

Maternal Prenatal Stress, Oxidative Stress and Fetal Programming: Integrating Placental, Endocrine, Mitochondrial and Epigenetic Mechanisms and Emerging Therapeutic Strategies

Aliyu Buhari^{1*}, Lawali Ibrahim²

¹Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria

²Department of Physiology, Faculty of Basic Medical Sciences, Zamfara State University, Talata Mafara, Nigeria

DOI: <https://doi.org/10.51584/IJRIAS.2026.11080181>

Received: 31 August 2026; Accepted: 05 September 2026; Published: 22 September 2026

ABSTRACT

Background: Maternal stress during pregnancy is increasingly recognized as an important environmental determinant of fetal development and lifelong disease susceptibility. Although prenatal stress has been associated with adverse neurodevelopmental, cardiovascular, metabolic and behavioural outcomes, the biological pathways linking maternal stress to persistent offspring phenotypes remain incompletely integrated.

Objective: This systematic review aimed to synthesize evidence concerning the molecular and physiological mechanisms linking maternal prenatal stress with fetal programming, with particular emphasis on hypothalamic–pituitary–adrenal-axis activation, placental glucocorticoid metabolism, oxidative stress, mitochondrial dysfunction, inflammation and epigenetic regulation. A secondary objective was to examine emerging nutritional, antioxidant, hormonal and phytochemical strategies that may attenuate stress-induced developmental programming.

Methods: The review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework [1,2]. PubMed/MEDLINE, Embase, Scopus, Web of Science, Google Scholar and the Cochrane Library should constitute the principal information sources. Eligible evidence comprises human observational/interventional studies and experimental animal studies investigating maternal stress during pregnancy and biological or clinical outcomes in offspring. Study characteristics, exposure characteristics, mechanistic pathways, offspring outcomes and interventions will be extracted. Risk of bias will be evaluated using design-appropriate validated instruments. Because substantial heterogeneity is anticipated across populations, species, stress models, developmental windows and outcome measures, the principal synthesis will be narrative and mechanistic.

Results: Available evidence indicates that maternal prenatal stress can influence offspring development through interacting endocrine, placental, oxidative, inflammatory, mitochondrial and epigenetic mechanisms. Maternal stress activates the hypothalamic–pituitary–adrenal axis and alters glucocorticoid signalling, while the placenta regulates fetal exposure to maternal glucocorticoids through mechanisms including 11 β -hydroxysteroid dehydrogenase type 2. Human and experimental studies implicate altered placental function, oxidative stress and epigenetic modification in offspring programming [3–8]. Prenatal stress has been associated with altered cardiovascular, metabolic, neuroendocrine and behavioural phenotypes [3,4]. Experimental evidence further indicates that placental oxidative stress may mediate effects of maternal stress on offspring brain and behaviour and that antioxidant treatment can attenuate selected phenotypes [9]. Emerging evidence also implicates mitochondrial mechanisms in prenatal stress-induced offspring abnormalities [10].

Conclusion: Maternal prenatal stress should be considered a multisystem developmental exposure involving the maternal–placental–fetal axis rather than an isolated psychological event. Oxidative stress may represent an important mechanistic bridge between maternal endocrine activation, placental dysfunction, mitochondrial disturbance, inflammation and epigenetic programming. Antioxidant, mitochondria-targeted, melatonin-based and selected phytochemical strategies represent promising research directions, but their efficacy and safety during pregnancy require rigorous experimental and clinical investigation.

Keywords: Maternal stress; Prenatal stress; Fetal programming; Oxidative stress; Placenta; Glucocorticoids; Mitochondrial dysfunction; Epigenetics; Offspring; Developmental origins of health and disease.

INTRODUCTION

Pregnancy is a period of profound physiological adaptation and developmental plasticity. Environmental exposures during this period can influence fetal growth, organ maturation and the subsequent risk of disease. The developmental origins of health and disease (DOHaD) framework proposes that environmental conditions during critical periods of development can produce persistent biological alterations that influence health across the life course [11]. Maternal stress is one of the environmental exposures increasingly implicated in developmental programming. Stress during pregnancy may arise from psychological distress, anxiety, depression, socioeconomic adversity, traumatic experiences, environmental challenges or experimentally induced physiological stress. Epidemiological evidence has associated maternal prenatal stress with adverse offspring outcomes spanning neurological, behavioural, cardiovascular and metabolic domains [3,12].

A systematic scoping review of maternal stress and glucocorticoid exposure identified evidence linking prenatal exposure with offspring obesity, hyperglycaemia, insulin resistance, diabetes, metabolic syndrome, cardiovascular disease, hypertension and altered fetal growth [3]. A separate systematic review and meta-analysis involving more than 65 million women reported associations between high maternal stress during pregnancy and medical and psychiatric disorders in offspring [12]. However, the biological mechanisms underlying these associations are complex.

Maternal stress activates the hypothalamic–pituitary–adrenal (HPA) axis, resulting in increased secretion of corticotropin-releasing hormone, adrenocorticotrophic hormone and glucocorticoids. The resulting endocrine response can alter maternal metabolism, placental function and fetal development [3,13]. The placenta is particularly important because it represents the principal interface between maternal and fetal environments. It regulates nutrient transport, oxygenation, endocrine signalling and fetal exposure to maternal glucocorticoids. Placental 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) converts active cortisol/corticosterone to less-active metabolites and therefore contributes to protection of the fetus from excessive maternal glucocorticoid exposure [13,14]. Evidence from human pregnancy research demonstrates an association between maternal stress and altered cortisol/cortisone relationships at birth, supporting a potential role for placental glucocorticoid metabolism [14]. However, glucocorticoid signalling alone does not adequately explain the broad spectrum of programmed outcomes. Increasing evidence implicates oxidative stress, inflammation, mitochondrial dysfunction and epigenetic alterations as interacting mechanisms.

Oxidative stress and fetal programming

Oxidative stress results when the generation of reactive oxygen species exceeds antioxidant defence capacity. The placenta has substantial metabolic requirements and is therefore particularly sensitive to disturbances in redox homeostasis. Experimental evidence provides compelling support for placental oxidative stress as a mediator of prenatal stress effects. In a rat model of maternal psychosocial stress, maternal stress increased circulating corticosterone and induced oxidative stress in the placenta. Importantly, antioxidant treatment prevented selected prenatal-stress-associated anxiety and neurobiological abnormalities in male offspring [9].

This finding is important because it suggests a pathway beyond simple maternal cortisol transfer:

Maternal stress → maternal endocrine activation → placental oxidative stress → altered placental signalling → fetal developmental changes → offspring phenotype.

The placenta may therefore act as an active biological transducer of maternal stress rather than merely a passive barrier.

Placental glucocorticoid metabolism

Placental glucocorticoid metabolism represents another important pathway. Under physiological conditions, 11 β -HSD2 limits fetal exposure to maternal glucocorticoids. Excessive maternal glucocorticoid exposure or altered placental enzyme expression may modify this protective mechanism [13,15].

Experimental evidence indicates that high maternal glucocorticoid exposure can alter placental 11 β -HSD2 expression and contribute to differences in placental and fetal development between male and female offspring [15]. This supports the possibility that sex-specific placental responses may contribute to differences in vulnerability to prenatal stress.

Mitochondrial dysfunction

Mitochondria are central to energy metabolism, redox regulation, apoptosis and cellular signalling. Because mitochondrial function is closely coupled to reactive oxygen species generation, mitochondrial disturbance may establish a positive feedback loop:

Prenatal stress → mitochondrial dysfunction → increased ROS → oxidative damage → further mitochondrial dysfunction.

Recent experimental evidence has implicated CRF/CRFR1 signalling, mitochondrial calcium overload and mitochondria-associated membrane remodelling in prenatal fear-stress-induced hippocampal injury in offspring [10]. Although these findings are relatively new, they reinforce the importance of incorporating mitochondrial biology into models of fetal programming.

Inflammation

Oxidative stress and inflammation are closely interconnected.

Potential inflammatory pathways implicated in prenatal stress include:

NF- κ B signalling;

TNF- α ;

IL-6;

IL-1 β ;

altered immune-cell signalling;

endothelial dysfunction.

Inflammatory signalling can further impair mitochondrial function and amplify oxidative injury. Conversely, excessive ROS can activate inflammatory transcription pathways.

This creates a potentially self-reinforcing:

stress–oxidative stress–inflammation cycle.

Epigenetic programming

Epigenetic regulation provides a plausible mechanism through which a transient prenatal exposure can produce persistent biological changes.

Major mechanisms include:

DNA methylation

Maternal prenatal stress has been associated with altered DNA methylation in offspring. A systematic review reported evidence linking maternal prenatal stress with NR3C1 methylation and infant stress reactivity, although findings across other candidate genes were inconsistent [5].

This is particularly relevant because NR3C1 encodes the glucocorticoid receptor and therefore directly connects epigenetic regulation with HPA-axis function.

Epigenome-wide evidence

However, the evidence should not be overstated.

An epigenome-wide meta-analysis involving 1,740 mother–infant pairs found no genome-wide significant association between a composite prenatal maternal stress measure and neonatal DNA methylation, emphasizing the importance of replication and the possibility that effects may be small, tissue-specific or exposure-specific [16]. More recent meta-analytic evidence involving 12 cohorts and 5,496 participants identified differential methylation associated with cumulative maternal stressful life events during pregnancy, including loci involving ALKBH3, APTX, MYD88, UHRF1 and SDCCAG8 [17].

These apparently contrasting findings highlight an important conclusion:

Prenatal stress may influence epigenetic programming, but the molecular signature is unlikely to be uniform across all populations, tissues, stressors or developmental windows.

Placental epigenetic programming

The placenta deserves special attention because it is both a mediator and potential molecular record of prenatal environmental exposure.

In the PRISM cohort, cumulative maternal lifetime stress was associated with differential DNA methylation at multiple placental CpG sites, with enrichment involving pathways related to endocytosis, tight-junction biology and metabolism [18]. Such findings suggest that maternal stress may influence placental development through epigenetic mechanisms, potentially altering placental transport, barrier function and endocrine signalling.

Cardiovascular programming

Prenatal stress has been associated with cardiovascular phenotypes including:

altered blood pressure;

vascular reactivity;

sympathetic regulation;

endothelial function;

cardiac development.

The cardiovascular effects of prenatal stress are particularly relevant to DOHaD because subtle alterations during fetal development may become clinically important later in life.

The systematic scoping review by Eberle et al. concluded that prenatal stress and glucocorticoid exposure were associated with several cardiovascular and metabolic outcomes, although the evidence was heterogeneous [3].

Metabolic programming

Prenatal stress may influence:

glucose regulation;

insulin sensitivity;

adiposity;

pancreatic development;

appetite regulation;

metabolic syndrome.

The mechanisms potentially involve altered fetal glucocorticoid exposure, placental nutrient transport, oxidative stress and epigenetic regulation [3,13]. These mechanisms provide a biological basis for the hypothesis that prenatal stress can increase later-life susceptibility to cardiometabolic disease.

Neurodevelopmental and behavioural programming

The nervous system appears particularly vulnerable to prenatal environmental stress.

Maternal stress has been associated with:

altered HPA-axis regulation;

anxiety-like behaviour;

cognitive changes;

emotional dysregulation;

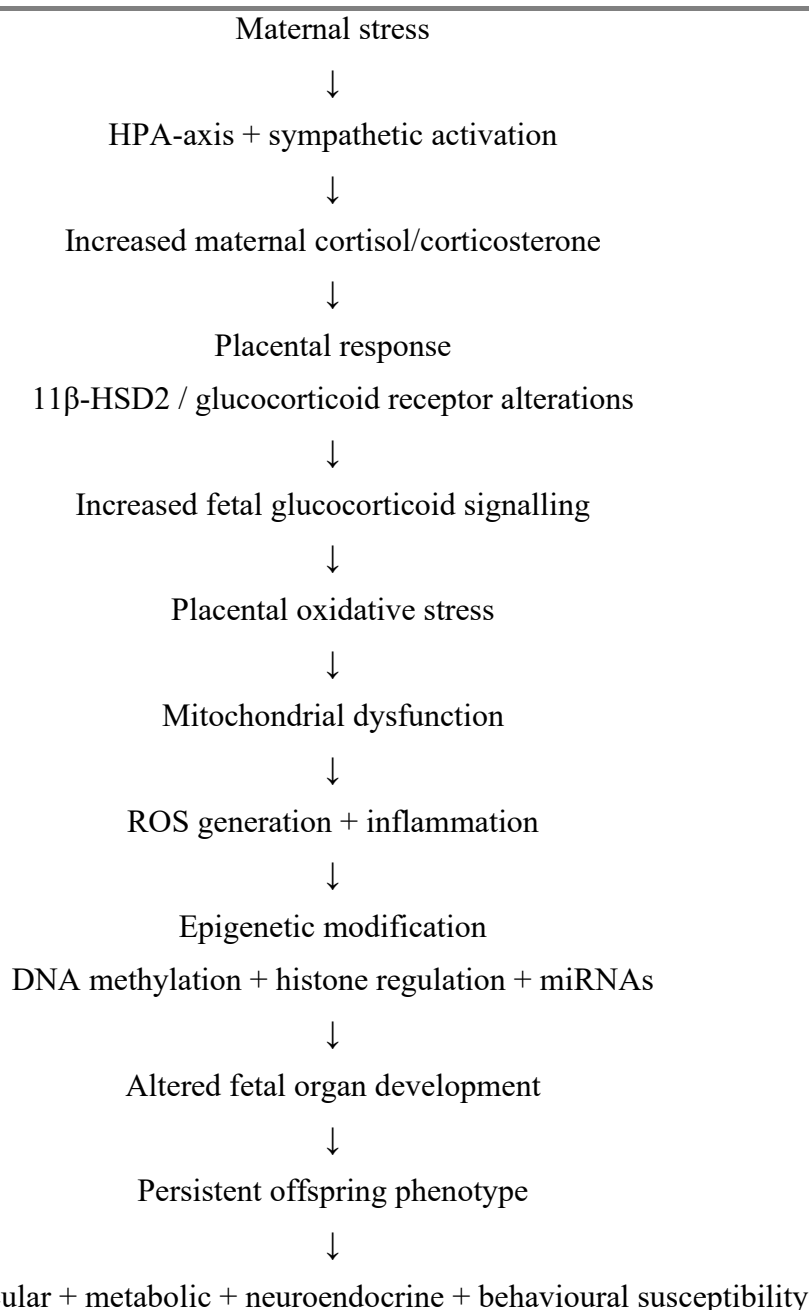
altered hippocampal development;

psychiatric vulnerability.

The experimental study by Holland et al. provides particularly important mechanistic evidence because placental oxidative stress was associated with adverse offspring brain and behavioural outcomes and antioxidant intervention attenuated selected effects [9]. The involvement of placenta-derived factors, including altered microRNAs, further supports the concept of placenta-to-brain signalling [9].

Integrated maternal stress–placenta–fetal programming model

The evidence synthesized in this review supports the following conceptual pathway:



This integrated framework represents the principal conceptual contribution of the review.

Emerging therapeutic strategies

Antioxidant therapy

Antioxidants represent one of the most biologically plausible intervention strategies because oxidative stress appears to participate in several stages of the programming cascade. However, the evidence remains predominantly experimental. The rat study demonstrating that maternal antioxidant treatment prevented selected prenatal-stress-induced brain and behavioural abnormalities provides proof-of-concept evidence but does not establish clinical efficacy in pregnant women [9].

Melatonin

Melatonin is particularly interesting because it possesses antioxidant, mitochondrial and anti-inflammatory properties.

Potential mechanisms include:

- direct radical scavenging;
- stimulation of antioxidant enzymes;
- mitochondrial protection;
- modulation of inflammatory signalling;
- regulation of circadian/endocrine pathways.

Nevertheless, pregnancy-specific safety and efficacy require careful evaluation before clinical recommendations can be made.

Hibiscus sabdariffa and anthocyanins: an emerging research opportunity

Hibiscus sabdariffa L. contains several potentially bioactive constituents, including phenolic acids, hibiscus acid and anthocyanins such as delphinidin-3-sambubioside and cyanidin-3-sambubioside [19]. Experimental and pharmacological literature has reported antioxidant, antihypertensive, antidiabetic, lipid-modulating and anti-inflammatory activities associated with *H. sabdariffa* preparations [19]. Delphinidin-3-sambubioside has also demonstrated biological activity involving oxidative and inflammatory pathways in experimental systems [20,21]. However, a critical distinction must be made:

There is currently insufficient evidence to conclude that *Hibiscus sabdariffa* or delphinidin-3-sambubioside prevents maternal-stress-induced fetal programming in humans. Consequently, this review proposes *H. sabdariffa* and its anthocyanins as candidate research interventions, rather than established pregnancy therapies. This distinction is important for scientific accuracy and clinical safety.

Novel therapeutic hypothesis

The evidence supports a testable hypothesis:

Targeting placental oxidative stress and mitochondrial dysfunction may interrupt the biological cascade linking maternal stress to fetal programming.

A second, more specific hypothesis is:

Phytochemically characterized anthocyanins, including delphinidin-3-sambubioside, may modulate oxidative and inflammatory signalling within the maternal–placental–fetal axis and thereby attenuate selected consequences of prenatal stress. This hypothesis requires experimental validation.

It is also worth noting that *H. sabdariffa* preparations are chemically heterogeneous, and previous reviews have emphasized the need for better-designed studies using phytochemically characterized preparations [19]. Therefore, future studies should quantify the active anthocyanin content rather than treating all *H. sabdariffa* extracts as biologically equivalent.

Evidence synthesis

Mechanistic pathway	Evidence	Principal implication
HPA-axis activation	Human + animal	Increased maternal glucocorticoid signalling

Placental 11 β -HSD2	Human + animal	Altered fetal glucocorticoid exposure
Oxidative stress	Strong experimental evidence	Potential mediator of fetal programming
Mitochondrial dysfunction	Emerging experimental evidence	Possible amplifier of ROS and cellular injury
Inflammation	Experimental + observational	Potential interaction with oxidative stress
DNA methylation	Human evidence, heterogeneous	Potential persistent molecular programming
miRNA	Experimental evidence	Possible placenta-to-fetus signalling
Cardiovascular programming	Human + animal	Later-life cardiovascular vulnerability
Metabolic programming	Human + animal	Obesity, glucose and insulin abnormalities
Neurobehavioural programming	Human + animal	Altered HPA function and behaviour
Antioxidants	Experimental	Promising but not clinically established
Melatonin	Experimental/preclinical	Potential antioxidant/mitochondrial intervention
H. sabdariffa	Pharmacological/preclinical	Candidate phytochemical intervention
Delphinidin-3-sambubioside	Experimental	Mechanistically interesting candidate

Strengths of the evidence

The literature has several important strengths.

First, evidence comes from both human observational research and controlled experimental models.

Second, several biological mechanisms converge on the maternal–placental–fetal interface.

Third, experimental antioxidant studies provide preliminary causal evidence that oxidative stress may mediate selected prenatal-stress effects [9].

Fourth, emerging epigenetic and mitochondrial studies broaden the mechanistic framework [10,17,18].

Limitations of current evidence

Several limitations prevent definitive causal conclusions.

Heterogeneous definition of stress

Studies measure stress using questionnaires, life events, anxiety/depression scales or experimental stress paradigms.

Species differences

Rodent models allow mechanistic experimentation but cannot reproduce the full complexity of human psychosocial stress.

Timing

The consequences of stress may depend on the developmental stage at exposure.

Sex-specific effects

Male and female fetuses may differ in placental and developmental responses.

Tissue specificity

DNA methylation findings in cord blood cannot necessarily be assumed to represent methylation patterns in the brain, placenta or other target organs.

Confounding

Human observational studies can be influenced by socioeconomic status, nutrition, smoking, medications, maternal psychiatric illness and other environmental exposures.

Intervention evidence

Evidence for antioxidants, melatonin and phytochemicals remains insufficient for clinical recommendations.

Research priorities

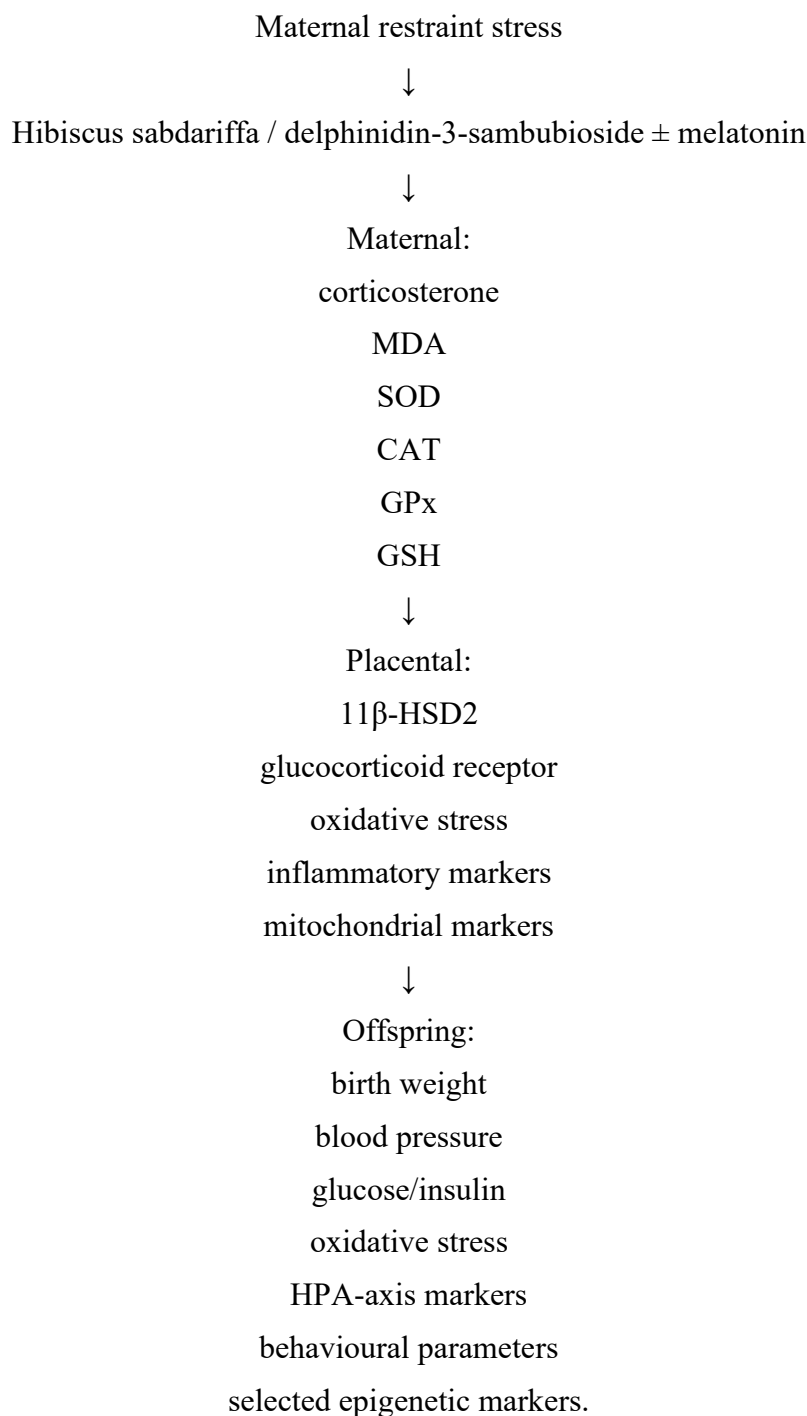
Future studies should:

- Measure maternal stress and biological stress markers simultaneously;
- Measure placental 11 β -HSD2 and glucocorticoid-receptor signalling;
- Quantify oxidative stress and antioxidant defence;
- Examine mitochondrial function;
- Characterize inflammatory pathways;
- Incorporate epigenomic analyses;
- Investigate male–female differences;
- Use longitudinal offspring follow-up;

- Standardize stress exposure definitions
- Use chemically characterized phytochemical interventions;
- Establish dose–response relationships;
- Evaluate pregnancy-specific safety before clinical translation.

Proposed future experimental model

A particularly valuable experimental study emerging from this review would investigate:



This would provide a mechanistically coherent platform for translating the systematic-review findings into experimental research.

CONCLUSION

Maternal prenatal stress is increasingly recognized as an important contributor to developmental programming and later-life disease susceptibility. Evidence synthesized in this review indicates that its biological effects are mediated through interacting endocrine, placental, oxidative, mitochondrial, inflammatory and epigenetic mechanisms. The placenta appears to occupy a central position in this process, integrating maternal stress signals and translating them into alterations in the fetal developmental environment. Among the emerging mechanisms, placental oxidative stress and mitochondrial dysfunction may represent critical points at which maternal stress signals are converted into persistent fetal biological changes.

Antioxidant and mitochondria-targeted approaches, including melatonin and selected phytochemicals, warrant further investigation. Hibiscus sabdariffa and its anthocyanin delphinidin-3-sambubioside are particularly interesting candidates because of their documented biological activities; however, direct evidence for prevention of maternal-stress-induced fetal programming remains inadequate.

Future research should therefore progress from broad antioxidant claims toward mechanistically defined, phytochemically standardized and pregnancy-safe interventions.

REFERENCES

1. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71.
2. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160.
3. Eberle C, Fasig T, Brüseke F, Stichling S. Impact of maternal prenatal stress by glucocorticoids on metabolic and cardiovascular outcomes in their offspring: a systematic scoping review. *PLoS One*. 2021;16(1):e0245386. doi:10.1371/journal.pone.0245386.
4. Caparros-Gonzalez RA, et al. Stress during pregnancy and the development of diseases in the offspring: a systematic review and meta-analysis. *Midwifery*. 2021;97:102939.
5. Sosnowski DW, Booth C, York TP, Amstadter AB, Kliwer W. Maternal prenatal stress and infant DNA methylation: a systematic review. *Developmental Psychobiology*. 2018;60:127–139. doi:10.1002/dev.21604.
6. Nowak AL, Anderson CM, Mackos AR, Neiman E, Gillespie SL. Stress during pregnancy and epigenetic modifications to offspring DNA: a systematic review. *Journal of Perinatal & Neonatal Nursing*. 2020;34:134–145.
7. Matthews SG, et al. Prenatal stress, glucocorticoids and the programming of adult disease. [Relevant developmental-programming literature].
8. Seckl JR, Meaney MJ. Glucocorticoid programming. *Developmental programming literature*.
9. Holland C, et al. Maternal antioxidant treatment prevents the adverse effects of prenatal stress on the offspring's brain and behavior. 2020.
10. Recent experimental study of CRF–CRFR1 signalling in prenatal fear stress-induced hippocampal mitochondrial damage in offspring. 2026.
11. Barker DJP. Developmental origins of adult health and disease and the DOHaD framework.
12. Systematic review and meta-analysis of maternal stress during pregnancy and offspring medical and psychiatric outcomes.
13. Literature concerning prenatal glucocorticoid exposure, placental glucocorticoid metabolism and developmental programming.
14. Maternal stress and placental function: cortisol/cortisone measurements and placental 11 β -HSD2 activity in 273 pregnancies.
15. Yu P, et al. Differential expression of placental 11 β -HSD2 induced by high maternal glucocorticoid exposure mediates sex differences in placental and fetal development. *Science of the Total Environment*. 2022. doi:10.1016/j.scitotenv.2022.154396.

16. Rijlaarsdam J, Pappa I, Walton E, et al. An epigenome-wide association meta-analysis of prenatal maternal stress in neonates: a model approach for replication. *Epigenetics*. 2016;11(2):140–149. doi:10.1080/15592294.2016.1145329.
17. Epigenome-wide meta-analysis of prenatal maternal stressful life events and newborn DNA methylation. International Pregnancy and Childhood Epigenetics Consortium.
18. Brunst KJ, Tignor N, Just A, Liu Z, Lin X, Hacker MR, et al. Cumulative lifetime maternal stress and epigenome-wide placental DNA methylation in the PRISM cohort. *Epigenetics*. 2018;13(6):665–681. doi:10.1080/15592294.2018.1497387.
19. Da-Costa-Rocha I, Bonnlaender B, Sievers H, Pischel I, Heinrich M. Hibiscus sabdariffa L.—a phytochemical and pharmacological review. *Food Chemistry*. 2014;165:424–443. doi:10.1016/j.foodchem.2014.05.002.
20. Hou DX, Tong X, Terahara N, Luo D, Fujii M. Delphinidin 3-sambubioside, a Hibiscus anthocyanin, induces apoptosis in human leukemia cells through reactive oxygen species-mediated mitochondrial pathway. *Archives of Biochemistry and Biophysics*. 2005;440(1):101–109. doi:10.1016/j.abb.2005.06.002.
21. Study of the anti-inflammatory activity and molecular mechanism of delphinidin-3-sambubioside. International Union of Biochemistry and Molecular Biology literature. 2015.