The role of melatonin in pregnancies complicated by placental insufficiency: A systematic review

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ABSTRACT

Placental insufficiency affects about 10% of pregnancies and can lead to pre-eclampsia, fetal growth restriction, and preterm birth. Despite significant advances in early prediction and prevention of preterm pre-eclampsia with aspirin, the effects of prophylaxis on fetal growth restriction are less certain, and the rates of late-onset pre-eclampsia are not influenced by aspirin treatment. Pregnancies complicated by placental insufficiency are characterized by increased oxidative stress, and recent studies suggest that melatonin has antioxidant properties and contributes to maintaining placental homeostasis.

We aimed to systematically review the available literature about melatonin in pregnancies complicated by placental insufficiency, specifically preeclampsia and fetal growth restriction, exploring three different aspects: 1) maternal melatonin levels; 2) expression and activity of melatonin placental receptors; 3) effects of maternal melatonin administration. PubMed (Medline) and Scopus were searched until December 2020. Identified studies were screened and assessed independently by two authors. Data were extracted and compiled in qualitative evidence synthesis.

The circadian pattern of melatonin secretion seems to be altered in pregnancies complicated by placental insufficiency reflected by lower production of melatonin, with consequent lower systemic and placental concentrations and lower expression of melatonin receptors, thus reducing the local release of the indole and its autocrine function. Small intervention studies also suggest that treatment is safe and may lead to prolongation of pregnancy and better outcomes, but double-blind, randomized placebo-controlled trials are lacking.

Introduction

Pregnancy is a peculiar time of a woman's life where the body has to adapt to several changes to sustain fetal growth and wellbeing and protect itself from the stress induced by the pregnancy status [1]. When such adaptive changes fail, the risks of complications and adverse pregnancy outcomes are increased [2–3]. As in all mammals, the circadian rhythm, which reflects the normal light: dark cycle over 24 h, was evolutionarily set to regulate all biological functions to ensure they are carried out at the proper time of the day, increasing the chance of survival. The central master clock of the circadian rhythm is located in the suprachiasmatic nuclei (SCN) of the hypothalamus, which communicates with the body through the production of molecules that act on peripheric clock genes. Melatonin is the most known of these molecules and plays a crucial role in several essential physiological functions, including the regulation of the sleep-wake cycle but also acting as an antioxidant, anti-inflammatory, anti-apoptotic and anti-tumoral agent [4–6].

During pregnancy, melatonin seems to have an important role in preserving placental homeostasis. As shown in animal models, oral supplementation with melatonin reduces blood pressure, increases the production of angiogenic factors, increases the uterine arterial flow, and the total serum antioxidant capacity [7–8]. Such function could be helpful in placental insufficiency-related disorders, like preeclampsia (PE) and fetal growth restriction (FGR), characterized by increased oxidative stress and pro-inflammatory status [1].

Considering these aspects, the effect of melatonin in pregnancy has been studied to explore systemic maternal melatonin levels in women with placental insufficiency-related disorders and the impact of maternal melatonin administration on such pregnancy complications.

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This systematic review aims to summarize the scientific knowledge about melatonin in the human population, specifically focusing on placental insufficiency, particularly PE and FGR.

Material and methods

A comprehensive systematic review was performed to identify studies evaluating the role of melatonin in pregnancies affected by placental insufficiency. The Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) guidelines [9] were followed in the report of this review. The study was registered with the International Prospective Register of Systematic Reviews database (PROSPERO registration number: CRD42021231936) [10].

Study identification and selection

A systematic English literature search was conducted from inception until December 2020 in PubMed (Medline) and Scopus. The search strategy consisted of relevant Medical Subject Headings (MeSH) terms and keywords, including "melatonin", "preeclampsia/eclampsia", "placental insufficiency", "intrauterine growth restriction (IUGR)"/" fetal growth restriction (FGR)" (Supplementary material Table S1). The search was conducted using single MeSH terms in order to include all possible articles published on the topic. Reference lists of relevant articles were searched manually to identify papers not found using the electronic search.

The inclusion criteria of our research strategy were clinical trials and research articles on this topic. Study protocols, case reports, review articles, editorials, letters to the editor, *in vitro* studies, experimental animal studies, and conference proceedings/posters that did not appear as full-text papers were not included in the review. The following data were extracted: authors, study title, year of publication, study period, objective, number of participants recruited, methods, pregnancy outcomes, and key results.

The study eligibility assessment, data extraction and methodological quality assessment of the included studies were completed by two independent investigators (SB, IF). Data from each eligible study were extracted without modification of original information onto custom-made data collection forms. Disagreements were resolved by consensus with a third reviewer (DLR).

The selected original articles were divided into three subgroups to improve the synthesis and understanding of the different topics on this theme. The first group involves articles that assessed blood, salivary, and/or urinary levels of melatonin in women with PE/FGR; the second group is formed by studies on placental tissue in women with PE/FGR; the third group refers to intervention studies in which melatonin was administered in a selected population of women with PE and/or FGR to evaluate pregnancy outcomes.

Quality assessment

The quality assessment of each included study was performed using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria [11] for observational studies of melatonin or placental receptor levels and utilizing the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool for intervention studies [12]. With QUADAS-2, each study was assessed in four domains related to the risk of bias: patient selection, index test, reference standard, and flow and timing. Each domain was categorized as "low risk", "high risk", or "some concerns" of bias if data regarding the domain were "reported and adequate", "reported but inadequate", and "not reported", respectively, and the first three domains were assessed regarding applicability. Each domain was categorized as "low risk", "moderate risk", "serious risk", "critical risk" of bias, or "no information", with the help of a series of signaling questions aiming to facilitate the process. The overall judgement was then established based on the rating of the individual domains. After applying the two separate quality criteria, the Robvis tool web app [13] was then used to visualize the risk-of-bias assessments creating "traffic-light plots" and weighted bar plots (Supplementary material Table S2).

Evidence synthesis and statistical analysis

Initially, we planned to obtain pooled summary estimates of the mean difference and 95 % confidence interval of serum melatonin levels and expression of placental melatonin receptors between pregnancies affected by placental insufficiency and those unaffected, overall and stratified by complication (PE or FGR), through meta-analyses using random-effects models. However, quantitative synthesis through meta-analysis was not possible due to the small number of studies on melatonin in pregnancy and the considerable heterogeneity of the studied populations and outcomes reported. Instead, the evidence was synthesized through qualitative description.

Results

Search results

After a systematic search of the available literature, an overall number of 642 studies was found. After removing duplicates, 153 research studies were obtained (103 articles about melatonin and PE/eclampsia and 50 articles on melatonin and FGR). Fig. 1 shows the flow diagram of the study selection. Review studies (64 articles) and study protocols (five articles) were excluded, as well as all articles not suitable for study type (i.e., book chapters, conference proceedings) or topic (not related to the research) (23 articles). A further 49 articles were excluded because of reporting *in vitro* (15 articles) or animal studies (34 articles). Therefore, 12 manuscripts were included for the systematic review: eight articles about melatonin and PE/eclampsia [14–21] and four about melatonin and FGR [22–25].

Risk of bias within studies according to QUADAS and ROBINS-I criteria

Ten observational studies were included in the review. In the "patient selection" domain, two studies were classified as high risk because the patients were selected randomly at different gestational ages [18,22]. The remaining eight studies were considered low risk. In the "index domain", one study was classified as high risk because the gestational age of the included population was limited to the early first trimester of pregnancy [23]. The remaining nine studies were considered low risk. In the "reference range" domain, four studies were classified as "some "concerns" of bias because the definition of PE/FGR was not reported [16,20,22–23]. The remaining six studies were considered as low risk. In the "flow and timing" domain, all studies were considered as low risk (Fig. S1). The two intervention studies identified [21 25] demonstrated the same critical issues and were considered at serious risk of bias because of: the absence of a protocol of randomization ("classification of interventions" risk of bias domain); absence of blinding at intervention ("measurement of outcomes" risk of bias domain) (Fig. S2).

Due to inconsistent methods and reporting of estimates of the included studies, meta-analysis was not possible.

Description of the studies included

Maternal systemic melatonin levels in pregnancies affected by placental insufficiency.

During pregnancy, melatonin production maintains a circadian rhythm with night-time levels significantly higher than day-time levels [5]. While keeping this circadian rhythm, melatonin production slightly decreases during the first and second trimesters. It then increases, reaching its peak values after 32 weeks of gestation, followed by a rapid fall after birth [20–22]. Some authors investigated if this pattern is

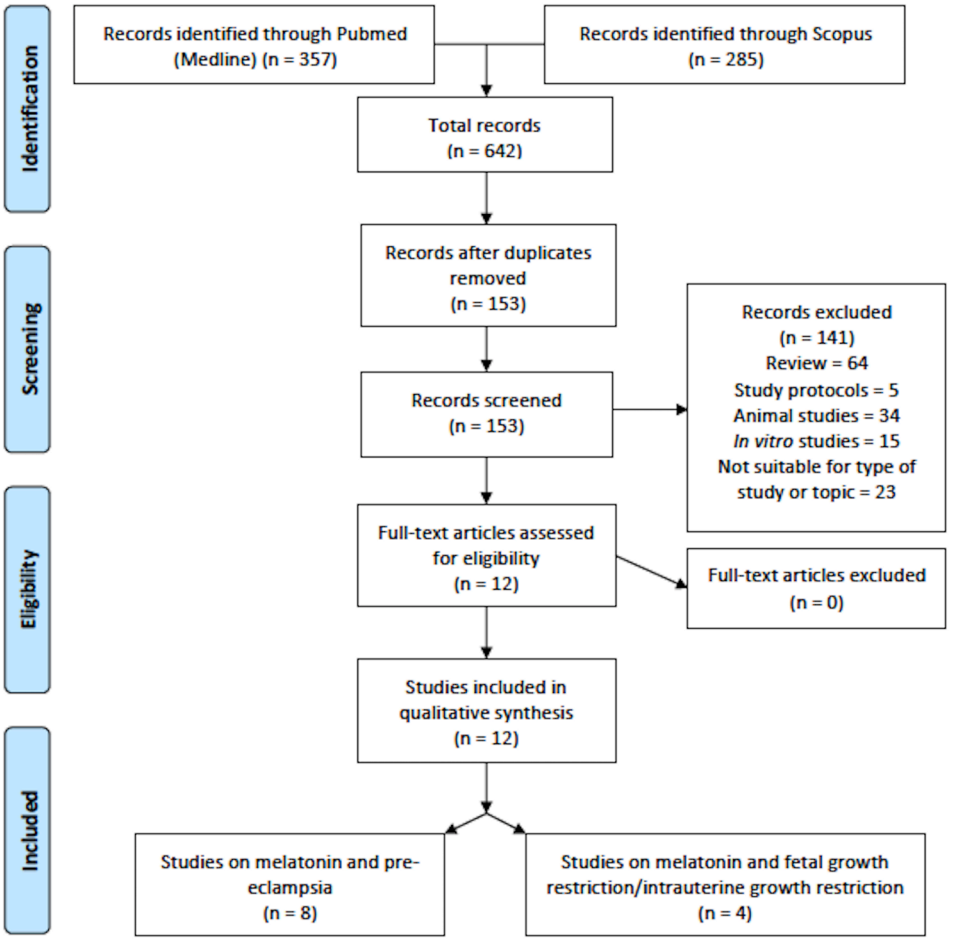

Fig. 1. Study flow diagram.

preserved in pregnancies with placental insufficiency or if the oxidative stress characterizing these pregnancies is reflected in a disruption of this pattern.

Overall, seven studies addressed the issue of melatonin levels in pregnancies complicated by placental insufficiency, five concerning PE and two about FGR.

The main characteristics and results of the included studies are summarized in Table 1.

In four studies, maternal circulating melatonin levels were significantly lower in patients with PE compared to controls: Nakamura *et al.* found that patients with severe PE had significantly lower serum nighttime melatonin levels than women with both mild PE and uneventful pregnancies at 32–36 weeks' gestation ($p < 0.01$) and at any gestational age below 36 weeks ($p < 0.05$) [14]; Bouchlariotou *et al.* found that nocturnal levels of melatonin were significantly lower in patients with PE at >32 weeks than in normal pregnancies (48.4 ± 24.7 vs 85.4 ± 26.9 pg/mL, $p < 0.001$) [15], Zeng *et al.* found that, at disease presentation, circulating levels of melatonin were significantly reduced in women with PE ($p = 0.001$) [17]; Shimada *et al.* found that salivary melatonin levels were significantly lower in complicated pregnancies than in healthy pregnancies at any time of the day assessed ($p < 0.001$) [18]. Only one study reported higher melatonin levels in women with PE compared to healthy pregnancies (29.4 ± 1.9 vs 22.7 ± 1.8 pg/mL, $p < 0.001$) [16].

Two studies addressed the question of melatonin levels in pregnancies complicated by FGR alone: Berbets *et al.* found lower melatonin levels (126.87 ± 14.87 vs 231.25 ± 21.56 pg/mL, $p < 0.001$) in singleton pregnancies complicated by FGR in the third trimester [22]; conversely, Ramiro-Cortijo *et al.* did not find differences in maternal serum levels at 9–11 weeks' gestation in twin pregnancies subsequently complicated by FGR [23].

Placental melatonin receptors in pregnancies affected by placental insufficiency

Following the study of Lanoix *et al.* [26] that showed the presence of MT1 and MT2 melatonin receptors in the placenta of healthy pregnancies providing evidence of local hormone production, some authors started to investigate whether in pregnancies complicated by placental insufficiency there is a down-regulation of these two receptors, responsible for lower systemic levels of melatonin. Four studies addressed this issue, three concerning PE and one about FGR.

The main characteristics and results of the included studies are summarized in Table 2.

In 2012, Lanoix *et al.* [19] demonstrated a lower expression of both receptors in eight placental tissue samples from women with PE ($p = 0.042$) associated with higher placental levels of serotonin, the precursor of melatonin ($p = 0.0095$). The mechanism behind this finding is likely related to the reduced placental gene expression ($p < 0.05$) and activity ($p < 0.001$) of the two enzymes responsible for the conversion of serotonin in melatonin, and both present in the chorionic villi, the AANAT (arylalkylamine *N*-acetyltransferase) and ASMT (acetylserotonin methyltransferase) enzymes. These data were confirmed by Zeng *et al.* [17] who also reported significantly lower expression of MT1 receptors in 27 placentas of women with PE ($p < 0.05$). Different results were reported by Yamamoto *et al.* [20], who found higher expression of MT1 receptors in 20 placentas of women with hypertensive disorders of pregnancy ($p < 0.001$), mainly in cases with gestational hypertension;

Table 1
Main characteristics and results of included studies on systemic maternal melatonin levels in pregnancies complicated by placental insufficiency.

Authors, year of publication	Population (N) (type)	Diagnostic criteria for PE and/or FGR	Gestational age	Time of melatonin dosage	Site	Controls (N)	Main results	Mean values of melatonin (pg/ml) in cases vs controls	P value
Nakamura et al., 2001 [14]	33 (19 PE + 14 FGR)	**PE:** BP ≥ 140/90 mmHg and proteinuria ≥ 0,3 g in a 24-h urine collection after 20 weeks **FGR:** EFW (BPD + AC) < 10°pc	From diagnosis until the 2nd day of the puerperium	2 a.m. and 2p.m.	Maternal blood	46	• Lower melatonin levels in women with severe PE	NA	$p < 0.01$
Bouchlariotou et al., 2014 [15]	31 PE	BP ≥ 140/90 mmHg and proteinuria ≥ 0,3 g in a 24-h urine collection after 20 weeks	> 32 weeks	2p.m. and 10p.m.	Maternal blood	20	• Lower melatonin levels in women with PE	48.4 ± 24.7 vs 85.4 ± 26.9	$p < 0.001$
Tranquilli et al., 2004 [16]	16 (8 PE + 8 with 24-h altered blood pressure pattern)	BP ≥ 140/90 mmHg and proteinuria ≥ 0,3 g in a 24-h urine collection after 20 weeks	36 weeks	Every 4 h for 24 h	Maternal blood	8	• Higher melatonin levels in PE	29.4 ± 1.9 vs 22.7 ± 1.8	$p < 0.001$
Zeng et al., 2016 [17]	113 PE	BP ≥ 140/90 mmHg and proteinuria ≥ 0,3 g in a 24-h urine collection after 20 weeks	At disease presentation	At disease presentation	Maternal blood	60	• Lower melatonin levels in women with PE	NA	$p = 0.001$
Shimada et al., 2016 [18]	58 high-risk pregnancies	Not specified	Second or third trimester	Before breakfast, lunch, dinner and sleep	Maternal saliva	40	• Lower salivary melatonin levels in high-risk pregnancies ($p < 0.001$)	NA	$p < 0.001$
Berbets et al., 2019 [22]	46 FGR	Not defined	Third trimester	8 a.m.	Maternal blood	20	• Lower melatonin levels in FGR ($p < 0.001$)	126.87 ± 14.87 vs 231.25 ± 21.56	$p < 0.001$
Ramiro-Cortijo et al., 2020 [23]	12 FGR	EFW < 3°pc or EFW < 10°pc + abnormal flow in UA, MCA and/or UtA at Color doppler	9–11 weeks	8–9 am	Maternal blood	72	• No differences in melatonin levels in FGR compared to controls	NA	NS

PE, preeclampsia; FGR, fetal growth restriction; BP, blood pressure; EFW, estimated fetal weight; pc, percentile; N, number; UA, umbilical artery; MCA, middle cerebral artery; UtA, uterine artery; NA, not assessed; NS, not significant.

Table 2
Main characteristics and results of the included studies on the placental expression of melatonin receptors.

Authors, year of publication	Population	Controls	Results
Lanoix et al., 2012 [31]	8 PE	8 normal	• Reduced expression of MT1 and MT2 receptors in PE ($p < 0.005$) • Reduced gene expression and activity of both AANAT and ASMT enzymes in PE ($p < 0.001$ and $p < 0.05$, respectively)
Zeng et al., 2016 [17]	27 PE	27 normal	• Reduced expression of MT1 ($p < 0.05$) • No difference in MT2
Yamamoto et al., 2013 [20]	25 HDP	25 normal	• Higher expression of MT1 expression in all types of HDP ($p < 0.001$)
Berbets et al., 2020 [24]	32 FGR	30 normal	• Reduced expression of MT1 and MT2 in FGR ($p < 0.001$)

PE: preeclampsia; HDP: hypertensive disorders of pregnancy; FGR: fetal growth restriction.

however, their expression was lower in cases with PE and even more so in PE superimposed on chronic hypertension.

A reduced expression of MT1 and MT2 receptors in pregnancies complicated by FGR has been reported by Berbets *et al.* [22]. The optical density of both MT1 and MT2 receptors was lower in pregnancies complicated by FGR than in controls ($p < 0.001$), and the difference in receptor expression was more evident in the apical than in the stromal part of the syncytiotrophoblast of FGR placentas ($p < 0.001$).

Effects of melatonin administration in pregnancies complicated by placental insufficiency

To date, there are only two clinical trials on the effect of melatonin administration in women complicated by PE or FGR [21,25]. Although these were not double-blind placebo-controlled trials, they showed that melatonin therapy is safe for both the mother and the fetus. Moreover, concerning PE, treatment with 10 mg x3/day of melatonin prolonged the interval from diagnosis to delivery by approximately-six days ($p < 0.05$), and fewer antihypertensive drugs were required to treat the disease compared to an historical cohort of controls ($p < 0.05$) [21]. On the contrary, treatment with 4 mg x2/day of melatonin from diagnosis to delivery in pregnancy complicated by FGR did not show an

improvement in birth weight ($p = 0.8$), but there is evidence of lower placental oxidative stress by lower placental concentrations of malondialdehyde (MDA), a marker of late stage lipide peroxidation ($p = 0.04$) [25].

The main characteristics and results of the study included are summarized in Table 3.

Discussion

Main findings

The main findings of this systematic review are that in pregnancies complicated by placental insufficiency, there is: firstly, a significant reduction in maternal systemic serum levels of melatonin, and secondly, a significant reduction in the expression of placental melatonin receptors.

Strengths and limitation

To our knowledge, this is the first systematic review on the role of melatonin in pregnancies complicated by placental insufficiency. The main limitations are the total number of studies included, the relatively small sample sizes, and the population heterogeneity, making it impossible to perform a meta-analysis and obtain reliable summary estimates. Despite these aspects, most studies obtained similar results when comparing uneventful pregnancies and pregnancies complicated by placental insufficiency. In those that did not find a significant association, there were some flaws in the inclusion criteria. In the group of studies that evaluated circulating levels of melatonin, the only one reporting higher levels of the indole in pregnancies complicated by placental insufficiency was Tranquilli *et al.* [16]; however, besides the small sample size, they also included women with an altered circadian rhythm of blood pressure and not only women with a strict diagnosis of PE [16]. Similarly, in the placental melatonin receptor group of study, the group of Yamamoto *et al.* found higher expression of MT1 receptor in the placentas of pregnancies with HDP; however, when stratified according to the subgroup of hypertension, expression was higher in cases with gestational hypertension, which is the milder form of the disease, lower in cases with PE and even more so in PE superimposed on chronic hypertension [20].

Interpretation

The importance of a normal circadian rhythm in pregnancy has been demonstrated by studies that showed that pregnant women working night shifts or exposed to jetlag were more likely to suffer adverse pregnancy outcomes such as miscarriage, preterm labor, and low neonatal birth weight [3]. Moreover, the maintenance of a circadian rhythm is also essential for the health of the cardiovascular system and to reduce the rate of hypertension. The effect of sleep disturbance patterns on maternal blood pressure and uterine perfusion has been addressed in the study by Tang *et al.* [27] that showed that maternal systolic, diastolic, and mean arterial blood pressure was significantly lower in women with longer duration and better quality of sleep. In contrast, poorer sleep quality was associated with higher resistance in the uterine arteries.

In pregnancies complicated by placental insufficiency, especially PE, there is evidence of an imbalance between the excessive production of reactive oxygen species (ROS) and defensive antioxidative mechanisms, such as the production of melatonin. The most acknowledged cause of impaired placental development is an insufficient remodeling of the spiral arteries in the first trimester, leading to increased uterine artery resistance. This triggers a cascade of events resulting in placental dysfunction, ischemia–reperfusion damage, increased placental production of ROS, reduced production of angiogenic factors (such as placental growth factor [PlGF] and pregnancy-associated plasma protein A [PAPP-A]), and increased production of antiangiogenic factors (soluble fms-like tyrosine kinase 1 [s-Flt1]) [1,28]. From this perspective, melatonin may play an essential role as a free radical scavenger, directly and through its numerous metabolites, and by stimulating the activity of antioxidant enzymes, such as glutathione peroxidase, in a circadian rhythm fashion [5]. The results from the group of Lanoix *et al.* [26], showing that the placenta can synthesize melatonin through the presence of the AANAT and ASMT enzymes on the chorionic villi, suggested that the pineal gland is not the only source of melatonin. They also showed that the chorionic villi express the two main melatonin receptors, MT1 and MT2, through which melatonin can exert its functions by systemic and autocrine routes [19]. The chorionic villi are formed by two major parts: the internal cytotrophoblast and the more external syncytiotrophoblast. The cytotrophoblast has proliferative and antiapoptotic functions and its cells fuse and form the more external syncytiotrophoblast, which does not have the ability to regenerate itself and is more exposed to oxidative stress. Damages of the cytotrophoblast are therefore reflected in lower production of syncytiotrophoblast cells and placental damage. Both syncytiotrophoblast and villous trophoblast cells are capable of synthesizing melatonin. The melatonin produced locally exerts its functions not only by interacting with MT1 and MT2 receptors but also through a receptor-independent mechanism. Due to its lipophilicity, melatonin crosses the cell membrane and can act as a free radical scavenger by activating directly different signaling pathways without needing a receptor-mediated mechanism [6]. The advantage of this autocrine production is that melatonin produced by the placenta can have a rapid action as an antioxidant agent. However, unlike the melatonin produced by the pineal gland, which follows a circadian rhythm, there is evidence that the placental production of melatonin is constant [29]. The topic has been debated because clock genes have been detected at the placental level [30]. The continuous availability of this hormone could be explained by the need to neutralize locally produced oxygen free radicals ("on-site protection" [5]), especially as the pregnancy progresses when the placenta becomes increasingly senescent. In addition, it could have a local effect by controlling the function of the placenta [29]. Receptor-independent action could, in

Table 3
Main characteristics and results of the included studies on the effect of maternal administration of melatonin in pregnancies complicated by placental insufficiency.

Authors, year of publication	Population (N) (type)	Weeks of evaluation	Controls (N)	Dosage	Primary outcome	Main results
Hobson et al., 2018 [34]	20 PE	$24–35^{+6}$	48	30 mg/day	• Maternal and perinatal safety • Prolongation of pregnancy	• Melatonin is safe • Melatonin prolongs the interval from diagnosis to delivery (mean 6 days; $p < 0.05$) • Melatonin reduces the antihypertensive drugs needed to treat hypertension
Miller et al., 2014 [25]	12 FGR	25–27	6	8 mg/day	• Maternal and perinatal safety • Levels of lipid peroxidation in FGR	• Melatonin is safe and tolerated • Melatonin reduces oxidative stress in FGR

PE: preeclampsia; FGR: fetal growth restriction; N: number.

this context, ensure faster action of the hormone for greater efficacy of the organ. In fact, *in vitro* placenta studies showed that melatonin has the ability to stabilize the villous trophoblast by inhibiting apoptosis of the cytotrophoblast through its antioxidant properties and action on MT1 and MT2 receptors, increasing the regeneration of the syncytiotrophoblast [29], and stabilizing placental homeostasis. This aspect may be of paramount importance in pregnancies complicated by placental insufficiency characterized by a primary dysfunction of the trophoblastic unit. As summarized in this review, the presence of lower systemic and placental levels of melatonin and lower expression and function of placental receptors may reflect placental impairment, specifically in the chorionic villi unit. *In vivo* studies have shown that exogenous administrations of melatonin can effectively increase its placental levels, as reported by Okatani *et al.* [30], who demonstrated higher melatonin concentration in chorionic villi of women who underwent chorionic villous sampling after being given an oral melatonin dose of 6 mg. Moreover, the activity of the antioxidant enzyme glutathione peroxidase was tested in chorionic homogenates between one and three hours after melatonin administration, and its activity increased significantly, with peak levels occurring at three hours ($p < 0.001$). Therefore, oral melatonin administration effectively increases melatonin placental concentration and its antioxidant activity but whether oral melatonin administration can reduce the dysfunction of pregnancies with placental insufficiency is still to be determined.

Historically, the treatment for PE is the delivery of the baby with the removal of the placenta. More recently, the introduction of effective screening programs able to identify women at high risk for PE followed by the daily administration of aspirin at a dose of 150 mg at 11–14 weeks of gestation has been shown to reduce by 62 % the rate of PE requiring delivery before 37 weeks of gestation [31]. However, aspirin administration is less effective for preventing late PE and FGR. In normal pregnancies, melatonin levels tend to be normal or lower in the first and second trimesters while they increase thereafter, reaching a peak after 32 weeks. This pattern possibly reflects the preparation of the pregnant uterus for parturition by being exposed to molecules that increase its sensitivity to the action of oxytocin. However, it could also express the need to balance the increased oxidative stress and metabolic demands of a senescent placenta and a growing fetus. From this perspective, increased melatonin production in the third trimester could be a critical factor in maintaining placental homeostasis towards the end of pregnancy.

Even though there are only two studies on the effect of melatonin administration on placental insufficiency, there is some evidence that using this indole in high-risk pregnancies could reduce oxidative stress, preserve placental function and stability, and improve fetal neurological development. [21,25] Moreover, the results on melatonin administration are promising in terms of neonatal outcomes due to the antioxidant action of the indole: data on animal studies demonstrated that the daily intravenous administration of 6 mg of melatonin in 14 FGR-induced ewes entailed an improvement of lipid peroxidation in the cortical white matter with an improvement of the organization and density of the white and grey matter and an axonal damage rejection evaluated by hematoxylin and eosin stain. However, larger prospective randomized trials are needed to establish the real effect of melatonin in these pregnancies, two of them currently ongoing: one evaluating the prophylactic role of melatonin in women at increased risk of PE [32], and one assessing the role of melatonin in promoting neurodevelopment in FGR infants [33].

Conclusions

As reviewed herein, the physiological and circadian pattern of melatonin secretion seems to be altered in pregnancies complicated by placental insufficiency. This is reflected by lower production of melatonin, with consequent lower systemic and placental concentrations, and lower expression of melatonin receptors, thus reducing the local release of the indole and its autocrine function. Further studies need to address if melatonin administration in pregnancy could prevent or improve the outcome of pregnancies complicated by pre-eclampsia and fetal growth restriction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2022.08.029.

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