

Circadian timing of antenatal corticosteroids: Impact on neonatal respiratory support and phototherapy requirements

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Abstract

This study aimed to investigate the impact of Antenatal Corticosteroid (ACS) administration timing, aligned with maternal circadian cortisol rhythms, on neonatal outcomes in pregnancies at risk of preterm birth. A total of 262 singleton pregnancies between 26+0/7 and 33+6/7 weeks of gestation that received ACS were retrospectively analyzed. Participants were categorized into three groups based on the timing of the first ACS dose: morning (03:00–12:00), daytime (12:00–21:00), and evening (21:00–03:00). Neonatal outcomes, including respiratory support type, phototherapy requirement, and Neonatal Intensive Care Unit (NICU) length of stay, were compared. Significant differences were observed among groups: the evening group had the longest NICU stay (20 days vs. 18 days, $p = 0.001$), the highest rate of Continuous Positive Airway Pressure (CPAP) use (84.6% vs. 55.2%, $p = 0.001$), and the greatest need for phototherapy (46.2% vs. 19.3%, $p = 0.036$). Logistic regression analysis identified ACS timing as an independent predictor of phototherapy requirement, with morning administration associated with the lowest risk ($p = 0.002$, OR = 9.81, 95% CI: 2.31–41.69). These findings suggest that the efficacy of ACS may depend on maternal circadian rhythm, and that morning administration could optimize respiratory outcomes, reduce phototherapy needs, and shorten NICU stay. Aligning ACS dosing with maternal cortisol peaks may therefore enhance perinatal outcomes and warrants validation in prospective studies.

Keywords: Antenatal corticosteroids, Circadian rhythm, Preterm birth, Neonatal outcomes, Phototherapy, Respiratory support

Introduction

Preterm Birth (PTB), defined as delivery prior to 37 completed weeks of gestation, represents a significant global public health challenge, with adverse neonatal outcomes, including morbidity and mortality, occurring with increasing frequency in proportion to the gestational age at birth (1). Evidence indicates that tocolytic drugs, used to prevent PTB, delay the onset of labour by a period of between 48 hours and seven days compared to no treatment (2). They also provide the opportunity for the Administration Of Antenatal Corticosteroids (ACS). In light of the evident advantages and low risk profile, a single course of ACSs can be regarded as the standard of care for women at risk of PTB in perinatal and neonatal mortality, Respiratory Distress Syndrome (RDS), Intraventricular Haemorrhage (IVH) and necrotising enterocolitis (NEC) (3). ACSs are fluorinated corticosteroids that exhibit glucocorticosteroid activity with no accompanying mineralocorticoid effect (4). The impact of modifying the pharmacokinetics of ACS in accordance with circadian rhythms on efficacy has thus remain

uninvestigated.

Pregnancy is characterized by a transient state of hypercortisolism, driven by elevated levels of CRH and ACTH (5). Notwithstanding the aforementioned increase in cortisol levels, it is established that the circadian cortisol rhythm remains intact, exhibiting a profile comparable to that observed in non-pregnant individuals (6). There is a paucity of extant studies on the circadian rhythm of human fetal cortisol. A study examining the hourly variation of fetal umbilical artery cortisol levels revealed the presence of a 24-hour circadian rhythm, although this rhythm exhibited some differences from the maternal cortisol pattern (7). In the same study revealed that maximum fetal umbilical artery cortisol values were recorded at 12:00-14:00 and 16:00-18:00, and minimum values were observed at midnight-02:00 and 04:00-06:00. Cortisol levels reach their peak at 8:00 a.m. and subsequently decline at 12:00 p.m in the maternal diurnal rhythm (8).

The hypothesis of this study is that ACS application in PTB risk has a circadian effect rhythm, similar to the

circadian cortisol rhythm, and may affect perinatal outcomes. The perinatal outcomes that were considered to be potentially affected by ACS application included APGAR score, umbilical artery blood gas pH value, the necessity for neonatal Intensive Care Unit (NICU) admission, the length of stay in the NICU, the requirement for phototherapy, the requirement for ventilation support and the type of ventilation required. To test this hypothesis, a retrospective observational study was planned, and the timing of ACS application in pregnant women admitted with PTB risk was recorded, with the aim of analyzing the relationship between ACS administration and perinatal outcomes.

Methods

Study design and participants

This retrospective study included 262 pregnant women who had administered ACS treatment for PTB risk management at Mersin University Faculty of Medicine Hospital Perinatology Clinic between January 2018 and December 2022. The study was approved by the Mersin University Clinical Research Ethics Committee (Decision No. 2023/42) and adhered to the universal standards outlined in the Declaration of Helsinki. All data were obtained from the hospital's electronic database. Due to the retrospective design of the study and the use of anonymized data extracted from the hospital's electronic database, the need for informed consent was waived by the Ethics Committee. This waiver aligns with national regulations and the Declaration of Helsinki guidelines for retrospective studies involving anonymized data.

Inclusion criteria: The singleton pregnancy meets the criteria for a risk of preterm birth between 26+0/7 and 33+6/7 weeks of gestation. In accordance with our clinical protocol and current guidelines (9), all women were administered two 12-mg doses of betamethasone intramuscularly, with a 24-hour interval between doses, to accelerate fetal lung maturity. Patients with premature rupture of membranes were initiated on a combination of intravenous ampicillin and oral azithromycin (10). Those experiencing contractions were administered oral nifedipine as a tocolytic agent (11), while magnesium sulfate therapy was employed as a neuroprotective agent in gestations <32+0/7 weeks

(12). The perinatal processes, encompassing pregnancy follow-up, delivery, and neonatal care, were conducted at our hospital for all pregnant women enrolled in the study. In our clinic, all premature births are attended by a team comprising a paediatric resident, a neonatology fellow and a neonatal nurse.

Exclusion criteria: Maternal chronic disease, pregnancy achieved by assisted reproductive technology, ACS treatment applied after 34 weeks of gestation, known or suspected fetal anomaly and aneuploidy, missing data.

Determination of ACS circadian rhythm

Hospital database records were used to determine the exact time of the initial dose of ACS for all patients enrolled in the study. Maternal cortisol levels display a circadian regularity, rising from 03:00, peaking between 12:00 and 13:00, and subsequently decreasing to their nadir between 19:00 and 01:00 (13, 14). To analyze the effect of the timing of ACS administration on perinatal outcomes in parallel with the circadian cortisol rhythm, participants were divided into three groups according to the time of receiving the first ACS dose: 03:00 AM - 12:00 PM, 12:00 PM - 09:00 PM and 09:00 PM - 03:00 AM.

Statistical analysis

Data analysis was performed using SPSS software, version 26 (IBM Corp., Armonk, NY, USA) and jamovi (2024 - version 2.5). We assessed data normality using Kolmogorov-Smirnov tests, Shapiro-Wilk tests and visual inspection of histograms. For variables that followed a normal distribution, we compared group differences using independent t-tests and expressed results as mean $\pm$ Standard Deviation (SD). Variables that did not follow a normal distribution were analyzed using the Mann-Whitney U test to compare median values, which are reported as median (range). Categorical variables were assessed using the chi-squared test, with results presented as counts and percentages (n, %). Logistic regression analysis was used to investigate predictors of phototherapy requirement. The effectiveness of this model in determining the need for phototherapy was assessed using ROC curve analysis. Statistical significance was set at a p-value of less than 0.05, with all tests performed as two-tailed.

Results

This study investigated the effect of adjusting the timing of ACS administration according to circadian rhythm on perinatal outcomes in pregnant women followed up for the risk of PTB. A total of 262 pregnant women at risk of PTB who met all inclusion and exclusion criteria were included in the study. The participants were divided into three groups based on the timing of the administration of ACS, in alignment with the circadian cortisol rhythm. The morning group consisted of 98 pregnant women whose ACS was administered between 03:00 AM and 12:00 PM, the daytime group consisted of 123 pregnant women

whose ACS was administered between 12:00 PM and 09:00 PM, and the evening group consisted of 41 pregnant women whose ACS was administered between 09:00 PM and 03:00 AM.

Table 1 presents the baseline characteristics of the participants, the distribution of etiologies causing PTB risk, the gestational age at which ACS was administered, and the interval between ACS and delivery. The groups demonstrated homogeneity with regard to gravidity, parity, gestational age (GA) at which ACS was administered, the interval between ACS administration and delivery, the aetiology of PTB and MgSO₄ administration ($p>0.05$).

Table 1. Baseline characteristics of groups categorized by timing of Antenatal Corticosteroid (ACS) administration

Characteristics		Morning (03:00 AM - 12:00 PM, n=98)	Daytime (12:00 PM - 09:00 PM, n=123)	Evening (09:00 PM - 03:00 AM, n=41)	p-value
Maternal age (years)		29.59 ± 6.61	30.15 ± 6.21	30.02 ± 6.05	0.809
Gravidity		2.68 ± 1.81	2.42 ± 1.47	2.49 ± 1.50	0.494
Parity		1.24 ± 1.26	1.06 ± 1.08	0.90 ± 1.04	0.263
PTB etiology	PTL with intact membranes	36 (36.7%)	35 (28.5%)	14 (34.1%)	0.094
	PPROM	25 (25.5%)	25 (20.3%)	14 (34.1%)	
	PIH	21 (21.4%)	47 (38.2%)	9 (22.0%)	
	Other	16 (16.3%)	16 (13.0%)	4 (9.8%)	
GA at ACS Administration (weeks)		31.82 ± 3.24	31.58 ± 3.39	31.83 ± 3.09	0.839
ACS Treatment-to-Delivery Interval (days)		5.95 ± 8.43	6.17 ± 8.15	5.93 ± 12.20	0.978
Use of MgSO ₄ (%)		28 (28.6%)	43 (35.0%)	15 (36.6%)	0.517

PTB, Preterm birth; PTL, Preterm Labour; PPRM, preterm prelabour rupture of the membranes; PIH, pregnancy-induced hypertension; GA, gestational age; ACS, antenatal corticosteroids

Table 2 presents the effects of ACS administration according to circadian cortisol rhythm in the groups. No statistically significant difference was observed between the groups in terms of GA at birth, birth weight, first- and fifth-minute Apgar scores, gender distribution, umbilical cord arterial pH values, NICU admission, surfactant requirement, and neonatal death. The rate of cesarean section was lowest in the evening group (73.2%) and highest in the daytime group (91.1%), with a statistically significant difference observed between the groups ($p = 0.012$). The number of days of stay in the NICU was 20 days in the evening group; there was a statistically significant difference from the morning (18 days) and daytime (18 days) groups ($p=0.001$).

Table 2 also highlights the key neonatal outcomes

that demonstrated statistical significance. There was a statistically significant difference between the groups regarding the primary type of ventilation support ($p = 0.001$). The ventilation rate on room air was highest in the daytime group (21.2%) and lowest in the morning group (13.8%). The need for high-flow nasal cannula (HFNC) was greatest in the morning group (17.2%), while no patients in the evening group required HFNC. Regarding continuous positive airway pressure (CPAP) ventilation, its use was most frequent in the evening group (84.6%) and least frequent in the daytime group (55.2%). The rate of intubation requiring mechanical ventilation was highest in the daytime group (21.2%), whereas no patients in the evening group required intubation. A statistically significant difference was observed among the groups regarding the incidence of hyperbilirubinemia requiring phototherapy ($p =$

0.036). The evening group demonstrated the highest prevalence of phototherapy use (46.2%), whereas the morning group exhibited the lowest prevalence (19.3%).

Table 2. Effect of antenatal corticosteroid (ACS) administration in the morning, daytime and evening groups according to the circadian cortisol rhythm on neonatal outcomes

Outcome		Morning (03:00 AM - 12:00 PM, n=98)	Daytime (12:00 PM - 09:00 PM, n=123)	Evening (09:00 PM - 03:00 AM, n=41)	p-value
Birth Week		32.59 ± 2.87	32.54 ± 3.22	32.70 ± 2.34	0.947
Birth Weight (grams)		1979.81 ± 663.68	1933.85 ± 719.33	2032.56 ± 706.87	0.725
Caesarean delivery rate		86 (87.8%)	112 (91.1%)	30 (73.2%)	0.012
Apgar score 1st minute		6.29 ± 1.95	6.18 ± 1.90	6.34 ± 1.91	0.863
Apgar score 5th minute		7.92 ± 1.67	7.94 ± 1.51	8.05 ± 1.30	0.870
Umbilical cord arterial pH, mean±SD		7.31 ± 0.09	7.30 ± 0.09	7.31 ± 0.09	0.759
Gender (%)	Female	52 (53.1%)	71 (57.7%)	25 (61.0%)	0.644
	Male	46 (46.9%)	52 (42.3%)	16 (39.0%)	
Admission to NICU		74 (76.3%)	91 (74.0%)	33 (80.5%)	0.696
Length of stay in NICU (days)		18 (1 – 134)	18 (1 – 222)	20 (1 – 85)	0.001
Primary respiratory support	Breathing room air	8 (13.8%)	14 (21.2%)	4 (15.4%)	0.001
	HFNC	10 (17.2%)	1 (1.5%)	0 (0.0%)	
	CPAP	32 (55.2%)	37 (56.1%)	22 (84.6%)	
	Intubation	8 (13.8%)	14 (21.2%)	0 (0.0%)	
Surfactant treatment		19 (33.3%)	21 (31.8%)	6 (23.1%)	0.628
Phototherapy use		11 (19.3%)	17 (25.8%)	12 (46.2%)	0.036
Neonatal death		7 (12.3%)	8 (12.1%)	2 (7.7%)	0.806

NICU, neonatal intensive care unit; HFNC, high-flow nasal cannula; CPAP, Continuous positive airway pressure ventilation

In this study, logistic regression analysis was employed to identify factors influencing the need for phototherapy in newborns. The logistic regression model demonstrated a good fit, with a deviation of 132 and an Akaike Information Criterion (AIC) of 176. The model's predictive power was evaluated using various R^2 measures: McFadden's R^2 was 0.238, Cox and Snell's R^2 was 0.242, and Nagelkerke's R^2 was 0.352, indicating that the model accounted for 23.8% to 35.2% of the variance in phototherapy requirements.

The analysis identified several significant predictors. Birth weight was inversely associated with the need for phototherapy, indicating that higher birth weights were associated with a lower likelihood of requiring phototherapy ($p = 0.018$, OR = 0.998, 95% CI: 0.996–1.000). The timing of antenatal corticosteroid (ACS) administration also had a significant impact.

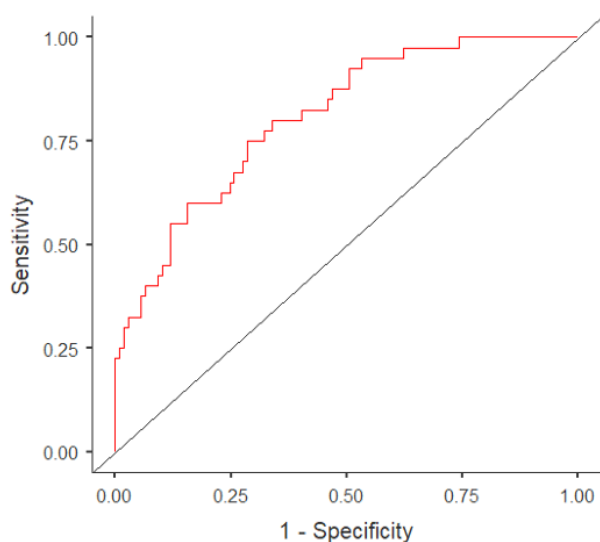
Administration during the daytime (12:00 PM–09:00

PM) compared to the evening (09:00 PM–03:00 AM) significantly increased the likelihood of phototherapy ($p = 0.041$, OR = 3.60, 95% CI: 1.06–12.24). Similarly, administration during the evening compared to the morning (03:00 AM–12:00 PM) was associated with a substantially higher likelihood of phototherapy ($p = 0.002$, OR = 9.81, 95% CI: 2.31–41.69). Primary respiratory support was another critical determinant. Compared to room air breathing, the use of high-flow nasal cannula (HFNC) significantly increased the likelihood of phototherapy ($p = 0.009$, OR = 49.62, 95% CI: 2.69–914.05), and continuous positive airway pressure (CPAP) also showed a significant association ($p = 0.048$, OR = 10.95, 95% CI: 1.02–117.76). In contrast, other variables such as gestational age at ACS administration, the interval between ACS treatment and delivery, the etiology of preterm birth, and Apgar scores did not exhibit statistically significant associations with the need for phototherapy (Table 3).

Table 3. Logistic regression analysis of factors affecting the need for phototherapy

Predictor		B	SE	β	P value	OR	95% CI
Constant		-34.59	22.99	-1.50	0.133	9.54	2.54 - 35807
Maternal age (years)		0.08	0.04	1.86	0.063	1.08	0.99 - 1.17
Gravity		0.10	0.17	0.59	0.553	1.11	0.79 - 1.55
Parity		0.08	0.27	0.30	0.762	1.09	0.63 - 1.86
GA at ACS Administration (weeks)		-0.28	0.35	-0.80	0.421	0.76	0.38 - 1.49
Birth Week		0.61	0.38	1.63	0.103	1.85	0.88 - 3.86
ACS Treatment-to-Delivery Interval (days)		-0.04	0.06	-0.70	0.485	0.96	0.84 - 1.08
Birth Weight (grams)		-0.00	0.00	-2.37	0.018	0.998	0.996 - 1.000
ACS Administration	Daytime & Morning	1.28	0.63	2.05	0.041	3.60	1.06 - 12.24
	Evening & Morning	2.28	0.74	3.09	0.002	9.81	2.31 - 41.69
Use of MgSO ₄		-0.40	0.75	-0.54	0.590	0.67	0.15 - 2.90
Caesarean delivery & normal vaginal birth		0.06	0.78	0.08	0.936	1.07	0.23 - 4.94
Male & Female		0.05	0.50	0.09	0.927	1.05	0.39 - 2.80
Forms of ventilation	HFNC & Room air	3.90	1.49	2.63	0.009	49.62	2.69 - 914.05
	Intubation & Room air	2.25	1.38	1.64	0.102	9.50	0.64 - 141.03
	CPAP & Room air	2.39	1.21	1.97	0.048	10.95	1.02 - 117.76
Apgar score 1st minute		-0.17	0.23	-0.73	0.468	0.85	0.54 - 1.33
Apgar score 5th minute		0.17	0.30	0.56	0.576	1.18	0.66 - 2.11
Umbilical cord PH		2.65	2.97	0.89	0.372	14.21	0.04 - 4798.07
PTB etiology	PPROM & PTL with intact membranes	1.31	0.79	1.66	0.097	3.70	0.79 - 17.28
	PIH & PTL with intact membranes	0.37	0.84	0.45	0.656	1.45	0.28 - 7.53
	Other & PTL with intact membranes	1.09	0.82	1.33	0.185	2.99	0.59 - 15.02

GA, gestational age; ACS, antenatal corticosteroids; HFNC, high-flow nasal cannula; CPAP, Continuous positive airway pressure ventilation; PTB, Preterm birth; PTL, Preterm Labour; PPRM, preterm prelabour rupture of the membranes; PIH, pregnancy-induced hypertension

**Figure 1.** ROC curve analysis of logistic regression model predicting neonatal phototherapy need

Our logistic regression model achieved a prediction accuracy of 77.9%. The model demonstrated high specificity (90.8%), indicating its strong ability to correctly identify newborns not requiring phototherapy. However, the sensitivity was moderate at 42.5%, reflecting a limited capacity to detect all true cases requiring phototherapy. The Area Under the Curve (AUC) was 0.807, signifying good overall discriminatory performance in distinguishing between newborns who require phototherapy and those who do not (Figure 1).

Discussion

In this study, our aim was to investigate the effects of ACS administration, timed according to maternal circadian cortisol rhythms, on maternal and fetal outcomes in pregnancies at risk of PTB. By categorizing participants into three distinct groups—morning (peak cortisol levels), daytime, and evening

(lowest cortisol levels). We identified significant variations in fetal outcomes, particularly in the need for primary respiratory support and the incidence of jaundice requiring phototherapy. Notably, the evening group exhibited a higher rate of phototherapy, while the morning group demonstrated more favorable respiratory outcomes, potentially reflecting the differential efficacy of ACS based on circadian synchronization. To our knowledge, no previous study has systematically investigated the fetal effects of ACS administration in the context of maternal circadian cortisol patterns, highlighting the novelty and clinical relevance of our findings.

The maternal circadian cortisol rhythm plays a critical role in homeostatic regulation. While it is known that the pre-pregnancy diurnal cortisol rhythm is preserved during pregnancy, except in cases of mood disorders or obesity its broader implications remain poorly understood (15-17). In our study, we focused on maternal and fetal outcomes in pregnancies without maternal comorbidities, under the assumption that the pre-pregnancy circadian cortisol rhythm remained intact (Table 1, 2). Regarding maternal outcomes, ACS administration across the three-time groups showed no significant differences in PTB etiology, MgSO₄ administration, GA at birth, or the interval between ACS administration and delivery, indicating that the groups were homogeneous in these aspects.

During pregnancy, the maternal circadian rhythm plays a critical role in regulating the developing fetus's circadian rhythm. However, in cases of PTB and subsequent NICU admission, disruptions or delays in this synchronization process occur, potentially affecting the establishment of the infant's circadian rhythm and overall development (16). Notably, our study found that the NICU length of stay was longest in the evening group ($p=0.001$). To the best of our knowledge, this is the first study to indicate that ACS administration during the evening hours (9:00 p.m.–3:00 a.m.), when maternal cortisol levels are at their nadir, may be associated with a prolonged NICU stay compared to administration during the morning and daytime, when cortisol levels are elevated. Given that the length of NICU stay is a critical factor in neonatal morbidity and mortality (18), it may be prudent to align ACS administration with the maternal circadian rhythm in cases where

timing is flexible and immediate intervention is not required.

Currently, there is insufficient data regarding the distribution of cesarean section rates throughout the day in PTB managed with ACS. However, studies in the general population have demonstrated that the rate of cesarean deliveries is significantly higher between 9:00 AM and 3:00 PM compared to the period between 12:00 AM and 6:00 AM (19). Similarly, in our study, we found that the cesarean section rate was statistically higher in the daytime group among pregnant women who received ACS ($p = 0.012$). Another study examining the diurnal distribution of unscheduled cesarean deliveries, similar to our findings, reported that 40.4% occurred during the 8:30 AM –4:30 PM shift (20). Based on these results, it can be inferred that ACS administration in alignment with the circadian cortisol rhythm may not have a significant impact on the timing of cesarean deliveries throughout the day.

The selection of respiratory support modalities is contingent upon the clinical presentation of the patient. In neonates presenting with isolated hypoxemia in the absence of respiratory distress, HFNC is deemed adequate for maintaining oxygenation (21). Conversely, in cases where there is a pronounced risk of RDS, nCPAP is the intervention of choice (22). The highest rate of HFNC use was observed in the morning group, while the need for more advanced respiratory support, CPAP, was significantly lower in this group compared to the evening and daytime groups. This finding may be attributed to the enhanced efficacy of ACS administration when aligned with maternal circadian rhythms, potentially optimizing fetal lung maturation and respiratory outcomes. To our knowledge, these results are the first study on the effect of ACS administration time on the type of respiratory support.

Among the groups, the need for phototherapy followed a pattern similar to respiratory support, highlighting the potential influence of circadian-aligned ACS administration. Notably, the evening group exhibited a significantly higher phototherapy rate (46.2%) compared to the morning group (19.3%). While ACS is well-established in reducing both respiratory complications and the incidence of jaundice requiring phototherapy (23), our study is

the first to demonstrate that the timing of ACS administration may critically influence its efficacy. The elevated phototherapy need in the evening group may be attributed to lower maternal cortisol levels during evening hours, which could diminish the therapeutic impact of ACS compared to morning administration. These findings suggest that the timing of ACS administration may play a significant role in its efficacy, and further studies are needed to confirm the relationship between ACS timing and phototherapy requirements.

Logistic regression analysis identified the timing of ACS administration as an independent predictor of phototherapy requirement; with morning administration being associated with the lowest risk. Specifically, neonates exposed to ACS in the evening had a significantly higher likelihood of requiring phototherapy compared to those who received ACS in the morning ($p = 0.002$, OR = 9.81, 95% CI: 2.31–41.69). This finding suggests that ACS effectiveness may be modulated by the maternal circadian rhythm, potentially influencing bilirubin metabolism and neonatal jaundice severity. Given that phototherapy is a widely used but resource-intensive intervention, optimizing ACS timing could have important clinical and healthcare implications by reducing the need for neonatal phototherapy and associated NICU interventions.

While aligning the timing of ACS administration with the maternal circadian rhythm may not always be feasible, our findings suggest that in cases of less severe PTB risk—such as preterm labor with insufficient contractions or preterm rupture of membranes—administering ACS during the morning hours, in sync with the maternal circadian rhythm, may positively influence the type of respiratory support required, reduce the need for phototherapy, and shorten the NICU length of stay. These potential benefits highlight the clinical relevance of optimizing ACS timing. However, our findings require validation through prospective studies to establish definitive recommendations.

Strengths and limitations

This study has several strengths. First, it is the first to systematically investigate the effects of ACS administration timing, aligned with maternal circadian cortisol rhythms, on perinatal outcomes in

pregnancies at risk of PTB. By categorizing participants into three distinct groups based on the timing of ACS administration, we were able to identify significant variations in neonatal outcomes, particularly in respiratory support requirements and phototherapy needs. The homogeneity of the groups in terms of PTB etiology, gestational age at ACS administration, and other maternal characteristics strengthens the internal validity of our findings. Additionally, the use of a large sample size and robust statistical methods enhance the reliability of our results.

However, this study also has limitations. As a retrospective study, it is subject to potential biases inherent in such designs, including selection bias and unmeasured confounding factors. Furthermore, the study was conducted at a single center, which may limit the generalizability of the findings to other populations or settings. The lack of direct measurement of maternal cortisol levels at the time of ACS administration is another limitation. As we relied on the assumption that the pre-pregnancy circadian rhythm remained intact. In a prospective study design, incorporating maternal salivary cortisol sampling to categorize participants based on their circadian cortisol levels could yield more precise and clinically relevant results. Additionally, it should not be overlooked that the risk of PTB itself may lead to disruptions in the maternal circadian rhythm. Future prospective studies with direct cortisol measurements and multicenter designs are needed to validate these findings and explore the underlying mechanisms.

Conclusions

This study provides novel insights into the potential influence of maternal circadian rhythms on the efficacy of ACS administration in pregnancies at risk of preterm PTB. Our findings suggest that the timing of ACS administration, particularly during the morning hours when maternal cortisol levels are at their peak, may optimize neonatal outcomes by reducing the need for advanced respiratory support and phototherapy. Conversely, ACS administration during the evening, when cortisol levels are at their nadir, was associated with a higher incidence of phototherapy and prolonged NICU stays. These results highlight the importance of considering maternal circadian rhythms in the timing of ACS

administration, especially in cases where immediate intervention is not required. However, further prospective studies are needed to confirm these findings and establish clinical guidelines for optimizing ACS timing in the management of PTB. This study underscores the potential for circadian-aligned interventions to improve perinatal outcomes and reduce neonatal morbidity.

Abbreviation

ACS, Antenatal Corticosteroids; PTB, Preterm Birth; PTL, Preterm Labour; PPRM, Preterm Prelabour Rupture of the Membranes; PIH, Pregnancy-Induced Hypertension; GA, Gestational Age; HFNC, High-Flow Nasal Cannula; CPAP, Continuous Positive Airway Pressure Ventilation;

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Competing interests

The authors declare that they have no competing interests.

Ethical standards

The study was approved by the Mersin University Clinical Research Ethics Committee (Decision No. 2023/42). Due to the retrospective design of the study and the use of anonymized data extracted from the hospital's electronic database, the need for informed consent was waived by the Ethics Committee. This waiver aligns with national regulations and the Declaration of Helsinki guidelines for retrospective studies involving anonymized data. The authors affirm that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the 1975 Declaration of Helsinki, as revised in 2008.

Data availability statement

The datasets generated and analyzed during this study are not publicly available due to patient confidentiality and institutional policies. However, anonymized data can be made available upon reasonable request from the corresponding author, pending approval from the Mersin University Ethics Committee.

Clinical trial number

Not applicable.

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