCG)/LH, prolactin [144], cytokines [145], and growth factors [146], induce progesterone production while prostaglandin F-2α [147], oxytocin [148], cytokines [149] and reactive oxygen species [150] suppress progesterone production. Prostaglandin F-2α is of particular importance because of its potential autocrine/paracrine actions which induce corpus luteum regression. A relationship between melatonin and prostaglandins has been reported as well as an inhibitory effect of melatonin on prostaglandin F-2α production in ewes [151]. Melatonin also increases prolactin secretion [152] and inhibits oxytocin release [153], suggesting that melatonin is important in maintaining progesterone production and luteal function.

6. Melatonin and pre-eclampsia

Pre-eclampsia is a major disorder of human pregnancy. Pre-eclampsia is characterized by pregnancy-induced hypertension ($\geq$140 mm Hg systolic and/or $\geq$90 mm Hg diastolic blood pressure: BP) and the onset of proteinuria ($\geq$300 mg protein/day) occurring in the second half of pregnancy [154]. It has been estimated that 5–7% of pregnancies worldwide are complicated by this disorder resulting in a very large disease burden [155,156]. Potential fetal complications include low birth weight, prematurity and death. Maternal complications include renal failure, HELLP syndrome (hemolysis, elevated liver enzymes, and thrombocytopenia), liver failure, cerebral edema with seizures and rarely death.

The human placenta is classified as hemochorial, and the establishment of the maternal placental circulation is influenced by trophoblastic invasion. Extravillous trophoblastic invasion transforms the low-caliber, high-resistance spiral arteries into high-caliber, low-resistance, and high-capacity uteroplacental arteries. At 10–12 weeks gestation, changes in the placenta result in an oxidative burst. Abnormal placentation has been implicated in the pathogenesis of pre-eclampsia and miscarriage.

Pre-eclampsia is characterized as a state of elevated oxidative stress resulting from increased generation of free radicals and decreased levels of antioxidants, which normally scavenge free radicals. The rise in placental oxidative stress may be involved in the etiopathogenesis of pre-eclampsia. Pre-eclampsia has been proposed as a two-stage disorder. In the first stage, the placenta produces a cytotoxic factor. In the second stage, the maternal response to the placental factor occurs and includes the formation of highly toxic ROS. Abnormal placentation leads to placental ischemia [157]. The ischemia/reperfusion injury to the placenta exaggerates the generation of placental oxidative stress. Free radical generation and the resulting oxidative damage are believed to be involved in the pathophysiology of abortions and pre-eclampsia [158,159]. The generation of free radicals increases during pregnancy with the placental mitochondria being the major source of ROS production. The peroxidation of lipids by ROS results in primary lipid peroxidation products such as lipid hydroperoxides and secondary products such

as malondialdehyde and lipid peroxides. The lipid hydroperoxides that are formed bind to lipoproteins. These are then transported to distant sites where the hydroperoxides promote ongoing lipid peroxidation resulting in systemic oxidative stress.

The placenta is very likely the site of generation of the lipid peroxides [160]. Elevated generation of lipid peroxides has been reported in the placenta of pre-eclamptic women [161]. Compared with normotensive pregnant women, women with pre-eclampsia have significantly higher plasma levels of malondialdehyde [162,163]. Conversly, antioxidant levels in pre-eeclampsia are reported to be lower than normal. Decreased placental glutathione peroxidase and glutathione levels has been observed in pre-eclamptic women [162]. Significantly reduced whole blood glutathione levels [164], superoxide dismutase activity [163] and vitamins C and E levels [165,166] are likewise lower in women with pre-eclampsia.

We observed that the patients with severe pre-eclampsia showed significantly lower nighttime serum melatonin levels than in individuals with mild pre-eclampsia or normal pregnant women after 32 weeks of gestation (Fig. 3) [53]. Elevated generation of $O_2^{\bullet -}$ in pregnant women has been observed [103,104] and melatonin levels were increased progressively during gestation in normal pregnant women [53,54]; this rise in melatonin, due to its potent antioxidant properties, is likely to reduce oxidative damage from ROS in the placenta and systemic endothelial cells. Melatonin as well as its metabolites are potent direct free radical scavengers [114,115] and indirect antioxidants by virtue of their ability to modulate gene transcription for antioxidative enzymes [117].

The antioxidant properties of melatonin have been extensively studied and the use of this molecule as a cell protector and as a potential disease-preventing agent has been summarized [167–169]. Walters-Laporte et al. [170] demonstrated that melatonin inhibits in vitro low-density lipoprotein (LDL) peroxidation; furthermore, melatonin is cytoprotective against the toxicity of oxidized LDL in endothelial cells. In fact, oxidative damage (malondialdehyde concentrations) was increased in lung, uterus, brain, kidney and thymus of pregnant rats soon after delivery compared with levels of this oxidation product in non-pregnant rats, whereas pinealectomy 1 month before pregnancy enhanced the level of malondialdehyde in the uterus and lung [171]. Although the exact mechanisms of vascular endothelial damage in pre-eclampsia are unclear, increased lipid peroxidation may lead to endothelial cell dysfunction [172]. Compared with normotensive pregnant women, those with pre-eclampsia have reduced expression of endothelial mRNA and protein for endothelial nitric oxide synthase (eNOS). Reduced expression of constitutive NOS in the vascular system leads to lower production of NO. NOS inhibition causes increased endothelial permeability and an abnormal response of the endothelial cells to the stress challenge of pre-eclampsia [173]. Wakatsuki et al. [174] reported that melatonin protects against oxidized LDL-induced inhibition of NO production in the endothelium of human umbilical arteries; it therefore appears likely that melatonin may inhibit LDL oxidation and protect against oxidized LDL-induced impairment of endothelial function in pre-eclamptic women.

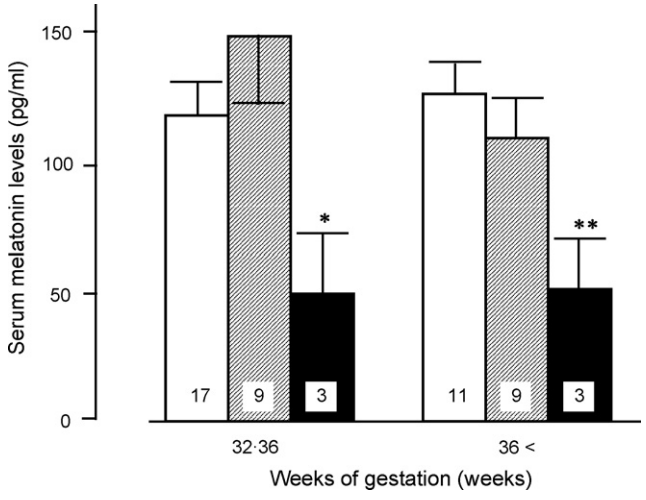

Fig. 3. Serum melatonin levels in normal pregnancy (clear column) or pregnancy with mild pre-eclampsia (hatched column) or severe pre-eclampsia (black column). Values are means ± S.E.M. for the number of patients indicated in each column. $^{*}P < 0.01$, $^{**}P < 0.05$ compared with mild pre-eclampsia. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with normal pregnancy. From Nakamura et al. [53].

Melatonin has been found to play a role in cardiovascular regulation. The nocturnal increase in melatonin exhibits an inverse temporal relationship with changes in cardiovascular activities [175]. It has been shown that surgical removal of the pineal gland elevates blood pressure (BP) in rats [176] while the administration of exogenous melatonin blocks the rise in BP in pinealectomized rats [177]. Accumulated data indicate that melatonin may play an important role also in controlling hypertension in humans since blood melatonin levels are significantly increased in hypertensive patients [178,179]. This rise in melatonin is believed to be a compensatory response to the elevated BP. Moreover, melatonin administration to healthy young women decreases systolic, diastolic and mean arterial pressure [180]. The anterior hypothalamic area may be one of the important central areas where melatonin exerts its modulatory effects on BP and heart rate [181]. An earlier study demonstrated a suppressive effect of melatonin on the sympathetic nervous system in rats [182], which is responsible for the nighttime rise in melatonin production. It has been documented that the circadian melatonin rhythm is lost in pregnant woman with pre-eclampsia; these women with an altered circadian melatonin fluctuation are at increased risk for pre-eclampsia [183].

During pregnancy, high maternal BP values are reported to adversely affect fetal growth and to be associated with an increased risk of intrauterine growth restriction [184]. BP exhibits a circadian periodic variation with lower values during the night and higher values during the day [185], and this rhythmicity is also present throughout pregnancy [186]. An altered circadian pattern has been reported in pregnancy-induced hypertension [187]. Nakamura et al. [53] reported that nighttime melatonin levels were significantly lower in pregnant women with pre-eclampsia than in normal pregnant women. Apparent decreases in maternal melatonin levels in pre-eclampsia suggest the involvement of melatonin in the pathogenesis of pre-eclampsia. There is precedence for melatonin decreasing BP [178].

Eclampsia includes the development of convulsions and/or unexplained coma during pregnancy or postpartum in patients who experienced signs and symptoms of pre-eclampsia. This serious complication in severe pre-eclampsia has an incidence of 1 in 2000 to 1 in 3448 pregnancies [188,189]. The pathogenesis of eclamptic convulsions continues to be the subject of extensive investigation and speculation. Some of the etiologic mechanisms that are suggested for the pathogenesis of eclamptic convulsions include cerebral vasoconstriction or vasospasm hypertensive encephalopathy. Light exposure is a well-known trigger for an eclamptic seizure. To prevent these seizures, it is not uncommon to keep these patients in a darkened ward. Melatonin is stimulated during darkness and is known to have anticonvulsant activity in humans [190], rats [191], and mice [192]. In mice, melatonin (25–100 mg/kg) dose dependently decreased the duration of tonic hind limb extension during electroshock [192]. The anticonvulsant effect of melatonin was blocked by luzindole, an MT1 receptor antagonist suggesting MT1 receptors may play an important role in

mediating the anticonvulsant activity of melatonin. Pinealectomy increased the number of chemically (pilocarpine)-induced seizures in rats, and melatonin treatment (four injections of 2.5 mg/kg melatonin before and after pilocarpin administration) partially inhibited the seizures [191]. In addition, six children (aged 2–15 years), with severe intractable seizures, were treated with 3 mg of oral melatonin 30 min before bedtime; melatonin was given in addition to their usual antiepileptic drug treatment for 3 months. Mean seizure rate decreased from 3.6 ± 3.9 to $1.5 \pm 1.8\,day^{-1}$ during the combinal treatment ($p < 0.05$) [190]. The implication is that decreased melatonin concentrations could be one of the triggers for an eclamptic seizure.

There is a recent report noting that antioxidants (vitamins C and E) effectively prevent pre-eclampsia in women at increased risk of the disease [193]. Thus, melatonin also could be useful as an antieclamptic drug in patients with pre-eclampsia. Melatonin administration to the pregnant women increases serum melatonin levels and it readily crosses the placenta. Melatonin also prevents the oxidative vascular endothelial impairment of systemic vessels and the placenta. Melatonin may well have important functions beyond the circadian signal it provides to the fetus. Reductions in maternal melatonin levels in severe pre-eclampsia suggest the involvement of this indoleamine in the pathogenesis of toxemia.

7. Melatonin and fetal hypoxia

Depressed fetal heart rate (FHR) variability following the onset of recurrent late or severe variable decelerations is accepted as the evidence of developing tissue hypoxia and acidosis; presently, the determination of umbilical arterial acid–base status provides the only widely accepted assessment of perinatal asphyxia [194]. Periventricular leukomalacia (PVL), the main substrate for cerebral palsy, is characterized by diffuse injury of deep cerebral white matter, accompanied in its most severe form by focal necrosis, and is associated with subsequent development of cerebral palsy and cognitive impairment [195]. The precise etiology of white matter damage remains unclear, but ischemia/reperfusion and generation of free radicals [196] and cytokine toxicity (especially given the epidemiologic association of PVL with maternofetal infection) [197] are believed to play an important role. Hypoxic attacks to tissues cause the formation of oxygen-derived free radicals, which have the capability of inducing a variety of pathologies including permanent neurological injury and multisystem organ failure [198,199].

Recently, determination of oxygen-free radical activity was confirmed in the evaluation of perinatal hypoxia. Wang et al. [200] demonstrated an association between lipid peroxide production and acid–base balance at delivery and suggested that oxidatively damage lipid measurements offered a more appropriate outcome measure as they reflect the extent of cell membrane damage and may be a more sensitive indicator of fetal stress than acid–base balance. Moreover, Rogers et al. [201] demonstrated cellular damage by free radical activity following hypoxia and reperfusion during labor, and supported the use of lipid peroxidation level as a marker of fetal hypoxia in preference to acid–base balance. Cells and tissues are normally protected against the breakdown of lipids by the antioxidant defense system; antioxidant enzymes of particular importance include SOD, catalase, GPx and glutathione-*S*-transferase. The levels of both lipid peroxidation products and antioxidant enzyme activities were significantly increased in the placenta and fetus in pregnancies complicated by non-reassuring FHR status during labor as a result of acute hypoxia. The elevations observed in antioxidative defense system were believed to be a compensatory response in an attempt to protect the fetus from damaging free radicals. Dede et al. [202] also demonstrated that malondialdehyde and SOD levels in placenta and umbilical cord blood were higher in patients with non-reassuring FHR status when compared with the normal FHR.

In adult animals, melatonin is neuroprotective in models of focal cerebral ischemia [203], and the pretreatment of melatonin (10 mg/kg intraperitoneal injection) reduces microglia activation in the hippocampus after kainic acid-induced inflammation in rats [204]. The glutamatergic analog ibotenate induces white matter cysts mimicking human PVL, melatonin (5 mg/kg injection) also attenuated ibotenate-induced white matter cysts in neonatal mice [205]. Septic newborns treated with melatonin (20 mg melatonin was given orally within the first 12 h after diagnosis) showed reduced serum malondialdehyde concentrations compared with the septic newborns without melatonin treatment [206]; treatment with melatonin (80 mg: 8 doses of 10 mg each separated by 2-h intervals) in asphyxiated newborns also reduces the levels of malondialdehyde and nitrite/nitrate in the blood [207]. Previous reports showed that melatonin is rapidly transferred from maternal to fetal circulation in pregnant women near term [59] and to fetal brain tissue in rats [208]. Maternally administered melatonin (10 mg/kg intraperitoneal injection) prevents oxidative lipid, DNA, and mitochondrial damage in the brain of mature [209] and premature fetal rats [210]. Recently, Welin et al. [211] demonstrated that post-asphyxial melatonin treatment (20 mg/kg infusion) attenuated the increase in activated microglia and 8-isoprostane (marker of lipid peroxidation) production and, at the same time, reduced the number of TUNEL-positive cells in the cerebral white matter in mid-gestation fetal sheep. Maternally administrated melatonin (1 mg bolus, then 1 mg/h for 2 h) reduces $^{\bullet}OH$ generation and lipid peroxidation in the fetal sheep brain in response to asphyxia following umbilical cord occlusion [212].

Homocysteine is an excitatory amino acid which markedly enhances the vulnerability of neuronal cells to excitotoxic and oxidative injury [213]. When hyperhomocysteinemia was induced in female rats by administration of methionine during pregnancy, increased malondialdehyde levels, DNA fragmentation and p53 mRNA expression were observed in the brain of the pups, while a significant reduction was seen in the neural levels of anti-apoptotic Bcl-2. However, melatonin administration (10 mg/(kg day) subcutaneously throughout pregnancy) prevented markers of lipid peroxidation and biochemical signs of apoptosis [214]. These protective actions of melatonin are likely due to its direct scavenger activity [107] and its indirect effects on antioxidative enzyme activities [116].

Okatani et al. [208] showed that melatonin given to the pregnant rat increases antioxidant enzyme activities in the fetal brain which, thereby, providing indirect protection against free radical injury. In this study, the administration of melatonin augmented the activities of SOD and GPx in near-term fetal rat brain. A recent report demonstrated that pretreatment with melatonin increases catalase activity in hypoxic rat brain tissue [215].

Many studies have shown that maternal administration of melatonin before hypoxia significantly decreases oxidative damage in the fetal brain. The choice of melatonin used alone or in combination with other antioxidants and conventional treatments may lead to the development of a new therapeutic approach for hypoxic fetal neural injury. Melatonin could become an important medication for preventing fetal brain damage for pregnant women whose fetus is in the non-reassuring fetal status.

8. Melatonin and parturition

Although the exact nature of the periodicity of human birth is debated, both seasonal and daily rhythmic patterns have been identified [216,217]. Birth after the spontaneous onset of labor has been reported to be more common in the morning or early after-

noon, suggesting that the onset of labor is more likely at night [216]. Although the mechanism determining parturition time is unclear, several reports have implicated the light:dark cycle (photoperiod) in the control of parturition in the human [218,219] and rats [220]. Rats typically give birth during the day-light hours [220], even if the light on/off time is artificially shifted [221]. Continuous darkness abolishes the photoperiodic timing of parturition [222], and light pulse can delay or advance the time of delivery of the young [223]. Thus, photopriod is likely to be an important factor in the control of parturition time.

The maternal pineal gland and its secretory product melatonin are essential components in the mechanism that transfers light/dark signals to the fetus. The daily duration of elevated melatonin in the maternal circulation has been hypothesized to convey day length information to the fetus in hamster [224]. Thus, melatonin is likely to be the photoperiod mediator regulating parturition time. Takayama et al. [225] observed that pinealectomized female rats, while showing no disturbances in estrous cyclicity nor in their ability to become pregnant, nonetheless failed to deliver their young exclusively during the daytime (the normal birthing phase); rather they gave birth across the 24 h light–dark cycle. Melatonin replacement was effective in restoring the daytime birth pattern when administered in the evening, but was ineffectual when given in the morning or when it was continuously available from a subcutaneous reservoir. This clearly demonstrates that the timing of birth in the rat is under circadian control, and that melatonin may serve as a key circadian signal for this event.

In the human, initiation of labor, defined clinically as a softened cervix and cervical dilatation, exhibits a 24-h distribution with a maximum between 24:00 and 05:00 h [226]. There are several reports which investigated the relation between parturition and melatonin in amniotic fluid or the maternal and fetal circulation [227,228]. These studies showed that melatonin levels in the amniotic fluid [229] or urine [230] of pregnant women increased around the period of delivery. The fetus also is thought to play an important role in determining parturition time. The precise duration of gestation in the human is disrupted in anencephaly, a malformation in which the fetal hypothalamus is severely abnormal [231]. Lesions of the fetal paraventricular nucleus and the fetal SCN prolong gestation in sheep [232]. It becomes evident that there is an important communication link between mother and fetus that may play a role in determining the time of the day at which delivery occurs. Changes in the circulating melatonin levels, which are synchronized with the light/dark cycle, are likely to be an important determinant of parturition time in pregnant women.

9. Concluding remarks

The vast amount of research on melatonin has led to great progress being made in understanding regulation of its synthesis and in characterizing its mechanisms of action. In pregnant women, a placental hormone seems to up-regulate melatonin synthesis in the maternal pineal gland. Elevated melatonin functions in a variety of ways as a circadian rhythm modulator, endocrine modulator, immunomodulator, direct free radical scavenger and indirect antioxidant and cytoprotective agent at all levels in the maternal–placental–fetal unit, and it appears to be essential for successful pregnancy. Altered patterns and/or reduced levels of melatonin secretion may be a cause of some pregnancy complications including those related to abortion, pre-eclampsia and neonatal neurological disability. Interruption of the daily dark period with light suppresses the production of endogenous melatonin and pregnant women who are often exposed to light at night or who have irregular activity cycles exhibit an increase incidence of pregnancy complications. These complications may be in part related to a relative melatonin deficiency in these individuals due to excessive light exposure.

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