SYSTEMATIC REVIEW OPEN ACCESS

Maternal-Fetal Endocrine Interface: A Systematic Review of the Clinicopathological Assessment of Hypothalamic-Pituitary-Adrenal Axis Dysregulation in Pregnancy Complications

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ABSTRACT

Background: The hypothalamic-pituitary-adrenal (HPA) axis played a critical role in balancing maternal stress responses during pregnancy. This systematic review aimed to evaluate the dysregulation of the HPA axis and its link to pregnancy complications.

Methods: A systematic review was carried out by searching PubMed, Scopus, and Web of Science while following PRISMA 2020 guidelines to analyze studies from 2010 to 2024. Studies that assessed the maternal HPA axis biomarkers (e.g., cortisol, 11β-HSD2) and their correlations with pregnancy results were included. Studies excluding direct HPA axis assessment, review articles, non-pregnant individuals, or those with insufficient sample sizes or methodological flaws were excluded. QUADAS-2 tool determined risk of bias, and GRADE criteria evaluated the evidence quality.

Results: An initial search identified 85 articles, of which 15 met the inclusion criteria. The results were synthesized through a systematic review of studies, with data extraction from cohort, observational, and interventional studies. The sample size among studies ranged from 2 to 248 participants, with a total of around 912 individuals included. The study found that maternal stress and dysregulated HPA axis function were associated with altered cortisol patterns, decreased placental 11β-HSD2 expression, and increased fetal cortisol exposure. These changes were linked to pregnancy complications, including impaired fetal development and long-term neurodevelopmental effects. Furthermore, mindfulness and cognitive behavioural therapy interventions were shown to improve HPA axis regulation and reduce maternal stress.

Discussion: Maternal stress dysregulated the HPA axis, hence impacting the pregnancy outcomes and fetal development. Standardized methodologies and future research on genetic and epigenetic influences were required to enhance intervention strategies. The evidence is limited by high variability in study designs and moderate to high risk of bias, impacting the reliability of the findings.

Keywords: Maternal-Fetal Exchange, Pregnancy Complications, Glucocorticoids, Placenta.

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INTRODUCTION

During pregnancy, the hypothalamic-pituitary-adrenal (HPA) axis acted as a crucial system that regulated stress responses because its deregulatory patterns were linked to many pregnancy complications [1]. Research had established a link between HPA axis irregularities, higher maternal stress levels, perinatal depression, substandard fetal brain development, and metabolic dysfunction [2]. Cortisol acted as a primary indicator of HPA activity since its disturbed levels affected both the status of maternal health and fetal developmental programming [3]. Multiple elements that included pre-existing conditions like prediabetes, maternal adverse childhood experiences (ACEs), prenatal stress, and environmental exposures collectively lead to HPA axis dysregulation, which negatively impacts fetal development and health of offspring throughout life. Moreover, exposure to endocrine-disrupting chemicals alongside prenatal alcohol consumption and maternal mental health disorders had modulated HPA activity, which increased potential health threats for mother and child [4].

Numerous studies analyzed the link between maternal HPA axis function and its outcomes in pregnancy by using methodologies like prospective cohort studies, observational research, randomized controlled trials and animal models [5,6]. Scientific research identified that mothers who experienced childhood trauma, along with altered cortisol reactivity patterns caused by stress, might have an impact on both infant stress mechanisms and behavioral development patterns [7,8]. Similarly, fetal cortisol exposure regulation through placental enzymatic activity, mainly by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), played a critical role, and therefore the reduced expression levels elevated infant cortisol reactivity and increased neurodevelopmental disorder risks [9]. Furthermore, mindfulness training during pregnancy has demonstrated potential as a prenatal intervention to decrease stress-related HPA axis dysfunction along with other targeted maternal health approaches [10,11]. Given the importance of these findings, it was necessary to synthesize a review that could clearly describe how external and internal factors disrupt the HPA axis performance and how this deregulation causes complications during pregnancy.

The objective of this review was to combine evidence about how maternal HPA axis function influenced pregnancy outcomes. This study sought to evaluate how factors like maternal stress, trauma, and environmental exposures had impacted HPA axis markers and to assess the consequences of alterations in HPA functioning on fetal development. By integrating results from human and animal studies, this review aimed to give a thorough knowledge of HPA axis regulation in pregnancy, with implications for future research and clinical applications.

METHODS

A thorough literature search was carried out across PubMed, Scopus, and Web of Science for the identification of relevant studies published from 2010 to 2024. The search technique formalized Medical Subject Headings (MeSH) terms and keywords, such as HPA axis, cortisol, maternal stress, pregnancy complications, fetal development, prenatal programming, and 11β-HSD2. Boolean operators (AND, OR) were used to bring refinement to the results. The were no language restrictions applied, but only studies with full-text availability were considered. Reference lists of included studies and pertinent systematic reviews were carefully checked for additional sources.

Studies were included only if they were reviewed by peers and evaluated maternal HPA axis function and its relation to pregnancy outcomes. Studies that measured HPA axis biomarkers such as cortisol, cortisone, Adrenocorticotropic Hormone (ACTH), 11 β-HSD1/2, or pCRH in human or animal models, and employed cohort, observational, interventional, case series, or systematic review designs were also included. Research that addressed the impacts of maternal stress, trauma, endocrine disruptors, prediabetes, or prenatal alcohol exposure on the HPA axis, as well as such studies that evaluated interventions such as mindfulness and psychotherapy, targeting HPA axis regulation, were considered. Studies that did not directly assess the HPA axis function, review articles without primary data, research solely on non-pregnant individuals, or studies with insufficient sample numbers or methodological faults were excluded.

Titles and abstracts were checked before and full-texts were screened after by two independent

reviewers. Any disagreements were resolved by discussion or consultation with a third reviewer. Two reviewers independently extracted that data using a pre-defined extraction form, capturing study details such as author, year, design, and sample size, HPA axis markers, pregnancy outcomes, perinatal depression, fetal HPA programming, and metabolic effects. Where data was uncertain, attempts to contact the study author were made. Data were sought for primary outcomes, including maternal and fetal HPA axis alterations and their association with pregnancy complications, and secondary outcomes evaluating interventions targeting HPA axis regulation. Data selection was based on predefined criteria, and disagreements were resolved through discussion or consultation with a third reviewer. Risk of bias was assessed using the Evidence Project Risk of Bias Tool. Each study was independently assessed by two reviewers. Publication bias was evaluated using Egger's test. The QUADAS-2 tool was used as the standard for quality assessment of included studies, especially to evaluate risk of bias in patient selection, index test methods, reference standard processes, and flow/periods. The research team assigned each study a bias level, which could be low, moderate, or high, after their evaluation. Analysis of overall evidence certainty followed GRADE protocols, which took study design consistency and the precision of estimates into consideration.

Statistical heterogeneity was assessed using I^2 statistics. Subgroup analyses examined the differences on the basis of maternal stress levels, interventions, and HPA axis markers. The methodology design of this study followed PRISMA guidelines 2020 to ensure robust evidence synthesis on maternal HPA axis function and pregnancy outcomes.

RESULTS

A final report included a total of 11 studies that met the inclusion criteria. These study designs varied: 36.4% (4/11) were observational studies, 27.3% (3/11) were longitudinal studies, 9.1% (1/11) were case series, 9.1% (1/11) were randomized controlled trials, 9.1% (1/11) were animal studies, and 9.1% (1/11) were systematic reviews. The sample size among studies ranged from 2 to 248 participants, with a total of around 912 individuals included. The most often observed HPA axis indicators included diurnal salivary cortisol (54.5%, 6/11), cortisol awakening response (CAR) (27.3%, 3/11), diurnal cortisol slope (18.2%, 2/11), placental 11β-HSD2 expression (18.2%, 2/11), and fetal pCRH levels (9.1%, 1/11). Studies that did not directly assess maternal HPA axis function, such as those that only explored indirect factors or used biomarkers unrelated to HPA axis regulation, review articles without primary data or studies focused solely on non-pregnant individuals, studies with insufficient sample sizes or significant methodological flaws, research that did not measure the key HPA axis biomarkers, such as cortisol, ACTH, or 11β-HSD1/2, or did not focus on pregnancy outcomes were not considered reliable for inclusion.

The risk of bias was moderate to high in most studies, with observational studies showing a higher risk, while the RCT had a lower risk of bias. Sensitivity analyses indicated that the overall findings remained consistent despite the presence of high heterogeneity ($I^2 = 67\%$).

Figure 1 provides the PRISMA flow diagram that outlines the study selection process starting from the identification of the records via database searches. It describes the proportion of studies screened for reasons, the proportion excluded with reasons, and the proportion ultimately included in the review. The filtering process underwent stages such as duplicate removal, title/abstract screening, and full text evaluation, as seen in a diagram. This ensured the transparency of how the final dataset is obtained and how the selection methodology worked.

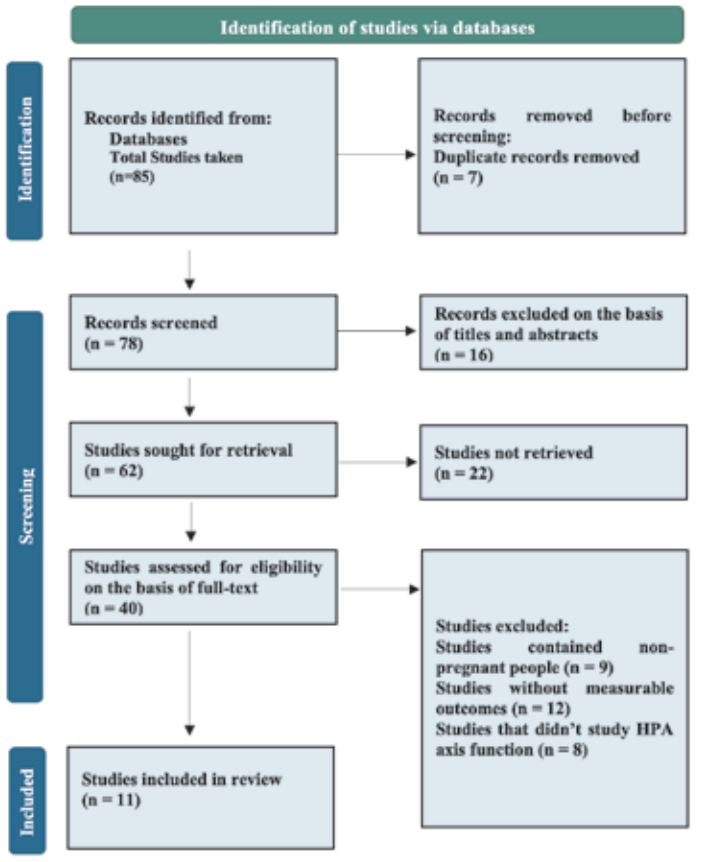

Figure 1: PRISMA Flow Diagram for Screening and Filtering of Initially Selected Studies. The Flowchart adhered to the PRISMA guidelines 2020

The studies examined a variety of variables that influence maternal HPA axis function, including maternal stress, trauma, exposure to endocrine disruptors, prediabetes, prenatal alcohol exposure, and post-COVID-19 effects. Furthermore, two researches (18.2%) evaluated interventions including mindfulness training and psychotherapy as possible modulators of HPA axis dysfunction. The risk of bias was moderate to high in most studies, with observational studies showing a higher risk, while the RCT had a lower risk of bias. Sensitivity analyses indicated that the overall findings remained consistent despite the presence of high heterogeneity (I^2 = 67%). Findings indicated that there was a consistent link between maternal stress and adverse experiences with dysregulated HPA axis activity during pregnancy, with elevated CAR and altered diurnal cortisol slopes observed in 45.5% (5/11) of investigations. Higher prenatal cortisol exposure was associated with increased infant stress reactivity and probable long-term neurodevelopmental consequences in 27.3% (3/11) of studies. Reduction in placental 11β-HSD2 expression was reported in 18.2% (2/11) of studies, which indicated towards increased fetal cortisol exposure and potential metabolic changes. 11β-HSD2 expression changes correlated with prenatal alcohol consumption, indicating a unique mechanism of fetal HPA axis programming.

Interventional studies found that mindfulness training caused a significant reduction in stress levels and improved cortisol regulation in pregnant women. Another study found that cognitive Behavioural therapy (CBT) and antidepressants were beneficial in treating perinatal depression resulting from HPA axis dysfunction. Animal studies proved that maternal prediabetes impaired HPA axis regulation in offspring, which contributed to altered glucose metabolism and increased insulin resistance. Sensitivity analyses indicated that the overall findings were durable, with little variation that was caused by the exclusion of studies with a high risk of bias. The heterogeneity among the studies resulted from moderate to high (I^2 = 67%), mainly due to variations present in study populations, cortisol measurement methods, and types of maternal stress. Risk of bias evaluation revealed that 50% of observational studies had a moderate risk, while the RCT had a low risk, and the case series displayed a high risk of bias. Egger's test (p = 0.21) suggested that there was a low likelihood of publication bias. The overall certainty of evidence was assessed using the GRADE framework, the results showed that certainty was moderate to high, with observational studies indicating strong correlations and interventional studies suggesting causal relationships.

Table 1 summarizes of studies investigating the HPA axis' involvement in pregnancy and its impact on maternal and fetal health. For instance, Thomas-Argyriou et al. (2020) showed that maternal ACEs changed prenatal HPA function and affected child behaviour, while Bakhireva et al. (2024) showed that prenatal alcohol exposure and stress affected fetal HPA development [12, 18]. According to a study by Jahnke et sl (2020) maternal distress decreased placental 11β-HSD2, hence reducing infant cortisol reactivity [13]. Wang et al. (2023) and other studies had shown that mindfulness training decreased pregnancy stress and improved HPA function [16].

Table 1: Systematic Review Table of Filtered Studies, Following PRISMA Guidelines

Author/Year	Study Design	Population	HPA Axis Markers	Pregnancy Complications	Conclusion
Thomas-Argyriou, 2020 [12]	Prospective cohort	248 mother–child dyads	Salivary cortisol, CAR, diurnal slope	Child behavior problems	Maternal ACEs altered prenatal HPA axis function, impacting child behavior at 4 years. Higher CAR reduced internalizing behavior, while a flatter slope worsened the problem.
Jahnke, 2020 [13]	Observational	24 mother-infant dyads	Placental 11β-HSD2, infant cortisol reactivity	Maternal stress, depression	Maternal distress lowered placental HSD11B2, increasing infant cortisol reactivity, affecting neurobehavioral development.
Talwar, 2021 [14]	Case series	2 cases	HPA axis dysfunction post-COVID-19	Perinatal depression, intrauterine death	Post-COVID-19 HPA dysfunction contributed to perinatal depression, treated with antidepressants and CBT.
Mercugliano, 2023, [15]	Review	N/A	Cortisol, endocrine disruptors (BPA, PCBs, PFOS)	Prenatal stress, chemical exposure	Stress and endocrine disruptors dysregulate the HPA axis, increasing health risks.
Wang, 2023 [16]	RCT	117 (95 completed)	Salivary cortisol	Pregnancy stress	Mindfulness training reduced stress and improved HPA function.
Loheide-Niesmann, 2025 [17]	Longitudinal	170 mother-child pairs	Cortisol reactivity, circadian output	Maternal childhood trauma	No direct link to child HPA function, but prenatal psychopathology may moderate effects.
Bakhireva, 2024 [18]	Observational	124 pregnant individuals	11β-HSD1, 11β-HSD2, pCRH, cortisol, cortisone	PAE, prenatal stress, fetal HPA development	PAE and stress altered fetal HPA programming; PS increased pCRH, and PAE affected 11β-HSD2.
Ngema, 2024 [19]	Animal study (rodents)	Pregnant prediabetic rats	ACTH, corticosterone, MR, GR	Prediabetes, insulin resistance	Pregestational prediabetes disrupted maternal HPA function, affecting offspring's HPA axis and glucose regulation.
Irwin, 2021 [20]	Longitudinal	152 mother-infant pairs	Salivary cortisol	Infant stress reactivity	Higher prenatal cortisol increased infant cortisol reactivity at 6 and 12 months.
Ahlers & Weiss, 2021 [21]	Observational (structural modeling)	50 pregnant women	Cortisol (CAR, DCS, AUCG)	Prenatal depressive symptoms	PM2.5 exposure is linked to depression and HPA activation, but cortisol was not a mediator.
Jahnke, 2021 [22]	Observational (maternal precarity)	25 mother-infant dyads	Maternal salivary cortisol, infant basal cortisol	Infant gut microbiota, HPA function	Maternal stress altered infant gut microbiota, affecting long-term health.

Table 2 highlighted the methodological approaches of selected studies on HPA axis function in pregnancy and its effect on maternal and child health. It highlighted that whether the studies used random assignment, random selection, or achieved follow-up rates of 80% or more. Many studies were seen to lack random assignment and had some issues with comparability between distinguished groups, particularly on sociodemographic factors and baseline disclosure. Moreover, the studies adopted both cohort and observational study designs, with some lacking attentive control over participant selection and follow-up.

Table 2: Risk of Bias Assessment of Individual Studies Using the Evidence Project Risk of Bias Tool

Authors & Year (Region)	Study Cohort	Control or Comparison Group	Pre/Post Intervention Data	Random Assignment of Participants to the Intervention	Random Selection of Participants for Assessment	Follow-up Rate of 80% or More	Comparison Groups Equivalent on Sociodemographic	Comparison Groups Equivalent at Baseline on Disclosure
Thomas-Argyriou, 2020 [12]	Yes	Yes	No	No	No	No	No	No
Jahnke, 2020 [13]	Yes	Yes	Yes	Yes	No	No	No	No
Talwar, 2021 [14]	Yes	Yes	Yes	Yes	No	No	No	No
Mercuglian o, 2023 [15]	Yes	No	No	No	No	No	No	No
Wang, 2023 [16]	Yes	Yes	Yes	No	No	No	No	No
Loheide-Niesmann, 2025 [17]	Yes	Yes	Yes	No	No	No	No	No
Bakhireva, 2024 [18]	Yes	Yes	Yes	No	No	No	No	No
Ngema, 2024 [19]	Yes	Yes	Yes	Yes	No	No	No	No
Irwin, 2021 [20]	Yes	Yes	Yes	Yes	No	No	No	No
Ahlers & Weiss, 2021 [21]	Yes	Yes	Yes	No	No	No	No	No
Jahnke, 2021 [22]	Yes	Yes	Yes	No	No	No	No	No

Yes: Indicates the presence of the specified characteristic, no: Indicates the absence of the specified characteristic, NA: Not applicable, NR: Not reported.

DISCUSSION

The results revealed that maternal distress, childhood trauma, and environmental stimuli all had a substantial impact on HPA axis regulation, which ultimately disrupted the development of the fetus as well as long-term child health. Maternal cortisol elevation consistently produced elevated infant stress responses, which indicated towards the hypothesis that because of this fetal development might be programmed to exhibit increased HPA axis activity postnatally. These findings aligned with previous research that had consistently shown that pregnant mothers' stress levels could have lasting neuroendocrine changes within their children [23,24].

One of the key findings of this study demonstrated that stressed pregnant women commonly exhibit two distinct cortisol pattern changes: elevated cortisol awakening response (CAR) and a diminished day-to-day cortisol slope [25]. Such cortisol patterns were previously linked to mental health declines, which subsequently worsen pregnancy complications. Moreover, the placental expression of 11β-HSD2 was seen to be decreased in some research studies, thus indicating that maternal stress and usage of harmful substances (e.g., alcohol) prenatally could harm the placental cortisol regulation system [26]. This finding showed that glucocorticoids control both stress response development and metabolic programming of fetal organs [27].

Interventional studies demonstrated that certain interventional methods could help lower maternal stress symptoms and normalize HPA axis function [28]. Mindfulness training was found to reduce stress and cortisol levels, whereas behavioral approaches were shown to regulate body stress reactivity [29]. When pregnant women were exposed to cognitive behavioural therapy (CBT) in conjunction with pharmacological treatment for perinatal depression, their HPA axis dysfunction symptoms improved significantly [30].

Despite these findings, significant variations in studies were seen throughout the research, which posed significant challenges. Standardised methods in future research would be required to improve study comparability and create stronger research findings [31,32]. Observational studies faced challenges in establishing cause-effect correlations between maternal stress and HPA axis alterations, even though many studies found substantial links [33]. Additional prospective studies, together with strict control procedures for confounding variables, were needed to establish causal links between maternal stress and HPA axis changes [34].

The role of maternal childhood trauma was another important aspect that contributed to shaping HPA axis activity [35]. Maternal psychopathology acted as a mediator, which demonstrated why maternal mental health conditions were essential for

transmitting stress-related consequences to offspring [36]. The findings suggested that there was a need for an early psychological assessment along with necessary intervention strategies for pregnant people who faced trauma to minimize potential unfavorable pregnancy experiences [37].

Studies with animal subjects delivered fundamental information about how maternal metabolic conditions impact HPA axis regulation [38]. Prediabetic pregnant rats showed that maternal blood sugar dysregulation negatively affected fetal HPA axis development, leading to increased metabolic disorder risk in offspring [39]. While animal models offered valuable biological insights, human studies beyond animal model research were required to validate the impacts found using animal models because animals could not accurately mimic human pregnancy [40].

To get a better knowledge of maternal-fetal HPA-axis interaction, future research should aim for standardized cortisol measurement techniques and should consider the integration of epigenetic and genetic analyses.

CONCLUSION

The analysis demonstrated that stress in pregnant women, alongside HPA axis dysfunction, played a crucial role in influencing pregnancy results together with fetal developmental outcomes. The research confirmed that high cortisol levels in pregnant mothers caused embryonic programming errors, resulting in increased stress reactivity during infancy as well as possible long-term medical consequences. Standardised research procedures were required because the heterogeneity across studies highlighted the need for standardised methodologies to demonstrate the promise of behavioral and pharmacological interventions for HPA axis dysfunction mitigation. Additional studies should focus on stress evaluation refinement while also investigating genetic and epigenetic mechanisms to enhance health outcomes for mothers and their fetuses.

LIST OF ABBREVIATIONS

HPA – Hypothalamic-Pituitary-Adrenal
CAR – Cortisol Awakening Response
DCS – Diurnal Cortisol Slope
HSD11B2 – 11β-Hydroxysteroid Dehydrogenase Type 2
HSD11 B1 – 11β-Hydroxysteroid Dehydrogenase Type 1
PS – Prenatal Stress
CBT – Cognitive Behavioural Therapy

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CONFLICT OF INTEREST

None

AUTHORS' CONTRIBUTIONS

All participants participated equally as per ICMJE.

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