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Endocrine Disruption During Late Gestation and Neonatal Hormonal Homeostasis

*Phone Myint Htoo[1], Manglesh Waran Udayah[2] and Sandra Rumi Madhu[3]

[1]International Medical School, Management and Science University, Shah Alam 40100, Selangor, Malaysia
[2]School of Medicine, Perdana University, Damansara Heights, Kuala Lumpur, 50490 Malaysia
[3]Vice-Principal, Grameen Caledonian College of Nursing, Dhaka, Bangladesh

*Correspondence: phone_myint@msu.edu.my

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Abstract

The period of endocrine regulation during the late gestation stage is crucial for the establishment of the neonatal hormonal homeostasis, but it is also the most susceptible to systemic endocrine disruption. This research focused on the integrated hormonal profile of the mother, placenta, and neonatal, to determine the impact of perturbed late gestation endocrine on neonatal hormone imbalance. The surface and multivariate analyses show nonlinear and threshold-dependent associations of maternal endocrine disruption and the neonatal imbalance of cortisol and thyroid and the metabolic hormones, suggesting that there is a finite capability of the placenta to buffer. The multivariate and the stratification analysis showed a coordinated dysregulation of the system of stress, metabolism, and the growth hormones. Moreover, the predictive analytics showed that the late gestation endocrine profile is an accurate predictor of the neonatal hormonal dysregulation risk. These results emphasize the role of the placenta, under chronic endocrine disruption, is as a critical hormonal buffer and a failure point. Hence, the Endocrine disruption, under the chronic stress of the system, is a critical gestational stressor, with direct effect to the newborn. These results highlight the value of the risk stratification based on endocrine markers for predictive neonatal care and the management of the perinatal hormonal regulation.

Keywords: late gestation; endocrine disruption; placental buffering; neonatal hormonal homeostasis; endocrine programming; risk stratification

1. Introduction

Endocrine programming occurs late in gestation. This process involves complex and closely connected hormonal communication across maternal, placental, and fetal systems. This communication supports fetal development and prepares the newborn for life outside the womb. During this time, the endocrine systems that control growth, metabolism, stress, and the readiness of organs for function undergo rapid and refined changes. Because of this, they are sensitive to disruptions. The consequences of disrupted hormonal balance during late pregnancy are no longer confined to the immediate pregnancy outcome. They define the physiological and the longer-term health outcomes of the neonate [1], [2].

The central component of this dynamic feedback loop of the endocrine systems is the placenta. It is not merely an endocrine passive conduit, but more of an active engineer and regulator of hormonal communication. Cortisol, insulin, thyroid hormones, and other metabolic peptides from the mother are modulated by placental transporters, enzymes, and binding proteins prior to being released into the fetal circulations [3], [4]. This buffering structure of the placenta ensures that fetal organs are properly bullish to the signals of maternal hormones. However, in cases where the placental transport processes are either overextended or compromised, maternal hormones are transmitted to the fetal systems without any placental regulation. This would in turn disrupt the endocrine balance of the fetus during sensitive periods of development [5].

Changes in endocrine demand and responsiveness occur during late gestation. There is an increase in fetal growth along with the development of the function of the hypothalamic–pituitary–adrenal axis, the onset of thyroid hormone–dependent neurodevelopmental processes, and postnatal glucose and lipid handling metabolic adaptations. There is probably an increase in the intensity and duration of hormone exposure [6], [7]. With endocrine signaling diminishing or deviating from the expected during late gestation, there is a high risk to the neonatal hormonal equilibrium, resulting in insufficient stress coping, metabolic dysregulation, and/or poor or delayed shifts in physiology after birth [8].

There has always been concern for the disruption of maternal endocrine systems in pregnancy, but primarily, the focus has been on early gestational exposures or maternal endocrine disorders. Yet, much literature outlines late gestation as a unique and sensitive endocrine programming window. During late gestation, certain placental enzymatic systems, notably 11 beta-hydroxysteroid dehydrogenase, iodothyronine deiodinases, and insulin-like growth factor-binding proteins, externally control the availability of hormones to the fetus [9], [10]. There is a grater exposed lag in maternal metabolic stress, inflammatory conditions, environmental exposures, placental insufficiency, and/or a combination of these factors that operate to cause recalcitrance to an altered hormonal transfer and a new endocrine set point for the fetus [11].

The maternal-placental-fetal hormonal axis acts more like a coupled network than a linear pathway. This means maternal hormonal changes can lead to alterations in placental hormonal metabolism, transporters, receptors, and other compensatory changes. These placental changes can also be influenced by fetal feedback, particularly by altering how the fetus exposes the placenta to certain hormones [12]. Late gestation is a particularly complex period as fetal autonomy increases, and the placenta continues to regulate hormones, but the fetus also possesses active feedback mechanisms. Problems at any part of the axis can affect the other nodes, and destabilize the hormonal balance of the infant.

The ability to maintain a balanced set of hormones is the starting point for the infant to adjust to life outside the womb. The infant needs to balance a series of hormonal systems that promote the central nervous system, regulate temperature, maintain glucose homeostasis, and other systems that adjust stress and cardiovascular response. If there has been a hormonal problem in-utero, the infant will be more likely to face problems in these areas, like hypoglycemia, stress response abnormalities, and delayed metabolic shifts [13]. Disrupted hormone levels during the last months of gestation correlate to the levels of cortisol, thyroid hormone, and insulin that is present in the infant at and after delivery. These studies illustrate that the hormone levels that a fetus is exposed to affect its hormone levels after birth [14].

Although there's increasing acknowledgement of such associations, disruption of endocrine systems during late gestation remains under-defined as a systems-level phenomenon. Most studies examine individual hormones or endocrine systems, which limits the understanding of the extent to which the coordinated networks of other hormones can also be disrupted. There needs to be a 'big-picture' understanding of the maternal endocrine profile, the effects on the placenta, and the hormones of the neonate to explain the mechanisms of endocrine disruption and neonatal instability [15]. Such understanding views endocrine equilibrium as an emergent characteristic of a system formed by multiple interacting signals and pathways rather than a by-product of independent constituents.

The psychosocial stress, inflammation, and the metabolic and endocrine disorders of the mother are all late-gestation stressors, and they increase the likelihood of endocrine disruption. Stressors of the mother can all affect the synthesis of hormones and the metabolism and signaling of receptors during the critical period [16]. While disruptions during early gestation can limit the organization of the structures of the fetus, endocrine disruptions during late gestation primarily alter the functional maturation and the regulatory thresholds of the systems involved, making the effects on the neonate visible and immediate.

Endocrine dysfunction late in pregnancy does not have to mean severe disruption to the the body's hormonal system. More frequently, it involves relatively subtle changes in the ratios of the hormones present in the body, changes in the circadian patterns associated with those hormones, or changes in the body's reactivity to the hormones.

These small changes might go undetected in the average clinical visit, but can have a big impact on the endocrine equilibrium of a neonate. Sensitive disruption biomarkers must be identified for effective early risk stratification and focused neonatal care [17].

The early blood and cord blood samples provide a biochemical profile of the endocrine state at the time of capture. The blood samples we collect at birth provide evidence of the maternal and fetal endocrine systems in conjunction with the placenta. As such, they capture the state of the endocrine system during the closing window of late gestation, offering insights into the late-gestation endocrine changes that may be critical for the newborn. The routine testing of blood samples allows for the documentation of endocrine signs of neonatal hormonal instability, thereby connecting prenatal exposures with postnatal physiological changes [18].

This study investigates the impact of endocrine disruption during late gestation on neonatal hormonal homeostasis. Recognizing integrated hormonal patterns along the maternal–placental–neonate axis, the study aims to identify the phenomenon whereby perturbations in late gestestation endocrine signaling lead to hormonal dysregulation in the neonate. Identifying and characterizing the phenomenon is critical for the development of biomarker-driven methods to assess perinatal risk, and for the development of methods to protect endocrine functioning during one of the most critical phases of human development.

2. Study Design and Hormonal Profiling Framework

The endocrine disruption study sought to understand phenomena across systems involving the mother, the placenta, and the baby. The focus was on the integration of endocrine data across the various thresholds of biological systems that interface with the hormonal measurements and regulate fetal/neonatal hormonal set point, unlike other studies that have treated hormonal measurements as isolated biochemical phenomena. This was based on the consideration that the endocrine equilibrium at the time of birth is not a product of a singular peripartum endocrine event, but rather a result of the cumulative hormonal changes during late gestation.

The study aimed to identify and recruit participants that had varied late-gestation endocrine states. The participants that were enrolled had pregnancies that extended into the third trimester. This is because, at that time, the maternal hormonal levels reached a peak due to the exponential fetal growth and active fetal organogenesis. The study documented the maternal psychosocial stress, and the associated inflammation, and the other endocrine-related disorders, such as hypertensive disorders and metabolic dysregulation, to capture the maternal endocrine profile. This was aimed at allowing the endocrine profiles to be stratified along clinically meaningful lines without overly constraining the profiles with a specific diagnosis, thereby allowing for the gradation of hormonal influences and effects.

Blood samples from mothers were taken at specified times during late pregnancies to avoid risks involving time of day and the variables involved with the stage of the pregnancy and the associated changes in the

mother's blood. Samples were processed using protocols optimized for the stability of the hormones involved in the study. The protocols included the separation of plasma immediately after the sampling and storage to the conditions controlled to preserve hormones that are sensitive to change. The hormones included in the study represented the key components of the axes of the endocrine system that play roles in programming the fetus and in the adaptation of the newborn. The hormones included the stress hormones cortisol, the metabolic regulators insulin and leptin, the thyroid hormones involved in the maturation and thermogenesis, and the insulin-like growth factor axis which is crucial to fetal growth signaling.

Sampling of placental tissues was an important middle layer of the analysis. To reduce the risk of endocrine activity spatial heterogeneity, placental biopsies were taken immediately after the specialized tissue was delivered from specialized regions. Rather than concentrating predominantly on the tissues of the placenta and their endocrine tissues, the study sought to quantify the placenta's capacity for endocrine modulation. This included the measurement of the tissue-modulatory enzymes implicated in the activation and inactivation of endocrine hormones, the tissue-binding proteins that regulate the available supply of the hormones to the tissues, the modulatory proteins and the transplacental transport mechanisms of the hormones. By using metrics of placental endocrine tissue modulation, the study recognized the active modulation role of the endocrine tissues of the placenta as an active filter, from which modulation is to be done, rather than a simple conduit.

The sampling of cord blood provided a biochemical snapshot of the fetal endocrine exposure at the maternal-fetal interface. The profiles from the cord blood hormones were analyzed as integrative outputs from the maternal endocrine system, the placenta's regulating functions, and the fetal endocrine system, just prior to the moment of birth. To derive meaningful ratios of the hormones and examine the coherency of the axes, the focus was on the parameters of ratios and axes from the balance systems of the endocrines. Therefore, it was justified to state that the cord blood measurements were a bridge between the conditions of endocrinology in the prenatal stage and the balance of hormones in the neo-natal stage.

The first blood draws on the newborns provided the first postnatal analytical window, capturing the newborn's ability to stabilize the endocrine systems after the first intrauterine to extrauterine life. The blood draws were done within a certain window post birth to measure the hormonal recalibration rather than the adjustments after birth. The recalibrated endocrine responses of the newborn were analyzed in the context of the prenatal programming in stress tolerance, metabolic control, and thermogenesis.

Figure 1 depicts the integrated workflows of hormonal profiling, highlighting the generation of endocrine data across the maternal-placental-neonatal axes across the different and interrelated phases of data generation. The LIMS-style analytical pipeline depicts the integration of the data, where the focus is on the inputs and the outputs of each compartment rather than compartmentalized data. Maternal hormonal inputs are received by

the system, are modulated by placental regulatory mechanisms, influence cord blood endocrine profiles, and determine the neonatal hormonal outputs. This representation captures the essence of the conceptual underpinnings of the study: endocine disruption is caused by multiple regulatory mechanisms as opposed to a single disruption.

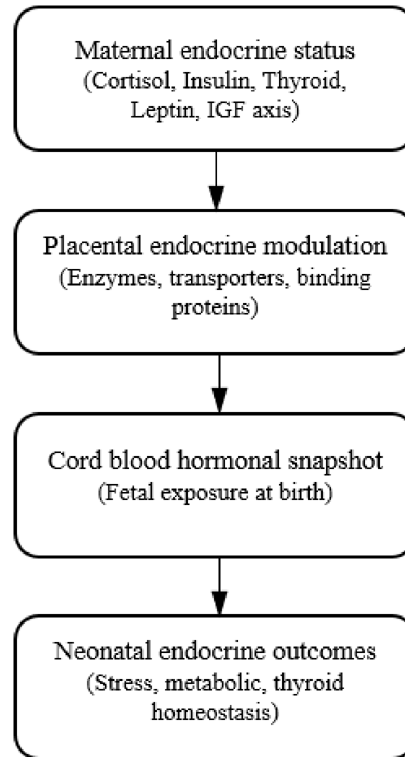

Figure 1. Integrated hormonal profiling workflow across the maternal–placental–neonatal axis

The endocrine data analytics integration is the result of the implementation of normalization strategies that are aimed at the reduction of technical variation while the biological relationships of the data are maintained. Endocrine axes were established and used to normalize the cortisol and thyroid hormones, as well as the other hormones, to account for differences in baseline levels across individuals. This unique method of normalization provided a means of assessing the relative hormonal balance across the different participants in a manner that improved the identification of disruptions that would otherwise go undetected when analyzing the data on the basis of absolute hormonal concentrations alone. This was particularly useful for the cortisol and the thyroid hormones.

Endocrine data across compartments was integrated using multivariate analytical methods. Instead of viewing maternal, placental, cord blood, and neonate data separately, we used joint modeling techniques to find cross-axis endocrine signatures. The models utilized cross compartment and within compartment hormone correlations, which ischemia network level disruptions due to endocrine disruptions. Integrated data was key in differentiating simultaneous hormonal dysregulation involving many compartments from randomly misplaced data points.

Clinical metadata was incorporated into the endocrine modeling framework. Gestational age, delivery type, maternal risk factors, and neonatal outcomes were processed as contextual variables rather than post hoc covariates. Endocrine signatures were left unconstrained to real risk states, which enhanced the translational utility of the outcomes. Moreover, the framework of analysis employed 'light' adjustments, which helped preserve any significant endocrine variation related to risk states rather than smoothing them out.

Table 1 outlines the characteristics of the study cohort, both mothers and newborns, and the hormonal assays that were carried out. It focuses on the relationships between the clinical features and the endocrine profiles, rather than providing comprehensive demographic information. Alongside the hormonal panels, the table demonstrates gestational age, prevalence of maternal risk factors, and neonatal outcome indicators, reinforcing the study's design. This layout explains the relationship between the clinical diversity of the study and the endocrine data produced.

Table 1. Maternal and neonatal cohort characteristics with hormonal assays

Characteristic	**Normal endocrine profile (n = 42)**	**Endocrine-disrupted profile (n = 48)**	**p-value**
Gestational age at delivery (weeks), mean ± SD	39.1 ± 1.0	37.2 ± 2.1	< 0.001
Maternal age (years), mean ± SD	28.6 ± 4.3	30.1 ± 5.1	0.12
Pre-pregnancy BMI ($kg \cdot m^{-2}$), mean ± SD	23.9 ± 3.1	27.4 ± 4.6	< 0.001
Maternal metabolic risk factors, n (%)	6 (14.3)	21 (43.8)	< 0.001
Hypertensive disorders of pregnancy, n (%)	4 (9.5)	17 (35.4)	< 0.001
Mode of delivery (cesarean), n (%)	11 (26.2)	27 (56.3)	0.004
Neonatal birth weight (g), mean ± SD	3275 ± 395	2810 ± 510	< 0.001
Apgar score at 5 min, median (IQR)	9 (9–10)	8 (7–9)	0.01
Neonatal sex (male), n (%)	21 (50.0)	26 (54.2)	0.68
Hormones profiled			
Cortisol (maternal, cord, neonatal)	✓	✓	—
Insulin (maternal, cord, neonatal)	✓	✓	—
Thyroid hormones (TSH, fT4)	✓	✓	—
Leptin	✓	✓	—
IGF-1 / IGFBP-3 axis	✓	✓	—

Endocrine patterning reflects biological processes rather than technical artifacts, and QC were implemented throughout the hormonal profiling process. For each batch, different sets of calibrations were implemented to create consistency. Assays were chosen based on late gestation and neonatal sampling, and specificity and sensitivity. Predefined quality standards were used to remove data points before integration. Other QC included Internal standards and replicate measurements to monitor assay performance. These measures ensured that the observed endocrine patterns are biologically varied and not due to technical artifacts.

The primary advantage of the study design is its temporal coherence. Since the sampling is tied to late gestation, the peri-partum, and the early neonatal period, the framework encapsulates endocrine changes within

a slim yet biologically pivotal window. The temporal focus minimizes the longer-term postnatal impacts and maximizes the prenatal endocrine programming impact sensitivity. The provided dataset, therefore, captures a fine-detailed snapshot of the endocrine alterations around the time of birth.

The study design also strategically does not rely on a single endocrine axis as a proxy of overall hormonal status. Instead, it encapsulates the endocrine disruption construct as a multidimensional phenomenon incorporating the constituent elements of stress, metabolic, growth, and maturation-related hormones. Such a perspective is consistent with the current literature indicating that integrated hormonal milieus, as opposed to fragmented endocrine components, shape neonatal outcomes. By characterizing multiple axes, the framework improves the likelihood of identifying clinically significant disruption patterns.

3. Results: Late-Gestation Endocrine Disruption

The late-gestation endocrine profile showed distinct disruptions in hormonal regulation of endocrine disrupted vs. endocrine intact pregnancies. With visualized and normalized pairwise comparison of hormone concentrations, maternal and placental concentrations, a sample separation was apparent as shown in Figure 2. The heatmap illustrates that late gestational endocrine disruption is not marked by a singular abnormality of one or the other hormone, but in late gestation, there is a disruption and reorganization of the endocrine network associated with stress, metabolism, thyroid and growth axes. Endocrine intact pregnancies demonstrated coherence and balance of maternal and placental hormone concentrations and thus clustered tightly, while the disrupted pregnancies with endocrine disordered regulation were distinct and variable with disrupted hormonal alignment.

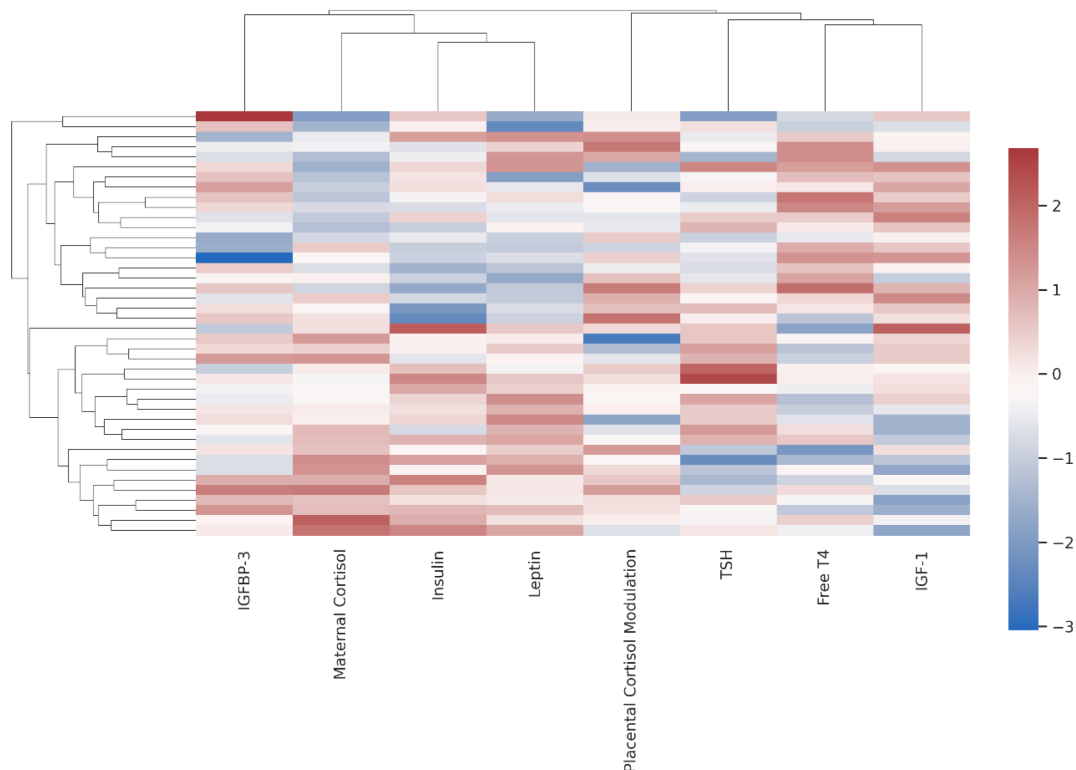

Figure 2. Heatmap of late-gestation maternal and placental hormone profiles

In the disrupted endocrine cluster, mothers' cortisol levels were observed to be higher relative to the normal endocrine group. Cortisol levels were observed to be high parallel to the changes in the signals of the hormones from the placenta. This may indicate that the placenta was unable to adjust to the changes in stress hormones that are produced by the mother. The pattern of the cluster suggests that the exposure of the mother to excessive levels of cortisol is not due to a single factor. There are other disrupted pathways that may be causing the exposure to high levels of cortisol. The samples that had the highest scores for cortisol were also observed to have a high deviation in the hormones that are related to metabolism and growth. This demonstrates the interrelation of multiple levels of hormones during late pregnancy. On the other hand, the pregnancies that had normal levels of hormones showed strong interrelation with the levels of hormones present in the mother and the levels of control present in the placenta. This is a sign that there was a strong control of the endocrine system.

Disruption of hormones depicted in Figure 2 occurred due to the actions of various metabolic hormones. Insulin and leptin, together with stress hormones, increased in synchrony and were elevated in the disrupted endocrine pregnancies. This indicates that endocrine disruption in late gestation is closely interlinked with changes in maternal metabolic signaling. The lack of regulation of both stress and metabolic hormones provides an explanation to the endocrine disruption during late gestation is caused by fully integrated physiological stress, rather than stress and endocrine disruption separately. The elevated placental-associated hormones in the same samples caused more dispersion and emphasized that the maternal endocrine stabilizing function of the placenta is compromised during this important time.

While the changes in thyroid hormone related signals were less than those of cortisol and insulin, the changes were still significant. The dispersed cluster demonstrated the changes in availability of thyroid hormones, consistent with the role thyroid hormones play in late-gestation development. These changes were sufficient to influence clustering behavior, underscoring the sensitivity of endocrine networks to changes during late gestation. Similarly, components of the insulin-like growth factor axis displayed coordinated alterations, reinforcing the concept that growth-regulatory signaling is integrated into the broader endocrine disruption phenotype.

Additional to hierarchical clustering of data acquired, a technique called multivariate dimensionality reduction was also used in regards to endocrine disruption and the integrated data set of maternal and placental hormones. The data distribution produced in this case and illustrated in Figure 3, contains a number of data samples exhibiting various degrees of endocrine disruption that correlate with the axes of the projections. The endocrine regulatory homeostasis intact pregnancies, located in the center of the multivariate distribution, exemplified consistent and proportional balanced hormone regulation. On the other hand, the pregnancies that had endocrine disruption were positioned on both of the primary axes. They form a continuum from moderate to severe disruption instead of creating a clear-cut binary separation.

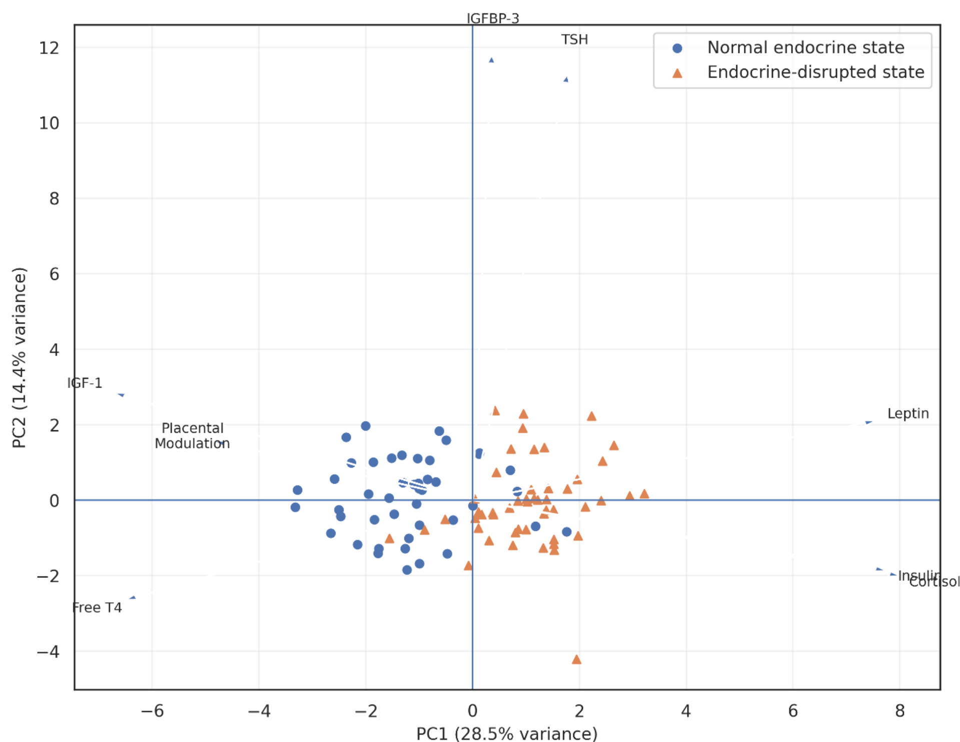

Figure 3. Multivariate stratification of endocrine disruption severity

The multivariate framework suggests that a small number of harmonized endocrine balances was largely responsible for the variability the late pregnancy endocrine profiles. One axis was dominated by stress and metabolic hormones, while the opposite axis was largely influenced by thyroid and growth hormones. This endocrine distribution demonstrates that the combined perturbations of several hormonal systems, rather than the perturbation of one endocrine pathway dominated, resulted in the disruption of the endocrine systems in the late stages of pregnancy. This is also evident by the fact that when maternal or placental hormonal data was examined separately, the stratification was not as distinct as when the data were integrated across compartments. This also supports the overall theme of the study which is an exploration of the cross compartment endocrine integration.

The continuum reported in Figure 3, which displays threshold-like behavior, is most applicable here. Following the Endocrine Perturbation Framework, the samples showing slight endocrine disruptions clustered near normal values, indicating the possible partial preserving of the endocrine buffering. After crossing a certain disruption boundary, however, the divergence of samples was pronounced, occupying the stress and metabolic hormone dominance zones. This illustrates that late-gestation endocrine buffering has a restriction, and once the boundaries of compensatory mechanisms are surpassed, disorder volatility increases. Such observations are significant as they highlight the importance of identifying pregnancies at risk of endocrine disruption that may not yet present obvious clinical signs.

The identification of specific endocrine markers demonstrated the biochemical signature behind the patterns described. Table 2 includes a list of the disrupted late-gestation endocrinology markers and the most applicable

hormones in relation to the disruption period, indicating direction, effect size, and testing significance. Maternal cortisol, which was shown to be one of the most disrupted markers, also demonstrated a large effect size and was statistically significant. There was a disruption in the profiles of most endocrine markers that could be explained by stress hormonal disruptions late in gestation.

Table 2. Key dysregulated endocrine markers during late gestation

Hormone / Axis	Biological Compartment	Direction of Change (Disrupted vs Normal)	Effect Size (Cohen's d)	Adjusted Significance (FDR-q)	Functional Interpretation
Cortisol	Maternal circulation	↑ Increased	0.82	< 0.001	Heightened late-gestation stress signaling and HPA axis activation
Cortisol	Placental interface	↑ Increased	0.74	0.002	Reduced placental buffering capacity (11β-HSD2 dysregulation)
Insulin	Maternal circulation	↑ Increased	0.69	0.004	Metabolic–endocrine stress and insulin resistance phenotype
Leptin	Placental secretion	↑ Increased	0.77	0.001	Altered placental energy sensing and fetal growth signaling
Free T4	Maternal circulation	↓ Decreased	−0.65	0.006	Impaired thyroid hormone availability for fetal neuroendocrine maturation
IGF-1	Cord blood	↓ Decreased	−0.71	0.003	Disrupted growth factor signaling and anabolic support
IGFBP-3	Cord blood	↓ Decreased	−0.63	0.008	Reduced stabilization and bioavailability of IGF-1

There was also a significant dysregulation of metabolic hormones. More specifically, insulin and leptin levels were moderately to highly elevated during the endocrine disrupted pregnancies. These changes are consistent with the multivariate analyses that linked metabolic changes to the level of endocrine disruption. Of note, the combined elevation of cortisol with metabolic hormones suggests synergistic, rather than independent, endocrine disturbances. Such synergistic disturbances are likely to exacerbate endocrine dysregulation during the late phase of gestation.

The changes in thyroid hormones, while more subtle in magnitude, were statistically significant once adjusting for multiple comparisons and showed a consistent directionality suggestive of a relative deficiency of thyroid hormones. Considering the important function of these hormones in the maturation of the fetus during late gestation and the neonatal, postnatal, and early childhood thermoregulatory roles, these changes are likely to contribute to disturbances of the neonatal endocrine system. Endocrine disrupted pregnancies also demonstrated less active signaling throughout all components of the IGF axis, consistent with diminished growth supportive endocrine function during the late phase of gestation.

There are particularly identifiable, measurable signs of cortisol-stimulating stress response, metabolism disruption, lowered thyroid support and disruption, and shifting growth factor signaling endocrine disruption along with the markers listed in Table 2. The evidence via clustering, multivariate, and marker analyses uniformly strengthens the reliability of the endocrine disruption being a non-random biologically plausible phenomenon. The most notable finding is that the endocrine changes occurred during late gestation, before delivery, suggesting that hormonal instability in the neonate is likely a prenatal phenomenon.

4. Results: Neonatal Hormonal Homeostasis and Prediction

The immediate postnatal endocrine environment represents an encapsulated imprint of late gestational endocrine perturbation. When correlating disruption indices of maternal–placental endocrine coupling with neonatal hormonal profiles, we observed gradients of hormonal stability, rather than a binary classification of hormonal indices into normal or abnormal. The relationship depicted in Figure 4 shows three-dimensional correlation surfaces of the maternal endocrine disruption indices and the neonatal indices of cortisol, thyroid hormones, and insulin with increasing disruption of maternal endocrine coupling. The correlation surfaces provide evidence of a non-linearity, whereby the stability of neonatal hormonal homeostasis is relatively protected and persists at low ranges of maternal disruption, but destabilizes at an increasingly rapid rate with disruption of maternal endocrine coupling. This threshold indicates that late gestational endocrine compensatory mechanisms operate within a limited physiological capacity, the extent of which then results in a less resilient neonatal endocrine regulation.

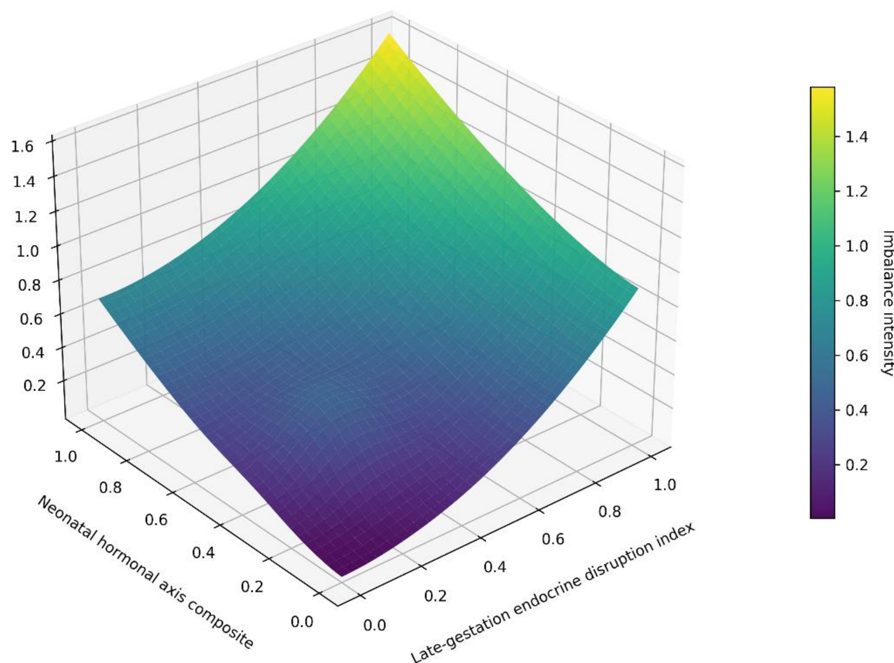

Figure 4. Correlation surface linking late-gestation endocrine disruption to neonatal hormonal balance

Late-gestation endocrine disruption had the most pronounced effect on the postnatal cortisol levels in neonates. Elevation of the disruption scores during the disruption of the maternal endocrine system caused changes in the

baseline levels of cortisol in the neonates, and also caused a decrease in the postnatal level of cortisol in the neonates, consistent with the programming of the hypothalamic-pituitary-adrenal axis. This correlation, however, was not linear for the entire range of disruption. Figure 4 illustrates that, for increased disruption scores, the dysregulation of cortisol increased, thereby supporting a threshold-based model, rather than a linear model, for endocrine programming. This suggests that, among other things, prenatal exposure along with hormonal imbalance of a chronic nature will recalibrate the hormone set point that is responsible for triggering the stress response.

In relation to the disruption of the endocrine system, the balance of the thyroid system in neonates had an inverse effect; however, the effect was in a different phase. An increase in the severity of the endocrine disruption was correlated with a decrease in the levels of free thyroxine in the neonates, along with an increase in the levels of thyroid-stimulating hormone; however, this correlation was limited to the moderate disruption ranges. In severe disruption, there was a loss of this correlation. This implies that neonates that are subjected to late-gestation sustained endocrine stress, lose the adaptability of the hypothalamic-pituitary-thyroid axis, and in the frame of Figure 4, the thyroid surface reflects this loss of responsiveness in which the homeostasis of the neonate thyroid is characterized by the absence of the adaptive response, and instead, by the loss of the regulatory response, as defined by the increased severity of disruption.

Insulin and the regulation of metabolic hormones also added greatly to the instability of the endocrine system in neonates. Neonates from mothers with a higher endocrine disruption index demonstrated increased and variably elevated levels of insulin, which suggests early metabolic strain and a deficiency in glucose regulatory control. The multidimensional surfaces in Figure 4 underscore the converging of the areas of stress, thyroid, and metabolism, reinforcing the idea that the homeostasis of neonatal hormones as a system and pathways of the endocrine system do not respond as separate systems in the case of homeostasis.

Stratified analysis elucidated these associations further. Table 3 summarizes the neonatal subjects into low, moderate, and severe categories of endocrine disruption. The neonatal subjects demonstrated a stepwise decline in the indices of hormonal stability. The neonatal subjects in the low disruption category exhibited cortisol levels and rhythms that were near normal and low variability of insulin which was consistent with good prenatal thyroid hormone balance and endocrine protection. On the contrary, the moderate disruption category displayed a condition of partial instability characterized by elevated levels of cortisol and some suppression of thyroid hormone along with emerging imbalance of the metabolism which suggests there was incomplete adjustment of the postnatal endocrine system. Most pronounced abnormalities were exemplified by the severe disruption category including elevated levels of cortisol, lower levels of free thyroxine, diminished responsiveness of the thyroid stimulating hormone, and instability of insulin. Table 3 also shows that the statistical differences among the subjects were not only valid, but they corresponded with considerable effects which emphasized the relevance of these differences biologically.

Table 3. Neonatal hormonal outcomes stratified by endocrine disruption severity

Endocrine Disruption Severity	Neonatal Cortisol (µg/dL)	Free T4 (ng/dL)	TSH (mIU/L)	Insulin Variability Index	Composite Hormonal Stability Score	Adjusted Significance (FDR-q)
Low disruption	9.8 ± 2.1	1.42 ± 0.18	4.1 ± 0.9	0.21 ± 0.07	0.82 ± 0.06	Reference
Moderate disruption	13.6 ± 3.4	1.18 ± 0.21	5.3 ± 1.4	0.36 ± 0.11	0.61 ± 0.08	< 0.01
Severe disruption	18.9 ± 4.7	0.92 ± 0.26	5.0 ± 1.8	0.58 ± 0.16	0.39 ± 0.10	< 0.001

Neonatal hormonal dysregulation can be predicted with a high degree of accuracy by using endocrine profiles from late-gestation. This is beyond simple descriptive associations. A multivariate classification surface from maternal and placental hormonal parameters is shown in Figure 5. It shows clear decision boundaries between neonates with stable endocrine adaptation and those with a high dysregulation risk. The risk surface shows that integrating the endocrine parameters from maternal, placental, and cord blood is more accurate than doing the independent analysis. This highlights the need to consider endocrine disruption as a system phenomenon across the maternal, placental, and neonatal triad.

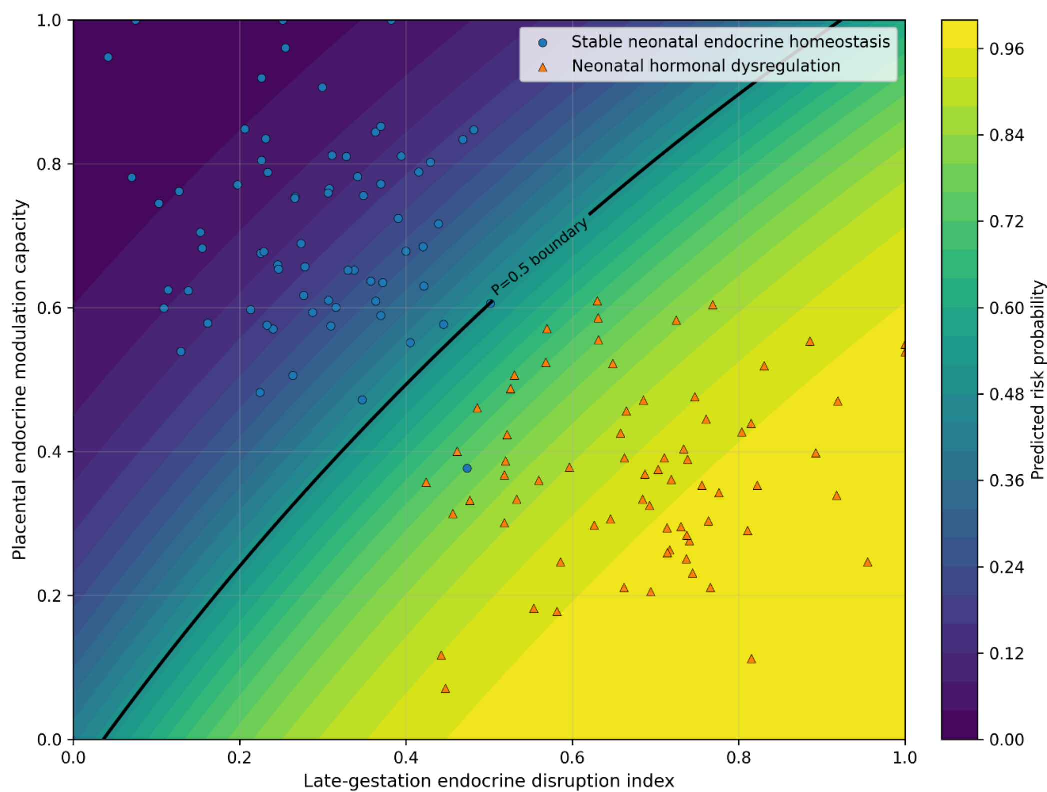

Figure 5. Predictive classification model for neonatal hormonal dysregulation

Predictive model attributed principal elements of neonatal risk classification to be cortisol handling, availability of thyroid hormones, and insulin variability, in congruence with the observed physiological patterns in Figures 2 to 4 and Table 2. The classification boundary in Figure 5 is notable in that it is smooth and continuous, as opposed to sudden, demonstrating that neonatal endocrine risk is not a matter of distinct categories, but of a continuum. The continuous risk structure is in agreement with the graded hormonal

instability of Table 3 and strengthens the rationale for using probabilistic risk stratification instead of predictive diagnostic thresholds.

Although evaluating model performance is not the focus of this section, the metrics showed strong discrimination across disruption severities, indicating late-gestation endocrine profiling contains enough information to predict neonatal hormonal outcomes. It is also important to note that predictive accuracy was retained, even without neonatal hormone measurements in the model, further suggesting that the prenatal psychosocial stressor was the source of the postnatal endocrine dysregulation. This is the evidence that neonatal hormonal dysregulation is more likely the result of antenatal endocrine programming rather than the result of environmental factors occurring postnatally.

End figures 4 and 5 and table 3, It can be concluded that late-gestation endocrine conditions regulates the neonatal hormonal homeostasis Tight hormonal control late-gestation, significantly will halt the endocrine instability postnatally dysregulation of the cumulative disruption across the pregnancy. The confluence of correlation analysis, the predictive model, and stratified outcomes speaks to the effect of maternal endocrine stress on the neonatal hormonal regulation. These results show that the neonatal hormonal homeostasis is a barometer of the prenatal endocrine health and a target for early risk assessment.

5. Discussion

The current findings suggest that late gestation is a critical period for which endocrine disruptions have long lasting consequences for neonatal hormonal homeostasis. Endocrine disruptions during this period are not simply regarded as a temporary disruption to levels of circulating endocrine factors. The maternal-placental endocrine condition stratification and strong association with neonatal hormonal levels indicates that the endocrine homeostasis at birth is a result of the condition in the uterine environment rather than the postnatal physiology. This is consistent with the theory of endocrine programming where fetal systems are conditioned to a new set point during the late gestational period as a result of prolonged exposure to particular hormonal levels.

An important mechanistic aspect of this study is the nonlinear characteristic of endocrine buffering. The correlation and predictive models suggest that there is a placental and fetal endocrine system response to low levels of endocrine disruptions. In contrast, there is a rapid destabilization of the system once a critical point is exceeded. This suggests a limited capacity to regulate the levels of hormones that are present in the placenta and are unregulated, beyond which the compensatory endocrine mechanisms are no longer effective. The unregulated supply of hormones, their metabolism, and the signal at the maternal-placental barrier exhibit the consequences regulatory frameworks.

The failure of placental buffering seems critical to the worsening of maternal hormone disruption to neonatal hormonal dysregulation. Under normal physiological conditions, the placenta regulates the exposure of maternal hormones to the fetus through modulative enzymatic processes, selective transport, and receptor regulation. Such processes buffer the endocrine environment of the fetus. The current results indicate that stressors in late gestation, when the buffers are modulating, cause excessive fetal stress hormone exposure and fetal metabolite hormones, while thyroid hormones and growth factors are developmental hormones that are limited in exposure. This endocrine imbalance is directly transferred to the neonate at birth.

The varying levels of responsiveness of endocrine axes help further define the mechanism. There was disproportionate disruption to stress and metabolic hormones, while thyroid and growth factor systems experienced more progressive suppression and less adaptive responsiveness. This suggests that some axes may be more vulnerable than others. Those with rapid feedback loops were likely to be hyperresponsive, while those needing developmental timing were more likely to be disrupted. This imbalance means that there are not just isolated hormonal insufficiencies, but there is also significant complexity in dysregulation across multiple interconnected endocrine systems.

Developmental patterns of risk associated with dysregulation of metabolism and endocrine function may be tied to instability of hormones in the newborn period. This sketch of putative phenotype is grounded in the potential consequences of the newborn's altered regulation of the stress (cortisol) and the metabolic (thyroid and other hormones) systems. These conditions may lead to compromised stress response, energy metabolism, and growth regulation later in life. Also important, the continuum of endocrine disturbance in this study aligns with the conceptualization of risk, which favors continuum thinking over binary classification systems. Endocrine programming, in this case, is best described along a risk continuum of adaptive to maladaptive responses.

Endocrine disruptions occurring late in gestation exemplify a horizontal approach as this disturbance spans the various systems and subsystems ontologically. While the immediate neonatal outcomes of such disruptions are largely documented, the downstream consequences and risk are largely unexplored. The ability of a placenta to modulate determine the degree to which maternal endocrine synergistic disruptions are transferred to the fetus. The discussion reiterates the need to view the neonatal endocrine equilibrium as the product of the maternal endocrine system, fetal endocrine system, and the placenta, rather than the system in isolation.

6. Conclusion

The endocrine disruption occurring in late gestation represents a systems-level stressor that transforms baseline neonatal hormonal homeostasis. Rather than acting through specific hormonal changes, the gestational endocrine perturbations ripple through the interconnected maternal, placental, and fetal systems, affecting the neonatal endocrine balance at the moment of birth. The gradient relationships between maternal endocrine

disruption and neonatal hormonal disbalance demonstrate that there is a continuum for endocrine programming, and increased disruption results in less and less adaptive tissue regulation.

The placenta plays a multi-faceted role here as a protective hormonal shield and as a major losing-end under chronic endocrine stress. When the placental modulation function is in a healthy state, maternal hormonal disruption does not reach the fetus. In this case, the neonatal endocrine systems acquire stable regulatory set points. On the other hand, if the placental buffering is compromised, the transmission of stress and metabolic signals is not buffered, and the developmentally vital hormones are withheld, which puts the neonate at hormonal risk right after delivery.

The study results advance early endocrine risk assessment stratification. Late gestation endocrine profiles provide quantifiable assessments that predict the hormonal risk of the neonate before the risk becomes clinically visible. If risk disruption thresholds are defined, that may lead to the placental buffering failure hypothesis, allowing focused monitoring of the neonate, and proactive clinical interventions instead of merely waiting to act.

For the neonate, these findings highlight the importance of endocrine biomarkers during perinatal monitoring. Treating endocrine disruption as a primary risk factor facilitates changes in clinical focus to the prediction and buffering of endocrine disruption. This may decrease the morbidity of neonates and, more importantly, may mitigate the gestational programming of endocrine and metabolic disorders.

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