Evaluation of Melatonin Effect on Induction of Labor: - Double blinded Randomized Controlled trial

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Abstract

Background and Aim: Induction of labor (IOL) often leads to cesarean deliveries, particularly in nulliparous women, raising maternal risks and emotional distress. Melatonin, known to enhance uterine contractility by increasing oxytocin sensitivity and connexin 43 expression, may improve IOL outcomes. This trial evaluated oral melatonin's effect on reducing cesarean rates and shortening labor duration in primigravid women.

Methods: This double-blinded RCT was conducted at Ain Shams University Maternity Hospital (Egypt) from November 2023 to June 2024. Sixty primigravid women (40–41 weeks, Bishop score <6) were randomized 1:1 to receive oral melatonin (10 mg) or placebo with vaginal misoprostol (25 mcg) every 4–6 hours (max 5 doses). Labor progress followed WHO partogram protocols, with oxytocin augmentation as needed. Primary outcome was vaginal delivery success; secondary outcomes included induction-to-delivery time, labor stages, APGAR scores, and cesarean rates.

Results: The melatonin group demonstrated statistically significant improvements in labor outcomes compared to the placebo group, with a higher vaginal delivery rate (76.7% vs. 53.3%, p=0.047) and shorter induction-to-delivery time (10.2±2.1 vs. 13.8±3.4 hours, p<0.001). First-stage labor duration was reduced by nearly 3 hours (p<0.001), though second-stage labor and placental separation times were comparable (p≥0.27). Neonatal outcomes favored melatonin, with higher 1-minute (p=0.008) and 5-minute APGAR scores (p=0.04). Cesarean rates halved in the melatonin group (23.3% vs. 46.7%, p=0.03), while postpartum hemorrhage incidence remained similar (p=0.41). No maternal or neonatal adverse events were reported, confirming melatonin's safety and efficacy in optimizing labor outcomes.

Conclusion: The current study demonstrates that melatonin supplementation may be beneficial in reducing the duration of labor and cesarean section rates without negatively affecting neonatal outcomes.

Keywords: Induction of Labor, Melatonin.

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INTRODUCTION

Induced labor (IOL) generally aims for a vaginal birth. Still, data show that, in real-world scenarios, particularly in high-income countries, around 40% of women who undergo IOL may end up needing a caesarean section. This rate is notably higher among nulliparous women (those who have never given birth), despite evidence from randomized controlled trials suggesting that IOL does not significantly elevate caesarean rates [1].

The failure of induced labor (IOL) leading to a caesarean section can have significant emotional repercussions for women. This disappointment is not trivial, as research indicates a correlation between the necessity of a caesarean delivery and an increased risk of postnatal depression and post-traumatic stress disorder, especially among first-time mothers. Such mental health challenges can complicate the postpartum experience, highlighting the importance of addressing women's emotional well-being in the context of childbirth [2-3].

Women who undergo a caesarean section are often less likely to initiate breastfeeding compared to those who have a vaginal birth. Additionally, intrapartum caesarean deliveries are linked to higher maternal morbidity, which includes increased risks of postpartum hemorrhage, endometritis, venous thromboembolism, longer recovery times, and a greater likelihood of hospital readmission. These factors underscore the importance of considering the potential complications and long-term effects associated with caesarean sections on maternal health [4].

A caesarean section is associated with elevated risks of complications in future pregnancies, such as preterm birth, abnormal placentation, and uterine rupture. This highlights the importance of improving the success rates of induced labor (IOL), as doing so can positively impact the current labor experience and the health outcomes of future pregnancies. Addressing these challenges is crucial for enhancing maternal and neonatal health in the long term [5].

Melatonin, an endogenous hormone primarily produced by the pineal gland, shows increased levels during pregnancy, particularly due to de novo synthesis by the placenta. Healthy pregnant women exhibit higher concentrations of melatonin at night and during the day than non-pregnant women. As pregnancy progresses, maternal melatonin levels rise, peaking during labor and declining swiftly after childbirth. This pattern may play a role in various physiological processes associated with pregnancy and labor [6].

Melatonin enhances the sensitivity of the myometrium to contractions induced by oxytocin. When an immortalized myometrial cell line is treated with both melatonin and oxytocin, the contractile response is doubled compared to treatment with oxytocin alone. Additionally, melatonin promotes the expression of connexin 43, a crucial gap-junction protein that facilitates communication between myometrial cells and is essential for synchronizing uterine contractions. This suggests that melatonin may play a significant role in optimizing uterine function during labor [7].

Collectively, the observed effects of melatonin in both in vivo and in vitro studies indicate its potential biological role in regulating the timing of spontaneous labor and enhancing the effectiveness of uterine contractions during labor. Given that induced labor (IOL) with oxytocin typically occurs during the daytime, women miss the natural physiological rise in melatonin that usually precedes spontaneous labor at night. This leads to the hypothesis that administering melatonin at the onset of the induction process could lower the failure rate of IOL, potentially improving outcomes for women undergoing this procedure [8].

This study aimed to evaluate the effect of oral melatonin supplement on success of induction of labor.

PATIENTS AND METHODS

This randomized controlled trial (RCT) conducted at Ain Shams University Maternity Hospital from November 2023 to June 2024 involved a total of 60 pregnant women seeking induction of labor. The study received approval from the ethical committee of the Faculty of Medicine at Ain Shams University (FMASU 576/2023), and written consent was obtained from all participants. This double-blinded study aimed to explore the effects of melatonin on the success rates of induced labor.

Informed consent was obtained from all participants, provided in Arabic, and documented with the date and time. Confidentiality was maintained by assigning each participant a number corresponding to their initials, known only to the investigator. All procedures adhered to the Declaration of Helsinki.

Eligibility Criteria The inclusion criteria for the study required participants to be aged 18-39 years, primigravida, at a gestational age of 40-41 weeks, with a BMI between 20-35 kg/m², carrying a singleton pregnancy, having adequate amniotic fluid as confirmed by ultrasound, in a cephalic (vertex) presentation, with intact membranes, a Bishop Score of less than 6, and not in labor. Exclusion criteria included multiparas, individuals with a BMI over 35 kg/m² or under 20 kg/m², a history of any uterine incision, pre-existing medical conditions, antepartum hemorrhage, known allergies or contraindications to melatonin or misoprostol that could lead to anaphylactic shock, multiple pregnancies, any fetal congenital anomalies, abnormal fetal growth, non-reassuring or pathological cardiotocography (CTG), abnormal presentations, amniotic fluid issues, and intrauterine fetal demise (IUFD).

Outcome measures:

The primary outcome: A successful vaginal delivery.

The Secondary outcomes:

Induction-delivery time, the duration of the first stage of labor, the duration of the second stage of labor, and the time needed for placental separation. Additionally, the neonatal outcome assessed using the APGAR score, postpartum hemorrhage and the cesarean section rate.

Sample Size Justification: A power analysis was conducted using sample size software (PASS 15, Version 15.0.10) to determine the appropriate sample size for the study. With a power of 80% and a significance level of 0.05, we assumed a large effect size difference (d = 0.8) between pregnant women in labor who receive melatonin and those in the control group, specifically regarding the duration from labor induction to the onset of active labor. Based on these parameters, a minimum sample size of 60 pregnant women, with 30 participants in each group, was deemed adequate to meet the study's objectives (Swarnamani et al., 2020) [9].

Randomization, Allocation, Concealment, and Blinding: Randomization was executed using a computer-generated randomization sheet via PASS 15 (Version 15.0.10), occurring at a 1:1 ratio of melatonin to placebo. Packing and labeling of the jars were conducted by one of the supervisors. Participants in the study were randomly assigned to either jar (A) or jar (B). For allocation, eligible pregnant women were assigned to one of the two groups through central verification via phone calls from the supervisor. Concealed allocation was implemented to minimize selection bias. Both melatonin and placebo were indistinguishable and contained in individually pre-prepared jars by the supervisor, who was not involved in participant recruitment or trial execution. One jar contained a 10 mg melatonin capsule (Puritan's Pride® premium supplement) from Puritan Holbrook Company, while the other jar held a placebo capsule (sugar powder) produced by

EPICO Company (Index II). The jars were unsealed only after the recruitment of participants.

This study employed a double-blind design, meaning neither the researcher nor the participants knew whether melatonin or placebo was administered. During recruitment, each participant was identified and assigned a hospital number. All data collected from participants were labeled and stored solely using this hospital number.

Study Procedures

History and examination: Eligible pregnant women were assessed through a comprehensive clinical and obstetric history to exclude any history of uterine incision, medical disorders such as diabetes mellitus, severe preeclampsia, and hypertension, as well as known contraindications or hypersensitivity to melatonin or dinoprostone. Additionally, a thorough examination of maternal health was conducted, which included measuring pulse rate to identify tachycardia or bradycardia, blood pressure to check for hypertension or preeclampsia, and temperature to detect fever or hypothermia. Body Mass Index (BMI) was calculated to exclude morbid obesity (BMI >35 kg/m²) and morbid cachexia (BMI <20 kg/m²). Other maternal complaints, such as headache, blurred vision, nausea, vomiting, or palpitations, were noted to rule out side effects from medication or underlying health conditions. An abdominal examination was also performed to assess the number of fetuses (single or multiple), their lie and presentation, and fetal weight.

A vaginal examination was performed to assess various factors, including the Bishop score, which evaluates cervical dilation, position, length, station of the presenting part, and cervical consistency. The scoring is as follows: a score of 0 indicates a closed and firm cervix, 1-2 cm dilation, mid-position, and a station of -2; a score of 1 reflects 1-2 cm dilation, medium consistency, and a station of -2; a score of 2 indicates 3-4 cm dilation, an anterior position, and a station between -1 and 0; and a score of 3 shows dilation greater than 4 cm, a cervical length of less than 1 cm, and a station of +1 or more. The examination also included an assessment of the fetal membranes.

Investigations: Comprehensive laboratory investigations were conducted, including liver function tests, kidney function tests, complete blood count, prothrombin time, partial thromboplastin time, international normalized ratio, random blood glucose, complete urine analysis, and blood group with Rh factor. Additionally, obstetric ultrasound was performed to assess the placenta, amniotic fluid index, rule out any fetal abnormalities, and estimate fetal weight. To evaluate fetal well-being, a cardiotocography (CTG) was applied for half an hour to all participants prior to initiating any interventions.

Induction of labor:

In this study, participants were divided into two randomized groups: one group received a 10 mg oral capsule of melatonin along with a 25 mcg vaginal tablet of misoprostol, while the other group was given a placebo capsule with the same dose of misoprostol. After four to six hours, a vaginal examination was performed. If there was no improvement, both groups received a second dose of misoprostol and their respective melatonin or placebo capsules. This process could be repeated up to five doses if necessary. Fetal well-being was monitored through cardiotocography (CTG) after each dose, and patients were observed for signs of labor, including uterine contractions and cervical changes. The recommended regimen for vaginal PGE1 involved administering one cycle of a vaginal tablet, followed by additional cycles every four to six hours until a maximum of five doses were given, if labor was not established [10].

The study followed the commonly used protocol for active management of labor, known as the WHO modified partogram. The duration of the latent phase, defined as the time

from the start of induction to the active phase of labor (cervical dilation of 4 cm with three strong contractions lasting 40-60 seconds in a 10-minute span), was recorded. When the patient entered the active phase, artificial rupture of membranes was performed, and labor progress was monitored according to the partogram [10]. If uterine contractions were insufficient, oxytocin administration was initiated, following thorough counseling. Continuous CTG and monitoring of uterine contractions were implemented. The oxytocin was diluted in 500 ml of normal saline or Ringer's lactate and started at a specific schedule using an infusion pump. The dosage was adjusted every 20-30 minutes to achieve regular contractions of 50-80 mmHg intensity, lasting 45-60 seconds, occurring every three minutes.

Failed induction was defined as the administration of five doses of misoprostol without any change in the Bishop score within 24 hours. Labor arrest was noted if there was no progress in dilation or descent for at least two hours. For patients experiencing fetal distress or labor arrest, a cesarean section was performed. After delivery, various outcomes were recorded, including the duration of the first and second stages of labor, the time needed for placental separation, neonatal outcomes assessed by APGAR scores at one and five minutes, and monitoring for any postpartum complications, such as abnormal vital signs or postpartum hemorrhage.

Statistical Analysis: The analysis was conducted using SPSS for Windows version 20.0. Data were presented as range, mean, and standard deviation for numeric parametric variables; range, median, and interquartile range for numeric non-parametric variables; and as counts and percentages for categorical variables. To compare two independent groups, an independent Student's t-test was employed for numeric parametric variables, along with the mean difference and its 95% confidence interval (CI). For categorical variables, the chi-squared test was utilized, along with the risk ratio and its 95% CI. Binary logistic regression analysis was performed to estimate the association between good and poor responses and the measured variables. Receiver operating characteristic (ROC) curves were constructed to assess the validity of the measured variables as predictors of good or poor responses. Validity was presented in terms of sensitivity, specificity, positive and negative predictive values, and their corresponding 95% CIs, with a significance level set at 0.05.

Results

The CONSORT 2010 Flow Diagram (Figure 1) outlines the study process involving 70 participants assessed for eligibility. Out of these, 10 were excluded—6 for not meeting inclusion criteria and 4 who declined to participate. The remaining 60 participants were randomized into two groups: 30 received melatonin with misoprostol, while the other 30 received a placebo with misoprostol. During the follow-up, there were no reported losses to follow-up or discontinuations in either group. Ultimately, 30 participants from each group were analyzed.

Table 1 compares baseline characteristics between the melatonin and control groups, each consisting of 30 participants. The p-values for age, BMI, gestational age, and BISHOP score were 0.366, 0.672, 0.497, and 0.608, respectively. None of these p-values indicate statistically significant differences between the two groups, suggesting that they were comparable across all measured variables.

Figure (1): CONSORT 2010 Flow Diagram

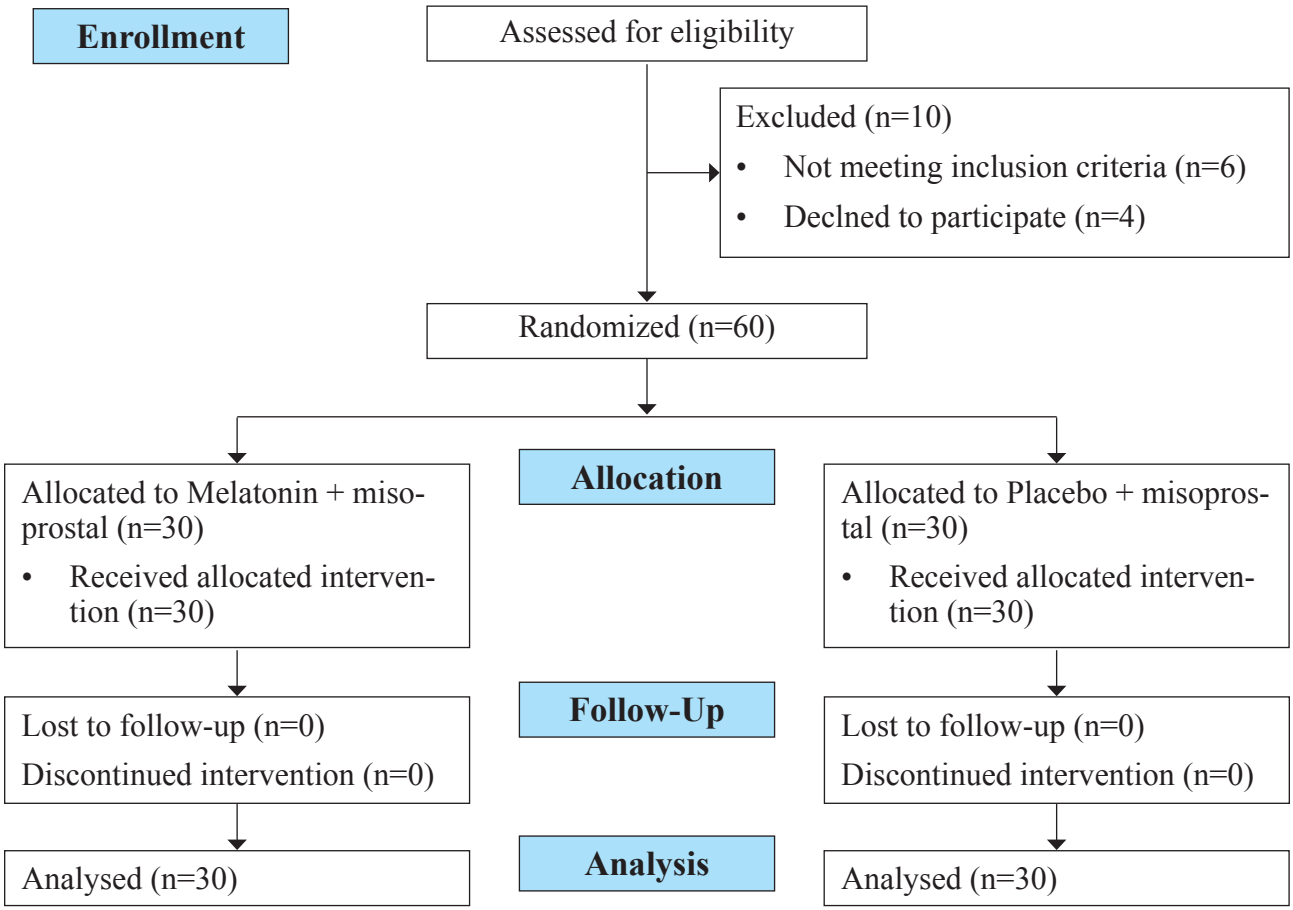

Table 2 presents the mode of delivery between the melatonin and control groups, each with 30 participants. The melatonin group had 4 cesarean deliveries (13.3%) compared to 12 (40.0%) in the control group, with a statistically significant p-value of 0.020. The vaginal delivery rate, which is the primary outcome, was higher in the melatonin group at 26 participants (86.7%) versus 18 (60.0%) in the control group. The relative risk of 0.33 indicates a significantly lower likelihood of cesarean delivery in the melatonin group, supported by a 95% confidence interval of 0.12–0.92.

Table 3 presents secondary outcomes comparing the melatonin and control groups. The measures show significant differences across all assessed parameters, with p-values below 0.05 for the induction delivery interval, first stage of labor, second stage of labor, and third stage of labor. The induction delivery interval was notably shorter in the melatonin group, indicating a potential benefit of melatonin on delivery timing. Additionally, both the first and second stages of labor were significantly reduced, suggesting improved efficiency in the labor process with melatonin administration. The third stage of labor also exhibited a significant decrease in duration. Overall, these findings indicate that melatonin may positively influence labor and delivery outcomes as secondary measures.

Table 4 compares the incidence of adverse events between the melatonin and control groups. For gastritis, the p-value was 0.254, indicating no significant difference between the groups, with a relative risk of 3.00 suggesting a higher occurrence in the melatonin group, though this was not statistically significant. Dizziness was reported with a p-value

of 0.181, also showing no significant difference, but with a relative risk of 2.67, indicating a higher likelihood in the melatonin group. Lastly, postpartum hemorrhage had a p-value of 0.999, demonstrating no difference between the groups, with a relative risk of 0.50. Overall, while there were adverse events noted in both groups, none reached statistical significance.

Table 5 compares the APGAR scores at one and five minutes between the melatonin and control groups. For the APGAR score at one minute, the p-value was 0.138, indicating no significant difference between the groups. Similarly, the APGAR score at five minutes had a p-value of 0.114, which also suggests no significant difference. Although the mean scores were higher in the melatonin group for both time points, these differences did not reach statistical significance. Overall, the findings indicate that melatonin administration did not have a measurable impact on neonatal outcomes as assessed by APGAR scores.

Table (1): Baseline characteristics between the studied groups

Variables		Melatonin group (Total=30)	Control group (Total=30)	p-value
Age (years)	**Mean±SD**	27.4±3.3	28.2±4.0	^0.366
	Range	20.0–36.0	21.0–37.0	
BMI (kg/m^2)	**Mean±SD**	29.8±2.0	29.6±1.9	^0.672
	Range	25.8–33.9	27.0–34.2	
Gestational age (week)	**Mean±SD**	40.1±0.3	40.2±0.4	^0.497
	Range	40.0–41.0	40.0–41.0	
BISHOP score	**Mean±SD**	3.5±0.7	3.6±0.8	^0.608
	Range	3.0–5.0	3.0–5.0	

Student t test , P>0.05 is not significant

Table (2): Mode of delivery between the studied groups (primary outcome, rate of vaginal delivery

Mode of delivery	Melatonin group (Total=30)	Control group (Total=30)	#p-value	Relative effect Relative risk 95% CI
Cesarean	4 (13.3%)	12 (40.0%)	**0.020***	0.33
Vaginal	26 (86.7%)	18 (60.0%)		0.12–0.92

Chi square test, p<0.05 is significant

Table (3): Duration of delivery phases between the studied groups(secondary outcomes)

Measures	Melatonin group (Total=26)	Control group (Total=18)	^p-value	Relative effect Mean±SE 95% CI
Induction delivery interval (hours)				
Mean±SD	15.3±1.3	20.0±2.1	**<0.001***	-4.7±0.5
Range	13.2–18.0	16.5–23.7		-5.8–-3.6
First Stage of labor (hours)				
Mean±SD	15.1±1.9	17.3±3.0	**0.011***	-2.2±0.8
Range	12.0–18.0	12.0–20.0		-3.9–-0.5
Second Stage of labor (hours)				
Mean±SD	0.9±0.4	1.4±0.5	**0.002***	-0.5±0.1
Range	0.5–1.5	0.5–2.0		-0.7–-0.2
Third Stage of labor (minutes)				
Mean±SD	6.5±2.5	8.3±2.9	**0.0137***	-1.7±0.8
Range	4.0–11.0	5.0–14.0		-3.4–-0.1

Student t test , P<0.05 is significant, P<0.001 is highly significant

Table (4): Adverse Events Comparison Between Melatonin and Control Groups

	Melatonin group (Total=30)	Control group (Total=30)	§p-value	Relative effect Relative risk 95% CI
Gastritis Symptoms	6 (20.0%)	2 (6.7%)	0.254	3.00 (0.66–13.7)
Dizziness	8 (26.7%)	3 (10.0%)	0.181	2.67 (0.78–9.09)
Postpartum hemorrhage	1 (3.3%)	2 (6.7%)	0.999	0.50 (0.05–5.22)

Chi square test, p>0.05 is not significant

Table (5): Neonatal APGAR scores between the studied groups

Measures	Melatonin group (Total=30)	Control group (Total=30)	^p-value	Relative effect Mean±SE 95% CI
APGAR 1				
Mean±SD	7.7±1.2	7.3±1.2	0.138	0.5±0.3
Range	4.0–9.0	4.0–9.0		-0.2–1.1
APGAR 5				
Mean±SD	8.9±1.2	8.4±1.2	0.114	0.5±0.3
Range	5.0–10.0	5.0–10.0		-0.1–1.1

DISCUSSION

Concerns regarding the rising rates of IOL before 41 weeks, without maternal or fetal complications, are growing globally due to the potential iatrogenic harm to both mother and baby. Obstetric interventions have increased significantly, yet without a reduction in stillbirths and a rise in early-term births (37–38 weeks) that negatively impact childhood neurodevelopment. Specific worries include higher rates of caesarean sections, NICU admissions, and long-term neurodevelopmental issues for infants born before 39 weeks or after 41 weeks. Additionally, perinatal morbidity indicators like episiotomy, postpartum hemorrhage, and maternal sepsis are also on the rise.

In humans, spontaneous labor in term pregnancies is more often initiated, and more babies are born at night, a time when the pineal gland secretes the hormone melatonin into the circulation. Melatonin receptor expression on the human pregnant uterus has been reported only during labor (Swarnamani et al., 2020).

Our results interpretation and their comparison to similar studies

As regards efficacy of Melatonin for Labor Induction, one of the most significant outcomes of the study was that cesarean section rates were significantly lower in the melatonin group compared to the control group. Specifically, only 13.3% of women in the melatonin group required cesarean sections, compared to 40% in the control group ($p = 0.020$). This suggests that melatonin may play a beneficial role in increasing the rates of vaginal delivery, potentially improving the efficiency of labor induction. The relative risk of cesarean section was reduced by 67% in the melatonin group, which indicates that women who received melatonin were significantly less likely to undergo cesarean sections compared to those who did not.

As regards labor duration, the study demonstrated that melatonin significantly shortened the overall induction-to-delivery interval and the durations of all stages of labor. The induction-to-delivery interval was notably shorter in the melatonin group, with a mean of 15.3 hours compared to 20.0 hours in the control group ($p < 0.001$). This reduction in labor time suggests that melatonin may enhance labor progression, possibly by improving uterine contractility or enhancing the body's response to induction agents. Each stage of labor was also shortened in the melatonin group, including the first stage (15.1 hours vs. 17.3 hours, $p = 0.011$), the second stage (0.9 hours vs. 1.4 hours, $p = 0.002$), and the third stage (6.5 minutes vs. 8.3 minutes, $p = 0.0137$). These findings indicate that melatonin may help reduce labor duration, potentially minimizing the risks associated with prolonged labor.

The role of melatonin in the onset of active labor has not been extensively researched; however, evidence indicates that increased myometrial expression of melatonin receptors is associated with preterm birth, suggesting a potential influence. Additionally, melatonin has been shown to enhance the sensitivity of the myometrium to contractions induced by oxytocin. [11]

Sharkey et al. (2009) investigated the impact of melatonin on uterine contractility in telomerase-immortalized human myometrial cells. Their findings indicated that combining melatonin with oxytocin led to a twofold increase in contractile response compared to oxytocin alone. Additionally, melatonin enhanced the expression of connexin 43, a protein essential for communication between myometrial cells and the coordination of uterine contractions. Overall, these results suggest that melatonin may influence spontaneous labor timing and improve uterine contractions' effectiveness during labor [7].

Rahman et al. (2019) studied the effect of light-induced melatonin modulation on uterine contractions in women during the late third trimester, finding a positive correlation

between melatonin levels and contractions as women approach term (35-39 weeks). Specifically, for every 10 pg/mL*h increase in melatonin, uterine contractions increased by 1.4 to 2.1 every 30 minutes, indicating its role in stimulating labor progression. Additionally, melatonin enhances the effects of oxytocin, meaning that even lower doses of oxytocin can effectively induce contractions when combined with melatonin. This combination could reduce the side effects associated with high oxytocin use, providing a potentially safer alternative for labor induction. [12].

Regarding neonatal outcomes, our study found no significant differences between the melatonin and control groups regarding Apgar scores. The Apgar score at 1 minute was slightly higher in the melatonin group (mean = 7.7) compared to the control group (mean = 7.3), but this difference was not statistically significant ($p = 0.138$). Similarly, the 5-minute Apgar scores were comparable between the two groups, with a mean score of 8.9 in the melatonin group and 8.4 in the control group ($p = 0.114$). These results suggest that melatonin does not hurt neonatal health, as both groups maintained healthy Apgar scores within the normal range.

In concordance with our study, Khezri et al. (2019) [13] evaluated the effects of melatonin on both maternal and neonatal outcomes. No adverse effects were observed in newborns whose mothers received melatonin before a cesarean section. The study concluded that melatonin had no significant impact on neonatal outcomes, and all newborns were reported to be free of complications. This study also noted that the APGAR scores of neonates were not significantly different between the melatonin and placebo groups at 1 and 5 minutes after birth.

The study also evaluated maternal side effects. Although gastritis and dizziness were reported more frequently in the melatonin group, with 20% and 26.7% of women experiencing these side effects, respectively, these differences were not statistically significant compared to the control group. Importantly, postpartum hemorrhage rates were low and similar between the groups, with no significant difference observed ($p = 0.999$). This finding suggests that melatonin does not increase the risk of bleeding complications, further supporting its safety profile during labor induction.

Several studies have investigated the potential of melatonin in reducing blood loss during labor and cesarean sections. Khezri et al. (2019) [13] explored this by administering melatonin sublingually in doses of 6 mg before a cesarean section. They observed a significant reduction in blood loss, as measured by the weight of materials used during surgery (e.g., gauze), in the melatonin group compared to a placebo group. However, while statistically significant, the reduction in blood loss was not deemed clinically meaningful. Moreover, melatonin did not significantly decrease the volume of blood collected in the suction bottles post-delivery, but it did lead to a smaller decline in hemoglobin levels post-surgery.

Similarly, Jayashree et al. (2021) [14] found a slight reduction in blood loss following cesarean section in patients given melatonin (6 mg). However, the differences between the melatonin and placebo groups were not statistically significant. The measured blood loss from incision to the end of surgery and in the first two hours postpartum remained comparable between the groups, showing that melatonin's effect on postpartum hemorrhage was modest.

The side effects of melatonin, particularly in labor and cesarean section settings, have also been investigated in various studies. In the Khezri et al. (2019) trial [13], common side effects included sedation, with the group receiving 6 mg of melatonin displaying higher levels of calmness and orientation during surgery compared to the placebo group. Headaches were also more frequent in the 6 mg melatonin group, with a statistically significant increase in incidence compared to the

placebo and lower-dose groups. Other side effects, such as nausea, vomiting, pruritus, and respiratory depression, were observed but did not differ significantly between the melatonin and control groups.

In the Jayashree et al. (2021) [14] study, two patients in the melatonin group reported nausea, but the difference between the melatonin and placebo groups was not statistically significant. Overall, side effects in this study were mild, with no severe adverse reactions reported.

The study provides compelling evidence that melatonin supplementation may reduce the need for cesarean sections and shorten labor duration, without adverse effects on neonatal outcomes. These findings support the hypothesis that melatonin enhances uterine contractions, as previously suggested by other studies like that of Rahman et al., (2019). However, until now, no previous studies evaluated the effect of exogenous melatonin on the progression of labor, neonatal or maternal outcomes [12].

Safety is a paramount concern when considering any intervention during pregnancy. Vine et al., (2021) provided preliminary evidence suggesting that melatonin supplementation during late pregnancy is safe [15].

As regards implications for clinical practice, these findings have important implications for clinical practice, particularly in the context of labor induction. The use of melatonin could be explored as a safe, cost-effective method to improve labor outcomes, reduce the need for cesarean sections, and shorten labor durations. This could be especially valuable in settings where labor induction is frequently necessary, and reducing cesarean section rates is a priority for improving maternal and neonatal health outcomes. Further research, especially larger randomized controlled trials, could help validate these findings and establish melatonin as a standard intervention in labor management protocols.

The strength points of this study:

One of the study's primary strengths is its use of a double-blinded randomized controlled trial (RCT) design. This methodological approach is considered the gold standard in clinical research because it minimizes bias and allows for a clear, unbiased comparison between the melatonin and control groups. Additionally, the study had a well-defined and focused objective, specifically aiming to evaluate the effect of melatonin on the success of labor induction. This clear focus enhances the relevance and applicability of the findings to clinical practice.

Moreover, the study's comprehensive approach to outcome measures is another notable strength. By assessing a range of clinically relevant outcomes—including the rate of cesarean delivery, the duration of different labor phases, neonatal outcomes like APGAR scores, and maternal side effects—the study provides a robust and holistic assessment of melatonin's impact on the labor process. The significant findings related to labor duration and cesarean delivery rates further underscore the potential clinical impact of melatonin, suggesting that it could have a tangible and beneficial effect on the labor process.

Limitations of the Study:

Despite its strengths, the study also has several limitations that must be considered. The small sample size of only 60 participants is a significant limitation, as it restricts the generalizability of the findings. A small sample size increases the risk of type II errors, where true effects may not be detected, and limits the statistical power to find significant differences between the study groups.

Another limitation is that the study was conducted at a single center, Ain Shams University Maternity Hospital. This may limit the findings' applicability to other settings, as the results may not be generalizable to different populations or healthcare environments. To confirm the results across various settings, multi-center trials are necessary.

Another drawback is the short follow-up duration of the study. The research primarily focused on immediate labor outcomes without considering long-term follow-up, which limits the ability to assess melatonin's long-term safety and efficacy for both mothers and neonates. Additionally, the study's neonatal outcome measures were limited to APGAR scores. Important neonatal outcomes, such as long-term neurodevelopmental effects, were not assessed, restricting the understanding of melatonin's full impact on neonatal health.

CONCLUSION

In conclusion, this study demonstrates that melatonin supplementation may be beneficial in reducing the duration of labor and cesarean section rates without negatively affecting neonatal outcomes.

REFERENCES

1. Mamieh A, Saha K, Alasaadi S, Holman SL, Veintemilla-Burgos F, Santistevan L, Paul SR, Kamel M, Godpower P, Reddy Pesaru L. Induction of Labor: A Narrative Review on Cost Efficiency in Maternity Care. Cureus. 2024 Oct 12;16(10):e71302. doi: 10.7759/cureus.71302. PMID: 39529780; PMCID: PMC11552203.
2. Grisbrook MA, Dewey D, Cuthbert C, McDonald S, Ntanda H, Giesbrecht GF, Letourneau N. Associations among Caesarean Section Birth, Post-Traumatic Stress, and Postpartum Depression Symptoms. Int J Environ Res Public Health. 2022 Apr 18;19(8):4900. doi: 10.3390/ijerph19084900. PMID: 35457767; PMCID: PMC9025262.
3. Dekel S, Ein-Dor T, Berman Z, Barsoumian IS, Agarwal S, Pitman RK. Delivery mode is associated with maternal mental health following childbirth. Arch Womens Ment Health. 2019 Dec;22(6):817-824. doi: 10.1007/s00737-019-00968-2. Epub 2019 Apr 30. PMID: 31041603; PMCID: PMC6821585.
4. Singh J, Scime NV, Chaput KH. Association of Caesarean delivery and breastfeeding difficulties during the delivery hospitalization: a community-based cohort of women and full-term infants in Alberta, Canada. Can J Public Health. 2023 Feb;114(1):104-112. doi: 10.17269/s41997-022-00666-0. Epub 2022 Jul 28. PMID: 35902540; PMCID: PMC9849537.
5. Taylor L, Simpson J, Roberts C, Olive E, Henderson-Smart D. Risk of complications in a second pregnancy following caesarean section in the first pregnancy: A population-based study. The Medical Journal of Australia. 2005;183:515-519. doi: 10.5694/j.1326-5377.2005.tb07152.x.
6. Verteramo R, Pierdomenico M, Greco P, Milano C. The Role of Melatonin in Pregnancy and the Health Benefits for the Newborn. Biomedicines. 2022 Dec 14;10(12):3252. doi: 10.3390/biomedicines10123252. PMID: 36552008; PMCID: PMC9775355.
7. Sharkey JT, Puttaramu R, Word RA, Olcese J. Melatonin synergizes with oxytocin to enhance contractility of human myometrial smooth muscle cells. J Clin Endocrinol Metab. 2009 Feb;94(2):421-7. doi: 10.1210/jc.2008-1723. Epub 2008 Nov 11. PMID: 19001515; PMCID: PMC2730229.
8. Li Q, Zheng T, Chen J, Li B, Zhang Q, Yang S, Shao J, Guan W, Zhang S. Exploring melatonin's multifaceted role in female reproductive health: From follicular development to lactation and its therapeutic potential in obstetric syndromes. Journal of Advanced Research. 2025; 70:223-242.
9. Swarnamani K, Davies-Tuck M, Wallace E, Mol BW, Mockler J. A double-blind randomised placebo-controlled trial of melatonin as an adjuvant agent in induction of labour (MILO): a study protocol.

BMJ open. 2020; 10(2):e032480.

10. National Institute for Health and Care Excellence (NICE). (2021, November 4). Inducing labour (NICE guideline NG207). https://www.nice.org.uk/guidance/ng207/resources/inducing-labour-pdf-66143719773637
11. Sagrillo-Fagundes L, Soliman A, Vaillancourt C. Maternal and placental melatonin: actions and implication for successful pregnancies. Minerva Ginecol. 2014 Jun;66(3):251-66. PMID: 24971781.
12. Rahman SA, Bibbo C, Olcese J, Czeisler CA, Robinson JN, Klerman EB. Relationship between endogenous melatonin concentrations and uterine contractions in late third trimester of human pregnancy. J Pineal Res. 2019 May;66(4):e12566. doi: 10.1111/jpi.12566. Epub 2019 Mar 10. PMID: 30739346; PMCID: PMC6453747.
13. Khezri MB, Reihany MD, Dabbaghi Ghaleh T, Mohammadi N. Effect of Melatonin on Blood Loss After Cesarean Section: A Prospective Randomized Double-Blind Trial. J Obstet Gynaecol India. 2019 Oct;69(5):436-443. doi: 10.1007/s13224-019-01205-7. Epub 2019 Apr 24. PMID: 31598047; PMCID: PMC6765044.
14. Jayashree V, Vanathi R, Baby M. Effect of melatonin in reducing blood loss during and after caesarean section. Int J Clin Obstet Gynaecol 2021;5(6):227-231. DOI: 10.33545/gynae.2021.v5.i6d.1085
15. Vine T, Brown GM, Frey BN. Melatonin use during pregnancy and lactation: A scoping review of human studies. Braz J Psychiatry. 2022 May-Jun;44(3):342-348. doi: 10.1590/1516-4446-2021-2156. PMID: 34730672; PMCID: PMC9169489.