

A SYSTEMATIC REVIEW ON THE IMPACT OF MELATONIN AND THE CIRCADIAN RHYTHM ON MATERNAL AND FETAL OUTCOMES

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BACKGROUND

- Melatonin
 - Helps regulate sleeping patterns and synchronize circadian rhythms
 - Plays a significant role in pregnancy, and ultimately maternal and fetal outcomes¹. This includes
 - Reducing maternal and fetal oxidative stress during pregnancy by acting as a direct free-radical scavenger² maternal to fetal transmission of photoperiodic information
 - Promoting proliferation of fetal cells e.g. trophoblasts for proper uteroplacental development²,
 - Promoting development of fetal immunological tolerance mechanisms within the uterus due to melatonin-binding sites on lymphocytes, monocytes, and granulocytes¹.
- Emerging evidence suggests potential therapeutic implications of melatonin supplementation in managing certain pregnancy-related conditions including postpartum maternal hemorrhage³, metabolic syndrome⁴, and compromised cardiovascular function e.g. pre-eclampsia⁵.

OBJECTIVES

- We aim to comprehensively analyze the influence of melatonin and circadian rhythm on maternal and fetal health outcomes on the pathogenesis of pregnancy complications, including
 - Pre-eclampsia
 - Intrauterine fetal growth restriction (IUGR)
 - Preterm labor, through increased oxidative stress³.

METHODS

- A systematic search was employed and used the following three electronic databases: Web of Science, Embase, and PubMed.
 - Search terms were "melatonin," "circadian rhythms," "pregnancy," "maternal outcomes," and "fetal outcomes."
- 3,764 studies were found.
- Articles were screened in a two-step process:
 - Titles and abstracts evaluated to assess relevancy to study objectives
 - Full texts of potentially relevant articles were first reviewed by abstract through the artificial intelligence program.
- The selection process was conducted independently by five researchers, and any discrepancies were resolved through consensus or consultation with a sixth researcher when necessary. Studies that met the inclusion criteria were further subjected to data extraction.
 - 1,840 studies were then excluded
- Inclusion criteria included
 - The studies to evaluate melatonin and/ or the circadian rhythm in the context of maternal and/or fetal outcomes.
 - Pregnant patients in any trimester, postpartum patients, and fetuses.
 - Studies published in English within the last 15 years.
- A total of eight studies were included for our systematic review;
 - Four about melatonin and preeclampsia
 - Three about melatonin and fetal growth restriction (FGR)
 - One about melatonin and oxidative stress.

RESULTS

Table 1: Summary results of studies on systemic maternal melatonin levels in pregnancies complicated by preeclampsia

Authors	Population (N)	Gestational Age	Controls (N)	Results	Mean values of melatonin (pg/ml) in cases vs controls	P value
Lanoix et al., 2012 [6]	8 PE	33.1- 36.1 weeks	8	- Lower melatonin production in preeclamptic placentas	NA	p ≤ 0.01
Zeng et al., 2016 [7]	113 PE	At disease presentation	60	- Reduced melatonin levels are associated with the development of preeclampsia	NA	p = 0.001
Diallo et al., 2023 [8]	9 PE	At disease presentation	20	- Melatonin concentration was strongly decreased in preeclamptic macrophage compared to a healthy donor	NA	p ≤ 0.001
Savka et al., 2023 [9]	32 PE	30- 32 weeks	33	- Lower concentrations of melatonin in women with PE	30.98 pg/ml vs 55.20 pg/mL	p = 0.029

Table 2: Summary results of studies on maternal melatonin levels in cases of fetal growth restriction

Authors	Population (N)	Gestational Age	Controls (N)	Results	Mean values of melatonin (pg/ml) in cases vs controls	P value
Berbets et al., 2021 [10]	46	Third trimester	20	- Decreased melatonin in pregnancies complicated by intrauterine fetal growth retardation	-126.87 ± 14.87 pg/ml, vs -231.25 ± 21.56 pg/ml	p < .001
Ramiro- Cortijo et al., 2020 [11]	14	9th- 11th week	90	- No significant differences in melatonin levels in twin pregnancies complicated by FGR vs control	NA	p = 0.679
Berbets et al., 2020 [12]	14	30- 36 weeks	13	- Significant decrease in melatonin concentrations in the umbilical blood at labor in pregnancies complicated by intrauterine growth restriction	7.50 pg/ml vs 14.60 pg/ml	p = 0.001

Table 3: Quantitative results of melatonin and markers in umbilical artery and vein vs delivery circumstances¹³

Marker/Group	No Labor UA	No Labor UV	Labor UA	Labor UV	Day UA	Day UV	Night UA	Night UV
Melatonin (pg/ml)	11.8	11.3	23.9	25.6	7.9	8.6	21.0	22.0
SOD3 (ng/ml)	95.0	67.9	141.7	97.4	118.8	80.8	100.8	75.3
Gpx3 (ng/ml)	3937	4081	4754	5070	4120	4394	4255	4398
8-OHdG (ng/ml)	3.8	3.3	2.7	2.6	3.3	2.9	3.6	3.2

UA= Umbilical Artery, UV=Umbilical Vein

DISCUSSION

- Our findings demonstrated a significant relationship between low maternal melatonin levels and those with preeclampsia.
- Similar findings with low melatonin levels were also seen in cases of fetal growth restriction.
- In the setting of delivery context, nighttime deliveries were associated with higher melatonin levels in the umbilical artery and vein and similar trends were noted with the onset of labor.

CONCLUSION

- Lower melatonin levels were found in the setting of placental insufficiency compared to control groups with a healthy pregnancy.
- Of the seven studies that evaluated melatonin levels in the setting of placental insufficiency, only Ramiro-Cortijo et al.'s study found no significant difference between both groups¹¹.
 - This was the only study that used twin pregnancies as the population of interest and evaluated participants between the 9th-11th week of gestation¹¹.
- Future studies should be directed at understanding whether appropriate melatonin administration for those at risk of developing placental insufficiency or fetal growth restriction can reverse the patient's trajectory and thus improve maternal and fetal outcomes.
- Limitations of this study include the total number of studies, small sample size, and no quantitative summarization.

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