

# Efficacy of Melatonin Administration in Pregnancy in Prevention of Neonatal Respiratory Distress Syndrome in Preterm Neonates: A Randomized Controlled Trial

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## Abstract

**Objective:** Respiratory Distress Syndrome (RDS) is a common complication in premature neonates due to immature lungs, and antenatal corticosteroid administration could reduce its incidence. We aim to investigate the role of antenatal melatonin administration in preventing RDS among women with placenta accrete spectrum who usually mandate early delivery.

**Materials and methods:** This is a single-blinded randomized controlled trial performed in a tertiary hospital among women with placenta accrete spectrum. The melatonin group received Melatonin 10 mg/daily for two weeks before elective cesarean section in addition to corticosteroids, and the control group just received corticosteroids. The RDS occurrence was compared between two groups.

**Results:** In total, 60 participants were involved in the study (30 in the melatonin group and 30 in the control group). RDS was diagnosed for five (16.7%) neonates in the melatonin group and nine (30.0%) neonates in the control group (P-value= 0.228). Among neonates with RDS, no neonate in the melatonin group required intubation, and six (66.7%) neonates intubation needed in the control group (P = 0.016).

**Conclusion:** Antenatal melatonin administration may reduce the need for intubation in preterm neonates with RDS, though the lower incidence of RDS observed in the melatonin group was not statistically significant. The small number of RDS cases limits the ability to draw definitive conclusions regarding intubation rates and hospitalization duration. Larger-scale, multicenter studies with long-term follow-up are needed to validate these findings and better understand melatonin's role in neonatal respiratory care.

**Keywords:** Melatonin; Respiratory Distress Syndrome; Placenta Accreta

## Introduction

Understanding the critical role of lung maturation in

late-stage fetal development underscores the importance of effectively managing fetal lung development and its subsequent impact on neonatal health, particularly in cases requiring early delivery, for various reasons. Conditions such as the placenta

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accreta spectrum (PAS) usually mandate early delivery (1-3), emphasizing the need for proactive management strategies. Respiratory distress syndrome (RDS) might result in other respiratory complications like pneumothorax, pulmonary hypertension, sepsis, and neonatal death (4). These situations make it crucial to administer appropriate management and prevention strategies. Antenatal corticosteroid therapy in women at risk of preterm delivery has demonstrated efficacy in reducing both the incidence and severity of respiratory distress syndrome (RDS) (5, 6).

Melatonin is a human hormone produced in the brain in response to darkness, and it is approved by the Food and Drug Administration (FDA) as a supplement (7) and it is safe during pregnancy and breastfeeding (8). Moreover, Melatonin has anti-inflammatory effects by reducing tissue restriction, scavenging free radicals, and reducing oxidative stress (9, 10). Also, melatonin activates various antioxidant enzymes that play key roles in neutralizing free radicals and safeguarding cells against oxidative harm (11-13).

Low melatonin levels are linked to the development of retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and late-onset sepsis, as supported by numerous studies (14). Studies have shown that melatonin administration during the late fetal and early neonatal stages holds promise in preventing lung damage (15), brain injury (16), and sepsis (17), offering potential health benefits and limiting complications occurring before and after delivery.

Animal and preclinical studies have suggested that melatonin may enhance lung maturation, mitigate oxidative stress-induced lung injury, and reduce inflammation in neonates (18, 19). Furthermore, clinical studies evaluating the direct administration of melatonin in neonates with RDS have demonstrated reductions in pro-inflammatory cytokines and improved clinical outcomes (20). While most studies have focused on melatonin administration after delivery and have been conducted in non-human models, Lee et al. demonstrated that maternally administered melatonin may help prevent fetal lung injury in rats (21).

Our goal is to explore the potential effects of taking melatonin during pregnancy on the occurrence of RDS in women who have PAS and require early delivery as part of a clinical trial. We aim to investigate the relationship between antenatal melatonin consumption

and RDS incidence in this population.

## Materials and methods

**Study design and population:** This is a single-blinded randomized controlled trial, which was performed at the Vali-e-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran between March 2023 and October 2023.

The inclusion criteria included singleton pregnancy, maternal age between 19 and 45 years, diagnosed with placenta accreta spectrum based on the Society for Maternal-Fetal Medicine (SMFM) criteria (22), and a gestational age between 32 and 34 weeks, ensuring that all neonates were preterm. Exclusion criteria included fetal anomalies, maternal underlying diseases, lack of consent to participate, and failure to adhere to the study protocol from administration until delivery. Before enrollment, all eligible women were informed about the study, with participants in the intervention group made aware of melatonin administration.

**Outcomes:** The primary outcome was comparing RDS in neonates of mothers who received Melatonin and mothers who did not. In addition, we compared intubation requirements, hospitalization days, APGAR score in the first and fifth minutes, and surfactant requirements between the two groups.

**Data collection and Measurements:** Participants were collected based on convenience sampling at the maternal-fetal clinic and randomly divided into two groups based on permuted block randomization. It was a superiority trial. The number of people needed for each group was 29, with power equal to 0.95 and type 1 error equal to 0.05 due to previous studies, and the Beta coefficient of 0.693 (23).

According to the dropout rate, 32 participants were considered for each group. The melatonin group received melatonin 10 mg/daily (2 tablets 5mg) for two weeks in addition to betamethasone, while the control group received only betamethasone. All pregnant women received two doses of betamethasone (each dose: 12 mg/intramuscular) at 28 weeks of gestation and one dose before delivery. All pregnant women underwent elective cesarean section due to suitable timing for pregnant women with PAS (22). The baseline characteristics, including maternal age, education, obstetrics history, type of PAS due to its invasion, maternal mortality, maternal ICU admissions, neonatal outcomes, including RDS, weight, sex, Apgar score, surfactant therapy, intubation, and hospitalization days are documented.

RDS is diagnosed based on clinical symptoms (increased work of breathing including tachypnea, nasal flaring, expiratory grunting, sub and intercostal retractions, reduced or absent breath sounds, cyanosis, and increased oxygen requirement), chest x-ray findings (a diffuse ground glass reticulogranular appearance with air bronchogram and low lung volume) (4) by an expert neonatologist. Surfactant was delivered in liquid form through an endotracheal tube and administered as a single bolus dose at a pace that the neonate could adequately tolerate with bolus administration. The first dose was 200 mg/kg, and the second dose was 100 mg/kg after 12 hours (24). The surfactant was administrated based on Canadian Pediatric Society (25).

**Statistical Analysis:** Statistical Package Social Sciences (SPSS) version 25 was used in the analysis. We used mean (standard deviation), median (minimum, maximum), and number (absolute percent) for quantitative data with normal distribution, quantitative data without normal distribution, and qualitative data, respectively. The normality was evaluated by the Kolmogorov-Smirnov test. Qualitative variables were analyzed using the chi-square test, and continuous quantitative variables with normal distribution were analyzed using the independent t-test. Mann-Whitney test was used for quantitative variables without normal distribution. A P-value less than 0.05 were considered statistically significant.

**Ethical Considerations:** The ethical committee of the Tehran University of Medical Science approved the study (code: IR.TUMS.IKHC.REC.1402.164), and It is registered in the Iranian Registry of Clinical Trials (code: IRCT20230801059003N1 on 2023-08-

16). The written consent was obtained from all participants, and The study was performed regarding the Helsinki Declaration (26).

**Data Availability:** The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

## Results

Overall, 64 participants were enrolled in the study. Of these, 32 were administered 10 mg of melatonin daily for two weeks, while the remaining participants served as the control group. Two participants in the melatonin group did not adhere to the prescribed regimen, and two participants in the control group opted to deliver at different hospitals. Consequently, 30 participants from each group were included in the final analysis (Figure 1).

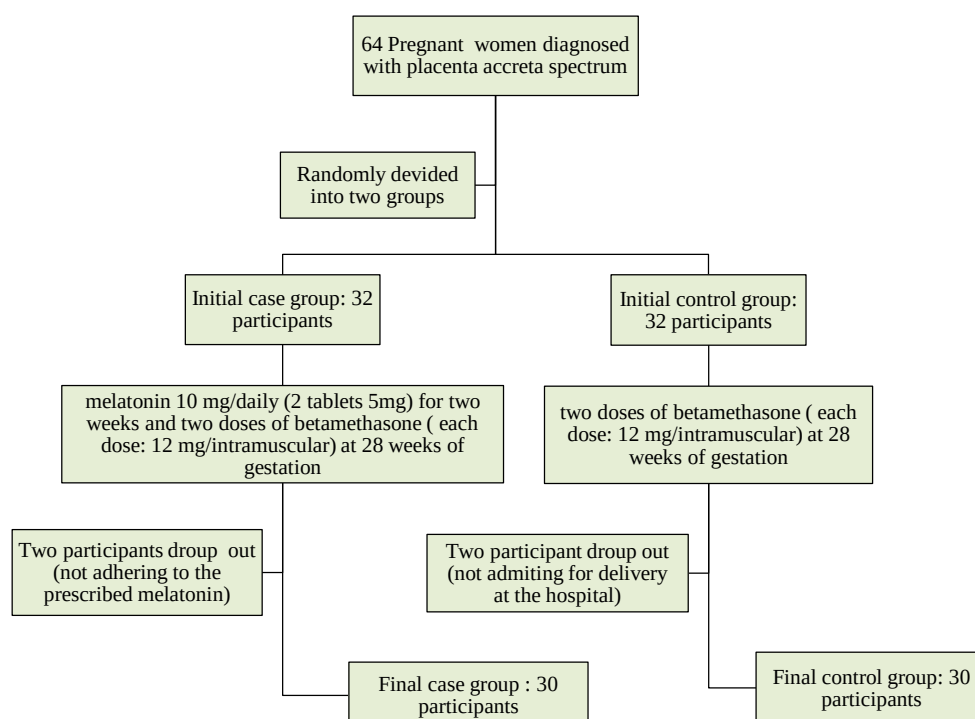
The age, education level, gestational age at delivery, obstetrics history, including gravid, parity, and cesarean history, and the type of the PAS were matched between the two groups (Table 1). All participants underwent elective cesarean section, and there was no mortality and ICU admission among women. There was not any dose interruption of melatonin recorded in the melatonin group, and no additional co-morbid conditions were mentioned.

Regarding neonatal outcomes, RDS was diagnosed for five (16.7%) neonates in the melatonin group, compared to 9 (30.0%) neonates in the control group (P-value= 0.222). The median of 1<sup>st</sup> and 5<sup>th</sup> minute Apgar scores in the melatonin group were 7.0 (3 to 8) and 9.0 (6 to 10), while there were 5.5 (1 to 9) and 8.0 (6 to 10) in the control group, respectively (P-value= 0.111, 0.083).

**Table 1.** The Baseline Characteristics of participants in the Trial

| Variables                           |                   | Melatonin group<br>(n=30) | Control group<br>(n=30) | P-value <sup>2</sup> |
|-------------------------------------|-------------------|---------------------------|-------------------------|----------------------|
| Age (years)                         |                   | 35.5(21,43)               | 35.6(23,45)             | 0.350                |
| Neonates sex (male)                 |                   | 15(50.0)                  | 16(53.3)                | 0.796                |
| Neonates weight (grams)             |                   | 2294(186)                 | 2378(267)               | 0.162                |
| Education                           | Before university | 27(90.0)                  | 26(86.7)                | 0.688                |
|                                     | University        | 3(10.0)                   | 4(13.3)                 |                      |
| Gestational age at delivery (weeks) | 33.3(32.2,35.5)   | 33.6(32.0,34.7)           | 0.618                   | 33.3(32.2,35.5)      |
| Gravid (number)                     |                   | 0.0(0,4)                  | 0.0(0,5)                | 0.523                |
| Parity (number)                     |                   | 0.0(0,3)                  | 0.0(0,4)                | 0.470                |
| Cesarean history                    |                   | 1.0(0,3)                  | 1.0(0,3)                | 0.639                |
| Type of PAS <sup>1</sup>            | Accreta           | 25(83.3)                  | 26(86.7)                | 0.615                |
|                                     | Increta           | 4(13.3)                   | 2(6.7)                  |                      |
|                                     | Percreta          | 1(3.3)                    | 2(6.7)                  |                      |

<sup>1</sup>: placenta accreta spectrum, <sup>2</sup>: p-value less than 0.05 is significant



**Figure 1.** The Flow Diagram of the Participants in the Study

Among neonates with RDS, no neonate in the melatonin group required intubation, while six (66.7%) neonates intubation was needed in the control group (P-value= 0.016). Also, 4 (80%) neonates with RDS needed surfactant therapy in the melatonin group, while 7 (77.8%) neonate needed it in the control group (P-value=0.725). The median of hospitalization days among neonates in the melatonin group was 1.0 (0,48) days, while 5.0 (0,16) days were in the control group (P-value=0.249). The neonatal outcomes between participants are shown in Table 2. No additional complications or neonatal mortality were reported. All neonates were discharged from the hospital in stable condition.

## Discussion

This study demonstrated that antenatal melatonin

administration did not significantly reduce the incidence of respiratory distress syndrome (RDS) in preterm neonates born to mothers with abnormal placental implantation. However, the incidence of RDS was lower in the melatonin group compared to the control group (16.7% vs. 30%). This investigation employed a novel approach by administering melatonin to pregnant women, in contrast to most studies, which primarily focus on direct neonatal administration, with only limited evidence from animal models (21,27). Notably, a significant reduction in the need for neonatal intubation was observed in the melatonin group compared to the control group. Gitto et al. (28) demonstrated that melatonin treatment reduces proinflammatory cytokines and improves clinical outcomes in infants with respiratory distress syndrome (RDS).

**Table 2.** The neonatal outcomes between participants whose Received Melatonin and Control Group

| Variables                                          | Melatonin group (n=30) | Control group (n=30) | P-value <sup>2</sup> |
|----------------------------------------------------|------------------------|----------------------|----------------------|
| RDS <sup>1</sup> (yes)                             | 5(16.7)                | 9(30)                | 0.222                |
| Apgar score                                        |                        |                      |                      |
| 1 <sup>st</sup> minute                             | 7.0(3,8)               | 5.5(1,9)             | 0.111                |
| 5 <sup>th</sup> minute                             | 9.0(6,10)              | 8.0(6,10)            | 0.083                |
| Surfactant therapy (among neonates with RDS) (yes) | 4(80)                  | 7(77.8)              | 0.725                |
| Hospitalization days                               | 1.0(0,48)              | 5.0(0,16)            | 0.249                |
| Intubation (among neonates with RDS) (yes)         | 0(0)                   | 6(66.7)              | 0.016                |

<sup>1</sup>: respiratory distress syndrome, <sup>2</sup>: p-value less than 0.05 is significant

Similarly, Gharehbaghi et al. (23) highlighted the beneficial effects of melatonin in reducing bronchopulmonary dysplasia (BPD), the duration of mechanical ventilation, mortality, and hospital stay. Although our study observed a reduction in the incidence of RDS in the melatonin group, the difference was not statistically significant, likely due to the small sample size. Notably, our findings showed a significant reduction in the need for intubation in the melatonin group.

Gharehbaghi et al. also reported a reduction in hospital stay, which was not statistically significant in our study, possibly due to the limited sample size and the lack of evaluation of other factors influencing hospitalization duration. Furthermore, Elfarargy et al. (29) identified significant improvements in clinical parameters and biomarkers associated with neonatal RDS, such as disease severity, oxidative stress, and inflammatory response, following melatonin administration in preterm infants. Melatonin, synthesized by the placenta during pregnancy through de novo placental synthesis (30), has demonstrated a favorable safety profile with no reported side effects (28,31). Consistent with these findings, our study observed no adverse effects associated with melatonin administration.

This study provides significant and novel insights into antenatal care by demonstrating a reduction in the need for intubation among preterm neonates with melatonin administration. The matching of neonates' sex, gestational age at delivery, and maternal age between the two groups minimized potential confounding factors, strengthening the validity of the findings. However, several limitations must be acknowledged. The relatively small sample size and single-center design may limit the generalizability of the results. Furthermore, the lack of long-term follow-up restricts the ability to evaluate the sustained effects of melatonin on neonatal outcomes beyond the immediate postnatal period. The absence of paraclinical data on pro-inflammatory cytokines also represents a significant limitation, as these biomarkers could provide additional mechanistic insights into the observed effects. Although hospitalization duration was reduced in the melatonin group, the difference was not statistically significant, and various factors influencing hospitalization rates warrant further investigation. Additionally, while both groups received antenatal corticosteroids, the high incidence of RDS observed in this study could be attributed to the subjective nature of RDS diagnosis and the

tertiary-level care setting of the treatment center. Moreover, the hospital records were incomplete, making it difficult to extract comprehensive neonatal data. As a result, we were unable to compare several variables, such as amniotic fluid volume and intubation duration, between the groups. Although our study observed a lower incidence of RDS in the melatonin group, the small number of RDS cases limits the ability to draw definitive conclusions regarding intubation rates and hospitalization duration. Future studies with larger, multicenter cohorts and comprehensive follow-up are essential to validate these findings and explore the broader implications of antenatal melatonin administration.

## Conclusion

This study suggests that antenatal melatonin administration may reduce the need for intubation among preterm neonates with RDS. However, while the incidence of RDS was lower in the melatonin group, the small number of RDS cases limits the ability to draw definitive conclusions regarding intubation rates and hospitalization duration. Additionally, the lack of long-term follow-up prevents assessment of sustained neonatal outcomes. Further large-scale, multicenter studies with extended follow-up are needed to validate these findings and better understand the potential role of melatonin in neonatal respiratory care.

## Conflict of Interests

Authors declare no conflict of interests.

## Acknowledgments

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