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UMBILICAL CORD CORTISOL LEVELS IN TERM AND LATE-PRETERM NEWBORNS

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Abstract

Cortisol, a glucocorticoid hormone secreted by the adrenal cortex, plays a pivotal role in human physiology, particularly in stress response regulation, immune function, and metabolic homeostasis. In the perinatal period, cortisol becomes a critical determinant of neonatal outcomes, as it drives the maturation of key fetal organs and facilitates the transition from intrauterine to extra uterine life. A surge in fetal cortisol levels during late gestation is integral to the development of the lungs, liver, and brain, which are essential for postnatal survival. Moreover, the umbilical cord, as the primary channel of maternal-fetal exchange, provides an invaluable window into the hormonal state of the fetus at birth.

An observational prospective study analyzing umbilical cord blood cortisol levels, focusing on their associations with gestational age, was conducted at the Mother Teresa Hospital in Skopje, and 88 samples were obtained for analysis.

The aim was to compare cortisol levels in healthy and appropriate for gestational age (AGA) newborns, depending on their gestational age.

The results showed a mean cortisol level of 93.41 [95%CI 82.72 – 104.10]. In term infants the mean cortisol level was significantly higher, with a mean value of 100.60 [95%CI 88.940 – 112.259], than in preterm ones where mean cortisol level was 51.91 [95%CI 40.528 – 63.301], with a statistically significant difference ($p<0.0012$).

The significant associations between cortisol levels and gestational age highlight the potential utility of umbilical cord blood cortisol as a biomarker for assessing neonatal stress and adaptation.

Keywords: cortisol, newborn, umbilical cord, delivery, gestational age, term, preterm.

Introduction

Cortisol, a glucocorticoid hormone secreted by the adrenal cortex, plays a pivotal role in human physiology, particularly in stress response regulation, immune function, and metabolic homeostasis. In the perinatal period, cortisol becomes a critical determinant of neonatal outcomes, as it drives the maturation of key fetal organs and facilitates the transition from intrauterine to extra uterine life.

A surge in fetal cortisol levels during late gestation is integral to the development of the lungs, liver, and brain, which are essential for postnatal survival. Moreover, the umbilical cord, as the primary channel of maternal-fetal exchange, provides an invaluable window into the hormonal state of the fetus at birth [1, 6].

Studies underscore the importance of umbilical cord blood cortisol as a biomarker of fetal adaptation to labor and delivery. For instance, research has shown that cortisol levels differ significantly between term and preterm neonates, with preterm infants typically exhibiting lower levels.

These diminished cortisol levels in preterm neonates contribute to complications such as respiratory distress syndrome (RDS), highlighting the need for timely clinical interventions, including antenatal glucocorticoid therapy [8, 9]. In term neonates, the cortisol surge during labor appears to confer adaptive benefits, promoting lung maturity and facilitating cardiovascular transition [6].

Beyond gestational age, a range of perinatal factors, including birth weight, neonatal gender, and the duration of labor influence umbilical cord blood cortisol levels. Birth weight has been positively correlated with cortisol levels, with lower levels observed in neonates with low birth weight, regardless of gestational age [8].

Furthermore, gender-specific differences have been identified, with male neonates generally displaying higher cortisol levels than their female counterparts under comparable stress conditions [7].

This gender disparity is thought to reflect intrinsic differences in hypothalamic-pituitary-adrenal (HPA) axis regulation between male and female fetuses [7, 10].

Labor duration also plays a crucial role in modulating cortisol levels. Prolonged labor often results in elevated cortisol levels due to sustained fetal stress, which can enhance neonatal organ readiness for extrauterine life in term infants. However, in preterm neonates, this stress-induced cortisol response may be insufficient to offset the challenges of prematurity, necessitating additional medical support [6, 10].

These findings highlight the complexity of cortisol dynamics and their dependence on multiple intersecting factors.

Despite extensive research, several gaps remain in our understanding of the determinants and implications of umbilical cord blood cortisol levels. While studies have documented the impact of gestational age and labor duration, fewer have addressed how maternal factors such as obesity or stress influence these levels. For instance, maternal obesity has been shown to lower glucocorticoid levels in maternal blood at delivery, though umbilical cord blood levels remain unaffected, suggesting a potential compensatory mechanism [1].

Additionally, the interaction between cortisol levels and neonatal anthropometric markers, such as birth length, remains underexplored [5].

This paper aims to address these gaps by presenting a comprehensive analysis of umbilical cord cortisol levels and their relationship with key perinatal factors, including gestational age, birth weight, gender, and labor duration.

By integrating findings from recent literature, this study seeks to elucidate the physiological and clinical significance of umbilical cord cortisol levels in fetal and neonatal development. Ultimately, the goal is to provide insights that could inform perinatal care strategies, particularly for vulnerable populations such as preterm or low-birth-weight neonates.

Methods

Study Design and Participants

This study was designed as a cross-sectional observational analysis of umbilical cord blood cortisol levels, focusing on their associations with gestational age. Neonates were recruited from the Special Hospital for Gynecology and Obstetrics "Mother Teresa" - Skopje, a level 2 maternity hospital. The study contains data from 88 newborns who met the inclusion criteria.

Healthy, AGA newborns from mothers with regularly monitored singleton pregnancies and with APGAR >= 7 were included. Inclusion criteria encompassing both term (≥37 weeks of gestation) and preterm (<37 weeks) births.

Exclusion criteria were designed to avoid all possible conditions that could alter and disrupt the normal physiological cortisol levels in both the mother and the newborn. Exclusion criteria involved: mothers with high-risk pregnancies, those receiving corticosteroids, genitourinary infections in the last trimester, and diagnosed psychological conditions.

Exclusion criteria also included maternal conditions that could independently alter cortisol levels, such as Cushing's syndrome, severe stress disorders, or chronic steroid use, as well as neonates with congenital anomalies or chromosomal abnormalities.

All necessary data on the course of pregnancy were provided from the mothers' obstetric histories and a standardized questionnaire. Informed consent was obtained for the inclusion of newborns in the study, after every mother was informed of the purpose of the research and notified that the sampling protocol would not cause additional stress or adverse effects to the newborn.

The participants were divided into two main groups:

1. **Term Neonates (n = 75):** Delivered at ≥37 weeks of gestation.
2. **Preterm Neonates (n = 13):** Delivered at <37 weeks of gestation.

Ethical Considerations

The study protocol was approved by the institutional and Medical Faculty at University Goce Delchev, Stip ethics committees. Written informed consent was obtained from the mothers prior to sample collection. All procedures adhered to the principles outlined in the Declaration of Helsinki.

Sample Collection

After delivery, either by spontaneous birth or cesarean section (SC), the umbilical cord was clamped, and before the delivery or extraction of the placenta, 2 ml of arterial blood was extracted from the umbilical cord using a sterile syringe and a 21G (0.8 mm) needle.

The aspirated blood was immediately transferred to a prepared serum tube with a red cap, which contained a gel separator and a coagulant.

The sample was left at room temperature to coagulate for at least 30 minutes and then centrifuged at 3000-3500 rpm for 10-15 minutes.

The separated serum remained above the gel, ready for analysis. Until 2 pm, the cortisol analysis was performed, and after 2 pm, the serum was separated and stored in a refrigerator at a temperature of 2-8 ℃ until next morning for analysis.

The cortisol level measurement itself was performed on an Access 2 Immunoassay System [11], operating by CLIA [12] method, with paramagnetic particles. All measured values were in $\mu g/L$.

Data Collection and Variables

In addition to cortisol levels, data on mothers and newborn characteristics were collected from medical records and standardized questionnaires:

1. **Maternal Variables:** Age, parity, mode of delivery (vaginal or cesarean section), history of drugs use, etc.
2. **Neonatal Variables:**
    - **Gestational Age:** Confirmed via ultrasound dating and Ballard scoring.
    - **Birth Weight and Length:** Measured immediately after delivery using calibrated equipment.
    - **Gender:** Documented from clinical records.
3. **Labor Characteristics:** Duration of labor (measured in hours) and any interventions used (e.g., oxytocin, epidural analgesia).

Statistical Analysis

Data processing was performed using the statistical software programs Microsoft Excel, MedCalc 23.0, and JASP.

Data are presented with their mean, standard deviation (SD), standard error (SE) and 95% CI, and for the descriptive parameters of the populations of interest with absolute numbers and percentages.

1. **Comparisons Between Groups:** Mann-Whitney U-test and ANOVA tests were used when comparing and testing hypotheses.
2. **Multivariate Analysis:** Linear regression models were used to determine independent predictor of cortisol levels, adjusting for confounding factors, in our case gestational age.

A p-value <0.05 was considered statistically significant.

Results

Participant Characteristics

A total of 88 neonates were included in the study, comprising 13 term neonates and 75 preterm neonates. Table 1 summarizes the demographic and clinical characteristics of the study population.

The characteristics of the study group, including maternal age, parity, mode of conception, cigarette, alcohol and drug consumption are presented in Table 1. Some of the more important medical data for the mothers such as hospitalizations during pregnancy, as well as some data from the birth process are presented in Table 2.

Table 1. – Statistical demographic data of mothers.

Mothers	**n**	**Mean (SD) or %**
Age	88	31.69 (6.56)
Ethnicity	88	
Albanian	40	45.46%
Bosnian	2	2.27%
Macedonian	38	43.18%
Roma	5	5.68%
Turkish	3	3.41%
Pregnancy in row	88	2.56 (1.91)
Way of getting pregnant	88	
In vitro	2	2.27%
Spontaneous	86	97.73%
Smoking	88	
Yes	14	15.91%
No	74	84.09%
Alcohol	0	0%
Drugs	0	0%

Table 2. – Medical and obstetric data of mothers.

Mothers	**n**	**Mean (SD) or %**
Previous hospitalizations	88	
Yes	11	12.50%
No	77	87.50%
Rupture of membranes (hours)	88	3.18 (6.47)
Duration of birth (hours)	88	4.15 (4.01)
Method of delivery	88	
SVD	42	47.73%

SC	46	52.27%
Presentation of fetus	88	
Head-first	78	88.64%
Breech	7	7.96%
Feet	3	3.41%

The maternal age ranged from 21 to 48 years, or an average of 31.69 (6.56). As shown in Figure 1, the age distribution, according to the methodology of the State Statistical Office used in the Census from 2021, is consistent with national data from that census. This suggests that our sample quite realistically reflects the maternal age distribution in the general population.

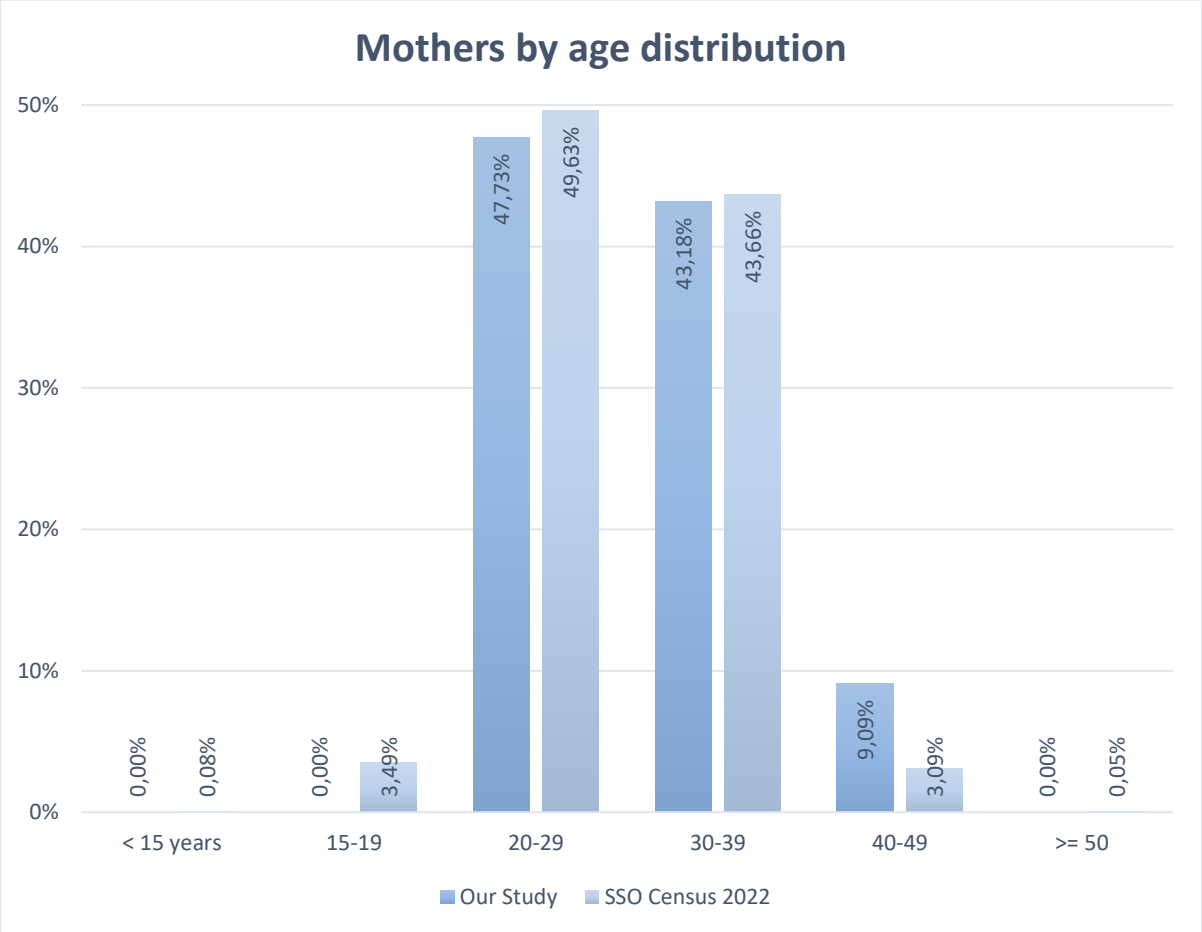

Figure 1. – Distribution of mothers by age compared to national data from the State Statistical Office.

We would like to emphasize that, although labor duration for vaginal delivery lasted from 3 to 11 hours (6.64 hours on average), regional analgesia was not used, and cortisol levels were not affected.

Basic characteristics of newborns, such as birth weight and length, gestational age, and APGAR scores at 1 and 5 minutes, are shown in Table 3.

Table 3. – Statistical data and results for newborns.

		$\bar{x}$	SD	95% CI
Gestational age (weeks)	Preterm (n=13)	35.92	0.28	35.92±0.15 [35.77- 36.07]
	Term (n=75)	39.43	0.87	39.43±0.06 [39.37- 39.49]
Birth weight (gr.)	Preterm (n=13)	2796.15	409.01	2796.15±222.34 [2573.81 – 3018.49]
	Term (n=75)	3353.60	453.57	3353.60±102.651 [3250.95 – 3456.25]
Birth length (cm)	Preterm (n=13)	47.77	2.09	47.77±1.14 [46.634 – 48.906]
	Term (n=75)	49.89	2.12	49.89±0.480 [49.410 – 50.370]
APGAR Score 1 min	Preterm (n=13)	8.69	0.63	8.69±0.342 [8.348 – 9.032]
	Term (n=75)	8.47	1.00	8.47±0.226 [8.244 – 8.696]
APGAR Score 5 min	Preterm (n=13)	9.15	1.07	9.15±0.582 [8.568 – 9.732]
	Term (n=75)	9.17	0.67	9.17±0.152 [9.018 – 9.322]

It is worth noting that the relatively high gestational age among preterm newborns (35.92 [95%CI 35.77- 36.07] gestational weeks) is largely due to the fact that SHGO Mother Teresa is a 2nd level maternity hospital as defined in the Master Plan for Regionalization of Perinatal Care adopted by the Government of the Republic of North Macedonia in 2024, and accordingly accepts mothers who have full 34 weeks of pregnancy for childbirth.

When analyzing cortisol levels by gender of the newborns (Table 4), no statistically significant differences were observed ($p = 0.424$), indicating that cortisol secretion in the immediate perinatal period was not significantly associated with baby's gender.

Table 4 – Cortisol level by gender of the newborns (μg/L).

	n	$\bar{x}$	SD	95% CI
Average of whole group	88	93.41	51.185	93.41 ±10.694 [82.716 – 104.104]
Male	49	89.49	52.161	89.49 ±14.605 [74.886 – 104.096]
Female	39	98.33	50.167	98.3277 ±15.745 [82.583 – 114.073]
p(M/F) = 0.424				

Umbilical Cord Cortisol Levels by Gestational Age

Cord blood cortisol levels were significantly higher in term neonates compared to preterm neonates as can be seen in data in Table 5. Among preterm neonates, cortisol levels increased with advancing gestational age, with the lowest levels observed lowest age preterm group (early 36 weeks).

Table 5 – Cortisol lavel depending on newborn gestational age (μg/L).

	n	$\bar{x}$	SD	SE	95% CI
Average of whole group	88	93.41	51.185	5.46	93.41 ±10.694 [82.716 – 104.104]
Term	75	100.60	51.518	5.95	100.60 ±11.659 [88.940 – 112.259]
Preterm	13	51.91	20.946	5.81	51.91 ±11.386 [40.528 – 63.301]
p<0.05		p(T/P) =0.0012			

Discussion

This study provides comprehensive insights into the variability of umbilical cord blood cortisol levels in neonates and their associations with gestational age and gender. Consistent with prior research, we observed that cortisol levels were significantly higher in term neonates compared to preterm neonates. Additionally, cord blood cortisol levels demonstrated no gender differences.

Gestational Age and Cortisol Levels

Our findings reinforce the critical role of gestational age in determining fetal cortisol levels. Term neonates exhibited significantly higher cortisol concentrations compared to preterm neonates, likely reflecting the fetal cortisol surge that occurs during late gestation.

This surge is crucial for the maturation of vital organs, particularly the lungs, liver, and brain, enabling neonates to transition to extrauterine life [6, 8]. Preterm neonates, especially those born before 28 weeks, lacked this surge, which may explain their vulnerability to complications such as respiratory distress syndrome (RDS) and impaired thermoregulation.

These results align with earlier studies that highlight the need for antenatal corticosteroid therapy in preterm births to mitigate these risks [9].

Gender-Specific Variability

Although female neonates exhibited slightly higher cortisol levels compared to males, this difference was not statistically significant in multivariate analyses. These findings are partially unconsistent with earlier research suggesting that male fetuses may have a heightened stress response due to differences in hypothalamic-pituitary-adrenal (HPA) axis regulation [7].

However, the lack of significance in our study may be attributed to sample size limitations or the influence of other confounding factors. Further research is warranted to explore the underlying mechanisms of gender-specific differences in cortisol dynamics.

Clinical Implications

The findings of this study have important implications for neonatal care. The significant associations between cortisol levels and gestational age highlight the potential utility of umbilical cord blood cortisol as a biomarker for assessing neonatal stress and adaptation.

For preterm neonates, strategies such as antenatal corticosteroid administration and postnatal glucocorticoid supplementation may help mitigate the consequences of inadequate cortisol production. Additionally, understanding the influence of labor duration on cortisol dynamics could inform decisions regarding labor management, particularly in high-risk pregnancies.

Limitations and Future Directions

This study has several limitations. First, the sample size was relatively small, which may have limited the statistical power to detect subtle differences, particularly in gender-specific analyses. Second, maternal factors such as stress, obesity, and mode of delivery were not extensively analyzed, despite their potential influence on fetal cortisol levels [1].

Also due to the fact that SHGO Mother Teresa is a 2nd level maternity hospital as defined in the Master Plan for Regionalization of Perinatal Care adopted by the Government of the Republic of North Macedonia in 2024, and accordingly accepts mothers who have full 34 weeks of pregnancy for childbirth..

Future research should focus on exploring the mechanisms underlying gender-specific differences in cortisol dynamics, as well as the role of maternal factors in modulating fetal cortisol production. Additionally, larger, multicenter studies could validate the utility of umbilical cord blood cortisol as a biomarker for neonatal adaptation and inform targeted interventions to optimize outcomes.

Conclusion

This study provides significant insights into the variability of umbilical cord blood cortisol levels and their associations with key perinatal factors, including gestational age, birth weight, gender, and labor duration. The findings confirm that term neonates exhibit higher cortisol levels compared to preterm neonates, underscoring the importance of the late-gestational cortisol surge in preparing the fetus for extrauterine life. Additionally, the positive correlation between cortisol levels and birth weight highlights the potential role of cortisol as a biomarker for neonatal stress and adaptation.

Labor duration emerged as a significant factor influencing cortisol levels, particularly in term neonates, where prolonged labor was associated with elevated cortisol levels.

This adaptive response underscores the role of labor-induced stress in promoting neonatal readiness for birth. However, preterm neonates did not exhibit the same cortisol increase with prolonged labor, likely reflecting their limited adrenal function. While gender differences in cortisol levels were observed, they were not significant after adjusting for other variables, suggesting that other factors may mediate these differences.

Clinically, the study highlights the utility of umbilical cord blood cortisol measurements in assessing neonatal stress and predicting outcomes, particularly for preterm neonates. The findings also underscore the importance of timely interventions, such as antenatal corticosteroid administration and tailored labor management strategies, to optimize neonatal outcomes in at-risk populations.

Future research should aim to address the limitations of this study, including exploring the impact of maternal factors and conducting larger, longitudinal studies to validate these findings. By deepening our understanding of the determinants and implications of umbilical cord cortisol levels, we can advance perinatal care strategies to improve neonatal health outcomes.

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