The Relationship of Melatonin to the Physiological Parameters of Pregnant Women During Period Pregnancy

Hanaa Dakheel Mezaala[1], Kh. G. Al-Fartosib[2], Mehdi El Arbi[3]

[1]*General Directorate of Education in Thi-Qar, Thi- Qar, Iraq*
[2]*Marshes Researches Center, University of Thi- Qar, Thi-Qar, Iraq*
[3]*Institut Supérieur de Biotechnologie de Sfax, Université de Sfax, Tunis, Tunisia*
Email: hanaadekheel78@gmail.com

Abstract: In recent times, there has been an explosive expansion in the comprehension of the hormone melatonin, particularly regarding its role in physiology, regulation, and therapeutic applications within various realms of clinical medicine. Melatonin serves as a vital biological agent capable of modulating mitochondrial performance, showcasing anti-inflammatory,antioxidant, and neuroprotective properties, promoting restful slumber, and bolstering the immune system. Moreover, it boasts bioavailability and minimal toxicity, positioning it as a promising candidate for the safe and effective treatment of an array of ailments while safeguarding human well-being. Within this manuscript, we endeavored to explore the significance of melatonin during the nascent stages of human existence, encompassing pregnancy, fetal development, and the newborn phase, through a thorough evaluation of contemporary literature.

Keywords: Melatonin, physiological parameters, pregnant women.

1. Introduction

Melatonin (N-acetyl-5-methoxy-tryptamine) is a mystical indole amine that the human body conjures from a myriad of origins. Its grand unveiling mainly takes place within the enchanted pineal gland, responding to the gentle embrace of darkness. This marvelous hormone is also crafted by a host of other organs, including the skin, bone marrow, lymphocytes, retina, and the wondrous gastrointestinal tract (Talib, 2018). Remarkably, the gastrointestinal tract (GIT) harbors an astonishing abundance of melatonin, boasting hundreds of times more than its pineal counterpart [S. R. Pandi-Perumal et al., 2006, R. Hardeland and B. Poeggeler, 2008]..,
Furthermore, melatonin serves not merely as a hormone produced by the pineal gland, but also as a cellular influencer and a hormone derived from leukocytes, exhibiting both paracrine and autocrine functionalities (D. X. Tan etal., 2003). Additionally, melatonin showcases remarkable antioxidant capabilities at elevated concentrations, functioning as a direct scavenger of radicals (D.-X. Tan 1993).
The identification of a target for melatonin's influence at this level appears to be quite compelling, supported by two elements: the accumulation within mitochondria and various findings regarding the intramitochondrial build-up of melatonin (A. López, 2009) M. Messner et al. [1998].
1-1 Effects of Melatonin
Melatonin, first discovered in bovine pineal gland [1], is primarily synthesized by pinealocytes using tryptophan as a biochemical precursor [2]. Though primarily known for its production by the pineal gland, melatonin is also synthetized in many other tissues, including, the retina, skin, digestive tract and bone marrow [3].

Melatonin undergoes metabolism predominantly within the liver and the kidneys, with 6-sulfatoxymelatonin being its primary urinary metabolite [4]..
Melatonin executes its physiological functions primarily through its interaction with melatonin receptor-1 (MT1) and melatonin receptor-2 (MT2), which belong to the large family of G-protein-linked receptors that are distributed throughout the various organs and systems of the body [5]. Although there is currently much debate about a putative nuclear receptor for melatonin being retinoid acid receptor (ROR) [6], the current evidence is still obscured in uncertainty [7].
Moreover, melatonin exhibits distinct non-receptor-dependent mechanisms of action, including the activation of protective cellular signaling cascades and its universal role as an antioxidant through its metabolites [4].
The physiological functions of melatonin are diverse and intricate, involving the fine-tuning of circadian rhythms, the regulation of blood pressure and autonomic cardiovascular activities, the modulation of the immune system, the oversight of energy expenditure and body weight, along with essential contributions to normal pregnancy and fetal growth [3,8,9].
The core processes that elucidate the antioxidant properties of melatonin encompass the capture of reactive oxygen species/reactive nitrogen species (ROS/RNS), the enhancement of the production of antioxidant enzymes (such as superoxide dismutase (SOD) and glutathione reductase), along with the heightened availability of nitric oxide (NO).

1.2. Melatonin in Pregnancy and Fetal Development

Melatonin plays an essential role in the complex regulation of reproductive functions, including ovulation, fertilization, embryo implantation, and guiding gestation processes [10]. In pregnant individuals, nocturnal plasma melatonin levels rise far higher than in the non-pregnant state, peaking at term and then gracefully returning to norm physiological ranges postpartum [10]. Melatonin from a maternal source easily crosses the placenta to provide signals of the day length as the fetus develops [11]. In addition to its genesis in the pineal gland, the placenta also exhibits impressive production of melatonin that occurs in a manner that is not clearly tied to circadian rhythms [12] This placental melatonin axis is a critical component in the neutralization of free radicals, and therefore alleviating oxidative stress during problematic pregnancies [13].

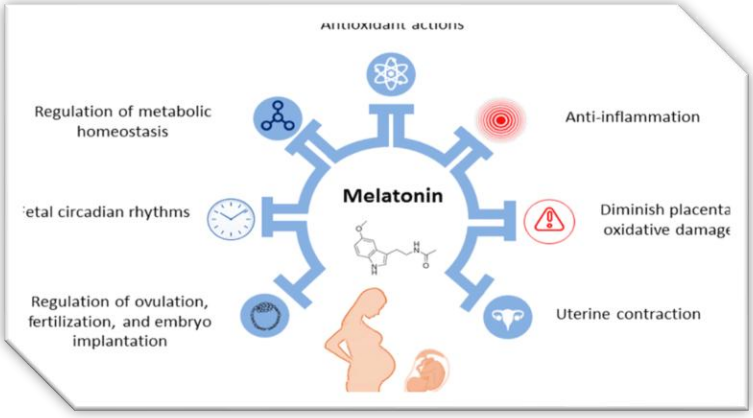


Figure 1. Role of melatonin in pregnancy.

1.3 Siruture and synthesis of melatonin

Melatonin was first extracted in 1958 by the skin specialist Aaron Lerner from the pineal gland of cattle (Fig. 1). Although its main production takes place in the pineal gland, there are various secondary sources like the retina, digestive system, skin tissue, blood platelets, and bone marrow, along with possibly other bodily structures; yet, their overall contribution to the system is minimal (Claustrat, B, et al. 2015).

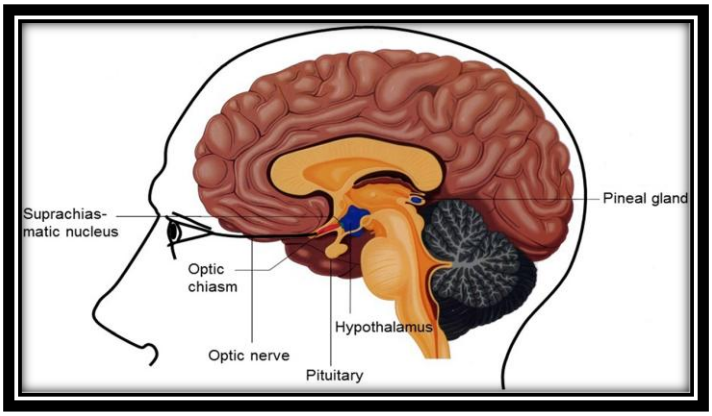


Fig. 2 A side view showing the brain's elaborate structure. This image of the brain in a sagittal view with suprachiasmatic nucleus, optic chiasm, optic nerve, hypothalamus, pituitary gland, pineal gland.

Melatonin synthesis within the mammalian pineal gland is tightly regulated by the master clock located in the hypothalamic suprachiasmatic nucleus (SCN), which is entrained by the light/dark cycle through retinal intrinsic photosensitive ganglion cells. These extraordinary cells send their axons to the SCN table, forwarding important environmental photoperiodic information, guaranteeing that melatonin production occurs only in the darkness of the night (Canteras NS., 2011). also important to know that melatonin production is inhibited by light exposure during the night (the retinal melanopsinergic system and a complex of neurons [Bartol I, et al.,1997; Klein DC, Weller JL1972] ultimately leading to reduced sympathetic outcomes negatively impact melatonin production in the pineal). In humans, this photoinhibition is predominantly influenced by blue light (460 to 480 nm) and at intensities beginning from <200 lux (60 to 130 lux) (AkiyamaT, et al., 2017). These pivotal aspects (entrainment of the light/dark cycle and nocturnal photoinhibition) contribute to the role ascribed to melatonin as a temporal signaling molecule that regulates the synchronization of the organism's internal circadian physiology with the geophysical changes in the external environment occurring between the daily and seasonal cycles of light and dark, as discussed in this narrative (see "Chronobiotic effects" and "Seasonal effects").

The enigmatic building block employed in the enchanting creation of melatonin within the human body is none other than tryptophan (Figure 3) (Salehi, B, et al., 2019), which holds the prestigious title of an essential amino acid.

The mesmerizing orchestration of biochemical reactions by tryptophan hydroxylase (TPH) and aromatic L-amino acid decarboxylase (AADC) propels the metamorphosis of tryptophan into the captivating neurotransmitter serotonin. In the following intricate biochemical dance, serotonin is transformed into melatonin through the deft catalytic prowess of arylalkylamine N-acetyltransferase (AANAT) and hydroxyindole-O-methyltransferase (HIOMT) (Figure 2) (Hardeland R et al., 2006).

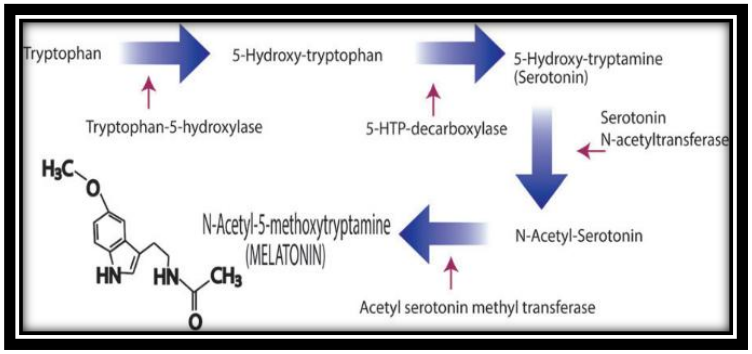


Figure 3. Melatonin biosynthesis in humans

The initial physiological event leading to melatonin synthesis is induced by highly sensitive ocular photoreceptors, which stimulate the production of melanopsin within a specific subset of photosensitive retinal ganglion cells (Gooley JJ, Lu J, et al., 2003). This process subsequently transmits signals to the pineal gland, regulating the release of melatonin, which is synthesized from serotonin, either through stimulation or inhibition (Cahill GM, 1991). Physiological concentrations of melatonin fluctuate between 5 to 200 pg/mL, contingent upon the diurnal cycle (Hickie IB, Rogers NL, 2011).

In human subjects, exposure to blue wavelength light (480 nm) perceived by melanopsin induces suppression of noradrenergic stimulation of serotonin N-acetyltransferase (SNAT) phosphorylation.

This culminates in the disruption and subsequent breakdown of the enzyme, which, in tandem with melatonin's fleeting presence in the circulatory system,, through nocturnal secretion of an increased amount of melatonin and scarce secretion by day. In diurnal species, melatonin increases at night promotes sleep, lowers core body temperature, reduces blood pressure, reduces glucose tolerance, and increases insulin resistance; while in nocturnal species, enhanced melatonin levels during the evening seem to have the opposite impact, producing greater activity levels by night (Cipolla-Neto J & Amaral FGD, 2018; Zisapel N, 2018).

The Therapeutic Wonders of Melatonin in Endometriosis

Endometriosis (EMS) is a persistent inflammatory condition influenced by estrogen, characterized by the atypical proliferation of endometrial tissue beyond the confines of the uterine cavity, often affecting the ovaries, various pelvic regions, or the peritoneal lining; it is believed that EMS primarily arises from the phenomenon of retrograde menstruation [14].

From a multifaceted vantage point, transcending the traditional manifestations of pelvic discomfort, EMS has been linked to diminished life satisfaction, decreased workplace efficiency, and a myriad of clinical disruptions that may lead to emotional upheaval, metabolic shifts, anxiety, inflammation, cardiovascular ailments, and an escalated risk of cancer [Nnoaham, K.E.; Hummelshoj, L.; Webster, P.; d'Hooghe, T, 2019].EMS is multi-factorial in nature, owing to genetic and environmental factors; however, its etiology is to be established further. Vigorous debates continue to swirl around the influence of endocrine-disrupting substances, regurgitated endometrial fragments, Mullerian vestiges, stem cells sourced from bone marrow, and the dual pathways of hematogenous and lymphatic dissemination in the development of EMS [Burney, R.O.; Giudice, L.C.,2019].

There is also a complex cancer signaling pathway, promoting inflammatory response, rising estrogen production, in EMS patients along with its receptor, ERβ, also one that correlates with elevated levels of cytokines, prostaglandins and metalloproteinases (MMPs) in the eutopic endometrium of EMS patients [Bulun, S.E.; Yilmaz, B.D.; Sison, C.; Miyazaki, K.; Bernardi, L.; Liu, S.,2019].

Many therapeutic measures (such as gonadotropin-releasing hormone antagonists and cyclooxygenase inhibitors) that suppress ovulatory menstruation and reduce estrogen formation are used along with the surgical excision of lesions to reduce pelvic pain [17]; yet, the complex disorder etiology remains a puzzle at a pathological level.

Disruption of circadian rhythms has also been shown to alter melatonin levels and are considered a risk factor for developing EMS [Marino, J.L.; Holt, V.L.; Chen, C., 2008].

Thus, a normal, functioning melatonergic pathway would be incapable of functioning in someone who suffers from EMS. In contrast, endometrial biopsies from women who had endometriomas (n = 20) or peritoneal lesions (n = 11) showed heterogeneity of melatonin receptor (MR1A and MR1B) expression based on ectopic tissue location [Mosher, A.A.; Tsoulis, M.W.; Lim, J.; Tan, C,2019; Luiz Gustavo de Almeida Chuffa, 2020, 20].

Melatonin, initially is an endogenous this exceptional hormone is known for its multitude of biological functions and even its striking antioxidative capacity. However, its capacity to reprogram CKM syndrome is still up in the air despite melatonin's wide potential in disorders

via oxidative stress that excel in cognition. The present review integrates the current appreciation of the role of oxidative stress in gestation and lactation that could render CKM characteristics in progeny and offers insights into the complex underlying pathways and molecular bases that govern this phenomenon.

This magical hormone and its many derivatives are some of the biggest protectors against oxidative chaos and wild free radicals. Previous studies have established that melatonin protects neural integrity under conditions of cerebral ischemia in adults, and an expanding amount of evidence continuously demonstrated that melatonin protects against abnormal myelination and inflammatory glial response during myelination of the developing central nervous system, both of which are critical components of white matter injury.

Melatonin Use in Pregnancy and Lactation in the Context of Oxidative Stress: Insights into Cardiovascular–Kidney–Metabolic Health of the Offspring,

Melatonin's multifarious role in redox homeostasis, fetal programming and protection of the offspring from unfavorable outcomes makes it a potential reprogramming strategy [24].

Quantifying melatonin detection Reagents need to be at room temperature (18-25°C) before use. 30 mL of Concentrated Wash Buffer must be mixed with 750 mL of deionized or distilled water. The excess solution must be stored at 4°C and the concentrate is heated in a water bath at 40°C (with a limit of 50°C), agitated gently until crystals are completely dissolved. The solution should be equilibrated to room temperature before application. Prepare the standard 15 minutes before use. Centrifuge for 1 minute at 10,000g and seal the Standard with 1.0mL of Reference Standard and Sample Diluent. Once the lid is securely crouched and allowed it to sit for 10 minutes, you invert the solution several times. Once the solution is fully dissolved, it is very important to pipet the solution fully. The stock solution is quantified after reconstitution to be at a concentration of 1000pg/mL.

Proceed with additional dilutions as necessitated (excluding those performed in the wells). The recommended concentrations include 1000, 500, 250, 125, 62.5, 31.25, 15.625, and 0 pg/mL. In an EP tube, it is advised to combine 0.5mL of the 1000pg/mL standard with 0.5mL of Reference Standard and Sample Diluent to constitute a 500pg/mL standard solution. The methodology for preparing the remaining concentrations adheres to the same protocol. The utmost standard concentration remains at 1000pg/mL in its undiluted form. The zero concentration signifies a reference standard and sample diluent concentration of 0 pg/mL. Standards may be diluted to a volume of 200L of the actual amount present in each tube.

Prior to the experimental procedure, it is essential to ascertain the requisite quantity of biotinylated detection antibody (50µL/well). An additional 100-200µL should be prepared for adequate preparation. The stock tube must undergo centrifugation, and the concentrated Biotinylated Detection Antibody should be diluted with a 1:100 Diluent prior to utilization. It is imperative to calculate the necessary concentration of HRP conjugate (100µL/well) before the commencement of the experiment. An extra 100-200µL should be prepared for sufficient preparation.

The HRP Conjugate Diluent (1:100) should be employed to dilute the concentrated HRP Conjugate to its working concentration. Due to the potential for degradation from light and contaminants, it is advisable not to open the vial until absolutely necessary! Any residual reagent remaining after aspirating the requisite dosage with sterile tips should not be discarded. Refrain from amalgamating the reagent within the Diluent vials provided in the kit. Contamination of reagent preparation water or containers can adversely affect the accuracy of findings.

2. Assay Method

1- Prepare reagents and samples at Reagents and samples were prepared at room-temperature. Sample Preparation for Assay Centrifuge a thawed sample again before assay. Swirl all reagents before pipetting. avoid foam. Repeat analysis of samples and standards.

Antigen, biotinylated detection Ab: Add 50µl of Standard, Blank, or Sample into each well. Suitable Reference Standard & Sample Diluent fill the blank. 330 µl Per blocker solution, and add 50 µl of Biotinylated Detection Ab solution in each well immediately. Apply our Plate sealer. Tap the dish lightly to settle the mixture. Incubate for 45 min at 37°C. Solutions are dispensed on the bottom of micro ELISA plates to avoid inner wall contacting and foaming.

2- Wash: Aspirate and wash each well three times. Fill each well with approximately 350µl of Wash Buffer using a squirt bottle, multi-channel pipette, manifold dispenser or automated washer. The charge transfer process relies upon complete liquid removal at every stage of the process. Aspirate or decant any residual Wash Buffer from the plate after the final Wash.

3- Distribute 100µl of the HRP Conjugate masterpiece into every well. Adorn with a new plate sealer. Settle it at a cozy 37°C for half an hour. Rinse: Execute the aspiration and wash routine five times as carried out in the previous step. Gently agitate.: Add 90µl Substrate Solution to each well. Place fresh plate sealer on. At 37°C, incubate 15 minutes. Keep light out. A change of colour may shorten or lengthen the response time, but not by more than 30 minutes. Termination of the reaction is based on the visible gradient of the standard wells. 50µl Stop Solution to each well. Instant yellow. Add stop solution in the same order as substrate. Optical density (OD) measurement: Measure the OD of each well at 450 nm using a microplate reader. Microplate reader: preheat and adjust testing settings..

4- latly Put unused reagents back in the fridge at the proper temperature until expiration after the experiment.

Prepare reagents and samples at room temperature. Before assay, centrifuge the sample again after thawing. Before pipetting, carefully swirl all reagents. avoid foam. Assaying samples and standards twice is suggested.

5- MX 8 Biotinylation Detection Ab: Add 50µl of Standard, Blank, or Sample to each well. Reference Standard & Sample Diluent completes the blank well. Immediately add 50 µl of Biotinylated Detection Ab solution to each well. Apply our Plate sealer. Gently tap the dish to combine. Subsequently, solutions are added to the bottom of micro ELISA plates at 37℃ for 45 min to prevent inner wall contacting and foaming..

6- Wash: Aspirate and wash each well three times. Add 350µl Wash Buffer to each well (using a squirt bottle, multi-channel pipette, manifold dispenser, or automated washer). Performance relies upon thorough liquid elimination at every stage. After the last wash, aspirate or decant any residual Wash Buffer and pat the plate against a few sheets of thick, clean absorbent paper while in inverted position..

7- Distribute 100µl of the HRP Conjugate working potion into every well. Adorn the plate with a pristine sealer. Allow it to incubate at a warm embrace of 37°C for half an hour. Cleansing: Execute the aspiration and wash ritual five times, as detailed in the Reagents and Conditions for Protein Phosphatase - Substrate. : 90µl Substrate Solution in each well. Place fresh plate sealer on. At 37°C, incubate 15 minutes. Keep light out. Colour change does not modify the time needed to respond, beyond 30 minutes. Stop the reaction when the gradient is visible on standard wells. currently Stop: Add 50µl Stop Solution to each of the wells. Instant yellow. Add stop solution in the same order as substrate. OD Measurement: The optical density of each well will be measured at 450 nm with a microplate reader. Microplate reader pre-heating and assay settings.

8- latly After experiment,store unused reagents back to designated temperature refrigerator till expiry.

Statistical Analysis

The numerical exploration was executed with the aid of Microsoft Excel 2010, and the findings were articulated as mean ± standard deviation (mean ± SD). A one-way ANOVA was employed to contrast the parameters across various examined groups. To unveil the interconnections among the parameters of the current investigation, Pearson's correlation was utilized. P-values

(P≤0.05) were deemed to hold statistical significance. The analysis of correlation was computed using Pearson's correlation coefficient..

3. Results

MELATONIN EMBODIES the quintessential hormone of the vertebrate pineal gland, cascading into the bloodstream in a rhythmic dance, reaching peaks in all species beneath the cloak of night. In mammals, the sweet cadence of melatonin is choreographed by an intrinsic circadian clock located in the suprachiasmatic nucleus of the hypothalamus, synchronized to the pulse of the light-dark cycle. Melatonin seems to be a crucial actor in a multitude of essential physiological mechanisms (Brzezinski A, 1997), regulating the modulation of circadian rhythms, as well as visual, reproductive, cerebrovascular, neuroendocrine and neuroimmunological activities. More recently, evidence also has emerged showing that melatonin plays a role in suppressing growth and function, specifically hampering LH release from the pars tuberalis (Nakazawa et al., 1991), and inhibiting proliferation of uterine antimesosomal stromal cells.
The journey of pregnancy ushers in a remarkable transformation in the mother's physiology, notably marked by an impressive surge in blood volume, soaring by around 45% [26].

Upon delving into the insights presented in Table No. 1, it became evident that there were subtle yet significant alterations (P≤0.05) in the biochemical analysis levels as pregnancy unfolded, particularly when juxtaposed with the control group. A keen examination of cholesterol levels revealed a notable shift from 101.50±13.6 to 183.48±25.6, highlighting a significant rise in cholesterol percentages as the months of pregnancy unfurled from their nascent stages to the final trimester. Similarly, a noteworthy increase in triglycerides was observed throughout the gestational period, with fat levels climbing from 93.2±11.01 in the early months to a striking 176.5±19.43 by the pregnancy's end when compared to the control group. Moreover, beneficial HDL fats exhibited a modest upward trend during the months of gestation, as their percentage ascended from 56.1±20.2 in the initial months to 70.56±16.2 in the concluding months of pregnancy, all at a significant level (P≤0.05). The percentage of VLDL also experienced an upward trajectory throughout pregnancy, rising from 25.5±17.3 in the early stages to 39.45±6.4 in the latter months. Additionally, LDL levels surged from 102.1±32.1 during the first month of pregnancy to an elevated 134.72±29.1.
This is also the case in Table 6. There was no difference in the tests or statistical analysis. It did not show significant differences at a significant level between employed women and non-employed women, as we did not notice a significant change in the percentages of the analyzes and there is a great similarity in the apparent results.
elevated blood sugar levels during pregnancy have been linked to a rise in newborn weight [Whyteetal, 2013, Kushtagi P, Arvapally2009]. Although various investigations have explored the connection between maternal lipid profiles in women with normal blood sugar and the size of their offspring [17,18].,

Table (1) Effect of pregnancy stages on anti-oxidant parameters of pregnant women

pregnancy stages	no	RBSg/l	UREAg/l	CREATI g/l	ALBUMIN g/dl
control	50	121±2.2a	3.41 ± 0.26 a	0.9±4.4b	25.96±0.03b
Fiest trimester	35	163.5±2.1a	3.17±0.34a	0.7±5.1	23.35±0.05a
Second trimester	35	200.8±3.4a	3.44±0.43b	0.6±2.5bc	23.51±0.08a
Third trimester	35	215.2±3.5a	2.88±0.45b	0.5±2.2a	20.67±0.02b
LSD		1.92	0.18	1.3	0.16

- The numbers in the table express average values ± standard deviation.
- The means the presence of varying letters assigned to each element indicates marked differences at the probability threshold (P≤0.05).

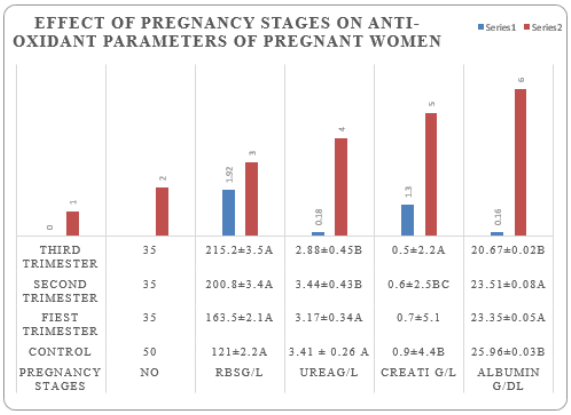


Table (2) Influence of Blood Type on Various Anti-Oxidant Metrics in Expecting Mothers.

Blood groop	no	RBS	UREA mg/dl	CREATI mg/dl	ALBUMIN mg/dl
A	22	192±22.4^{b}	32.75±3.05^{b}	0.7±3.5^{b}	3.77±0.02^{a}
B	32	175.5±32.5^{a}	30.2±3.5^{a}	0.8±2.06^{a}	2.98±0.03^{b}
AB	25	183.77±22.01^{b}	37.2±2.8^{a}	0.6±2.9^{b}	3.03±0.07^{a}
O	76	188.5±23.01^{b}	40.9±2.5^{a}	0.7±3.5^{a}	3.24±0.05^{a}
LSD		18.94	1.96	1.42	0.1

●The numbers in the table express average values ± standard deviation.

●The means Symbols representing various elements vary considerably at the significance threshold (P≤0.05).

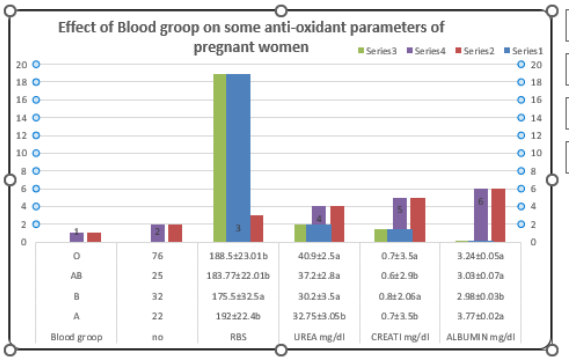
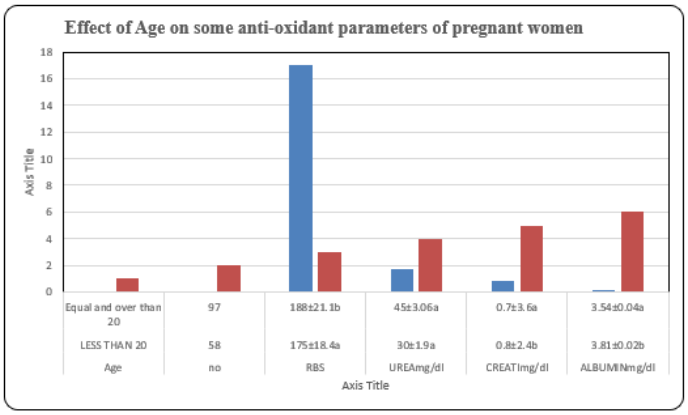


Table (3) Effect of Age on some anti-oxidant parameters of pregnant women.

Age	no	RBS	UREAmg/dl	CREATImg/dl	ALBUMINmg/dl
LESS THAN 20	58	175±18.4^{a}	30±1.9^{a}	0.8±2.4^{b}	3.81±0.02^{b}
Equal and over than 20	97	188±21.1^{b}	45±3.06^{a}	0.7±3.6^{a}	3.54±0.04^{a}
LSD		17.01	1.73	0.88	0.17

●The numbers in the table express average values ± standard deviation.

●The means distinct letters assigned to each variable showcase notable variations at the significance threshold (P≤0.05).



4. Discussion

Melatonin, a wondrous indoleamine, emerges from the essential amino acid, tryptophan (Reiter, R. et al., 2013). Its formation dances in harmony with the surrounding light, as illumination curbs its release. The suprachiasmatic nucleus, a master circadian conductor receiving luminous signals from the retina via the retinohypothalamic pathway, orchestrates the rhythmic production of melatonin (Berson, D.M., 2010). A growing body of evidence indicates that the rhythmicity of melatonin release, influenced by the cycles of light and dark, plays a pivotal role in regulating reproductive health. When oxygen is harnessed during metabolic activities, it gives rise to free oxygen radicals. These radicals possess “free” valence electrons, rendering them fiercely reactive and capable of inflicting damage upon cellular structures (Kojo, S., 2004). The phrase “reactive oxygen species” (ROS) encompasses not only these free radicals but also stable non-radical entities, like hydrogen peroxide, that can provoke oxidation (Bouayed, J. and Bohn, T. 2010). While ROS are vital for key physiological functions, an excess can lead to cellular harm, a phenomenon known as “oxidative stress” (Valko, M., 2007). Antioxidative agents, or oxygen-scavengers, can be found within the body and can also be introduced from external sources. They mitigate free radicals by bestowing electrons upon them, thereby achieving stabilization (Rahman, K., 2007).

Lipoproteins parameters

According to our intriguing discoveries, elevated levels of fat during the miraculous journey of pregnancy emerge as a typical phenomenon for expectant mothers due to an uptick in the release of lipids, while the weight of the mother tends to escalate as the foetus flourishes. As noted by Z. Matuszak et al. (1997), diminished levels of the hormone melatonin, secreted by the pineal gland, also contribute to the delicate balance of fat levels, aiming to mitigate potential side effects and diminish susceptibility. The current findings resonate with a cohort of researchers who have observed that a mother’s serum cholesterol levels surge by roughly 50–70% during pregnancy, starkly contrasting with standard levels [Husain F et al. 2006]. Other studies have indicated that, in comparison to their non-pregnant counterparts, total cholesterol levels can soar up to 39% in the later stages of pregnancy, while triglyceride levels may escalate by as much as 18% more than those seen in non-pregnant individuals during the same period (An-Na et al., 1995), achieving significance when evaluated against the control group ($P \leq 0.05$). The interplay of LDL and HDL with oxidative modification is noteworthy. Melatonin levels in humans are notably lower during the initial trimester, gradually increasing after the 24-week mark, peaking by the conclusion of pregnancy, as it is released from the pineal gland, acting as a formidable scavenger of oxygen-free radicals and effectively neutralizing hydroxyl radicals (D. Muller-Wieland et al., 2013). Consequently, a majority of expectant mothers embark on their prenatal care journey during the first trimester, even before the notable shifts in lipid metabolism become apparent. Furthermore, we uncovered a positive correlation between maternal melatonin levels and birth weight. Our results align harmoniously with other research that underscores the vital role this hormone plays in fostering healthy foetal growth and the development of vital organs (McCarthy, R., et al., 2019). One hypothesis suggests that maternal stress, which may alter cortisol and melatonin levels, leads to disruptions in circadian rhythms (Chen, Y., et al. 2013). The revelations from the current investigation harmonized with several other scholarly pursuits, notably one that examined the potential of exogenous melatonin to alleviate sleep disturbances. An up-to-date meta-analysis regarding melatonin's prowess in combating insomnia unveiled a remarkable decline in prolonged sleep latency and a noteworthy enhancement in overall sleep quality. Ferracioli-Oda E. et al. (2013) ensured that participants were enveloped in relatively dim illumination (15 lux) for three days preceding the light stimulation in this experiment. SA Jasser (2006) found that while a striking 86.2% of subjects experienced an early surge of melatonin (50 out of 58) when subjected to low light, 70.7% of individuals (41 out of 58) exhibited a postponed melatonin response in subdued light, echoing

the concept of circadian pacemaker drift (Czeisler CA, 1999). Collectively, these studies illustrate that irrespective of previous light exposure, both the suppression of melatonin and the phase shift reactions are attuned to the ambient light levels typically found in a standard room. Nevertheless, contrasting studies have surfaced that challenge the outcomes of the present research. In capuchin monkeys, more specifically, decreased maternal melatonin resulted in reduced cortisol production in the fetal adrenal gland, suggesting that lack of maternal melatonin or lack of circadian rhythm in fetal corticosterone contribute to intrauterine growth retardation (Torres-Farfan C., 2004). An additional study involving sheep indicated that insufficient melatonin directly hampers the fetal adrenal gland's capacity to release cortisol when stimulated by ACTH and the noradrenaline-mediated contraction of fetal cerebral arteries, brown adipose tissue, and glycerol. The drinking behavior of juvenile rats was also shown to be affected by maternal melatonin deficiency during early pregnancy; this effect could potentially be reversed by administering exogenous melatonin to the mother (Kennaway DJ, 1992). In contrast to the minimal quantities of melatonin secreted by the pineal gland, the findings of the current study may be regarded without detrimental alterations in lipids, indicating that both mother and fetus remain unscathed. The hormone melatonin, synthesized within the mitochondria and pivotal in regulating metabolism, yet not promptly released into the systemic circulation, might play a significant role in this context (Ahluwahia A., 2018). Furthermore, it also regulates the production of genes responsible for antioxidant enzymes and aids in the elimination of free radicals, as the mitochondrial membranes lining the stomach boast a high concentration of melatonin receptors (MT1 and MT2) (Ding, K. et al., 2014). This could serve as compelling evidence that the hormone melatonin, emanating from the mitochondria, governs the fetal environment and influences fat metabolism...

5. Conclusions

A multitude of studies have delved into the realm of melatonin over the last decade, unveiling its myriad traits that underscore its vital role in human well-being. The selected research for this review has unveiled fresh perspectives on melatonin's functions, showcasing its anti-inflammatory prowess against the perils of high-risk pregnancies, its remarkable skill in fine-tuning circadian rhythms—an element essential for the proper development of fetal brain function—and its remarkable ability to ignite the labor process, a critical key to achieving a successful vaginal birth. Moreover, the discoveries underscore its remarkable transit across the placenta, its vital role in breastmilk in promoting the circadian rhythms of infants and its capacity to defend against oxidative stress in neonates.

While there are a lot of studies showing positive effects of melatonin supplementation in pregnancy and postpartum mothers for mothers and babies, significant clinical trials are required to reach a conclusion regarding whether melatonin is a viable therapeutic approach for mothers and babies. This creates an interesting speculation that if melatonin is introduced in still very young years of life this could save the very phenomenon of being alive for generations ahead.

Extensive clinical trials are essential to achieve conclusive outcomes that form a unified agreement about the role of melatonin as a therapeutic option in pregnancy and for newborns, despite the multitude of studies affirming that melatonin supplementation during pregnancy and shortly after has beneficial effects on both mothers and their babies. This suggests that the administration of melatonin in early developmental stages could offer protection for future generations..

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Conflict of Interest

The authors would like to declare that they do not have any conflict of interests

References

1. Lerner, A.B.; Case, J.D.; Takahashi, Y.; Lee, T.H.; Mori, W. Isolation of melatonin, the pineal gland factor that lightens melanocytes. J. Am. Chem. Soc. 1958, 80, 2587.
2. Back, K.; Tan, D.X.; Reiter, R.J. Melatonin biosynthesis in plants: Multiple pathways catalyze tryptophan to melatonin in the cytoplasm or chloroplasts. J. Pineal Res. 2016, 61, 426–437.
3. Hardeland, R.; Pandi-Perumal, S.R.; Cardinali, D.P. Melatonin. Int. J. Biochem. Cell Biol. 2006, 38, 313–316.
4. Hardeland, R.; Tan, D.X.; Reiter, R.J. Kynuramines, metabolites of melatonin and other indoles: The resurrection of an almost forgotten class of biogenic amines. J. Pineal Res. 2009, 47, 109–126.
5. Slominski, R.M.; Reiter, R.J.; Schlabritz-Loutsevitch, N.; Ostrom, R.S.; Slominski, A.T. Melatonin membrane receptors in peripheral tissues: Distribution and functions. Mol. Cell Endocrinol. 2012, 351, 152–166.
6. Ekmekcioglu, C. Melatonin receptors in humans: Biological role and clinical relevance. Biomed. Pharmacother. 2006, 60, 97–108.
7. Ma, H.; Kang, J.; Fan, W.; He, H.; Huang, F. ROR: Nuclear Receptor for Melatonin or Not? Molecules 2021, 26, 2693.
8. Reiter, R.J.; Mayo, J.C.; Tan, D.X.; Sainz, R.M.; Alatorre-Jimenez, M.; Qin, L. Melatonin as an Antioxidant: Under Promises but over Delivers. J. Pineal Res. 2016, 61, 253–278.
9. Tordjman, S.; Chokron, S.; Delorme, R.; Charrier, A.; Bellissant, E.; Jaafari, N.; Fougerou, C. Melatonin: Pharmacology, Functions and Therapeutic Benefits. Curr. Neuropharmacol. 2017, 15, 434–443.
10. Carlomagno, G.; Minini, M.; Tilotta, M.; Unfer, V. From Implantation to Birth: Insight into Molecular Melatonin Functions. Int. J. Mol. Sci. 2018, 19, 2802.
11. Reiter, R.J.; Tan, D.X.; Korkmaz, A.; Rosales-Corral, S.A. Melatonin and stable circadian rhythms optimize maternal, placental and fetal physiology. Hum. Reprod. Update 2014, 20, 293–307.
12. Lanoix, D.; Guérin, P.; Vaillancourt, C. Placental melatonin production and melatonin receptor expression are altered in preeclampsia: New insights into the role of this hormone in pregnancy. J. Pineal Res. 2012, 53, 417–425. [CrossRef
13. Landgraf, D.; Achten, C.; Dallmann, F.; Oster, H. Embryonic development and maternal regulation of murine circadian clock function. Chronobiol. Int. 2015, 32, 416–427.
14. Bulun, S.E. Endometriosis. N. Engl. J. Med. 2009, 360, 268–279.
15. Nnoaham, K.E.; Hummelshoj, L.; Webster, P.; d'Hooghe, T.; de Cicco Nardone, F.; de Cicco Nardone, C.; Jenkinson, C.; Kennedy, S.H.; Zondervan, K.T.; World Endometriosis Research Foundation Global Study of Women's Health consortium. Reprint of: Impact of endometriosis on quality of life and work productivity: A multicenter study across ten countries. Fertil. Steril. 2019, 112, e137–e152.
16. Burney, R.O.; Giudice, L.C. Reprint of: Pathogenesis and pathophysiology of endometriosis. Fertil. Steril. 2019, 112, e153–e161.
17. Bulun, S.E.; Yilmaz, B.D.; Sison, C.; Miyazaki, K.; Bernardi, L.; Liu, S.; Kohlmeier, A.; Yin, P.; Milad, M.; Wei, J. Endometriosis. Endocr. Rev. 2019, 40, 1048–1079.

18. Marino, J.L.; Holt, V.L.; Chen, C.; Davis, S. Shift work, hCLOCK T3111C polymorphism, and endometriosis risk. Epidemiology. 2008, 19, 477–484.
19. Mosher, A.A.; Tsoulis, M.W.; Lim, J.; Tan, C.; Agarwal, S.K.; Leyland, N.A.; Foster, W.G. Melatonin activity and receptor expression in endometrial tissue and endometriosis. Hum. Reprod. 2019, 34, 1215–1224. [Google Scholar] [CrossRef]
20. You-Lin Tain 1,2,3 and Chien-Ning Hsu 4,5,"Melatonin Use during Pregnancy and Lactation Complicated by Oxidative Stress: Focus on Offspring's Cardiovascular–Kidney– Metabolic Health in Animal Models ", 2024
21. Luiz Gustavo de Almeida Chuffa , "Melatonin Promotes Uterine and Placental Health: Potential Molecular Mechanisms ".
22. Chen, B.H.; Park, J.H.; Lee, Y.L.; Kang, I.J.; Kim, D.W.; Hwang, I.K.; Lee, C.-H.; Yan, B.C.; Kim, Y.-M.; Lee, T.-K.; et al. Melatonin improves vascular cognitive impairment induced by ischemic stroke by remyelination via activation of ERK1/2 signaling and restoration of glutamatergic synapses in the gerbil hippocampus. Biomed. Pharmacother. 2018, 108, 687–697. [CrossRef] [PubMed]
23. Hu, Y.; Wang, Z.; Pan, S.; Zhang, H.; Fang, M.; Jiang, H.; Zhang, H.; Gao, Z.; Xu, K.; Li, Z.; et al. Melatonin protects against blood-brain barrier damage by inhibiting the TLR4/ NF-κB signaling pathway after LPS treatment in neonatal rats. Oncotarget 2017, 8, 31638–31654. Available online: https://pubmed.ncbi.nlm.nih.gov/28404943 (accessed on 1 October 2022). [CrossRef]
24. You-Lin Tain 1,2,3 and Chien-Ning Hsu 4,5,*Villapol, S.; Fau, S.; Renolleau, S.; Biran, V.; Charriaut-Marlangue, C.; Baud, O. Melatonin promotes myelination by decreasing white matter inflammation after neonatal stroke.Pediatr. Res.2011, 69, 51–55. Available online: https://pubmed.ncbi.nlm.nih.gov/20856166 (accessed on 1 October 2022). [CrossRef].
25. Melatonin Use during Pregnancy and Lactation Complicated by Oxidative Stress: Focus on Offspring's Cardiovascular–Kidney– Metabolic Health in Animal Models.