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REVIEW ARTICLE

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Early life corticosteroid overexposure: Epigenetic and fetal origins of adult diseases

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Abstract

The relationship between events occurring during intrauterine development and later-life predisposition to long-term disease, has been described. The fetus responds to excess intrauterine exposure to high levels of corticosteroids, modifying their physiological development and stopping their growth. Fetal exposure to elevated levels of either endogenous (alterations in fetal hypothalamic-pituitary-adrenal axis) or synthetic corticosteroids, is one model of early-life adversity; to developing adult disease. At the molecular level, there are transcriptional changes in metabolic and growth pathways. Epigenetic mechanisms participate in transgenerational inheritance, not genomic. Exposures that change 11β-hydroxysteroid dehydrogenase type 2 enzyme methylation status in the placenta can result in transcriptional repression of the gene, causing the fetus to be exposed to higher levels of cortisol. More precise diagnosis and management of antenatal corticosteroids for preterm birth, would potentially decrease the risk of long-term adverse outcomes. More studies are needed to understand the potential roles of factors to alter fetal corticosteroid exposure. Long-term infant follow-up is required to determine whether methylation changes in placenta may represent useful biomarkers of later disease risk. This review, summarize recent advances in the programming of fetal effects of corticosteroid exposure, the role of corticosteroids in epigenetic gene regulation of placental 11β-hydroxysteroid dehydrogenase type 2 enzyme expression and transgenerational effects.

KEYWORDS
adult diseases, early life programming, epigenetic, fetal corticosteroid overexposure, hypothalamic–pituitary–adrenal axis, prenatal corticosteroid administration, transgenerational effects

1 | INTRODUCTION

An association has been described between events occurring during prenatal life and diseases in adolescence or adulthood.[1–7] Prenatal adverse environments (such as xenobiotics exposure, malnutrition, infection, hypoxia, and stress) can cause overexposure of fetuses to excessive intrauterine corticosteroids.[6] Exposure of the fetus to excess corticosteroids leads to long-term programming of the function of the hypothalamic–pituitary–adrenal (HPA) axis (Figure 1) and the behavior of the organism.[4] The latest evidence indicates that transgenerational epigenetic transmission might be partly responsible for the multigenerational effects of corticosteroid exposure and maternal stress in pregnancy.[5]

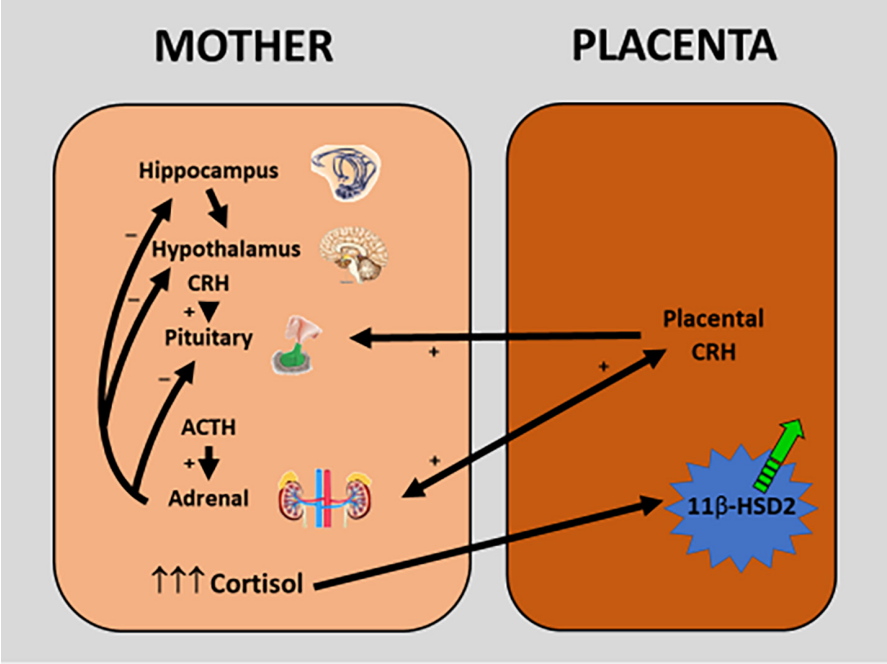

FIGURE 1 The maternal hypothalamic–pituitary–adrenal axis: cortisol is secreted from the adrenal glands and regulation is controlled by central negative feedback. In pregnancy, cortisol levels rise three-fold. Placental CRH stimulates both the maternal pituitary and adrenal glands, leading to increased cortisol production. Rising cortisol can also stimulate further placental CRH production. Passage of cortisol through the placenta is partially inhibited by placental 11β-HSD2. CTH, adrenocorticotropin-releasing hormone; CRH, corticotropin-releasing hormone; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2.

This review summarizes recent advances in the programming fetal effects of corticosteroid exposure, in the role of corticosteroids in epigenetic gene regulation of placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) enzyme expression, and transgenerational effects and provides some recommendations and guidelines for clinical care.

2 | EPIGENETICS AND FETAL ORIGINS OF ADULT DISEASE

The "programmed" changes may be the origins of a number of diseases in later life. New factors that interact with gene expression in utero are now known.[2–5,7–10] The developmental windows range from conception to the neonatal period.[4,5]

Epigenetic regulation is needed for normal fetal and placental development and function, explains the fetal origin of certain adult diseases, and is responsible for the transgenerational inheritance of acquired characters.[11,12] Genetics is the study of genes, genetic variation, and heredity of living organisms. Phenotypic traits are developed with the inheritance of genetic information in the form of genes.[11] Epigenetics is the alteration in heritable traits in gene expression that does not involve changes to the DNA sequence. Development of phenotypic traits occurs as the result of external factors such as environmental and behavioral factors. Hence, it is the change in the phenotype without changing the genotype. It can be caused by external and internal environments (such as availability, or not, of nutrients, or exposure to viruses or environmental contaminants), age and diseased conditions.[11,12] DNA methylation, histone modification, imprinting, and other epigenetic processes (noncoding mRNA-associated gene silencing, paramutation, X chromosome inactivation, bookmarking, and cloning) are mechanisms that initiate and uphold epigenetics (Table 1).[5,11,12] DNA damage may also cause epigenetic alterations.[11,12]

These changes may cause the modification of genes, but not of the nucleotide sequence of DNA, and may transmit from generation

TABLE 1 Types of epigenetic inheritance.[5,11,12]

1. DNA methylation: DNA cytosine methylation, which is a change in DNA in which a methyl group is transferred from *S*-adenosylmethionine to a cytosine C-5 position by a DNA-5 methyltransferase.
2. Transformation of histone proteins: more transient than methylation, especially through acetylation of the lysine. Histone modification include acetylation, methylation, and phosphorylation. More than 50 different epigenetic modifications of proteins have been identified of the histone.
3. Genetic imprinting or "imprinting": manifested only in higher organisms and refers to genes that can modify their function without the need for a change in the sequence of the DNA. It seems that there is a cellular mechanism that in someway "marks" or leaves an imprint on all genes.
4. Others epigenetic processes: noncoding RNA associated gene silencing, paramutation, X chromosome inactivation, bookmarking, and cloning.

to generation through a process called transgenerational epigenetic inheritance.[11,12] Epigenetic changes can have then a huge impact on human health. If these patterns of chemical modifications occur during a critical period of development, the pattern may remain for the rest of life. Most chronic diseases probably involve the interaction of multiple environmental stimuli with multiple genes.[12]

3 | EXOGENOUS CORTICOSTEROIDS AND FETAL ORIGINS OF ADULT DISEASES

Synthetic corticosteroids (betamethasone and dexamethasone) are routinely used in obstetrical practice in the management of women at risk of early preterm birth and for some other indications, such as asthma, autoimmune diseases, and congenital adrenal hyperplasia.[1,6,7,10,14–20] Exposure to excess corticosteroids before birth is hypothesized to be a key mechanism underlying the fetal origins of adult disease.[4,5,18,19,21–24] Recent epidemiologic evidence from human and animal studies suggests that there may be adverse long-term consequences (Table 2) of prenatal administration of corticosteroids.[4,5,10,18,19,21,24–26] In humans, current evidence shows that feto-neonatal risks with a single corticosteroid course between 24 and 34 weeks of pregnancy, are rare, transient, and reversible. Additionally, their benefits outweigh the risks, significantly reducing perinatal morbidity and perinatal and neonatal mortality.[10,12–19,21,23,24] Three reports of follow up of the original prenatal betamethasone trial indicate that there was no clinical effect on psychological, lung, and cardiovascular risk factors at 30–31 years of age; however, there were indications of insulin resistance, particularly in women.[27–29] Fluorinated synthetic corticosteroids, such as betamethasone and dexamethasone, are 25–30 times more potent than cortisol and have insignificant mineralocorticoid action. Because synthetics are poor substrates for metabolism by placental 11β-HSD2, the use of these pharmacologic agents has directly improved clinical outcomes.[15,30] Current ACS practice is to administer a single 2-day course of either betamethasone or dexamethasone to women in preterm labor between 24 and 34 weeks of pregnancy.[10,13–20]

TABLE 2 Associated effects of prenatal corticosteroid therapy in animal and human models.[1]

Animal models:
↓ Fetal growth (e.g. birth weight, head circumference, body length)
↓ Placenta weight
↑ Impairment of hypothalamic–pituitary–adrenal axis
↓ Locomotion, motivation, cognition
↓ Myelination
↑ Metabolic impairment (e.g. adiposity, hyperinsulinemia, hyperglycemia)
↑ Cardiovascular (hypertension)
↓ Fecundity
Humans:
↓ Fetal growth (e.g. birth weight, head circumference, body length)
↓ Placenta width
↑ Impairment of hypothalamic–pituitary–adrenal axis
↑ Neuropsychiatric and behavioral changes
↑ Metabolic impairment (e.g. adiposity, hyperinsulinemia, hyperglycemia)
↑ Cardiovascular (hypertension)
↑ Fetal heart rate variation
↓ Renal function (glomerular filtration rate)

Recent trials demonstrate modest benefits from a single corticosteroid course for late preterm (34–37 weeks of pregnancy), term elective cesarean deliveries, and periviable deliveries. However, many women, perhaps exceeding 50%, with threatened preterm deliveries receive prenatal corticosteroids but do not deliver until after 34 weeks of pregnancy or at term. These expanded uses expose populations to prenatal corticosteroids at gestational ages that have been minimally evaluated for efficacy or risk. These effects of corticosteroids suggest caution for the expanded use of prenatal corticosteroids beyond at-risk pregnancies at 24–34 weeks.[20,25,26]

Adverse medical events in human newborns have also raised concerns about the safety of multiple corticosteroid courses (weekly, repeated or, periodic courses; different from rescue courses).[10,13–17,30,31] Several studies have established the efficacy of multiple courses, but there are still questions about their safety.[10,32,33] The current position of the international governing authorities and scientific institutions is that the use of multiple courses is not recommended, so these concerns should go away.[10,13,14,16,30]

4 | ENDOGENOUS CORTICOSTEROIDS AND FETAL ORIGINS OF ADULT DISEASES

The HPA axis is a major neuroendocrine pathway that modulates the prenatal stress response.[8,20] The fetal adrenal gland makes unique contributions to both the regulation of fetal development and the timing of parturition and some earlier studies have shown that the fetal HPA axis is highly sensitive to excess levels of corticosteroids that could alter the regulation of HPA function.[6,8,34–36]

The ability of the early environment to modify HPA function in adulthood was described more than 60 years ago.[21,23,37] It has been proposed that programming of the HPA axis in utero (Figure 2), is linked to the development of cardiovascular disease, insulin resistance, and diabetes in later life.[2,24,29]

Prenatal corticosteroid administration to women with threatened preterm birth and high endogenous maternal corticosteroid levels during pregnancy are both associated with lower birth weight.[8,24] Long-term consequences for offspring include HPA axis activation, increased metabolic and cardiovascular disorders, and neurodevelopmental sequelae.[5,8,18,24] Corticosteroids have become a popular candidate for mediating the effects of prenatal stress on HPA function and behavior after birth.[4,5,23,38] The glucocorticoid cortisol is the principal end product of the HPA axis in humans and plays a fundamental role in maintaining homeostasis and in fetal maturation and development.[21,38,39] Increased circulating corticosteroids, as a result of stress, stimulate the sympatho-adrenal system, causing elevated adrenaline and noradrenaline release from the adrenal medulla. These stress-induced

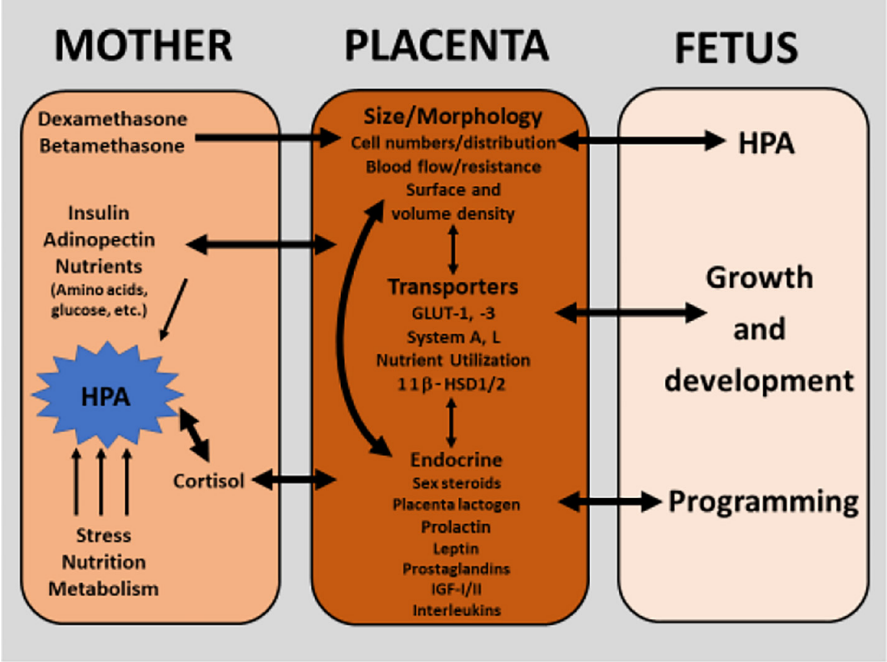

FIGURE 2 Perinatal programming of the hypothalamic–pituitary–adrenal axis, placental function, and long-term disease risk. HPA, hypothalamic–pituitary–adrenal; GLUT-1, glucose transporter 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; IGF-I/II, insulin-like growth factor I/II.

catecholamines have been shown to decrease 11β-HSD2 mRNA in the BeWo human choriocarcinoma cell line and in primary trophoblastic cells.[8]

Tissue corticosteroid levels are controlled by the 11β-HSD enzymes.[8] Under normal circumstances, access of maternal endogenous glucocorticoid (corticosterone or cortisol) to the fetus is low. This results from the placental expression of 11β-HSD. The 11β-HSD interconverts cortisol and corticosterone to inactive products (cortisone, 11-dehydrocorticosterone). There are two isoforms, 11β-HSD1, which is bi-directional, 11β-HSD2, which is uni-directional (cortisol to cortisone). Synthetic corticosteroids do enter the fetal circulation and bind to both glucocorticosteroid receptor and mineralocorticoid receptor—effects on the fetal brain are probably mediated by both of these receptors—or they may also bind to neurosteroid receptors. The receptor-ligand complexes translocate to the nucleus and bind to hormone response elements in the promoter regions of target genes to alter gene expression. HPA function in the adult offspring suggests that maternal corticosteroids, or a factor stimulated by corticosteroids, pass to the fetus to mediate prenatal stress-induced changes in HPA function. Further support for the "glucocorticoid hypothesis" has been provided by a blockade of 11β-HSD during pregnancy, and therefore an increased transfer of glucocorticoid from mother to fetus results in offspring that exhibit elevated basal and stress-stimulated HPA activity. There are exponential increases in fetal plasma cortisol concentrations in the last 10 days of gestation in humans, rising markedly to around three-fold the nonpregnant levels by the third trimester.[8,23] The prepartum surge of circulating fetal corticosteroids is vital for the development of many organ systems including the lung, liver, kidney, brain, and neuroendocrine development.[8,23] As early as 11–12 weeks of pregnancy, profound changes in the activity of the maternal HPA occur that lead to increased production in the maternal cortisol loop (Figure 1).[8] The HPA axis is regulated by the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which in turn stimulates the production of cortisol from the adrenal glands. Normally, cortisol regulates its own secretion through a negative feedback loop that inhibits the production of CRH and ACTH. However, during pregnancy, the placenta begins to release CRH into the maternal bloodstream and levels reach 1000–10 000 times those in nonpregnant women. This further increases the production of cortisol by the adrenal glands. Although cortisol usually negatively regulates the secretion of hypothalamic CRH, a rise in maternal cortisol actively stimulates the release of placental CRH, which further raises the levels of maternal cortisol progressively during pregnancy. This increase in maternal glucocorticoid levels has been proposed to be required for normal fetal organogenesis.[8] In addition, increased maternal catecholamine concentrations will lead to constriction of placental blood vessels and may lead to fetal hypoxia, which will in turn activate the fetal HPA axis. It is also possible that fetal hypoxia will lead to activation of the fetal sympathetic nervous system, which has also been shown to be programmed by the early environment. Programming of the sympathetic nervous system and neurotransmitter systems in the brain will ultimately lead to altered physiologic responses to stress in offspring.[23] Such modification will indirectly influence HPA function.[4,5,22] The fact that corticosteroids play a central role in the programming of HPA function logically leads one to question the impact of synthetic corticosteroids during pregnancy.[9,23]

5 | FETAL CORTICOSTEROID OVEREXPOSURE AND LONG-TERM CONSEQUENCES

One of the major hypotheses proposed to underlie developmental programming is overexposure of the developing fetus to corticosteroids. Much evidence to support this hypothesis has accumulated from animal studies of fetal overexposure to corticosteroids (betamethasone and dexamethasone).[8–10,21,23] Recent evidence indicates that they can exert powerful effects on the epigenome, including on DNA methylation, histone acetylation, and microRNA, to influence gene expression.[5] The clinical data in infants exposed to corticosteroids suggest altered HPA axis function over the short term. The longer-term consequences of prenatal corticosteroid exposure on HPA axis function are poorly understood.[21] Follow-up studies of preterm infants exposed to high levels of corticosteroids in utero have shown an increased incidence of behavioral disorders, altered immune responses, lower growth centiles, elevated blood pressure, and increased insulin resistance, along with changes in HPA axis baseline and stress responsiveness.[20] Observational studies in humans suggest that high maternal cortisol levels can overcome the protective 11β-HSD2 barrier and pass across the placenta, slowing fetal growth and/or gestation.[8]

Normally, the fetus is protected from the high levels of maternal cortisol by molecular mechanisms in the placenta that convert active cortisol to its inactive metabolite cortisone. Consequently, fetal cortisol levels are 10–13 times lower than maternal cortisol levels. The primary barrier between the maternal and fetal circulations is provided by two epithelial layers that cover the chorionic villi of the human placenta, syncytiotrophoblast and cytotrophoblast. Within these trophoblast layers, the enzyme 11β-HSD2 catalyzes the conversion of active cortisol into inactive cortisone, thus protecting the fetus from excessive cortisol exposure. Acute cortisol exposure reduces its expression, resulting in overexposure of the fetus to maternal corticosteroids. One of the consequences of fetal corticosteroid exposure, in addition to lowering birth weight, is alteration of the set point of the offspring's HPA axis, with activation of the HPA axis—a change that persists into adulthood. From an evolutionary perspective, such an adaptation to an intrauterine insult is thought to be beneficial in the short term and linked to increased chance of offspring survival in a predicted stressful environment.[8,20,23]

6 | PLACENTA, CORTICOSTEROIDS AND LONG-TERM DISEASE RISK

The placenta plays a key role in controlling growth and development.[39] Prenatal adversity, including xenobiotics exposure, malnutrition, infection, hypoxia, prenatal stress, or corticosteroid overexposure is either transmitted across the placenta or has direct influences on the development and function of the placenta.[6] Epidemiologic data have suggested that low placental weight at birth is associated with small babies and predicts hypertension and coronary disease in offspring.[3] Equally, a high placenta weight to birth weight ratio has been shown to be associated with coronary heart disease and hypertension.[1] It has been suggested that the association between placental surface area and the offspring's risk of hypertension depends on the mother's nutritional state, and that poor maternal nutrition may compound the adverse effects of small placental size.[35,39] Mechanisms by which corticosteroids impact placental growth and development still remain unclear.[6,39]

7 | EPIGENETIC REGULATION OF 11B-HSD2 EXPRESSION

It is now largely accepted that epigenetics can be modified by environmental exposures, particularly during development, when the epigenome undergoes profound changes. It has been suggested that the link between prenatal stress and the reduction in placental 11β-HSD2 expression may involve hypermethylation of the promoter, leading to a corresponding reduction in 11β-HSD2 expression.[5,8] Exposures that change 11β-HSD2 methylation status in the placenta can result in transcriptional repression of the gene, causing the fetus to be exposed to higher levels of cortisol that may adversely affect fetal development.[8] Prenatal stress and maternal exposure to exogenous corticosteroids can lead to permanent modification of HPA function and stress-related behavior.[4,5,8,23] Such fetal exposure permanently alters HPA function in pre-pubertal, post-pubertal, and aging offspring.[23] It is possible that the epigenetic status of placental 11β-HSD2 could also be a useful predictor of other adverse outcomes.[8]

8 | EPIGENETIC GENE REGULATION AND TRANSGENERATIONAL EFFECTS

Ancestral environmental exposures have been shown to promote epigenetic transgenerational inheritance and influence all aspects of an individual's life history. Because of their inherent plasticity, epigenetic mechanisms are susceptible to environmental influences; this susceptibility is thought to be greatest during early development. Over the last several years, epigenetic processes have emerged as important factors for many diseases, and the discovery of epigenetic processes in germ cells has raised the possibility that they may contribute to disease heritability and disease risk. The placenta, interposed between the mother and the fetus, is a potential mediator of this risk through epigenetic mechanisms, including DNA methylation, with possible fetal alterations and diseases later in life.[37,38]

The impact of early-life corticosteroid exposure on long-term HPA axis function is not simply limited to the immediate offspring of a pregnancy but may also affect subsequent generations, resulting in transgenerational effects.[4,5,12,35] One explanation is that fetal

exposure to corticosteroids induces alterations in the epigenetic regulation of gene expression, which are transferred to the next generation with subsequent changes in the physiology of this next generation.[1,12,35–37] In animal models, prenatal stress during pregnancy induces physiologic changes in the second generation, including modification in HPA axis and function, increased body length, insulin resistance, cardiovascular function, and anxiety or depression-like behavior.[12,36,37]

Whether exposure to elevated levels of glucocorticoids mediates placental gene expression through epigenetic and programming mechanisms remains to be elucidated. Multivariate linear regression reveals a significant association between differential methylation of the placental corticosteroid receptor gene and large for gestational age status. Placental 11β-HSD2 methylation is greatest in infants with the lowest birth weights and it is associated with reduced scores of early neurobehavioral outcomes in neonates. Specific patterns of placental DNA methylation have been recently identified. These data strengthen the notion that placental epigenetics is a critical potential modulator of long-term health and disease risk.[1,12,37–39]

9 | SUMMARY

Prenatal environment has profound influences on endocrine function throughout life. Although the short-term outcomes and benefits of exposure to single courses of synthetic corticosteroids in humans have been largely reassuring, there is reason for caution in extrapolating these findings for the long-term in humans. Animal studies indicate that HPA axis changes persist into adulthood and represent a programming effect that is transgenerational.

Corticosteroids can alter placental growth, the placental exchange surface area, and the abundance of early-life nutrient transporters. In humans, 11β-HSD2 gene mutations produce a low birth weight and reduced placental 11β-HSD2 activity. Low-birthweight babies have higher plasma cortisol levels throughout adult life, indicating that HPA axis programming also occurs in humans. The molecular mechanisms of corticosteroid programming involve permanent and tissue-specific changes in the expression of key genes. Hence, corticosteroid programming may explain the association between fetal events and subsequent disorders in adult life.

There has been increasing interest in the placenta as a suitable tissue for identifying biomarkers of disease. One potential biomarker is epigenetic modification, that is, changes in gene expression such as DNA methylation, histone modification, and chromatin packages, which do not involve changes in the DNA sequence and can be subject to environmental insults. DNA methylation is the most common mechanism studied to date and there is now preliminary evidence in humans that methylation levels of genes involved in corticosteroid action are altered by the early life environment and may also affect subsequent generations, resulting in transgenerational effects.

10 | RECOMMENDATIONS AND GUIDANCE FOR PRACTICE

More precise diagnosis and management of prenatal administration of corticosteroids for preterm birth, would potentially decrease the risk of long-term adverse outcomes. Emerging clinical strategies and interventions may help in the selection of mothers at risk for preterm birth who would benefit from prenatal corticosteroids, such as reducing morbidity (including respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis) and perinatal mortality.

Prenatal corticosteroid treatments that deliver the lowest fetal exposure for the shortest interval should be a goal.

More studies are needed to understand the potential roles of prenatal stress, nutrition, and lifestyle factors, and whether it is possible, to modify these to alter fetal corticosteroid exposure.

Longitudinal studies in pregnancy with long-term infant follow up are required to determine whether methylation changes in the placenta may represent useful biomarkers of later disease risk.

AUTHOR CONTRIBUTIONS

CBP and ERV conceptualized this review and drafted the initial manuscript. CBP, LBS, CBS, and ERV reviewed and corrected the initial draft and contributed to finalizing the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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