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Review IJC

Trauma-Its Transgenerational Inheritance and Associated Nuances in Perinatal Care: A Systematic Review

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Abstract

The research is a systematic review of the existing clinical and animal studies pertaining to effects of trauma on immediate offsprings and its transgenerational inheritance. The research also summarises the current statistical data on perinatal care globally with special emphasison India as a developing nation and the current strategies, government policies and international recommendations on maternal and child health as put forward in the Sustainabledevelopment goal 2030 by the United Nations. The study entails a detailed review from various databases like Google Scholar, Pubmed, and Scopus and it was found that both genetic and epigenetic mechanisms are instrumental in shaping the neurobiome of an embryo's brain. This plasticity can be further linked to future behavioural alterations and mental health disorders in the offspring. It summarises the cumulative effect of these Perinatal restraint stress (PNRS) which can be conceptualised as "scars" on the brain having detrimental neuropsychological and developmental changes termed as perinatal programming. This study aims to consolidate findings available on the subject with an intent to draw conclusions and define better child rearing practices and provides scope for further study. The study also identifies gaps in the literature and makes recommendations for future research directions and policy domains to enhance prenatal health outcomes, especially in low-resource environments. The research highlights the significance of early intervention and supportive care in reducing the negative effects of prenatal stress on future generations by incorporating insights from many studies.

Keywords. Transgenerational inheritance, perinatal stress, maternal stress, fetal health, mental health

INTRODUCTION

WHO defines perinatal period as the duration extending between the attainment of viability by foetus (i.e. a gestational weight of 1000g) at 28 weeks to completion of seven days of neonatal life, although the maternal and childcare program is initiated with the first antenatal visit much before viability is attained. WHO proposed prenatal and antenatal care in its first and second targets in the 13-point goal 3 in the sustainable development goal 2030.

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Perinatal Stress - Disease Model

In view of the hostile gestational and infant life conditions it can be deduced that survival of such an infant does not confer an immunity to long term chronic diseases in adulthood. The phenomenon was first explained in the early 1900s by Dr. David Barker, in the form of inherent memories of early life stressors manifested as diseases in adult life (Barker et al. 1993) [1]. He believed that perinatal plasticity arising from diverse environmental influences can lead to foetal growth restrictions. He proposed Foetal Origins of Adult Disease (FOAD), a concept highlighting that sensitive developmental

periods in foetal growth affected by environmental exposure can give rise to mutated or altered phenotypic expression, at times disobeying the original genetic code. The concept of epigenetic variation giving rise to transgenerational inheritance of phenotypic responses to stress was hence coined. The changes accumulated over generations get imprinted in a phenomenon of Genotypic Programming and form the basis of this transgenerational inheritance (Figure 1). Dr. David Barker further extended the hypothesis to the Developmental Origin of Health and Disease (DoHaD) that specified a critical developmental period of 1000 days (Conception to 2 yrs of life).

For any given individual,

$$p(complex\ disease) = f[exposure\ to\ risk\ factor\ X\ Susceptibility]$$
$$susceptibility = f[structure\ and\ function\ of\ physiological\ system]$$
$$structure\ and\ function\ of\ physiological\ systems = f[genes\ X\ early\ environment]$$

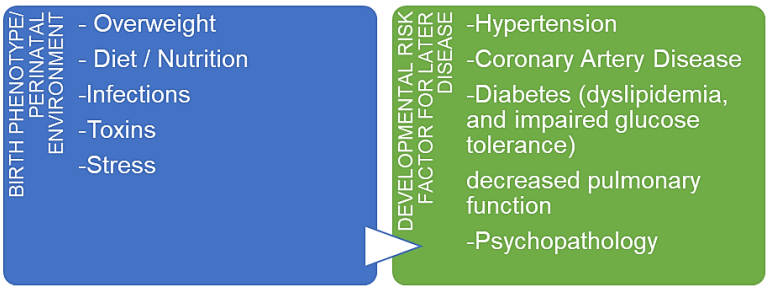

Figure 1. Flow chart explaining the relationship between perinatal (and antenatal events) and disease susceptibility in adulthood.

Factors Affecting Foetal Preprogramming

- Type of Stressor
- Gestational age at exposure
- Duration of Exposure
- Organ impacted
- Humoural factors

Ex: Maternal Nicotine intake is responsible for teratogenic exposure to conceptus. Nicotine induced stimulation of Acetylcholine Receptor (nAchR) leads to its upregulation halting the normal neurotrophic function of Ach in foetal development. This disrupts the preset timeline of normal programming causing abnormal brain development and associated future complications. Abnormal expression leads to untimely apoptosis of neurons in critical locations such as the hippocampus progenitor neuron, dentate gyrus and olfactory bulb. Subsequent gliosis leads to reduction in brain mass, cortical thickness and cell size (Figure 2).

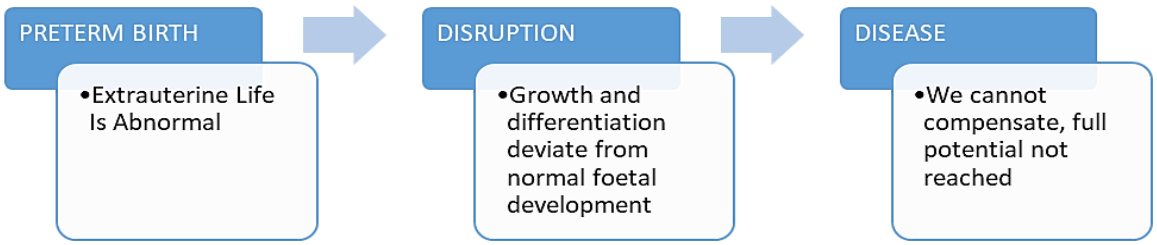

Figure 2. Flowchart explaining the progression of disease starting from an in-utero abnormality.

THE EFFECT OF STRESS ON VITAL PROCESSES

Placenta - Organ of Foetal Origin

The placental tissue not only acts as a nutritional support but is also an effector organ mediating the release of biological signals into the maternal compartment. It thus not only functions as the feeder

but also plays a vital role in cross-communication between mother and foetus. The maternal stress is often reflected in the foetus. This is mediated via the stress hormone - cortisol and limited by 11-beta-hydroxysteroid dehydrogenase type 2 (11b-HSD2) enzyme. Norepinephrine mediated placental vasoconstriction causes uteroplacental insufficiency in stress further causing hypoxia to the foetus (Figure 3).

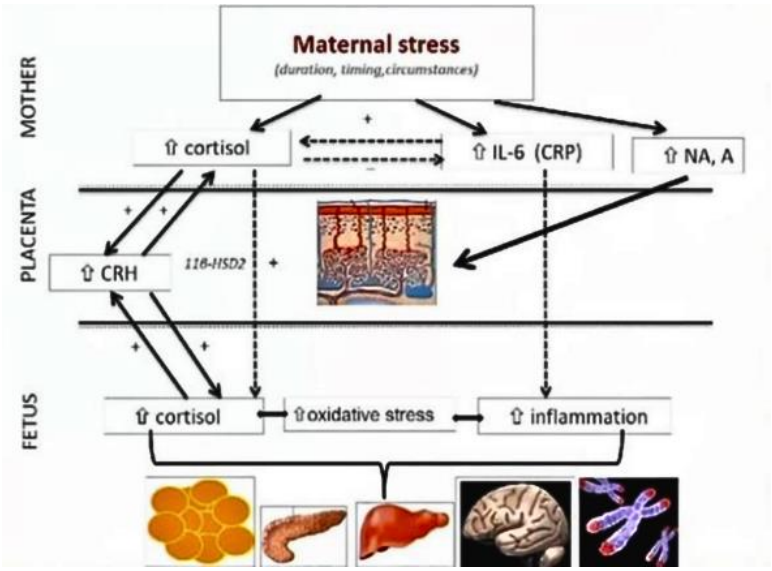

Figure 3. Explains the role of placenta in the mediation of foetal structural modifications in response to maternal stress.

Neonatal Cerebral Development

Neonatal hypoxic-ischemic encephalopathy (HIE) accounts for a large percentage of morbidity and mortality in newborns. Structural, physiological and humoural alterations are key mediators in the brain's response to the stressful event. The brain's cerebral cortex, hippocampal formation, and subventricular zone are the three areas most susceptible to hypoxia damage and subsequent impairments.

Cardiopulmonary Development and Remodelling

Fetal cardiac remodeling and increased vulnerability to ischemia and reperfusion injury in offspring are caused by gestational hypoxia.

Circulatory Factors

Increased foetal cortisol levels caused by a hypoxia-induced inhibition enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11b-HSD2) present in placenta leads to an increased foetal exposure to stress hormones i.e. cortisol hormone crossing placental barrier along with proinflammatory cytokines causing inflammatory processes within the foetal compartment . Stress associated with release of epinephrine and norepinephrine leading to vasoconstriction of placenta can induce hypoxic conditions detrimental to foetal brain development. Glucocorticoids play an essential role in normal maturation of various vital organs, especially lungs. Incessant exposure to glucocorticoids may cause derangement from normal developmental trajectory and reprogramming the vulnerability in later pathophysiology. Its role in initiation of terminal maturation to remodelling of axon and dendrite growth to cell survival is vital (Figure 4).

HPA - Axis

Exposure to glucocorticoids in-vivo or iatrogenic leads to higher levels in the foetus, causing down-regulation of GR and up regulation of HPA axis activity due to lack of negative feedback. The culmination of these alterations results in increased glucocorticoid exposure causing behavioural,

cognitive, emotional dissonance leading to multiple cardiovascular and metabolic syndromes in adulthood (Figure 5).

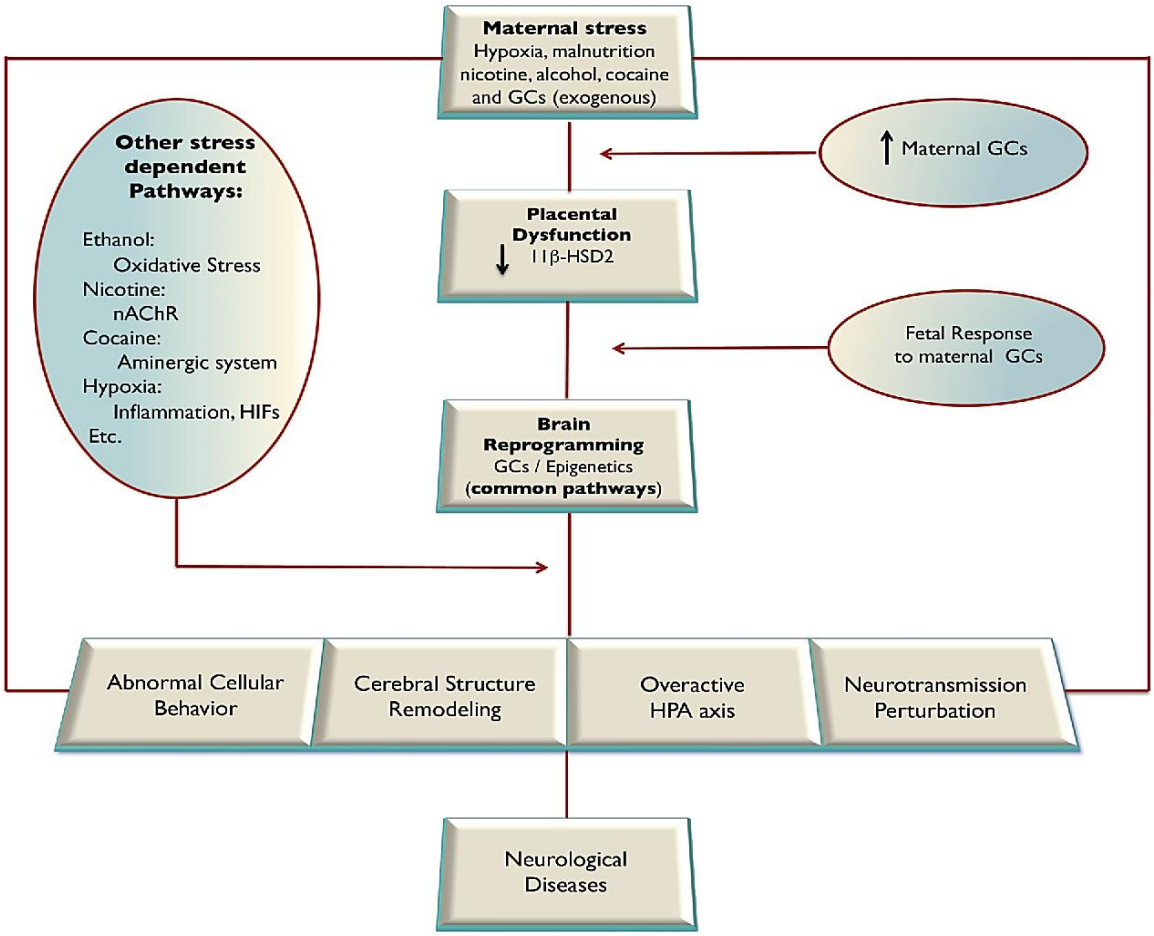

Figure 4. Explains the pathways of maternal stress leading to foetal neural reprogramming.

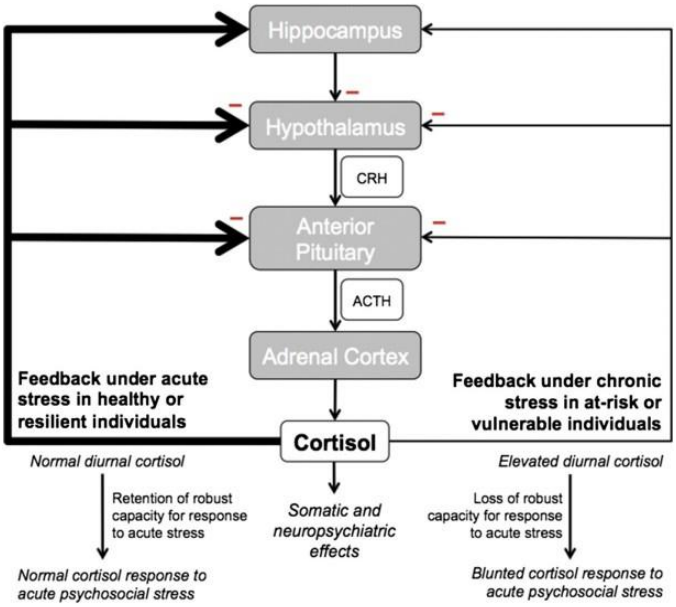

Figure 5. The Hypothalamic-Pituitary-Adrenal (HPA) axis, its feedback mechanisms, and the impact of stress on these processes.

MATERNAL MALNUTRITION

Malnutrition including both overnutrition (calorie, fat and protein rich) and undernutrition (diet deficient in all proximate principles and vitamins) leads to foetal susceptibility in altered body habitus in adult life. Epigenetic alterations in glucocorticoid receptor expression and hypothalamic genetic changes in proopiomelanocortin (POMC) gene expression is responsible for increased foetal vulnerability to obesity in adulthood. Undernutrition influences myelinogenesis and neural development (particularly vita B12 and Folic acid deficiencies) leading to altered sensorimotor functions in view of structural alterations in the brain (Figure 6).

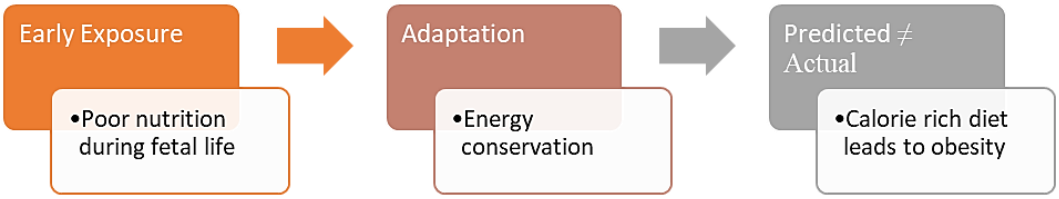

Figure 6. The flowchart explains the predisposition to obesity in certain newborns due to poor maternal nutrition in the antenatal period.

Malnutrition is associated with selective atrophy of hippocampal neurons and global nutrient deficiency (esp. reduced choline levels) affects neonatal development and is associated with intellectual disability and delayed milestones. Overnutrition on the other hand also alters brain anatomy. Evidence suggests increased hypothalamic neurogenesis, hippocampal remodelling and decreased cell death and neural differentiation in dentate gyrus in young adult offspring occurs on administration of lipid rich diet in mice.

Teratogenic Conceptus

Teratogens are substances that cause abortive or defective transformation in embryological development primarily during the period of first 16 weeks of gestation. Exposure to various pharmacological drugs and substances namely, lithium, valproate, thalidomide, nicotine alcohol, cocaine etc. have long term deleterious consequences during postnatal life. Recreational substances have been included in the current review.

Methodology

Aim: The study aims to review and compile the existing clinical literature available on the effects of trauma on immediate offsprings and its transgenerational inheritance.

Objectives: The study aims to provide a comprehensive systematic review of contemporary literature on the topic of impact of traumatic events on an offspring not directly exposed to a specific stressor. The research intends to highlight the current statistical data on perinatal care globally especially in India keeping in view the directives laid down by the United Nations Sustainable Development Goals 2030.

Research Design and setting: This study is a systematic review with data compiled from an online, in-depth search of various databases for keywords like “transgenerational inheritance”, “perinatal stress” and “maternal stress”. Various articles were reviewed regarding content pertaining to prenatal trauma, teratogenicity, and drug toxicity to select a final selection of research literature used for the study.

Procedure: In depth search was conducted on google scholar and Pubmed database using keywords “transgenerational inheritance”, “perinatal stress” and “maternal stress”. A total of 120 articles published in the year 2001-2023 were screened for the information about prenatal trauma, teratogenicity, and drug toxicity and a final set of 35 articles was obtained to be included in this review. Additionally, the thorough screening on youtube for recorded lecture material was done. Lastly information pertaining to UN SDG 2030 was obtained from the WHO website and information

regarding government policies of Indian origin was obtained from the National Health Mission website of Government of India. Following selection of the research articles, the information collectedwas summarised and tabulated to provide a summary of the current understanding of human and animal evidence available in the field.

REVIEW OF LITERATURE

Brain injury results from fetal hypoxic ischemia, a condition marked by a restricted oxygen flow to the brain. Micronutrients and essential nutrition play a critical role in growth. Exposure to teratogenic agents results in structural and metabolic alterations that are frequently irreversible.

Foetal Hypoxia-Ischemia

Afflicted Organ	Immediate Effect	Adult Implication
Cerebral cortex, hippocampus (most susceptible) and sub ventricular zone	Decreased myelin and axon expression of structural proteins of the white matter and acounter-increase in the glial cell. The Hippocampal cells include sub-region cytosolic PLA2(cPLA2) and CA1associated apoptosis.	Neurodevelopmental disorders put a person at risk for abnormalities in white matter in later life.
Foetal heart	Foetal heart remodelling increases heart susceptibility to ischemia and reperfusion injury in offspring. Hyper-reninism and associated release of Angiotensin and Aldosterone causes cardiac and pulmonary vascular remodelling. Stress associated continuous rise in RAS pathway mediators.	Pulmonary hypertension in newborns. Predisposition of neonatal heart to cardiomyopathies.
Lung	raise the mRNA expression in the lung, heart, and brain as well as the protein levels of interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-a) in the sera of fetal guinea pigs. Dong Y 2009 [2]	
Placenta	Increased foetal cortisol levels caused by a hypoxia-induced inhibition enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11b-HSD2) present in placenta.	Increased Stress hormone exposure

Nutrition

Afflicted Organ	Immediate Effect	Adult Implication
Metabolism	Changes in the epigenetics of the hypothalamus genes encoding proopiomelanocortin and the glucocorticoid receptor (Stevens et al. 2010) [3]	Obesity susceptibility due to changed GR expression, POMC, and Neuropeptide Y binding, which in turn affects how food intake, energy expenditure, and glucose homeostasis are regulated in later life
Brain: hippocampus	Major and minor cranial components hypertrophied, and sensorimotor function was affected. Malnutrition and hippocampal shrinkage are related in CA2, CA4, and DG but not in CA1 and CA3. (Florian et al. 2011) [4]. Maternal choline insufficiency during pregnancy not only reduces maternal nutrition intake globally but also modifies neurogenesis and angiogenesis in the developing fetal hippocampal regions.	
	Increased proliferation of neural progenitor cells in the hypothalamus of the fetus and newborn. Affected embryonic hippocampal development is indicated by changes in the proliferation of neural progenitors, decreased apoptosis, and modified neuronal differentiation inside the dentate gyrus.	reduced dentate gyrus neurogenesis in young adult offspring

Teratogens

Afflicted organ	Immediate Effect	Long term Implications
Nicotine	Anorexia in mothers and vasoconstriction due to catecholamine release causing chronic placental insufficiency. Motor and sensory deficits increased chance of cognitive, attention, and learning deficiencies, conduct disorder (CD), attention-deficit/hyperactivity disorder (ADHD), and drug dependence.	Poor nutrition status in Foetus. Increased externalised behaviour (such as oppositional, aggressive, overactive). Hyperactivity, reduced brain cell survival, abnormal synaptogenesis, increased anxiety, sensorial and cognitive dysfunction, neurochemical imbalance, and nicotine self-administration.
Cocaine	Cocaine inhibits monoamine uptake, causing disruption in autonomic function and aberrant neurotransmitter. Intense vasoconstriction and maternal vascular compromise, causing foetal hypoxia/ischemia and/or malnutrition. microcephaly, cerebral malformation, focal hypoxic/ischemic or intraventricular haemorrhage damage and perturbation of cerebral cytoarchitecture.	cognitive deficiencies at school age, such as impulsivity, aggressive behavior, weak resistance to distractions, and trouble focusing. Your IQ can fall within the usual range. Increased susceptibility to anxiety, depression, sleep disturbances, feeding difficulties, quadriparesis and seizure.
Alcohol (Foetal Alcohol Syndrome)	Pre and postnatal growth retardation and delayed neurological development.	Difficulty making friends, vulnerability, poor academic performance, increased aggression

Glucocorticoid Exposure

Afflicted organ	Immediate Effect	Adult Implications
Placenta	Maternal stress, psychosocial or harmful environmental factors lead to glucocorticoid release or disrupt the uteroplacental barrier, such as 11b-HSD2.	increased risk of hypertension, coronary heart disease, obesity, hyperlipidaemia, insulin resistance, type2 diabetes, stroke in adulthood
Brain	Anatomical alterations in hippocampus, amygdala, lateral septal nuclei and some other cortical areas.	
HPA axis hypothalamic-pituitary - adrenal	Prolonged elevations disrupt the equilibrium of neurotransmitters and synaptic plasticity, hinder fetal development, and reset the sensitivity of the HPA axis. Increased sensitivity to the HPA axis results in a better reaction to stress and challenges.	Contribute to aberrant neurodevelopment and the brain's increased susceptibility to illnesses in the postnatal period, such as affective disorders and cardiometabolic diseases.
		Correlated with learning disabilities or lower IQ, antisocial conduct, increased susceptibility to anxiety disorders, attention deficit/hyperactivity disorder (ADHD), schizophrenia, and behaviors suggestive of depression

DISCUSSION

The current article is a systematic review of the scientific evidence surrounding the epigenetic transmission of stress and the central role of maternal, foetal factors and biochemical mediators in the vertical transmission of traits. The inference from contemporary literature reveals that inflictions during intrauterine and early postnatal life “pave the way” for later processes in future ages with respect to the predisposition towards age related disorders While the scientific community is pondering over elements like the magnitude, duration of exposure and clinical significance to precisely determine the impact associated with the etiological agent, there remains to be a major lacuna in the following:

1. Most research is centred around animal models due to the ethical limitations

2. Longitudinal studies on the subject matter remain non-feasible due to resource constraints

It was found that foetal hypoxia lead to ischemia which decreased myelin and axon activity in white matter and an increased glial cell mass in cerebral cortex and subventricular zone (Wang et al. 2010) [5] along with PLA2 and CA1 associated hippocampal cell apoptosis (Arai et al. 2001) [6] leading to white matter dystrophies in adult life. Hypoxia leads to foetal cardiovascular remodelling, increased susceptibility to ischemia and increased incidence of persistent pulmonary hypertension of newborn. Associated RAS activation causes vascular remodelling in stress (Goyal et al. 2010) [7]. Increased foetal cortisol levels caused by a hypoxia-induced inhibition enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11b-HSD2) present in placenta leading to hypoxic changes preterm birth and exaggerated stress response in offsprings (Homan et al. 2006) [8].

Atrophy in the dentate gyrus of the hippocampal regions (CA2, CA4, and DG) is associated with malnutrition, but not with CA1 and CA3. Maternal choline deficit during pregnancy not only reduces maternal nutrition intake globally but also modifies neurogenesis and angiogenesis in the fetus's hippocampal region, as well as sensorimotor functions.

Exposure to teratogenic substances like nicotine leads to a plethora of side effects including decreased nutrition and anorexia in mothers, vasoconstriction (due to catecholamine release leading to chronic placental insufficiency), motor and sensory deficits and an increased risk of neuropsychiatric illnesses like attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD), and the risk for developing drug dependence (Eppolito et al. 2006) [9]. Poor nutrition status in offspring, increased externalized behavior (oppositional, aggressive, overactive, and hyperactive), hyperactivity, cognitive and somatosensory impairment, heightened anxiety, neurochemical imbalance, nicotine self-administration, decreased neural cell survival, and aberrant synaptogenesis are some ways in which this presents itself in adulthood. Contrarily, cocaine inhibits the uptake of monoamines, which results in abnormal neurotransmitter production, severe vasoconstriction, and maternal vascular impairment, which can lead to fetal hypoxia/ischemia and/or malnutrition. Numerous harmful fetal problems follow, including disruption of the brain cytoarchitecture, localized hypoxic/ischemic or intraventricular hemorrhage damage, and microcephaly. It has also been discovered that cocaine usage during pregnancy is linked to a number of cognitive deficiencies in school-age children, such as impulsivity, aggressive behavior, weak resistance to distractions, and trouble concentrating. (Ackerman et al., 2010; Richardson et al., 2011) [10,11]. Cocaine also increases the susceptibility of the offspring to anxiety, depression, sleep disturbances, feeding difficulties, quadriparesis and seizure. Alcohol consumption beyond the safe limit in pregnancy (Foetal Alcohol Syndrome) leads to pre and postnatal growth retardation and delayed neurological development resulting in a difficulty making friends, vulnerability, poor academic performance, increased aggression.

CONCLUSION

The current research data on transgenerational inheritance of stress induced phenotype focuses primarily on neuro endocrine alteration causing changes in body habitus. The role of glucocorticoids has assumed a central importance among other mediators like cytokines, angiotensin, acetylcholine, nicotine etc. This research has consolidated contemporary evidence in association to perinatal preprogramming and developmental plasticity. It further opened avenues extending into other fields such as perinatal care, neuropsychiatry, anthropology, genetics and allied research disciplines. One shortcoming, however, is the limited availability of human-foetal evidence due to violation of ethical principle. A second shortcoming is the lack of numerical evidence. As a psychologist we can utilise this newfound understanding of the mismatch theory to disseminate the information regarding the deleterious role of stress as well as the government initiative to counter it, amongst the masses through the existing Anganwadi system. The colloquial saying that a mother does not forget her treatment during pregnancy extends further as not just her but her children also are a carrier of biomarkers of stress

transforming their phenotype and the phenotype of successive generations. Apart from nutrition, and teratogen exposure, the well-researched role of management of stress and the role of psychological counselling has acquired importance and it has become essential to equip the upcoming psychologist with the understanding of perinatal counselling by means of a meticulously designed curriculum.

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