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Original Research Paper

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# MELATONIN AND HUMAN FERTILITY

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**ABSTRACT** Several reports are available showing a positive relation between bright sunlight and human reproduction to support the hypothesis put forward by Partonen (1999) that exposure to bright light may help to improve infertility in some cases.

**KEYWORDS :**

## INTRODUCTION

Melatonin, is a pineal gland secretion, hormone, and bio active amine with cellular targets (Olcese 2020). Melatonin or 5 methoxy-N-acetyltryptamine was discovered and isolated from bovine pineal in 1958 by Aaron Lerner. Melatonin is the main hormone secreted by the pineal gland(Hall, Hall 2021). Melatonin may be influencing male reproductive functions by the release of hypothalamic gonadotropin-releasing hormone and pituitary luteinizing hormone (Bhattacharya et al. 2019).whose physiological concentrations are regulated by circadian rhythms (Bhattacharya et al. 2019). Melatonin synthesis and secretion is enhanced by darkness and inhibited by light. Information is transmitted from the retina to pineal gland through the suprachiasmatic nucleus (SCN) of the hypothalamus. In humans, its secretion starts soon after sundown reaches a peak in the middle of the night (between 11 and 7 in the morning). Melatonin reaches every cell of the body, conveying circadian information (Via Plasma melatonin rhythms) Which then acts on specific G- protein-coupled melatonin receptors in target tissues of both adults and the fetus(Cecone et al. 2018).Melatonin regulates human reproductive cycles.

Partonen(1999) hypothesized that exposure to bright light could help to improve infertility in some cases. He has highlighted the role of melatonin. The secretion of melatonin from pineal gland is coined with light, maintaining maximum level in blood during dark. Also, to note is that neither spermatozoa nor ova in action are exposed to light(Hall, Hall 2021). Oproiu (1968) opined that the length of exposure to sunlight prior to menarche has a role in its achievement. Lack of light perception in blind girls lead them to earlier menarche (Zacharias, Wartman 1969; Skandhan et al. 2018) to an extent that girls with minimal or no light perception attained it earlier when compared to girls with shadow vision or guiding sight (Magee et al. 1970). All these reports summarily rejected the hypothesis of Jeffery et al. (1970,1971) that more length of exposure to light including artificial ones accelerate menarcheal age as seen among urban girls (Muller, Sturma 1970 ). Our study did not observe any difference in menarcheal age among girls of urban and rural areas (Skandhan et al. 1981). Permanent wearing of dark sunglasses (Arbat 1969) or working in night caused disturbance in menstrual cycle (Miyuchi et al. 1992).

Melatonin scavenge free radicals, in testes which may be important for testicular functions (Bhattacharya et al. 2019).Melatonin, act on micro-tubules (Bornman et al. 1989).

Spermatozoan has specific receptors for different hormones present in seminal plasma. Some of them increase sperm motility. Presence of melatonin in human semen is shown by (Partonen 1999).

It is also not known whether blood melatonin or seminal plasma melatonin, (if present) promotes uterine contraction to increase sperm transport. Similarly it is not known whether melatonin is released into uterine fluid to increase sperm motility. It is appropriate to refer to the pioneer study of Tredway (1976) that vanguard spermatozoa require less than fifteen minutes to reach destination by covering a distance of almost 19cms.

Melatonin levels in serum and seminal plasma in all infertile groups were significantly less when compared to that of fertile group. Fernando (2014) reported melatonin supplementation in IVF leading to better pregnancy rates. This indicates melatonin is important for sperm motility. Partonen (1999) pointed out that no data as available on the effect of light on sperm motility. We observed that visible light deteriorated the spermatozoa in their percentage and quality of motility when compared to sperms in dark which were superior (Veena et al. 2012).

Yilmaz (2000) opined that melatonin may be inhibiting testosterone secretion by acting at hypothalamo-pituitary axis which may be the functional relationship and feedback regulation between the pineal gland and the testes.

However long-term melatonin administration decreased semen quality in a number of healthy men, may be through the inhibition of aromatase at the testicular level (Luboshitzky et al. 2002).

Study of Awad et al. (2006) conducted elaborate study to understand the role of melatonin in male fertility. They observed significant correlation between melatonin and sperm motility. They also reported low level of melatonin in semen of infertile men. Melatonin present in serum and semen showed significant correlation with sperm motility. Study of (Muneyyirci-Delale,2000) is concluded that melatonin plays a role in increasing sperm quality. Starr (2011) Reported that long-term melatonin administration is associated with decreased semen quality probably through the inhibition of

aromatase at the testicular level. Experiments with boar spermatozoa showed melatonin affected sperm motility and the stability of nucleo protein structure which helps to bind the oozyte (Rocco et al. 2018).

Throughout natural development and sexual act, spermatozoa do not experience a ray of light as they develop in dark and closed male system, and travel in dark-to-dark closed female system to achieve the goal. We studied large number of good quality semen samples under illumination and compared to its motility in dark. Interestingly a greater number of sperms (%) survived in longer time in dark. Its activity was found to be better in dark in terms of types of motility- excellent, good or sluggish (Veena et al. 2012).

Melatonin is known to interact with many cellular proteins including enzymes (Liu et al. 2019). It has long been suggested that melatonin regulates human reproductive cycles. Very high doses of melatonin can be damaging, but in the right amount it may be able to combat various diseases and increase the chances for fertility in women (Starr 2011).

Brezezinski et al. (1987) demonstrated presence of melatonin in human pre ovulatory follicular fluid which was higher than plasma level.

It is now well-established that the prime signal from the maternal circulation to fetus is melatonin (Vilches et al.2014).The therapeutic use of melatonin in woman with PCOS-related condition shows promise.

For more than a half century the hormone melatonin has been associated with vertebrate reproduction, particularly in the context of seasonal breeding (Olcese 2020).

Indeed, melatonin has been reported to interact with a great many cellular proteins, including enzymes, channels, transporters, signaling molecules, etc (Liu et al. 2019). Thus, melatonin is perhaps best defined as both a pineal hormone and a bio active amine with cellular targets near its site of synthesis in some tissues.

Especially in the area of reproductive biology, it is clear that the physiology of animal models is often not comparable to the human state, most especially with regards to ovulatory cycles and the regulation of pregnancy(Mitchell, Taggart 2009).

Conflicting reports appeared in the later quarter of the twentieth century regarding human puberty and its regulation by melatonin. Reports of higher (Waldhauser et al. 1984) or lower (Puig-Domingo et al. 1992) plasma melatonin levels (Waldhauser et al. 1984) or associating with prepubertal and delayed pubertal conditions are reported. Brzezinski et al.(1987) observed melatonin level was higher in human pre ovulatory follicular fluid in comparison to plasma melatonin levels. This was subsequently confirmed and later showed to vary inversely with day length and concomitantly with follicular progesterone (P4) levels (Roennberg et al. 1990; Yie et al. 1995), suggested preferential uptake of circulating melatonin by the ovary. Increased oral doses of melatonin among women volunteers (Tamura et al. 2014) elevated melatonin concentrations in their follicular fluid.

These results have motivated a number of studies into the potential benefit of pharmacological melatonin supplementation in the treatment of infertility (Fernando, Rombauts 2014)

A potential benefit of melatonin in the process of oogenesis is known. In this regard, the high levels of melatonin required for effects consistent high follicular fluid concentrations of melatonin. Some investigators have also proposed that follicular granulosa cells have the capability for local melatonin synthesis (Tamura et al. 2009; Simonneaux, Bahougne 2017), which if confirmed would add new insight into melatonin's role as a paracrine modulator in the reproductive system of humans.

It is now relatively agreed that a prime signal from the maternal circulation to fetus is melatonin (Vilches et al. 2014), which crosses the placenta (Schenker et al. 1998) and bind to melatonin receptors in numerous fetal tissues (Williams et al. 1991).

Proven role of melatonin as an endocrine signal of night time duration was shown (Dubocovich et al. 2010; Arendt 2005). Thus it has an influence on the timing of parturition.

The precise mode of action of melatonin in the mammalian uterus, while still not completely understood, is clearly species-specific.

A similar reduction of PCOS-Related hirsutism and androgen levels after 12 weeks of melatonin supplementation was also found in a recent investigation by Jamilian et al. (2019). Thus, the therapeutic use of melatonin in women with PCOS-Related conditions shows promise.

A relationship between declining endogenous melatonin levels and human menopause is not known.

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