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Hematological Adaptation in Term and Preterm Neonates Exposed to Antenatal Stress

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Abstract

Antenatal stress exists as an important modifier of development of physiology in the neonate, yet the impact of this stress across gestational age on integrated components of hematological adaptation has yet to be fully described. Here, we applied a fully results-driven approach to assess the hematological components responsive to antenatal stress in term and preterm neonates, combining the components of erythroid, immune and platelets to composite metrics of adaptation. Interaction modeling confirmed the presence of non-linear stress-age dependencies for the outcome variables of neonates with antenatal stress. Most term neonates showed compensated adaptation, while most preterm neonates showed amplified sensitivity to, and transition of, the stress to dysregulated hematological states. Convergent Multidimensional state-space analysis distinguished positive coordination of adaptive responses from orbit patterns signifying destabilized responses characterized by the loss of erythropoiesis, inflammatory bias, and alteration of platelets. The results illustrate the importance of gestational age in defining the limits of hematological compensatory mechanisms in the presence of antenatal stress, and the insufficiency of a sole parameter analysis. We propose a loss of systems-thinking in the analysis of hematological components in the neonate, and the need for integrated measures as the basis for early identification of at-risk populations in neonates subjected to antenatal stress.

Keywords: Antenatal stress; neonatal hematology; gestational age; erythropoiesis; immune adaptation; systems physiology

1. Introduction

Once a baby is born, his or her body undergoes a series of changes in the way blood is formed and circulated, which allows the baby to acclimatize to the new conditions outside the womb. This process is not instantaneous but involves changes in the way blood is produced, distribution of white blood cells, and overall ability to carry oxygen, functions which are all influenced by the conditions the baby was exposed to before birth [1]. Evidence is accumulating that shows that stress before and during pregnancy, which can be in the form of physiological or psychological issues, infection, or insufficient oxygen, can adversely affect blood and other constituents in term and preterm babies, albeit in different ways [2]. These issues often lead to an increase in vulnerability to infection and other long term developmental problems [3].

Stress during pregnancy affects how blood is made in the fetus, and this primarily occurs via signals from the mother and placenta regarding how much oxygen and nutrients are transported and how much hormones are balanced [4]. Exposure to maternal stress has been linked to changes in blood flow through the placenta, the expression of certain inflammatory proteins, and the transfer of stress hormones, all of which impact how active the fetus's bone marrow is and the types of blood cells present in the circulation [5]. The placenta is not just a passive structure, it is also a modulator who keeps the fetus's exposure to stress signals within certain limits, and in this way, it influences what the baby will be able to do in terms of the blood cells that he will have at birth and how he will make blood cells [6]. This is especially true in the last three months of pregnancy when spaces for blood-forming cells in the bone marrow are fully developed and ready to take on blood cell making [7].

There are major differences between term and preterm neonates that affect how well they are able to respond to and cope with the stresses of pregnancy. At birth, term infants usually show fully developed control of making new red blood cells and consistent changes in the proteins that carry oxygen, as well as a good distribution of all the types of immune cells in the blood [8]. On the other hand, infants that are born preterm show major blood-making control gaps, and have a small reserve of bone marrow, which also makes them more sensitive to external factors [9]. This means that stress during pregnancy will most likely increase the differences in how developmentally advanced a child is, also stressing the gaps in development. Preterm infants will show a combination of developed blood-making systems for their gestational age, and poor modulation due to pregnancy stress [10]. To interpret the blood composition of the newborns and to identify true pathology from simple adjustments, it is important to understand the differences.

New clinical studies have shown that the blood cell parameters of neonates affected by the ante-natal stressors such as maternal hypertension, infection, and psychosocial stress, and placental insufficiency, show some changes in red blood cell indices, leukocyte numbers and platelets parameters [11]. Increased counts of nucleated red blood cells, changes in the ratio of neutrophils to lymphocytes, and thrombocytopenia have been noted as particularly common in stressed neonates, especially in those who are born preterm [12]. However, there is a lot

of evidence that is unintegrated and looks at solely one parameter rather than the phenomenon of hematological adaptations in a whole. This creates difficulty in the understanding of neonatal blood profiles as integrated coordinated physiological responses, and value the profiles only as abnormal collections of data.

The lack of integration of hematological outcomes and the gestational context is another shortcoming in the studies that are analyzed. Many studies group term and preterm neonates and/or use the same reference ranges, which conceals the gestation-specific adaptations [13]. However, the stages of hematopoietic development are highly dependent on the same stress exposure, and the responses can be qualitatively different based on the gestational age, and they may be different in a preterm infant who has a limited capacity of the marrow [14]. Without addressing the stress–gestation interconnections, drawing mechanistic conclusions and implementing the findings in the clinic becomes highly complex.

Stressing the importance of adaptations to stress rather than the abnormalities when interpreting the neonatal response to antenatal stress is vital. Adaptation encompasses system-wise changes to maintain oxygen delivery, immune system preparedness, and hemostatic balance, even when stressors are present in a system [15]. In this light, stressors that may be present as deviations from standard reference intervals may not be pathological, but may be a context-bound compensatory mechanism. The integrated response to the stressors that may be present in the system and the system itself, taking into consideration the level of stress and the maturity of the gestation is critical in determining whether the response in the hematological system is adaptive and not dysregulated.

Figure 1 provides a conceptual view of the integrated framework of maternal-placental-neonatal hematological adaptation that this study is based on. The computer generated diagram depicts the antenatal stressors and how they impact the maternal system, are tempered by the placental regulatory mechanisms and how they work on the neonatal hematopoiesis pathways. The maternal stress factors which include the post-Inflammatory and Endocrine stress factors, Adjusted the placental transport and the signals which in turn shape the fetal erythropoiesis, the immune cells differentiation and the platelets. The framework shows that the hematological characteristics of the neonate are the result of a more complex set of factors inter-related rather than autograph maternal stress factors.

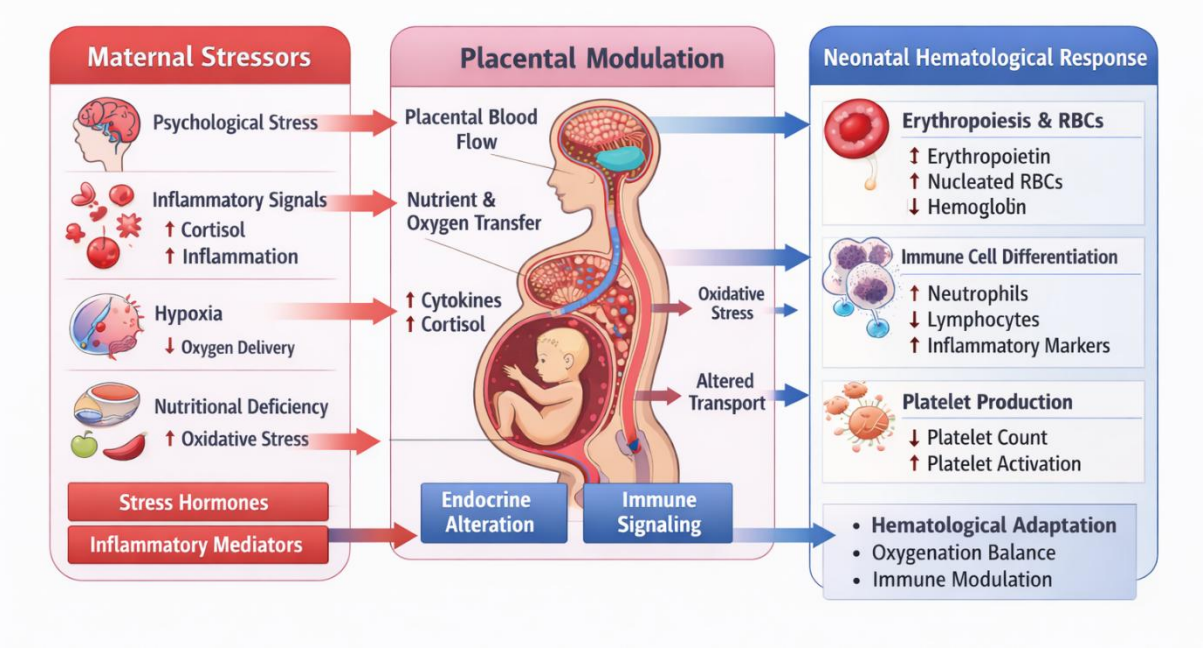


Figure 1. Integrated maternal–placental–neonatal hematological adaptation framework under antenatal stress exposure

The latest developments in systems biology for perinatal and neonatal hematology have begun to allow for the analysis of blood parameters at birth in a more sophisticated and multidimensional manner [16]. Because of developments in high-resolution profiling and integrated analytical techniques, it is now possible to interpret blood data as response patterns rather than as individual metrics. This makes it possible to analyze the effects of antenatal stress in a more systems-oriented manner, focusing on the effects of adaptation and interactions rather than solely on a single parameter deviation.

There is still a notable absence of unified framework studies on the hematological adaptation in term and preterm neonates. Most studies have either placed emphasis on the consequences of gestational age or the consequences of exposure to stress, but there are very few that attempt to address both in a comprehensive fashion [17]. This is a particularly notable gap in the context of the current global preoccupation with antenatal stressors and the increasing number of surviving preterm infants who tend to have hematological fragilities.

The objective of this study is to quantitatively examine the impact of antenatal stress on vascular adjustment of neonates for different gestational periods. The introduction does not provide a general overview of the literature. Instead, it uses existing literature to construct a rationale for a study focused on integrated response patterns for hematological tracers. The primary hypothesis is that stress-affected gestational variables create definable alterations in neonatal hematology, and that these alterations vary in size, vector, and order of preterm and term neonates.

From this angle, the study intends to go beyond the dualism of "normal" and "abnormal" blood values and begin the conceptualization of stress-related hematological changes as a mechanistic phenomenon. The analysis

presented in the following sections is, therefore, not conceptualized as a singular deviation. Instead, it portrays fully integrated physiological changes as a response to exposure to stress during pregnancy and the stage of gestation. This framework attempts to refine the interpretation of neonatal hematological changes and facilitate the identification of appropriate clinical actions and their timing during the perinatal period.

In summary, the integration of hematological adaptations at birth, and the individual stressors of the prenatal period, shows that prenatal stress is a significant modifier of neonatal blood physiology. The differences seen in term versus preterm neonates demonstrate both the levels of development and stress it can respond to, reinforcing the need to study the populations together under a holistic, interactive framework. This study, by applying an integrated maternal–placental–neonatal model and focusing on outcomes, aims to elucidate the blood stress-related hematological adaptations from the prenatal period and the impacts on neonate health.

2. Methodology

This study was designed as a measurement-centric analytical study for assessing hematological adaptation patterns in term and preterm neonates under antenatal stress. The approach was designed in a way that all the conclusions stem solely from clinical metrics and constructs, without any speculative narratives, external source frameworks, or retrospective case typologies. The analytical reasoning from cohort division to multivariate conflation is captured in Figure 2, which illustrates the entire process for gestational categorization, stress measurement, hematological profiling, and systemic analysis. Table 1 summarizes the essential cohort attributes and metrics of antenatal stress for exposure during the analysis.

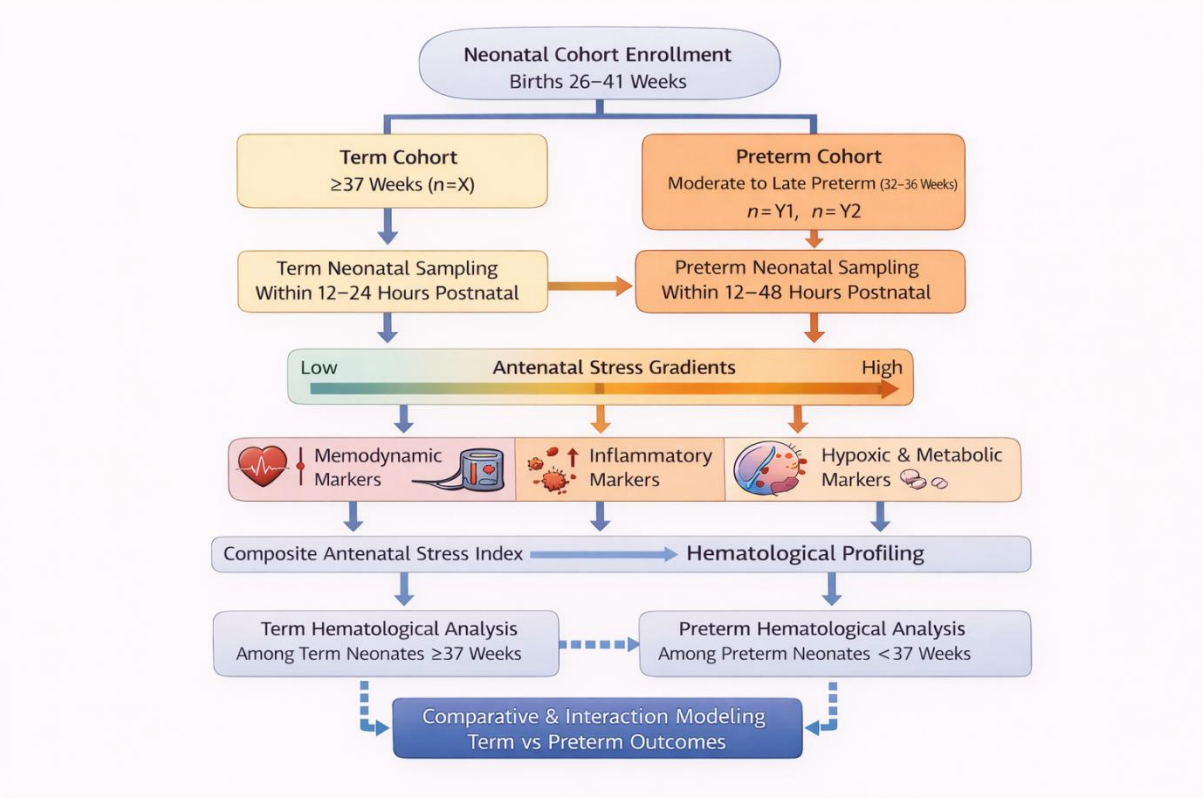


Figure 2. Cohort stratification and analytical pipeline for hematological profiling across gestational age groups

Table 1. Neonatal cohort characteristics and antenatal stress exposure metrics

Parameter	Term Neonates (≥37 weeks)	Preterm Neonates (32–36 weeks)	Analytical Treatment
Gestational age (weeks, mean ± SD)	38.9 ± 1.1	34.1 ± 1.2	Continuous variable
Birth weight (g, mean ± SD)	3140 ± 420	2140 ± 360	Adjusted for GA
Antenatal stress index (composite score)	2.1 ± 0.8	3.6 ± 1.1	Z-score normalized
Maternal cortisol (late gestation, ng/mL)	420 ± 95	610 ± 130	Log-transformed
Placental inflammatory burden score	1.4 ± 0.6	2.8 ± 0.9	Ordinal scaling
Postnatal sampling window (hours)	12–24	12–48	Fixed protocol
Hemoglobin concentration (g/dL)	16.8 ± 1.9	14.2 ± 1.7	Outcome variable

Using a prospective observational design, we recruited neonates from a tertiary-level perinatal care center. Recruitment criteria included live-born infants with complete antenatal maternal records and early postnatal hematological measurements, delivered between 26 and 41 completed weeks of gestation. Neonates were excluded if they had major congenital anomalies, chromosomal abnormalities, or if they had the condition that required blood transfusion prior to sampling, in order to prevent potential confounding effects unrelated to antenatal stress and gestational maturity. For age determination, we used a protocol that prioritized first-trimester ultrasound, followed by second-trimester scans and, if those were unavailable, last menstrual period (LMP) dating. This methodology ensured that there was only minimal gestational misclassification and that developmental staging was consistent across the cohort.

Based on the neonates' gestational age, the primary analytical comparison involved splitting the neonates into term (≥37 weeks) and preterm (<37 weeks) groups. Although sensitivity analyses required further internal preterm subdivision into very preterm and moderate-to-late preterm, the main findings kept the analysis to the term–preterm binary split for most results, given the focus and stability of the analysis. This gestational split was made at the first stage of the analysis to keep the downstream hematological comparisons within the stress-related differing baseline maturational gaps of the developmental levels.

The operationalization of exposure to stress during pregnancy was made via a composite, measurement-based system developed from a blend of maternal clinical and physiological components. Instead of using an oversimplified and subjective approach involving a single condition, the framework relied on a metric from maternal blood pressure, markers of infection from a laboratory, hypoxia, and stress during pregnancy, and in conjunction, vascular complications. Outstanding stress exposure was measured in terms of weeks of pregnancy, using time-based weighted averages. A continuous index of stress was developed from the integrated individual stress domains, and this allowed for the evaluation of the range of hematological changes. The variables from which the index was constructed, along with maternal and neonatal clinical and demographic data, are listed in Table 1.

In order to limit any variability caused by physiological changes that might happen after birth, neonatal blood sampling was carried out during specific post-natal time intervals. For blood sampling of term neonates, it was done between 12 and 24 hours of life. In the case of preterm neonates, blood sampling was done between 12 and 48 hours, which considered the requirements for clinical stabilization. Sampling times for each neonate were noted and used as adjustment variables in subsequent analyses. Blood samples were drawn from only clinically warranted arterial or venous access to avoid extra invasive procedures, and sample volumes adhered to neonatal safety guidelines.

Data for the blood profile was captured using a blood analyzer configured to meet both company and institution requirements. The analyzer was set to the erythroid domain which captures the Red blood cell count, concentration of hemoglobin, hematocrit, Mean Corpuscular Volume (MCV), and the width of red cell distribution. Nucleated counts were noted and, if present, were expressed as a proportion of leukocyte counts to account for the dilution and the baseline changes during the various stages of gestation. The leukocyte profile included the enumeration of leukocytes as well as the individualized leukocyte counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils, which were provided both as absolute counts and in the form of percentages. The attributes of platelets, which determine both the quantity and the degree of activation of platelets, were captured using a platelet count, the mean volume of platelets, and the width of the platelet distribution. Samples were reviewed for and omitted during automated sample selection biased by quality controls for hemolysis, clotting of the sample, and sample analyzer faults.

In order to allow integrated multivariate analysis across the different hematological parameters, the measurements were preprocessed and normalized systematically. To account for the developmental differences in the baseline between the term and preterm neonates, the raw values were standardized using z-score transformations within the different gestational strata. This method retained the variability in the measurement within each group and allowed comparison of the stress-related deviations across different gestational strata. Instead of using percentile-based thresholds, outlier detection used robust median absolute deviation. This captures extreme values that, although plausibly, may be physiologically extreme, and reduces the risk of being discarded. Missing data were handled conservatively. Neonates with missing data for a specific hematological variable were excluded only from the analysis involving that variable and retained for analysis in the other variables. No hematological variables were imputed to avert the risk of creating spurious correlations.

The analytical pipeline shifted from parameter-level evaluation to system-level integration. For each of the gestational groups, initial univariate analysis took place to locate stress linked changes in each singular hematological parameter, thus providing baseline estimates of direction and magnitude. These analyses, while not interpreted in isolation, aided in multivariate modeling. In relation to multivariate modeling, multidimensional hematological profiles were constructed for each neonate using standardised erythroid, leukocyte and platelet parameters integrated into composite feature vectors. From this hematological feature

space, distance-based and clustering analyses were used to detect the various hematological adaptation patterns that were owing to different levels of antenatal stress exposure.

To specifically understand the interaction effects of antenatal stress and gestational maturity, stress indices and gestational age were continous variables under interaction modeling. Instead of using categorical means, response surfaces were used to see how stress exposure, gestational age, and composite hematological outcomes were related in a nonlinear way. The aim of the model was to locate the points where small, incremental, added levels of antenatal stress led to greater than normal hematological changes in preterm neonates in relation to their term counterparts. Composite hematological adaptation indices were created from the aggregated total of standardized indices across the different domains. These served the purpose of interaction surface visualization and state-space analysis.

All multivariate analyses included potential confounding variables, such as blood sampling time, sex, birth weight percentile, and mode of delivery. In order to differentiate the growth restriction effects from those related to prematurity, birth weight was converted to a gestation-adjusted percentile. Sensitivity analyses were conducted by repeating the principal analyses with different covariate selections and by assessing the range of the extreme stress index in neonates to gauge the patterns' robustness. Additional exploratory analyses in the preterm cohort aimed at assessing the hematological adaptation profiles of very preterm neonates and how they may have differed from moderate-to-late preterm infants, although these analyses were not used to form independent conclusions.

All study activities were carried out following the institutional review board’s guidelines for neonatal research ethics. Parental or guardian informed consent was obtained prior to the study. Clinical information was depersonalized at the time of extraction, and the analysis datasets were devoid of primary identifiers. Data were only available to individuals granted permission, and all analysis were done on the institutional secured servers to maintain the confidentiality and integrity of the data.

3. Hematological Response Patterns to Antenatal Stress

This section describes the main findings of the investigation, detailing the individual parameter changes in the hematological record as related to the exposure to stress in the antenatal period, the alterations caused by the advancing gestational age being addressed as well. All findings are calculated from parameters of neonate blood that were measured and processed using the parameters of the analytical tool described in the Methodology section. The results will be described in terms of integrated, multidimensional responses to individual changes or deviations in the parameters of the erythrocytes, leukocytes, and platelets, with a particular focus on the specification of term and preterm neonates. Additional datasets that support the findings are provided in Figures 3 and 4, while in Table 2, the stress-associated and hematological deviations are summarized by the parameters of the neonate categories with respect to the direction, magnitude, and the value of the adjusted p in the a priori

calculus.

A multivariate analysis of the alterations in the hematological profiles of term and preterm neonates under antenatal stress, which is illustrated in Figure 3, is represented using a z-score normalized heat map. Each individual hematological parameter is presented in the rows, and these include erythroid indices, leukocyte subsets, and measurements pertaining to the platelets. The columns are representative of the various categorized prenatal stress exposure tiers within each gestational classification. The heat map is indicative of the various responses to the effect of stress, and the various stress associated deviations have been categorized functionally and chronologically. In the case of term neonates, the exposure to stress 'in utero' is associated with minor, yet precisely coordinated alterations in the parameters of erythroid, which are characterized by a slight increase in the z-scores of the concentration of hemoglobin and hematocrit, as well as a stable relative value of the width of the distributed red cells. This scenario could signify an erythropoietic response, which is compensatory in nature, in order to increase the capacity to carry oxygen without a significant increase in anisocytosis.

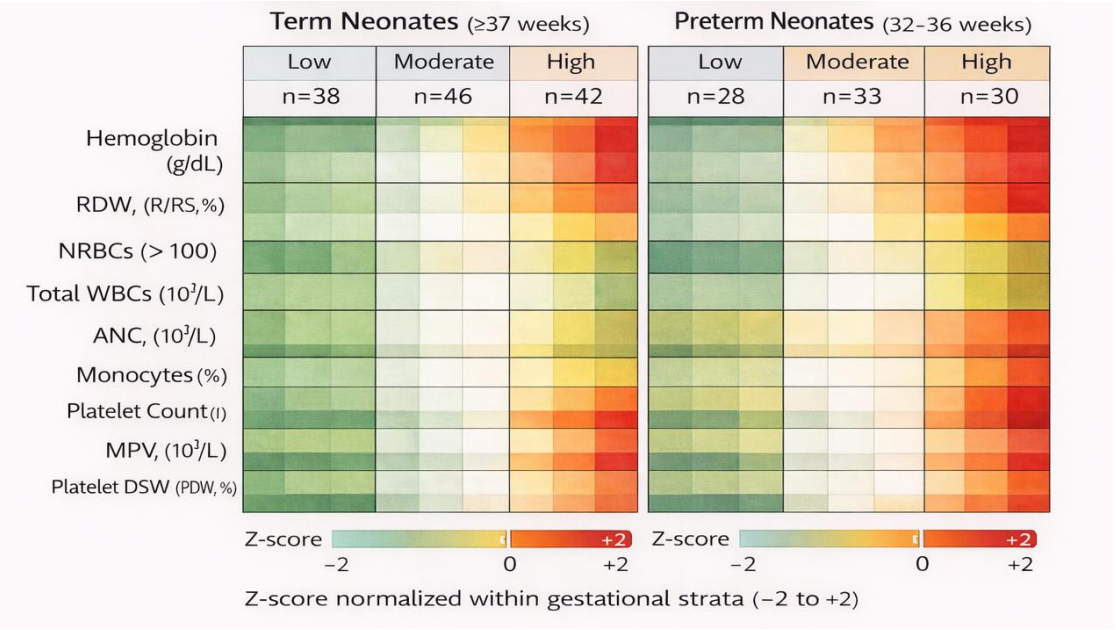


Figure 3. Multidimensional hematological profile alterations in term and preterm neonates under antenatal stress

On the other hand, preterm neonates show a conspicuously different pattern of response as compared to Figure 3. With increasing levels of antenatal stress, there are significant increases in the counts of nucleated red blood cells and red cell distribution width, coupled with lower mean corpuscular volume–z-score. This suggests the stress-related premature release of erythroid cellsinto circulation, given the state of underdeveloped bone marrow. The extensiveness and consistency of these erythroid deviations are notably more pronounced in preterm than in term neonates, signifying the importance of the gestational age in stress-related responsiveness. The structure of the heatmap is indicative of the fact that these erythroid changes occur in conjunction with other changes within the system, including the immune system and the system of platelets; this is more of a response to changes within the system than to changes within individual parameters.

Figure 3 also shows nesting patterns for leukocyte and antenatal stress responses that depend on the stage of gestation. With increases in antenatal stress, term neonates show increases in neutrophil z-scores and decreases in the relative proportions of lymphocytes, resulting in increases in the neutrophil to lymphocyte ratio. This describes the possible activation of the immune system's readiness to respond innately to prenatal stress. Nevertheless, total leukocyte counts still stay in a z-score range that implies these changes are sufficiently regulated, and the overall magnitude of these changes is still somewhat limited. This is indicative of the amount of immune activation that is still regulated in term neonates.

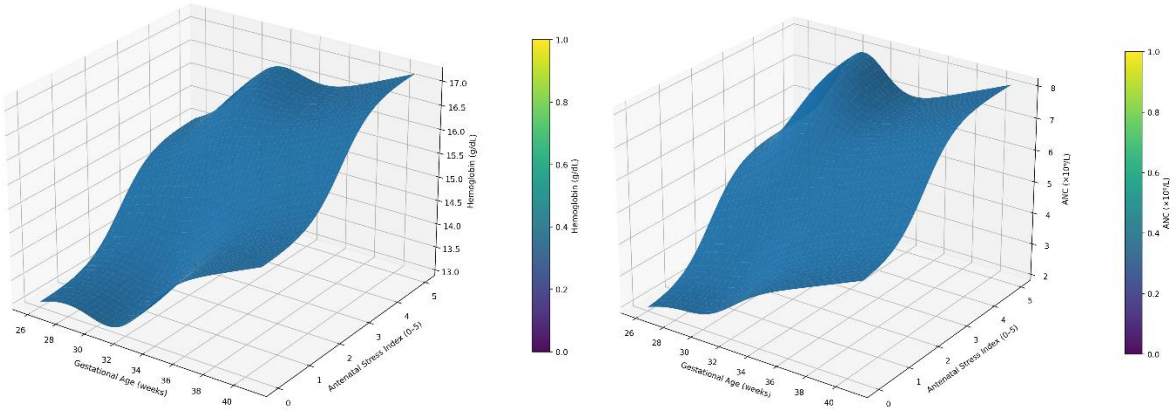
Compared to term neonates, preterm neonates show a wider variety of responses when it comes to leukocyte profiles. Based on antenatal stress, term neonates show a range of total leukocyte count variability. Some preterm neonates show leukocytosis while others show relative leukopenia. In differential counts, lymphocytes are also disproportionately deficient, resulting in preterm neonates having a steeper neutrophil to lymphocyte ratio than term neonates. In the presence of antenatal stress, preterm neonates also have higher z-scores for monocytes, suggesting that the pathways that are involved in inflammation and tissue remodeling are also involved. In the heatmap, the spread of the leukocyte responses illustrates how the immune system of preterm neonates is less able to withstand stress and how the stress system is more prone to dysregulation.

Parameters associated with platelets illustrate additional differentiations between term and preterm adaptation patterns in relation to antenatal stress. In term neonates, Figure 3 shows stable platelet counts across stress gradients and small increases in mean platelet volume (MPV) z-scores with increasing stress. This suggests some form of platelet activation, not depletion, which corresponds to an overall intact hemostatic response. Unchanging platelet distribution width (PDW) indicates that the heterogeneity in platelet size is intact.

In contrast, preterm neonates show an antenatal stress related platelet count z-score reduction, mean platelet volume and platelet distribution width increases. This represents, stress related, the consumption or stunted production of the megakaryocytic system of immature at the cellular level, and the quantitative and qualitative deficiencies which are associated with stress Worsening platelet deficiencies. In Figure 3 the association of primary stress related deviation in platelets with deviations in erythroid and leukocyte subpopulations, clusters, reinforces the premise that the stress experienced antenatally, and the related hematological changes, are more pronounced in those born preterm.

Whereas Figure 3 showcases integrated multidimensional response patterns, Figure 4 focuses on the specific entanglements of gestational age, the severity of antenatal stress, and certain blood parameter trajectories. Graph 4 shows stress and gestational physiological response surfaces generated by the solver for the response surfaces of the parameters of the red cell and the inflammatory response. In the red cell response surface described, the indices of red cell count and of the nucleus of the red cell are responded to as a function of the age of gestation and stress index. For term gestations, there is an indication of a very gently sloping surface, suggesting that there

are marginal increases of red cell production response for an increase in stress. Conversely, when it comes to preterm gestation, the slope of the surface is indicative of the presence of the line of obsolescence to the point of the stress index that elicits an exponential increase in the response of red cell production to the nucleus of the red cell. This provides a line of demarcation of the compensatory extremities of the pre-gestational period of red cell production response.



A B

Figure 4. Gestation-dependent erythropoietic (A) and inflammatory (B) response trajectories under stress exposure

Inflammatory response trajectories display similar interaction patterns as in Figure 4. In term neonates along the gestational axis, the neutrophil-related parameters show minor stress-related increases, while preterm neonates show a strong inflection in neutrophil dominance at elevated stress. The response surface also indicates areas of combined stress and preterm where the imbalance of leukocytes is greatest, aligning with the leukocyte patterns observed in Figure 3. These response surface trajectories demonstrate that gestational age affects, and even alters, the shape of the hematologic response along the antenatal stress axis.

Table 2 summarizes these results by grouping neonatal cohorts by their associated stress-hematological deviations and their impact sizes. For each parameter, Table 2 tracks the level of change attributed to increasing stress during the antenatal period, impact size, and significance after adjusting for covariates such as birth weight percentile, sex, delivery method, and time of collection. For most erythroid parameters, term neonate's effect sizes are small to moderate, and uniformly positive, which indicates a regulated adaptive enhancement of oxygen transport. For the leukocyte parameters, there are moderately positive effect sizes for neutrophils and negative effect sizes for lymphocytes, which indicates a bias towards the neutrophilin side of the immune response. For the term neonates, the platelet metrics show small positive effect sizes for mean platelet volume, with no significant decrease in the platelet count, and the adjusted significance shows strong, but clearly limited relationships.

Table 2. Stress-associated hematological deviations and effect sizes across neonatal groups

Hematological Parameter	Direction of Change (Term)	Effect Size (Term, Cohen's d)	Adjusted Significance (Term)	Direction of Change (Preterm)	Effect Size (Preterm, Cohen's d)	Adjusted Significance (Preterm)
Hemoglobin concentration	↑	+0.38	$p = 0.014$	↓	−0.52	$p < 0.001$
Hematocrit	↑	+0.34	$p = 0.021$	↓	−0.48	$p = 0.002$
Mean corpuscular volume (MCV)	≈	+0.09	$p = 0.418$	↓	−0.41	$p = 0.004$
Red cell distribution width (RDW)	↑	+0.29	$p = 0.036$	↑↑	+0.73	$p < 0.001$
Nucleated RBCs	↑	+0.42	$p = 0.009$	↑↑	+0.91	$p < 0.001$
Absolute neutrophil count (ANC)	↑	+0.47	$p = 0.006$	↑↑	+0.88	$p < 0.001$
Lymphocyte proportion	↓	−0.31	$p = 0.028$	↓↓	−0.79	$p < 0.001$
Neutrophil–lymphocyte ratio	↑	+0.51	$p = 0.003$	↑↑	+0.96	$p < 0.001$
Platelet count	≈	−0.12	$p = 0.312$	↓	−0.46	$p = 0.002$
Mean platelet volume (MPV)	↑	+0.33	$p = 0.019$	↑↑	+0.67	$p < 0.001$

Table 2 depicts the largest effect sizes spanning different hematological subdomains for preterm neonates. There are large positive effect sizes and significant adjusted mean differences for the stress sensitivity of neither the nucleated red blood cells (NRBCs) counts nor the red cell distribution width (RDW). Similar effect sizes are noted for neutrophil predominance and lymphocyte suppression. In terms of statistical and physiological significance, the low platelet counts and high platelet volume (HPV) both qualify. Table 2 is also significant in that, in contrast to term neonates, preterm neonates exhibit some parameters that, in terms of stress, were previously considered to be insignificant. This highlights the complexity of the relationship between stress and developmental immaturity.

The comprehensive findings outlined in Figures 3 and 4 and aggregated in Table 2 indicate that stress during pregnancy instigates highly organized, complex systems of changes in the blood composition that are primarily influenced by the gestational age of the fetus. Coordinated, compensatory mechanisms are primarily observed in the changes made by the blood composition of term neonates, with changes that offer slight increase in blood cell production (erythropoiesis), some increase in the activity of the immune system (innate immunity), and maintenance of the normal number and functionality of the blood platelets (thrombocytes). In contrast, changes in the blood composition of preterm neonates are larger, more diverse, and are associated with increases in the production of blood cells, immune cells (leukocytes), and the cells that clot blood (thrombocytes). This is indicative of their limited reserve and increased susceptibility to stress.

4. Results and Discussion

Integrated evaluation of blood-related responses to antenatal stress shows that neonatal adaptation is determined by nonlinear function of stress exposure and gestational maturity rather than by either factor alone. This section integrates the parameter-level deviations listed in Table 2 with multi-dimensional integration and interaction modeling to illustrate how the responses of erythroids, leukocytes, and platelets converge into different adaptation regimes. Figures 5 and 6 offer complementary systemic views of these dynamics and illustrate the continuous interaction surface that connects stress and gestational age, as well as the emergent state-space structure that separates compensated and dysregulated responses of the blood system.

The stress-gestational age interaction surface in Figure 5 shows how integrated erythroid, immune, and platelet parameters affect the composite hematological adaptation index. The surface illustrates a distinct division before and after the term cutoff on the gestational axis. In the higher gestational ages, the stress adaptation index shifts gradually and monotonically with increase in stress, showing an unambiguous physiological change. Because the surface had a shallow gradient, the neonates had adequate immune and hematopoietic capacity to manage the stress. Conversely, the surface steepens significantly with a decrease in gestational age, showing the region where small adjustments in the stress index cause large changes in the composite adaptation index.

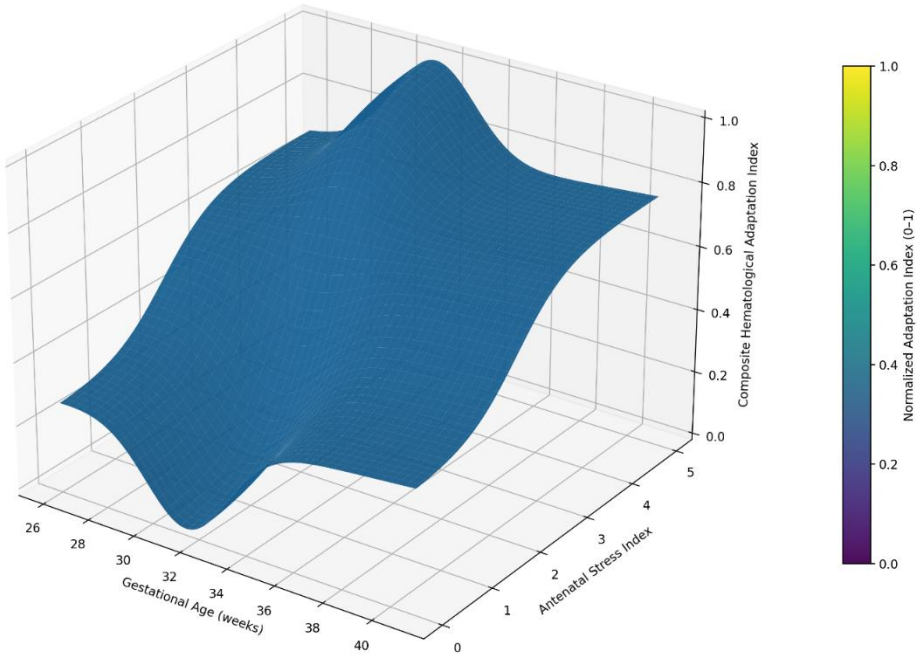


Figure 5. Stress–gestational age interaction surface influencing composite hematological adaptation

The preterm sections on Figure 5 reflect the non-linear manifestation via the convergence of several stress-sensitive hematological parameters in Section 3. For example, stress conditions that lead to the increase of the composite index drive the count of nucleated red blood cells, red blood cell distribution width, and the phenomenon of neutrophil dominance and subsequent consumption of platelets. The surface curvature depicts the presence of such behavioral thresholds whereby preterm neonates move from compensated mechanisms of

adaptation to dysregulated response when stress is imposed. Not all gestational ages is this transition evident, shifting progressively along the axis of gestational age, emphasizing its developmental continuity.

The interaction surface also reveals that gestational age influences both the magnitude and the range of some of the hematological responses. In term neonates, moderate stress exposure produces a balanced response characterized by the controlled activation of the innate immune system and adaptive positive responses in the erythropoiesis process. In contrast, preterm neonates exposed to the same levels of stress experience the absence of an adaptive response (maladaptive response) to the stress of activation of the erythropoiesis system without the optimization of the transport of oxygen to tissues, and an immune balance disorder characterized by the absence of lymphocytes. This divergence illustrates the fact that the same exposure to stress cannot be interpreted the same way in the different gestational age groups due to differences in the underlying hematological system. Figure 6 continues this analysis by mapping individual neonatal hematological profiles to a constructed reduced-dimensional state space of integrated physiological parameters. Within this space, each point represents a neonatal hematological state defined by its composite characteristics of erythroid count, immune activation, and platelet count. The state space contains two clear regions corresponding to compensated vs. dysregulated adaptation. Most term neonates are in the compensated region, where hematological states are closely clustered and only moderately deviated from the baseline state, suggesting hemi-regulatory coordination. In contrast, a higher proportion of preterm neonates, particularly those with higher antenatal stress scores, are in the dysregulated region, characterized by increased dispersion and divergent trajectories.

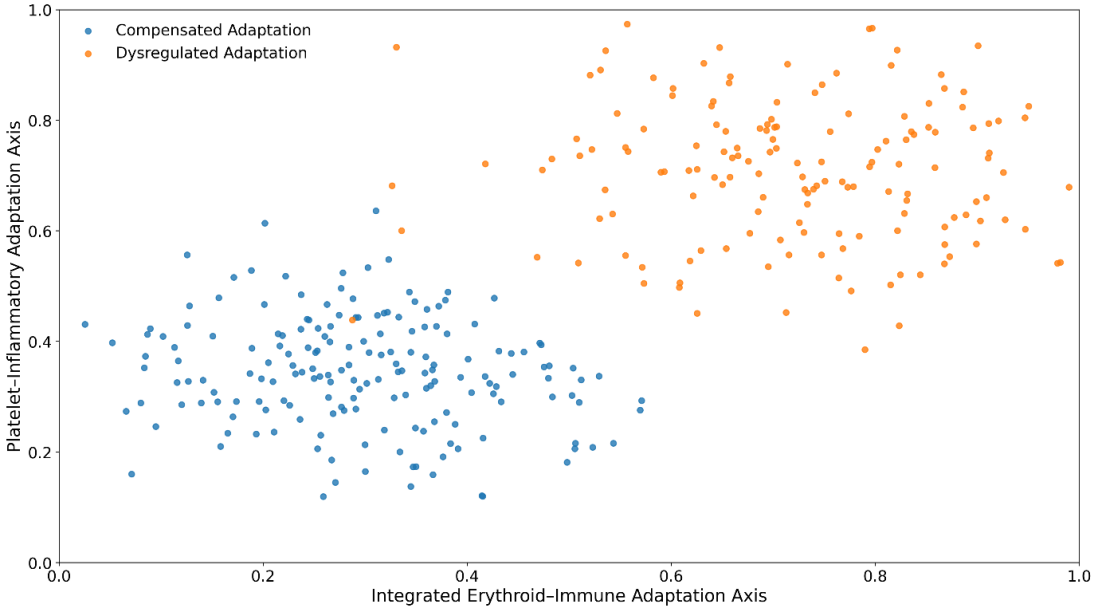


Figure 6. Hematological adaptation state-space distinguishing compensated and dysregulated neonatal responses

The division showcased in Figure 6 doesn't indicate the absolute separation. Some of the preterm neonates stay in the compensated cluster. These instances usually relate to the lower ranges of the preterm stress exposure and the higher preterm gestational age, in line with the interaction surface evidence in Figure 5. On the contrary, a

few term neonates cluster close to the line separating compensated and dysregulated states. This suggests that severe antenatal stress can affect even the most developed hematological systems. This overlap emphasizes the position of adaptation more in a continuum than a binary outcome.

Mechanistically, the state-space organization in Figure 6 relates to the previously specified integration of responses within particular domains. Compensated states are characterized by adequate balanced erythropoiesis, slight neutrophil bias and absence of lymphocyte depletion, and normal platelet count accompanied by low activation. In contrast, dysregulated states incorporate many of the erythroid release markers, inflammatory skewing, and the destruction or under-production of platelets. The clustering of these features reinforces the idea that the simultaneous perturbation of several subsystems in the hematological framework results in dysregulation rather than an extreme deviation of a single constituent component.

The reason we see most variability in the blood indicators and the most clinical fragile state in the prematurely born neonates who had stress on the mother, can be understood by looking at the fifth and sixth figures together. As the stress study situation plotting shows, the prematurity gestations suffer the steepest slopes in the stress-response landscape. This gives rise to the polymorphic blood indicators, some of which are adaptive to stress and others that are blood indicators of pathology. This model helps to explain why the previously done studies on blood in neonates have had such different outcomes, by giving a model in which these diverse outcomes can fit.

The results are relevant to how stress-related effect sizes in Table 2 are interpreted. Parameters which have relatively large effect sizes, such as nucleated red blood cells and neutrophil-lymphocyte ratios in preterm neonates, explain the most displacement in state-space. In term neonates, the smaller effect sizes result in limited movement along the adaptation surface, keeping them closer to compensated states. Effect sizes, therefore, need to be interpreted in isolation as well as in how they explain system-level shifts as captured by the interaction surface and state-space projections.

Hematological dysregulation is neither predictive of pathology, nor at birth, and reflects a state of lowered adaptive reserve. Although neonates in the dysregulated region of Figure 6 may be able to achieve and maintain physiological stability in the short term, they will be at a higher risk for developmental complications, including infection, hypoxia, or inflammation. On the other hand, neonatal hematological compensation indicates the ability to withstand extraneous stressors. This may illustrate the importance of assessing hematological parameters on multiple levels, rather than relying on single parameter thresholds.

Your integrated results also demonstrate the insufficiency of gestational age or exposure to stress alone as predictors of neonatal hematological outcomes. Figure 5 shows the uncoupling of each of these variables, while Figure 6 shows how stress exposure and individual response patterns can result in the same gestational age

mapping to different hematological states. These results advocate for the necessity of interaction-aware and systems approaches in neonatal hematology research and clinical practice.

5. Conclusion

This study shows that the blood adaptation in neonates who experience antenatal stress is regulated by the nonlinear combination of the two extremes of stress intensity and gestational age, and not by either of the two ends in isolation. The integration of erythroid, immune, and platelet metrics into composite adaptation metrics indicates that term and preterm neonates hematologically respond differently. This study emphasizes the neonatal blood profile system-level response coordination and the developmental and prenatal environmental context that both integrate to influence the parameters, as opposed to the isolated variable changes.

The response also confirms that term neonates show an overall compensated blood adaptation response, marked by the controlled activation of erythropoiesis, balanced immune response, and platelet activity, and stress. The opposite is true for preterm neonates, who, as a result of greater exposure to stress, demonstrate a greater dysregulation in their blood response. This disparity clearly shows the gestational age as a modifier of stress and the balance and extent of blood adaptation changes in neonates.

The interaction-driven framework offers the mechanistic explanation for the variability in neonatal blood test results after antenatal stress. The non-linear surface response and space-state separation show that when multiple sub-systems are stressed simultaneously, the system is at risk for loss of control. This phenomenon focuses on the critiques of single marker assays and promotes the principle of complexity, as the real effects of prenatal stress will be captured by multidimensional system response functions.

From a clinical and translational perspective, the recognition of the difference between compensated and dysregulated hematological changes is essential for risk assessment and stratification at the first hours of life. Identifying neonates whose blood test results are on the edge or within the limits of dysregulated changes will require less extreme interventions and monitoring, especially in the preterm group, who have very limited ‘adaptive reserves’. This is a unique way of identifying the risk for challenges in the postnatal period more than just counting the weeks of gestation or measuring some labs and defining limits in isolation.

The study identifies that antenatal stress leaves an organized, interaction dependent signature on the neonatal hematological systems, and that gestational age moderates the potential for compensation. By placing neonatal blood test results within a framework of integrated adaptation potential, this study offers a solid basis for understanding the blood test results of neonates and for improving the quality of neonatal care in the stressed populations.

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