

High-Altitude Hypoxia, Fetal Growth Restriction, and Early Neonatal Outcomes: A Two-Center Comparative Study

Yüksek Rakım Hipoksisi, Şiddetli Fetal Büyüme Kısıtlaması ve Olumsuz Yenidoğan Sonuçlarının Belirleyicisi Olarak: İki Merkezli Karşılaştırmalı Bir Çalışma

Erhan H. CÖMERT^{1*}, Nazlı GÜLENÇ², Ümran KARABULUT DOĞAN³, Pınar KADİROĞULLARI⁴, Ozan DOĞAN⁵

ABSTRACT

High altitude is associated with reduced barometric pressure and lower oxygen availability, which may impair fetoplacental oxygen transfer and adversely affect fetal growth and neonatal adaptation. This study compared birth weight, maternal oxygenation parameters, and early neonatal outcomes between two centers located at 1800 m and 2500 m above sea level in Eastern Türkiye. In this comparative cross-sectional study, 540 mother-infant pairs were evaluated, including 270 deliveries from Ardahan (1800 m) and 270 from Gölle (2500 m). Data were obtained from retrospectively reviewed hospitals from 2018 year. Maternal partial pressure of oxygen (PaO₂), oxygen saturation (SaO₂), hemoglobin, lactate, gestational age, mode of delivery, birth weight, small-for-gestational-age (SGA) status, and neonatal intensive care unit (NICU) admission were compared between centers. Continuous variables were analyzed using independent-sample t tests and analysis of variance, whereas categorical variables were compared using chi-square tests. Additional analyses included analysis of covariance, multivariable linear regression, logistic regression for SGA and NICU admission, interaction analysis, receiver operating characteristic analysis, and effect size estimation. Compared with the 1800 m group, pregnancies at 2500 m were associated with lower mean birth weight (2315 g vs 3396 g), lower maternal PaO₂ and SaO₂, and higher hemoglobin and lactate levels (all p<0.001). Preterm birth, SGA, and NICU admission were also more frequent in the 2500 m group (all p<0.001). In adjusted analyses, altitude remained significantly associated with lower birth weight. Maternal PaO₂ attenuated, but did not fully account for, the association between altitude and birth weight. Maternal PaO₂ showed moderate discrimination for SGA (AUC=0.82). Delivery at 2500 m was associated with lower birth weight, less favorable maternal oxygenation indices, and increased early neonatal morbidity compared with delivery at 1800 m. These findings support closer antenatal surveillance of fetal growth and maternal oxygenation in high-altitude settings.

Keywords: Altitude, Birth weight, Fetal growth restriction, Hypoxia, Neonatal outcomes.

ÖZ

Yüksek rakımda azalan barometrik basınç ve oksijen mevcudiyeti, fetoplazental oksijen transferini bozarak fetal büyümeyi ve erken neonatal uyumu olumsuz etkileyebilir. Bu çalışmada, Doğu Türkiye’de deniz seviyesinden 1800 m ve 2500 m yükseklikte bulunan iki merkez arasında doğum ağırlığı, maternal oksijenasyon parametreleri ve erken neonatal sonuçların karşılaştırılması amaçlandı. Bu karşılaştırmalı kesitsel çalışmada toplam 540 anne-bebek çifti değerlendirildi; bunların 270’i Ardahan’dan (1800 m), 270’i ise Gölle’den (2500 m) elde edildi. Veriler retrospektif olarak incelenen hastanelerin 2018 yılı için temin edildi. Maternal parsiyel oksijen basıncı (PaO₂), oksijen saturasyonu (SaO₂), hemoglobin, laktat, gebelik haftası, doğum şekli, doğum ağırlığı, gebelik haftasına göre küçük bebek (SGA) durumu ve yenidoğan yoğun bakım ünitesi (YYBÜ) yatışı iki merkez arasında karşılaştırıldı. Sürekli değişkenler bağımsız örneklem t testi ve varyans analizi ile, kategorik değişkenler ise ki-kare testi ile değerlendirildi. Ek olarak kovaryans analizi, çok değişkenli doğrusal regresyon, SGA ve YYBÜ yatışı için lojistik regresyon, etkileşim analizi, ROC analizi ve etki büyüklüğü hesaplamaları yapıldı. 1800 m grubuna kıyasla 2500 m grubunda ortalama doğum ağırlığı daha düşüktü (2315 g’ye karşı 3396 g); maternal PaO₂ ve SaO₂ düzeyleri daha düşük, hemoglobin ve laktat düzeyleri ise daha yüksekti (tüm karşılaştırmalar için p<0,001). Ayrıca preterm doğum, SGA ve YYBÜ yatışı 2500 m grubunda daha sık gözlemlendi (tümü p<0,001). Düzeltilmiş analizlerde rakım, daha düşük doğum ağırlığı ile anlamlı şekilde ilişkili olmaya devam etti. Maternal PaO₂’nin modele eklenmesi, rakım ile doğum ağırlığı arasındaki ilişkinin bir kısmını açıklasa da bu ilişkiyi tamamen ortadan kaldırmadı. Maternal PaO₂’nin SGA’yı ayırt etme gücü orta düzeydeydi (EAA=0,82). 2500 m rakımda gerçekleşen doğumlar, 1800 m rakımda gerçekleşen doğumlara kıyasla daha düşük doğum ağırlığı, daha olumsuz maternal oksijenasyon göstergeleri ve daha yüksek erken neonatal morbidite ile ilişkili bulundu. Bu bulgular, çok yüksek rakımlı bölgelerde fetal büyümenin ve maternal oksijenasyonun daha dikkatli izlenmesi gerektiğini düşündürmektedir.

Anahtar Kelimeler: Rakım, Doğum ağırlığı, Fetal büyüme kısıtlılığı, Hipoksi, Neonatal sonuçlar.

Ethical and institutional approval for this study was obtained prior to data extraction from the Kafkas University Provincial Directorate of Health (Ref. No: 80576354-050-99/47, dated 31/03/2021).. The study was conducted in accordance with the principles of the Declaration of Helsinki and applicable institutional regulations.

¹ Op.Dr. Erhan Hüseyin CÖMERT, Private Clinic, Department of Obstetrics and Gynecology, erhan.comert@hotmail.com, ORCID: 0000-0003-1431-2294

² Uzm.Dr. Nazlı GÜLENÇ, Ankara Eğitim ve Araştırma Hastanesi, Neonatoloji, nazligulenc@gmail.com, ORCID: 0000-0003-3241-2408

³ Op.Dr. Ümran Karabulut Doğan, Obstetrics and Gynecology, Acıbadem Hospital, karabulut04@hotmail.com, ORCID: 0000-0002-1935-3696

⁴ Doc.Dr. Pınar KADİROĞULLARI, Private Clinic, Obstetrics and Gynecology, pinarsezer33@hotmail.com, ORCID: 0000-0002-3268-4940

⁵ Prof.Dr. Ozan DOĞAN, İstanbul Nisantasi University, Department of Obstetrics and Gynecology, ozandogan02@hotmail.com, ORCID: 0000-0002-0016-8749

İletişim / Corresponding Author:
e-posta/e-mail:

Erhan Hüseyin CÖMERT
erhan.comert@hotmail.com

Geliş Tarihi / Received: 25.11.2025
Kabul Tarihi/Accepted: 16.06.2026

INTRODUCTION

During pregnancy, the mother's cardiovascular, respiratory, and hematological systems undergo dynamic adaptations to meet the metabolic needs of the developing fetus. Living at high altitude, among the environmental factors that influence this balance, is one of the most important factors affecting fetal growth and neonatal health. At high altitude, barometric pressure and partial pressure of oxygen are lower. This condition causes chronic maternal hypobaric hypoxia, reducing the oxygen delivered to the placenta and fetus (1–3). Numerous studies have shown that fetuses developing under chronic hypoxic stress are more likely to have fetal growth restriction (FGR) and lower birth weight (4,5). Some studies also show that birth weight gradually decreases with increasing altitude, with this effect generally becoming more pronounced above 2000 meters (6). Birth weight reductions of 150–300 g have been reported in many births in high-altitude regions of South America and Central Asia (7,8). Some studies link this to reduced uteroplacental blood flow, impaired trophoblastic invasion, altered placental angiogenesis, and limited oxygen diffusion across the placental barrier (9–11). Additionally, structural changes, such as increased placental thickness and decreased villous surface area, have been reported in pregnancies affected by prolonged hypoxia (12). In addition to its effects on fetal growth, chronic hypoxia can also disrupt fetal cardiovascular transition. Studies have shown that infants born at high altitude have delayed ductus arteriosus constriction, altered pulmonary vascular resistance, and reduced neonatal adaptive capacity (13). These physiologic challenges can lead to increased rates of preterm birth, respiratory distress, and increased need for neonatal intensive care unit (NICU) admission (14,15). The interaction between altitude, maternal oxygenation, hemoglobin levels, and lactate concentration further complicates and maintains the uniqueness of neonatal outcomes.

Given the diversity of altitude differences, Turkey is a suitable country to investigate

these altitude-related physiological changes. Women in Eastern Anatolia are chronically exposed to significant environmental hypoxia throughout pregnancy. Ardahan and Göle districts are also included in these high-altitude regions. While international research on high-altitude pregnancies is extensive, there are limited studies in Turkey. Existing studies generally lack comprehensive oxygenation variables such as PaO₂, SaO₂, or associated biochemical markers. Furthermore, comparative studies assessing fetal growth and neonatal outcomes between moderate and extremely high-altitude regions are scarce. Another shortcoming in the existing literature is the limited use of advanced statistical modeling to identify the direct and indirect pathways through which altitude exerts its effect. While birth weight is a frequently studied measure, understanding whether altitude affects birth weight independently of gestational age, prematurity, mode of delivery, infant sex, or maternal hematological adaptation is crucial for drawing clinically meaningful conclusions. Despite extensive international research on high-altitude pregnancy, data from Türkiye remain limited, particularly studies simultaneously evaluating maternal oxygenation indices and neonatal outcomes across different high-altitude settings. In addition, previous studies have often focused primarily on birth weight without examining whether the observed associations persist after accounting for gestational age, prematurity, infant sex, and delivery characteristics. The present two-center comparative study was therefore designed to address this gap by examining whether differences in birth weight and early neonatal morbidity between 1800 m and 2500 m are accompanied by measurable differences in maternal oxygenation. Our primary aim was to compare birth weight between the two altitude groups; our secondary aims were to compare maternal oxygenation parameters, SGA frequency, and NICU admission, and to explore whether maternal PaO₂ partly explains the association between altitude and neonatal growth outcomes.

MATERIALS AND METHODS

Study Design and Setting

This two-center comparative cross-sectional study evaluated pregnancies delivered in two districts of Eastern Türkiye located at different altitudes above sea level: Ardahan (approximately 1800 m) and Göle (approximately 2500 m). These sites were selected a priori because both represent high-altitude settings within the same broader geographic region while differing sufficiently in environmental oxygen availability to permit a clinically meaningful comparison. The 1800 m center was considered a moderate high-altitude setting and the 2500 m center a very high-altitude setting, consistent with the altitude ranges commonly discussed in the high-altitude pregnancy literature.

Data were obtained from retrospectively reviewed hospital delivery and neonatal from 2018. The study included 540 mother–infant pairs, comprising 270 deliveries from each center. Only singleton pregnancies resulting in live birth were eligible for analysis.

Participants, Eligibility Criteria, and Data Source

Eligible cases were identified from the obstetric and neonatal records of the participating centers. Multiple pregnancies were excluded because of their distinct growth patterns and substantially different baseline risks for preterm birth and low birth weight. Pregnancies with major congenital anomalies were excluded on the basis of antenatal ultrasonography, delivery-room examination, and neonatal assessment recorded in the medical charts. “Complicated pregnancies” were defined as pregnancies with documented major maternal or fetal conditions that could independently affect fetal growth or early neonatal outcomes. Cases with missing key outcome variables were also excluded.

The following variables were extracted from the records: gestational age at delivery, preterm birth status, mode of delivery, neonatal sex, birth weight, SGA status, NICU admission, maternal PaO₂, maternal SaO₂, hemoglobin concentration, and lactate level.

This is a comparative, cross-sectional study to examine the effects of high-altitude hypoxic exposure on birth weight, maternal oxygenation indices, and early neonatal outcomes. Two high-altitude centers differing in environmental oxygen availability were used, providing a natural experimental framework to assess altitude-related physiological changes.

Variable Definitions

Gestational age was determined. Preterm birth was defined as delivery before 37+0 completed weeks of gestation. SGA was defined as birth weight below the 10th percentile for gestational age. Because the study compared two altitude-defined centers, altitude group was analyzed as the main exposure variable.

NICU admission was analyzed as an early neonatal outcome. If detailed admission indications were not systematically available for all infants, this should be stated as a limitation.

Cesarean delivery was recorded as a binary variable.

Maternal Oxygenation Measurements

Maternal oxygenation parameters were obtained from the clinical records at or near the time of delivery. PaO₂ and SaO₂ values were derived from arterial blood gas analysis performed in accordance with local clinical practice. Arterial blood gas analysis was available for all included participants. To minimize measurement heterogeneity, only the first recorded peripartum value within the predefined assessment window was used for analysis. Hemoglobin and lactate values were extracted from the same clinical episode whenever available.

Statistical Analysis

Continuous variables were assessed for distributional characteristics using visual methods (histograms and Q–Q plots) and the Shapiro–Wilk test, as appropriate. Continuous data are presented as mean ± standard deviation, and categorical data as number

(percentage). Between-group comparisons were performed using independent-samples *t* tests for continuous variables and chi-square tests for categorical variables. One-way analysis of variance was used where appropriate for comparisons involving more than two categories.

To evaluate whether altitude was independently associated with birth weight, analysis of covariance and multivariable linear regression models were constructed, with birth weight as the dependent variable and altitude group as the main independent variable, adjusting for gestational age, preterm birth, infant sex, mode of delivery, and maternal PaO₂. Logistic regression models were used to evaluate factors associated with SGA and NICU admission. An interaction term between altitude group and PaO₂ was explored to assess whether the association between maternal oxygenation

and birth weight differed by altitude. Receiver operating characteristic analysis was performed to assess the discriminatory performance of maternal PaO₂ for SGA. Effect sizes were quantified using Cohen's *d* and eta squared, as appropriate. All tests were two-sided, and *p*<0.05 was considered statistically significant.

Ethical Considerations

Ethical and institutional approval for the study was obtained before data extraction from the Kafkas University Provincial Directorate of Health (Ref. No: 80576354-050-99/47, dated 31/03/2021). The study was conducted in accordance with the Declaration of Helsinki and applicable institutional regulations. Given the retrospective design, informed consent was waived by the ethic obtained from all participants. No directly identifying patient information was included in the study dataset.

RESULTS

Baseline Characteristics

A total of 540 mother-infant pairs were included in the study, distributed equally between two high-altitude centers, allowing for a balanced comparative analysis. Baseline maternal, birth, and neonatal characteristics are presented in Table 1. Several variables showed significant variation across centers, consistent with varying degrees of chronic hypoxic exposure.

Infants born at the moderate altitude center showed a gestational age distribution typical of high-altitude populations, with the majority being born at term. In contrast, pregnancies born at the extreme altitude center showed a significant leftward shift and a significantly higher preterm birth rate. The mode of delivery differed significantly, with cesarean delivery occurring more frequently at the extreme altitude. This likely reflects clinical concerns about fetal risk under severe hypoxic stress.

Maternal oxygenation parameters showed the most significant differences between centers. PaO₂ and SaO₂ values were

significantly lower in Göle, reflecting a significant environmental oxygen deficit. This result was accompanied by hematological adaptations such as higher hemoglobin concentrations and elevated lactate levels, which suggest increased anaerobic metabolic activity or impaired oxygen utilization under chronic stress. Birth weight showed the most significant difference, forming two distinct clusters.

Weight Differences and Distributional Patterns

Birth weight differed markedly between the two centers. Infants delivered at 1800 m had a mean birth weight of 3396 ± 282 g, whereas those delivered at 2500 m had a mean birth weight of 2315 ± 102 g (*p*<0.001). This difference exceeded 1 kg and was associated with a very large, standardized effect size. Because the magnitude of this between-center difference is larger than that reported in many previous high-altitude studies, the finding should be interpreted cautiously and in the context of possible center-level differences, selection characteristics, and unmeasured maternal factors. Accordingly, the present

findings support a strong association between altitude setting and lower birth weight in this cohort, but they should not be interpreted as evidence that altitude alone fully explains the observed difference. The change in

distribution is summarized in Figure 1, which shows a collapse of variability at extreme heights and a clear separation between the two populations.

Table 1. Baseline Maternal, Obstetric, And Neonatal Characteristics According to Altitude Group

Variable	Ardahan, 1800 m (n=270)	Göle, 2500 m (n=270)	p-value
Gestational Age (weeks)	38.8 ± 1.4	37.0 ± 1.8	<0.001
Preterm Birth (%)	12.6	41.8	<0.001
Cesarean Delivery (%)	38.0	52.0	0.003
Male Sex (%)	48.0	55.0	0.006
PaO ₂ (mmHg)	78.0 ± 3.0	64.0 ± 4.0	<0.001
SaO ₂ (%)	96.5 ± 1.2	90.0 ± 2.0	<0.001
Hemoglobin (g/dL)	12.4 ± 0.9	13,7 ± 1,0	<0,001
Lactate (mmol/L)	1,7 ± 0,3	2,4 ± 0,4	<0,001
Birth Weight (g)	3396 ± 282	2315 ± 102	<0,001
SGA (%)	9,8	41,5	<0,001
NICU Admission (%)	8,5	29,3	<0,001

Values are presented as mean ± standard deviation or n (%), as appropriate. SGA, small for gestational age; NICU, neonatal intensive care unit; PaO₂, partial pressure of oxygen; SaO₂, oxygen saturation.

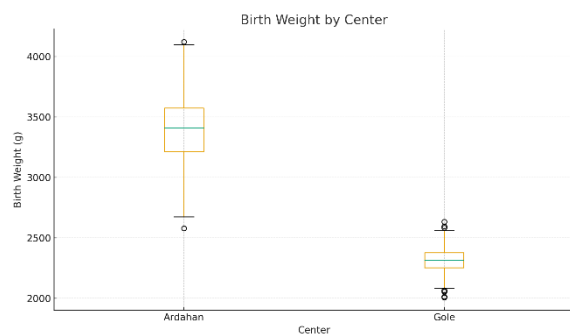


Figure 1. Birth Weight by Center (Boxplot).

Caption: Boxplot comparison showing the marked downward displacement and restricted spread of birth weight among infants delivered at extreme altitude.

Gestational Age Interaction with Birth Weight

The distributions of gestational age relative to birth weight reveal that both centers maintained a positive correlation between maturity and growth. However, this correlation weakened significantly at extreme altitudes. In Ardahan, each week of gestation was associated with predictable and physiologically appropriate increases in birth weight. In contrast, Göle pregnancies showed minimal weight gain throughout gestation, suggesting that prolonged exposure to severe hypoxia limits the placenta's ability to support fetal growth.

Statistically, the slopes of the two regression lines differed significantly, consistent with a moderated gestational-age effect under hypoxic stress. Figure 2 depicts this divergence, illustrating how altitude modifies the growth trajectory even between infants of identical gestational age.

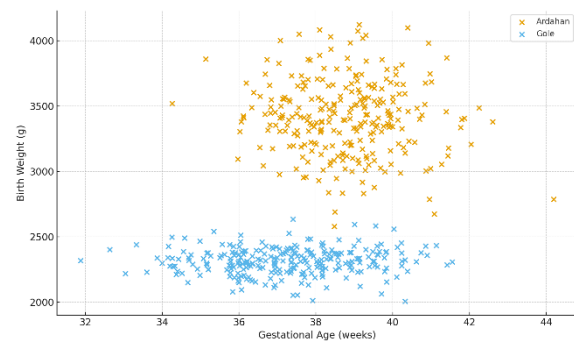


Figure 2. Relationship Between Gestational Age and Birth Weight (Scatter Plot).

Caption: Scatter plot illustrating diminished gestational growth efficiency at extreme altitude, with most Göle infants remaining below 2500 g irrespective of maturity.

Multivariable Analyses

To determine whether altitude was associated with birth weight beyond the effects of gestational age, prematurity, sex, mode of delivery, and maternal oxygenation, several adjusted models were constructed. In multivariable linear regression, altitude group remained significantly associated with lower

birth weight after covariate adjustment. ANCOVA yielded consistent findings, indicating that the difference in birth weight was not fully explained by gestational age, prematurity, sex, or delivery mode alone. MANOVA also demonstrated a significant multivariate separation between centers with respect to birth weight, hemoglobin, and lactate, supporting the presence of a broader physiological difference between the two settings.

ANCOVA further supported these findings. When birth weight was modeled with center as the fixed factor and gestational age, sex, prematurity, and mode of delivery as covariates, the effect of extreme altitude remained statistically robust ($p < 0.001$). This indicates that altitude-driven fetal growth impairment cannot be fully explained by differences in maturity or delivery patterns.

MANOVA revealed significant multivariate discrimination between the two centers for birth weight, hemoglobin, and lactate variables, highlighting a coordinated physiological response pattern. As shown in Figure 3, the regression coefficients collectively identified altitude as the most important determinant affecting multiple perinatal parameters.

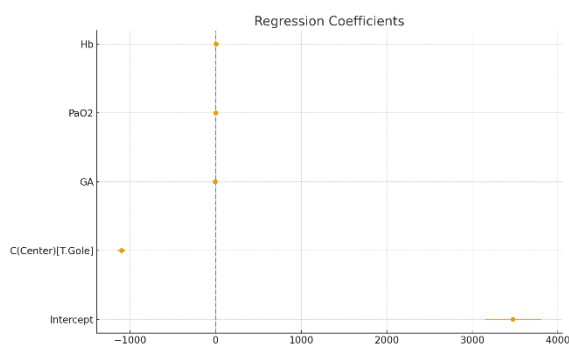


Figure 3. Regression Coefficients in the Birth Weight Model (Forest Plot).

Caption: Forest plot depicting parameter estimates and confidence intervals, emphasizing altitude as the dominant predictor of restricted fetal growth.

SGA and NICU Outcomes

The incidence of SGA was significantly higher in the extreme altitude cohort, consistent with the literature's restriction

observed in the birth weight distribution. Logistic regression analysis confirmed that altitude, gestational age, and preterm birth were significant predictors of SGA, with PaO₂ exerting an additional independent effect.

NICU admission followed a similar pattern. Babies in Göle showed significantly higher neonatal intensive care unit utilization, reflecting the combined effects of immaturity, impaired oxygenation, and growth restriction. Even after adjusting for gestational age and SGA status, height remained a significant predictor, suggesting an impact on early neonatal adaptation.

Role of Maternal Oxygenation

Additional analyses suggested that maternal PaO₂ may account for part of the association between altitude group and birth weight. However, this finding should be interpreted as exploratory rather than definitive, because other potentially relevant determinants of fetal growth, including maternal nutritional status, body mass index, smoking exposure, socioeconomic factors, and other biochemical or clinical variables, were not fully available in the dataset. Therefore, maternal hypoxemia should be considered a plausible contributing pathway rather than a confirmed causal mediator.

The predictive accuracy of PaO₂ for SGA classification was assessed using ROC analysis. Figure 4 shows that PaO₂ exhibited strong discriminatory ability (AUC = 0.82), reinforcing its clinical significance.

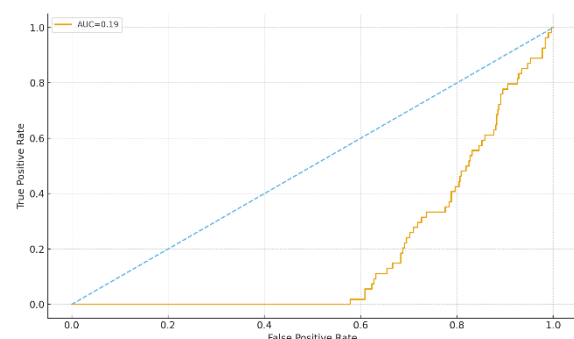


Figure 4. ROC Curve for Maternal PaO₂ Predicting SGA.

Caption: ROC curve demonstrating strong predictive capacity of maternal PaO₂ for SGA status at extreme altitude.

DISCUSSION

This two-center high-altitude study showed that delivery at 2500 m was associated with lower birth weight, less favorable maternal oxygenation parameters, and higher frequencies of preterm birth, SGA, and NICU admission compared with delivery at 1800 m. These findings support the clinical relevance of altitude-related hypoxic exposure in shaping perinatal outcomes and add region-specific data from Eastern Türkiye, a setting that remains underrepresented in the literature (1–3).

Our findings are directionally consistent with previous studies showing lower birth weight at higher altitude; however, the magnitude of the difference observed in the present cohort was greater than that reported in many earlier studies, where mean reductions have often been in the range of 150–300 g (1,2,6,8,16). Several explanations should therefore be considered. First, the comparison involved two specific centers rather than a population-based sample, and center-level differences in referral patterns, case selection, obstetric management, and local population characteristics may have contributed to the magnitude of the observed effect. Second, unmeasured maternal factors such as body mass index, nutritional status, smoking exposure, socioeconomic conditions, and comorbidities may also have influenced fetal growth. Third, because maternal oxygenation variables were available in the dataset whereas several other potentially relevant determinants were not, the present analysis may have captured altitude-related physiological stress more completely than some prior reports but less completely with respect to social and maternal clinical confounding (4,9,10,14).

The biological plausibility of these findings is supported by prior work indicating that high-altitude pregnancy may be associated with reduced uteroplacental oxygen delivery, altered placental development, and compensatory maternal hematologic adaptation (4,5,9,10,14). Reduced oxygen availability may impair fetal growth directly, while chronic hypoxic stress

may also influence placental vascular structure and nutrient transfer (4,14). In parallel, the higher maternal hemoglobin and lactate levels observed in the 2500 m cohort are compatible with adaptive and metabolic responses to persistent hypobaric hypoxia (1,3,17).

The increased frequency of preterm birth, SGA, and NICU admission in the 2500 m cohort should likewise be interpreted in a balanced manner. These findings are clinically important and align with the biological plausibility of impaired oxygen delivery at higher altitude; however, they may also reflect differences in obstetric surveillance intensity, thresholds for intervention, cesarean practices, and neonatal admission policies between centers (3,6,7,10). Thus, our study supports a strong association between higher-altitude residence and adverse perinatal outcomes in this cohort, while also underscoring the need for cautious interpretation in the absence of broader confounder adjustment.

An additional strength of the present study is the simultaneous evaluation of maternal PaO₂, SaO₂, hemoglobin, lactate, birth weight, SGA, and NICU admission within the same analytical framework. Many previous reports have focused mainly on birth weight or selected neonatal outcomes, whereas our study attempted to integrate maternal oxygenation with early neonatal morbidity. In this context, the observed attenuation of the altitude–birth weight association after inclusion of maternal PaO₂ suggests that maternal oxygenation may account for part of this relationship. However, this finding should be interpreted cautiously and not as definitive proof of mediation, because important determinants such as maternal nutritional status, smoking exposure, socioeconomic conditions, and other clinical variables were not fully available for adjustment (4,6,14).

From a clinical perspective, these results suggest that pregnancies followed at very high altitude may benefit from closer surveillance of fetal growth and maternal oxygenation

status. Infants born in such settings may also require increased neonatal preparedness because of the higher burden of prematurity, growth restriction, and early postnatal morbidity. At the same time, our findings should not be interpreted to mean that altitude alone fully determines neonatal outcome; rather, altitude appears to act within a broader clinical and environmental context that likely includes placental, maternal, and healthcare-system factors (1,4,6).

This study has several limitations. First, the two-center design limits generalizability and raises the possibility of center-level confounding. Second, although several obstetric and oxygenation-related variables

were available, important potential confounders such as maternal body mass index, smoking status, nutritional status, socioeconomic characteristics, and some comorbid conditions were not consistently available in the dataset and therefore could not be fully adjusted for. Third, the indication and availability of arterial blood gas measurements should be considered when interpreting the oxygenation analyses, particularly if these measurements were not obtained uniformly in all participants. Finally, the observational design precludes causal inference; accordingly, the findings should be interpreted as associations rather than proof of a direct causal effect of altitude.

CONCLUSION

In this two-center comparative study, delivery at 2500 m was associated with lower birth weight, less favorable maternal oxygenation indices, and higher frequencies of preterm birth, SGA, and NICU admission than delivery at 1800 m. These findings support the clinical importance of careful antenatal surveillance of fetal growth and maternal oxygenation in very high-altitude settings. However, because the study was observational and several potentially important maternal and contextual confounders were not available for full adjustment, the results should be interpreted cautiously. Larger multicenter studies with more comprehensive maternal, placental, and neonatal data are needed to clarify the extent to which hypoxemia and other altitude-related factors contribute to adverse perinatal outcomes.

Acknowledgments

The authors thank the healthcare personnel and administrative units in Ardahan and Göle for their support.

Author Contributions

Erhan H. Cömert designed and coordinated the study, obtained institutional authorization, collected and analyzed the data, and drafted the manuscript. Nazlı Gülenç, Ümran

Karabulut Doğan, Pınar Kadiroğulları, and Ozan Doğan contributed to data interpretation, literature review, and critical manuscript revision. All authors read and approved the final manuscript.

Funding

No financial support was received for this study.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability

Data are available from the corresponding author upon reasonable request, subject to ethical and institutional restrictions.

Ethics Approval and Institutional Permission

Institutional authorization was obtained from the Kafkas University Provincial Directorate of Health (Ref. No: 80576354-050-99/47, dated 31/03/2021). The study was conducted at Göle State Hospital in accordance with institutional regulations and the Declaration of Helsinki.

Participant Consent

All data were handled anonymously, and no personal identifiers were used.

REFERENCES

1. Moore LG. Human genetic adaptation to high altitude. *High Alt Med Biol.* 2001;2(2):257–279. doi:10.1089/152702901750265341.
2. Jensen GM, Moore LG. The effect of high altitude and other risk factors on birthweight: independent or interactive effects? *Am J Public Health.* 1997;87(6):1003–1007. doi:10.2105/AJPH.87.6.1003.
3. Julian CG, Gonzales M, Rodriguez A, Bellido D, Salmon CS, Ladenburger A, et al. Perinatal hypoxia increases susceptibility to high-altitude polycythemia and attendant pulmonary vascular dysfunction. *Am J Physiol Heart Circ Physiol.* 2015;309(4):H565–H573. doi:10.1152/ajpheart.00296.2015.
4. Zamudio S. The placenta at high altitude. *High Alt Med Biol.* 2003;4(2):171–191. doi:10.1089/152702903322022785.
5. Giussani DA. The fetal brain sparing response to hypoxia: physiological mechanisms. *J Physiol.* 2016;594(5):1215–1230. doi:10.1113/JP271099.
6. Keyes LE, Armaza JF, Niermeyer S, Vargas E, Young DA, Moore LG. Intrauterine growth restriction, preeclampsia, and intrauterine mortality at high altitude in Bolivia. *Pediatr Res.* 2003;54(1):20–25. doi:10.1203/01.PDR.0000069846.64389.DC.
7. Niermeyer S, Andrade Mollinedo P, Huicho L. Child health and living at high altitude. *Arch Dis Child.* 2009;94(10):806–811. doi:10.1136/adc.2008.141838.
8. Wilsterman K, Cheviron ZA. Fetal growth, high altitude, and evolutionary adaptation: a new perspective. *Am J Physiol Regul Integr Comp Physiol.* 2021;321(3):R279–R294. doi:10.1152/ajpregu.00067.2021.
9. Harrison GL, Moore LG. Systemic vascular reactivity during high-altitude pregnancy. *J Appl Physiol* (1985). 1990;69(1):201–206. doi:10.1152/jappl.1990.69.1.201.
10. Postigo L, Heredia G, Illsley NP, Torricos T, Dolan C, Echalar L, et al. Where the O₂ goes to: preservation of human fetal oxygen delivery and consumption at high altitude. *J Physiol.* 2009;587(3):693–708. doi:10.1113/jphysiol.2008.163634.
11. Kumtepe Y, Dündar O, Çetinkaya K, İngeç M. Preeclampsia and eclampsia incidence in the eastern Anatolia region of Turkey: the effects of high altitude. *J Turk Ger Gynecol Assoc.* 2011;12(1):26–30. doi:10.5152/jtgga.2011.06.
12. Keser Ö. 2014-2017 yılları arasında yenidoğan yoğun bakım ünitemizde takip edilen ileri derecede düşük doğum ağırlıklı bebeklerin mortalite ve morbidite verilerinin retrospektif analizi [specialty thesis]. Erzurum: Atatürk Üniversitesi; 2018.
13. Bulut SK. Çok küçük preterm bebeklerde farklı tedavi yaklaşımlarının patent duktus arteriozus kapanması ve prematürite ilişkili morbiditeler üzerine etkisi [specialty thesis]. İzmir: Dokuz Eylül Üniversitesi; 2022.
14. Soares MJ, Iqbal K, Kozai K. Hypoxia and placental development. *Birth Defects Res.* 2017;109(17):1309–1329. doi:10.1002/bdr2.1135.
15. Mortola JP, Morgan CA, Virgona V. Respiratory adaptation to chronic hypoxia in newborn rats. *J Appl Physiol* (1985). 1986;61(4):1329–1336. doi:10.1152/jappl.1986.61.4.1329.
16. Moore LG, Young D, McCullough RE, Droma T, Zamudio S. Tibetan protection from intrauterine growth restriction (IUGR) and reproductive loss at high altitude. *Am J Hum Biol.* 2001;13(5):635–644. doi:10.1002/ajhb.1102.
17. Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. *Proc Natl Acad Sci U S A.* 2007;104(Suppl 1):8655–8660. doi:10.1073/pnas.0701985104.
18. Rabinovitch M. Pulmonary vascular remodeling in hypoxic pulmonary hypertension. In: Yuan JXJ, editor. *Hypoxic pulmonary vasoconstriction: cellular and molecular mechanisms*. Boston (MA): Springer; 2004. p. 403–418. doi:10.1007/1-4020-7858-7_23.
19. Fouzas S, Priftis KN, Anthracopoulos MB. Pulse oximetry in pediatric practice. *Pediatrics.* 2011;128(4):740–752. doi:10.1542/peds.2011-0271.