Hum Reprod Update. 2014 Mar-Apr;20(2):293-307. doi: 10.1093/humupd/dmt054. Epub 2013 Oct 16.

Melatonin and stable circadian rhythms optimize maternal, placental and fetal physiology.

Reiter RJ[1], Tan DX, Korkmaz A, Rosales-Corral SA.

Author information

1 Department of Cellular and Structural Biology, University of Texas Health Science Center, San Antonio, TX, USA.

Abstract

BACKGROUND: Research within the last decade has shown melatonin to have previously-unsuspected beneficial actions on the peripheral reproductive organs. Likewise, numerous investigations have documented that stable circadian rhythms are also helpful in maintaining reproductive health. The relationship of melatonin and circadian rhythmicity to maternal and fetal health is summarized in this review.

METHODS: Databases were searched for the related published English literature up to 15 May 2013. The search terms used in various combinations included melatonin, circadian rhythms, biological clock, suprachiasmatic nucleus, ovary, pregnancy, uterus, placenta, fetus, pre-eclampsia, intrauterine growth restriction, ischemia-reperfusion, chronodisruption, antioxidants, oxidative stress and free radicals. The results of the studies uncovered are summarized herein.

RESULTS: Both melatonin and circadian rhythms impact reproduction, especially during pregnancy. Melatonin is a multifaceted molecule with direct free radical scavenging and indirect antioxidant activities. Melatonin is produced in both the ovary and in the placenta where it protects against molecular mutilation and cellular dysfunction arising from oxidative/nitrosative stress. The placenta, in particular, is often a site of excessive free radical generation due to less than optimal adhesion to the uterine wall, which leads to either persistent hypoxia or intermittent hypoxia and reoxygenation, processes that cause massive free radical generation and organ dysfunction. This may contribute to pre-eclampsia and other disorders which often complicate pregnancy. Melatonin has ameliorated free radical damage to the placenta and to the fetus in experiments using non-human mammals. Likewise, the maintenance of a regular maternal light/dark and sleep/wake cycle is important to stabilize circadian rhythms generated by the maternal central circadian pacemaker, the suprachiasmatic nuclei. Optimal circadian rhythmicity in the mother is important since her circadian clock, either directly or indirectly via the melatonin rhythm, programs the developing master oscillator of the fetus. Experimental studies have shown that disturbed maternal circadian rhythms, referred to as chronodisruption, and perturbed melatonin cycles have negative consequences for the maturing fetal oscillators, which may lead to psychological and behavioral problems in the newborn. To optimize regular circadian rhythms and prevent disturbances of the melatonin cycle during pregnancy, shift work and bright light exposure at night should be avoided, especially during the last trimester of pregnancy. Finally, melatonin synergizes with oxytocin to promote delivery of the fetus. Since blood melatonin levels are normally highest during the dark period, the propensity of childbirth to occur at night may relate to the high levels of melatonin at this time which work in concert with oxytocin to enhance the strength of uterine contractions.

CONCLUSIONS: A number of conclusions naturally evolve from the data summarized in this review: (i) melatonin, of both pineal and placental origin, has essential functions in fetal maturation and placenta/uterine homeostasis; (ii) circadian clock genes, which are components of all cells including those in the peripheral reproductive organs, have important roles in reproductive and organismal (fetal and maternal) physiology; (iii) due to the potent antioxidant actions of melatonin, coupled with its virtual absence of toxicity, this indoleamine may have utility in the treatment of pre-eclampsia, intrauterine growth restriction, placental and fetal ischemia/reperfusion, etc. (iv) the propensity for parturition to occur at night may relate to the synergism between the nocturnal increase in melatonin and oxytocin.

KEYWORDS: circadian rhythms; fetus; melatonin; placenta; pre-eclampsia

PMID: 24132226 DOI: 10.1093/humupd/dmt054

[Indexed for MEDLINE]