



WESTERN NIGERIA JOURNAL OF MEDICAL SCIENCES (WNJMS)

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FOR HEALTH IN ADULT LIFE**

IN UTERO EPIGENETIC IMPACTS OF MATERNAL NUTRITION, LIFESTYLE AND ENVIRONMENTAL FACTORS AND THEIR IMPLICATIONS FOR HEALTH IN ADULT LIFE

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ABSTRACT

The understanding of how gene and the environment interact in controlling disease can now be expanded to include epigenetic reprogramming, which is a key determinant of origins of human disease and development. Epigenetics is defined as heritable changes in gene expression that do not alter DNA sequence but are mitotically and trans-generationally inheritable. Epigenetic reprogramming is the process by which an organism's genotype interacts with the environment to produce its phenotype. This provides a framework for explaining individual variations and the uniqueness of cells, tissues, or organs despite identical genetic information. The main epigenetic mediators are DNA methylation, histone modification, and non-coding RNAs that regulate crucial cellular functions, and occur during human gametogenesis and early embryonic development along the germ line. Deficiencies in remodeling this epigenome can cause severe developmental defects, infertility, and long-term health issues in offspring. Parental diets, unhealthy parental habits and environmental factors such as exercise, social interaction and climate change may disturb the epigenetic reprogramming processes leading to an aberrant epigenome in the offspring. Here, we review the effects of parental environmental exposures on the epigenetics of gametes and the early embryo, and how those changes

influence transgenerational inheritance in humans and rats.

Keywords: Intrauterine Epigenetics, Epigenetic Reprogramming, Gametogenesis, Diet, Environment

INTRODUCTION

In the past, susceptibility to disease development was believed to be determined solely by inheritable information carried on the primary sequence of the DNA. Individuals are endowed with different genotypes that dictate how they respond to endogenous factors such as development cues, hormones, and cytokines or to exogenous influences, including nutrient availability, infection, physical activities, social behavior, and other environmental factors. Over time, these responses form the basis of genetic variability to disease susceptibility and aberrant changes in the linear DNA sequence result in mutations, deletions, gene fusion, tandem duplications, or gene amplifications causing dysregulation of gene expression that underlies the genesis of disease.¹

Epigenetics, coined by Conrad H. Waddington, a developmental biologist, encompasses heritable mechanisms of modulating gene expression that do not alter DNA sequence.² The three main mechanisms associated with epigenetic silencing of genes are DNA methylation, RNA associated

silencing and histone modification.³ Epigenetic modifications are mitotically and trans generationally inheritable.⁴ Its changes drive early embryonic and later stages of development through molecular mechanism, transcriptional process, influences on possible outcomes on cellular differentiation patterns in early life and throughout adulthood.⁵ Growing evidence supports the idea that proper epigenetic reprogramming is essential for gametogenesis and early embryo development.⁶

Current knowledge about early mammalian development has been studied from mice due to easy accessibility and fast breeding and importantly, because using mice involves fewer ethical issues. However, due to species-specific differences, such as developmental timing and cell lineage specifications, findings from experiments with mice cannot be directly extrapolated to human embryos.⁷ Scarcity of human embryo, technical limitations and restriction by ethical issues have hindered early work on human embryo development which focuses on embryo morphology, identifying factors that can improve in vitro culture, and profiling the expression of a few specific genes and proteins. Overtime, there have been development and implementation of low-input and single cell sequencing that have enabled researchers to profile the transcriptomes, DNA methylome, and chromatin accessibility of human gametes and early embryos in single cells with single-based resolution⁸ paving the way for dissection of the molecular regulation of human embryo development.

Reprogramming that is said to occur during gametogenesis and preimplantation is to ensure every generation receives the appropriate sex-specific imprint; of the genome undergoing reprogramming.⁹ However, studies have overtime uncovered when and how DNA methylation pattern occurs in germ line and the relevance of maintaining these patterns in early embryo. The role of some environmental contaminants in disease causation and development has also been identified. For instance, pesticides, cosmetics, thermal receipt papers are

examples of endocrine disrupting chemicals that humans are frequently exposed to in the environment that can alter the physiology and increase susceptibility to health issues such as cancer and obesity during development.¹⁰ Additionally, studies have shown that litters that are maternally exposed to epigenome-modifying chemicals such as bisphenol A used in making plastic products tend to have unhealthy phenotype and are prone to developing cancer.¹¹ Although, research has been concentrated on mouse model, relevant tools have also been developed to examine other species. This review focuses mainly on recent development in epigenetic dynamics in human and mice gametogenesis and early embryo development. The possible role of diet, life style and environment on fetal development is equally briefly discussed.

Epigenome during gametogenesis and early embryos

The epigenome coordinates the integration of instructions encoded within the genome with all the molecular and chemical constituents of cellular, extracellular and environmental origin. This, in conjunction with the genome, determines the unique gene expression of each cell to be identified during development or disease.¹² Global epigenetic reprogramming occurs during germ line development and early embryo development in mammals⁶ and the two most identified epigenetic mechanisms playing adaptive roles in developmental programming are: DNA methylation¹³ and histone modifications.¹⁴ DNA methylation is a covalent modification in which methyl groups are added to cytosine bases located at the 5' of guanosine (within cytosine-phospho-guanine (CpG) dinucleotide sequences) and is catalyzed by the DNA cytosine-5-methyltransferase (DNA-MTase) enzyme family and accessory proteins namely Dnmt1, Dnmt3a, Dnmt 3b, Dnmt2, and Dnmt 3L. This modification induces changes in chromatin structure and is generally associated with silencing of gene expression, thus providing a way to control gene expression.¹⁵

Diverse post-translational modifications also occur at amino termini of histone with

transcriptional activities being highly correlated with acetylation and methylation of lysine residues in the amino termini of histones H3 and H4.¹⁶ Histone acetylation is linked with transcriptional activation due to its lower affinity for DNA, which allows the relaxation of the chromatin. Conversely, deacetylation of histone corresponds with transcriptional silencing and the heterochromatic state. In addition to histone acetylation, methylation of histone H3 lysine 9 (H3 Lys9) correlates with a repressed state and heterochromatin assembly. Each lysine residue may be methylated in the form of mono-, di-, or trimethylation, adding to the complexity of the “histone code” and these modifications make up another important group of gene expression regulators.¹⁶ Non-coding RNAs are a heterogeneous group of RNA that do not encode proteins but play a role in gene silencing in biological, cellular and pathological processes making them the third epigenetic mechanism of gene regulation, hence their designation as either regulatory or housekeeping RNA.¹⁷

Epigenome during primordial germ cell development

Germ cell development begins with specification of primordial germ cells (PGCs) at the peri-gastrulation embryo stage at 2nd and 3rd week. Primordial germ cells are the precursors of sperm and oocytes which migrate from the yolk sac wall to the hind gut endoderm and finally to the developing gonads during embryogenesis in the fourth week. They proliferate rapidly during the migration stage and proceed on different path to differentiate into the sperm and oocytes after sex determination. The female gonadal primordial germ cells in the tenth week of development enter meiotic arrest in prophase I and remain quiescent in the developing gonad until puberty is reached.

The male gonadal primordial germ cells enter mitotic quiescence at this period but do not go on to meiosis until puberty. DNA demethylation in primordial germ cells takes place within the fourth- and seventh-weeks during embryogenesis.¹⁸ This is due to the

migratory primordial germ cells in the hind gut having a lower level of DNA methylation compared to adjacent somatic cells.¹⁹ The lowest level and the point at which methylation occurs among species vary, which might be due to different procedure. However, DNA demethylation dynamics in mouse primordial germ cell at embryonic days 10.5- 13.5 and those in human primordial germ cell during development between weeks 5-19 are consistent across literature.^{18, 19} The global clearance of DNA methylation observed in human PGCs leads to a great loss of DNA methylation in various regions, including CpG islands, transcription start sites, gene bodies, intergenic regions, repeats, and even most imprinting regions, which leads to the levels of DNA methylation in PGCs being the lowest among all the known human methylome.¹⁹ In the male gonocytes, a rapid increase of methylation is initiated during embryo development, and the methylome of male germ cells is fully established before birth.²⁰

In female germ cells, DNA methylation is re-established during the postnatal oocyte growth phase and is dependent on the functional interaction of the DNA methyltransferase Dnmt3a and the Dnmt3-like protein (Dnmt3L).¹⁸ DNA *de novo* methylation is completed when oocytes reach the germinal vesicle stage.²¹ After a period of intense activity during oocyte growth, transcription is ceased when the oocyte becomes arrested at the prophase of meiosis I, and this arrest is released after a preovulatory hormonal surge of gonadotropins.²²

Epigenome during Spermatogenesis and Oogenesis

Spermatogenesis

The gonadal germ cell undergoes spermatogenesis in male embryo to produce the male gamete and DNA methylation and histone modification brings about significant change during spermatogenesis. As earlier noted, a methyl group is added to the 5 carbon of pyrimidine ring of cytosine nucleotide found within the CpG Island.²³ This process is under the influence of DNA

methyltransferase (DNMT) enzymes that facilitate the movement of one methyl group from S-adenosyl methionine to cytosine.²⁴ Research has demonstrated a higher degree of methylation in sperm genome.²⁵ Histones are proteins located in the nuclei of eukaryotic cells packing DNA within lysosomes and their isomer proteins (H2A, H2B, H3 and H4) are located within the nucleosome binding to one another by H1 histone protein.²⁶

Epigenetic modification of histone protein is achieved through acetylation and acetylation of the histone subunits H3 and H4 facilitates chromatin configuration which is required for normal meiotic process and maturation of gamete.²⁷ This facilitates developmental changes in gamete and chromatin remodeling,²⁸ and results in the reorganization of the genome during post meiotic maturation of male germ cells and spermatids. Inheritance of somatic-like chromatin is based on these genomic organizations. Testis-specific basic proteins such as transition proteins and protamines replace histones during the maturation stage associated with nuclear DNA in the spermatozoa. They are responsible for the DNA being packaged in a very compact manner.²⁹ In human and mice, two protamines, Prm 1 and Prm 2 have been found in the sperm nuclei, where they play important roles in sperm function.³⁰ Haploinsufficiency resulting from targeted disruption of either allele of both *Prm 1* and *Prm 2* has led to a reduced amount of the respective protein, and also prevent genetic transmission of both mutant and wild type alleles.³⁰ Additionally, a direct link between haploinsufficiency of Prm 2 and spermatozoa with DNA damage and a reduced compaction of chromatin has also been demonstrated using single-celled DNA electrophoresis and ultrastructural analysis.³¹

Until recently, RNA in sperm is believed to be carryover or contamination from other cells. However, there is now a growing evidence suggesting RNA to be important in the various stages of spermatogenesis and epigenetic inheritance.³² It is noteworthy also that sperm transcriptomes are not the same in fertile and infertile males.³³ Small RNAs that

are differentially expressed between highly motile and less motile sperm depends on apoptosis and spermatogenesis alteration.³⁴ Aside the differentially expressed RNA, modification of these RNAs is also necessary for male fertility and epigenetic inheritance. For example, the inactivation of the N6-methyladenine RNA methyltransferase gene *Mettl3* or *Mettl4* by germ cells result in the loss of N6-methyladenine, a factor that has been implicated in the impairment of normal spermatogenesis.³²

Oogenesis

The formation of germ cells starts in the second week of post-fertilization called primordial germ cells.³⁵ Primordial germ cells produced by the female germ cells undergo mitosis to form oogonia and during subsequent oogenesis to become primary oocytes. These primordial germ cells migrate *in utero* into future ovary that undergo repeated mitotic cycles to form nests of germ cells.³⁶ In the female germ cells, DNA methylation is reproduced during the postnatal oocyte growth phase which is dependent on the functional interaction of the DNA methyltransferase Dnmt3a and Dnmt3-like protein (Dnmt3L).³⁷ *De novo* DNA methylation is completed when oocytes reach the germinal vesicle stage.²¹

During oocyte growth, transcription is ceased after a period of intense activity when oocytes become arrested at prophase of meiosis I, there is release of this arrest as a result of preovulatory hormonal surge of gonadotropins.²² The meiotic arrest is to possibly prevent oocytes from oxidative stress and DNA damage.³⁸ Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) are needed by these oocytes to finish meiosis I and go through meiosis II. Female germ cells remain hypomethylated after global DNA demethylation in early primordial germ cells maintaining meiotic arrest throughout the rest of embryonic development. Follicular growth is accompanied by the establishment of DNA methylation in oocytes which is largely completed at the germinal vesicle stage in mice. DNA methylation is highly enriched in the oocyte genome at the transcribed gene

bodies with absence of methylation at the intergenic regions and non-transcribing gene bodies resulting to a methylated domain.³⁹

Research in mice indicates that Dnmt3A and its cofactors are important in the reestablishment of DNA methylation in oocytes and the depletion of these enzymes results in global reduction in both CpG and non-CpG methylation in oocytes.⁴⁰ The functional role of DNA methylation in oocytes has not been elucidated. However, loss of DNA methylation in oocytes has been proven to be detrimental to its growth, maturation and fertilization in which embryos conceived from these oocytes die at 10.5 of embryonic day majorly due to deficiency of methylation at maternally imprinted regions.⁴¹ The reestablishment of imprints in females however begins considerably later after completion of meiosis I in the post embryonic phase.⁴² The establishment of imprinting in gametes is mediated by *de novo* methyltransferase in which Dnmt3A and Dnmt3L are the major gene for both sexes.⁴³ Disruption of this gene (Dnmt3L) was found to cause premature death of embryo in female and azoospermia in male.⁴²

Aside global *de novo* methylation, different histone modifications have been discovered during mouse oocyte maturation. Also, there is gradual increase in H3K9 acetylation as the oocytes grows, with chromatin histones undergoing widespread deacetylation during oocyte meiotic maturation.⁴⁴ Oocytes maturation can be blocked due to the deletion of the histone deacetylase genes *HDAC1* and *HDAC2* resulting to a decrease in overall transcriptional activity.⁴⁵ It has been noted also that the development of abnormal spindles in mouse oocytes is caused by knocking down mixed lineage leukemia (*MLL2*) gene that encodes the methyltransferase enzyme of H3K4, even though the affected oocytes can still grow to full size through meiosis.⁴⁶ It follows therefore that histone modification is crucial for oocyte maturation, and that the disruption of such modification may lead to defective chromosome condensation, segregation,

delayed maturation progression and even oocyte aging.

Epigenome during Early Embryo Development

Parental DNA is subjected to rapid and extensive demethylation during early embryogenesis (between fertilization and implantation), and subsequently resetting epigenetic information inherited from gametes in the preimplantation embryos.⁴⁷ A sharp decrease of DNA methylation occurs between fertilization and the two-cell stage in human embryos but the decrease of maternal DNA methylation is milder in relation to the paternal genome with the enzyme involved yet to be identified.⁴⁸ Dnmt1o is responsible for maintaining methylation during preimplantation development, and studies have shown that offspring of mothers deficient in DNMT1o died during late gestation and exhibit expression abnormalities limited to imprinted genes.⁴⁹ Dnmt1o is a specific form of Dnmt1 that has been implicated as the enzyme involved in DNA methylation in the female germ cell, although an earlier gene knock-out experiment in mouse has indicated that it is not actually required for methylation pattern in oocytes.⁴⁹

There are three waves of global demethylation that occur during development of human preimplantation embryos: one is between 10-12 hours after fertilization, another one occurs from the late zygote stage to the four-cell stage and the last is from the eight-cell stage to the blastocyst stage.⁵⁰ Completion of genome demethylation occurs at the four-cell stage and coincides with the point at which DNA methylation is at its lowest level in the blastocyst stage. Genome demethylation process has been shown to accompany preimplantation development with recent studies demonstrating that the global DNA methylation reprogramming is a dynamic balance between strong genome-wide demethylation and local re-methylation process. Additionally, due to the absence of H3K27me3, changes in human embryonic development from the eight-cell stage to

blastocyst stage have been linked to histone modification.⁵¹

Role of Maternal Diet and Lifestyle in Disease Causation

Maternal diet

The role of nutrition among other environmental factors in the epigenetic modifications of some enzyme-catalyzed metabolic processes has been noted.³⁵ In rat models, for instance, high fat-containing diets have been linked with an increase in DNA methylation levels and epigenetic silencing, while exposure to alcohol (ethanol) results in significant alterations in DNA methylation.³⁵ Folate, choline and some members of the B vitamins serve as precursors for S-adenosyl methionine (SAM).⁵³ SAM is an important substrate used by DNA and histone methyltransferase in the one-carbon metabolism pathway of DNA, RNA and histone modification that is required for molecular biosynthesis and epigenetic control of gene expression.⁵³

Epidemiological studies have also shown that parental malnutrition can affect offspring later in life and may extend to the future generation.⁵⁴ David Barker, the British epidemiologist, in 1990 hypothesized that malnutrition during pregnancy is one of the important origins of early adult heart and metabolic disorders.⁵⁵ He further emphasized that the intrauterine environment permanently shapes body structure, function, metabolism, and the possibility of disease in adulthood.⁵⁵ With the concept of developmental origins of health and disease, Barker's hypothesis is now widely accepted through different studies.⁵⁶ Pregnant mothers during the Nazi imposition of food crises in the Netherlands in 1944, known as Dutch hunger winter, had children with a broader range of health problems as adults which includes type II diabetes, obesity, cancer, cardiovascular diseases and schizophrenia⁵⁷ that may be linked to epigenetic changes *in utero*.

Maternal lifestyle

Maternal smoking in pregnancy remains a serious issue that gravely affects child health.

Fetal exposure to maternal smoking during pregnancy induces changes in DNA methylation of different tissues. The impact of prenatal exposure to tobacco smoke on DNA methylation was mostly analyzed in the cord blood and placenta of new borns.⁵⁸ It was discovered that maternal exposure to tobacco smoking results in a DNA methylation pattern that is associated with a low birth weight⁵⁹ and schizophrenia induction in adulthood.⁶⁰

Prenatal glucose levels also influence the risk of developing type II diabetes in later life, suggesting the presence of epigenetic memory that may persist in insulin/glucose target tissues.⁶¹ Furthermore, the development of obesity or type II diabetes is associated with glucose-induced, persistent changes in gene expression.⁶¹ Among the affected genes is glucose transporter 4 (GLUT4), which is a major glucose transporter in adipose tissue, and skeletal and cardiac muscles. With 3T3-L1 used as a cell model, it was discovered that both methylation of specific CpG sites and a methylation-sensitive transcription factor contribute to *GLUT4* gene regulation during pre-adipocytes to adipocytes differentiation.⁶¹ Maternal exposure to ethanol could result to aberrant DNA methylome regulation which can lead to potential health issues, such as postnatal growth restriction and craniofacial dysmorphology.⁶²

In in utero malnourished female offspring, oocytes meiotic competence is reduced, while expression of glucose transporters in ovaries and cumulus cells is affected at adulthood thereby compromising reproductive ability as observed in slower fertilization and cleavage rates as well as embryos with delayed development.⁶³ Stress is one of the environmental factors affecting human reproduction. Developmental problems in newborn emanating from physical and psychological health, the emotional wellbeing of the newborn in later life have been linked to preconception and frequency at which pregnancy is exposed to stress.⁶⁴ Infant mortality, and low birth weight have been implicated in maternal exposure to stress.⁶⁴ The increased DNA methylation of glucocorticoids receptor NR3C1 gene

promoter, which is linked to maternal stress through hypothalamic-pituitary-adrenal axis (HPA), has been indicated in human cord and new-born blood⁶⁵ Chronic maternal exposure to stress during pregnancy was accompanied by altered CpG methylation on glucocorticoids pathway genes in human placenta which indicates that placenta can be the main mediator between maternal and fetal stress.⁶⁶ Chronic prenatal exposure to stress has been shown to have negative impact on the overall health and development of the newborn.⁶⁷ In a study involving human subjects conducted in the Democratic Republic of Congo, chronic exposure to stress in the mother was found to be associated with epigenetic alterations in four key enzymes involved in the regulation of the HPA axis, namely *CRH*, *CRHBP*, *NR3C1*, and *FKBP5*.⁶⁷

Effects of Maternal diseases on Epigenetics

Studies have shown metabolic diseases to be the cause of abnormal intrauterine environment that resulting in epigenomic modifications in the fetus, while such modifications lead to metabolic disorders and diseases in adulthood. For instance, environmentally-mediated mutations in some genes may be transmitted to the next generation, resulting in the development of cancers. Insulin resistance in offsprings which is also a metabolic disorder have been linked with maternal obesity that can result to diabetes,⁶⁸ and may also affect vascular dysfunction resulting to cardiovascular diseases.⁶⁹ Maternal obesity has also been linked with altered mitochondria function and induction of epigenetic changes of mitochondrial DNA (mtDNA). For example, increased copy number, elevated expression of nuclear genes encoding mtDNA transcription factors *Tfam* and *Nrf1* have been detected in oocytes of obese mice.⁷⁰ In another study, maternal exposure to obesity-prone diets such as high-fat or high-sugar diet was linked to an elevated mtDNA content and increased expression of mtDNA biogenesis regulators *Tfam* and *Pgc-1a*, resulting in enhanced mitochondrial antioxidant defense, increased lipoxigenase expression, enhanced expression of transcriptional regulator *NF-B*,

and depletion of ovarian follicular reserve in female mouse offspring.⁷¹ Additionally, maternal dyslipidemia is reported to cause epigenetic change in placentas and fetal livers that may result in the accumulation of triacylglycerol in the fetal liver.⁷²

Environmental influence on epigenetics

Climate Change and Epigenetics

The process by which the environment affects a biological system forms the molecular basis involved in environmental epigenetics that have now been shown in all organism ranging from microbes to human. Environmental epigenetics explains how the environment impacts on the biology of any organism and therefore provides the molecular machinery for gene alteration and phenotypic variation in all organisms. Changes in these key environmental factors such as food availability, water availability and quality, air and temperature are due to climate changes which can bring about changes in epigenetics, physiology and phenotypes of all the organisms under examination. The resultant effects of such changes are passed on to subsequent generations through epigenetic transgenerational inheritance.⁷³

These environmental changes could be hazardous subsequently resulting to development of diseases,⁷⁴ that is passed down from one generation to another. Temperature is another environmental factor that can affect the epigenomic structure of the developing embryo, especially during incubation. For example, exposure of incubating wall lizard eggs to sub-critical temperatures results in significant alterations in gene expression.⁷⁵ In another study, a 1°C increase in incubation temperature of Pekin duck egg at critical stages of embryonic development, results in the up-regulation of DNMTs and embryonic stage specific enzyme activities of Dnmt 1 and Dnmt 3a within specific tissues, indicating the influence of temperature stress on epigenetic enzymes at stage specific development.⁷⁶

Effects of Exercise on Epigenetics

Exercise has been reported to be beneficial to health by ameliorating hypertension and decreases the incidence of proteinuria.⁷⁷ Physical exercise contributes to healthy cardiovascular and respiratory system.⁷⁸ There have been reports that exercise might bring about complications during pregnancy⁷⁹ but a recent study has shown that exercise actually has beneficial effects on both the mother and the fetus, provided it is adapted to the pre-pregnant medical history and fitness level of the pregnant woman.⁸⁰ Exercise as a potential epigenetic regulator results in the demethylation of gene promoter regions, CpG island and micro RNA thereby reducing mRNA expression in cardiovascular functions and by so doing restores the healthy homeostatic regulation of stress, cognitive and emotional status of an individual. Maternal exercise is reported to cause epigenetic changes in the *Atgr 1* alpha gene which enhances vascular function in offspring.⁸¹ Maternal exercise results in upregulation of some gene promoter methylation status with significant reduction in resting blood pressure and cardiovascular activity in subsequent generations.⁸²

Effects of Social Interactions on Epigenetics

Phenotypic diversity could be as a result of social experiences on biological processes which elucidate an inter play between the DNA and the environment. In humans, social interaction during infancy can have an impact on the developmental process of the child. A child that experiences neglect and other forms of child abuse may demonstrate severe cognitive and social deficit later in life.⁸³ The quality and frequency of parent-offspring interaction at postnatal period can be affected by stress, food availability and the environment in which the offspring is raised.^{84,85} The key element to the formation of strong child-to-mother attachment or relationship is parental sensitivity, and this has been found to determine sensitivity to stress and other negative effects among infants.⁸⁶ In humans, such impairments in attachment, resulting from different forms of disruptions in the parent-infant relationship,

have been linked to one form of personality disorder or the other later in life.⁸⁷

Most species engage in biparental or exclusive parental care of their offspring, and for a vast majority, it is through mother – infant interaction. The quality or otherwise of such early childhood interaction tends to have consequences both on their epigenetic (via DNA methylation and histone modification) as well as their phenotypic makeup in adolescence and adulthood.⁸⁸ For instance, chronic exposure to elevated levels of stress hormones (possibly arising from poor maternal child relationship) constitutes a major risk factor for the development of metabolic disorder such as obesity and insulin intolerance, and cardiovascular diseases such as hypertension later in life.⁸⁸ In rat models, differences in the frequency of some key maternal-infant behaviors or relationships such as nursing, licking or grooming of the offspring, have been shown to have strong correlation with how the offspring also behave and respond to stress when they become adults.^{88,89} Male rat offspring exposed to low frequency of licking/grooming tend to possess a higher hypothalamic- pituitary – adrenal responses to impaired cognition, stress and a reduction in hippocampal plasticity in adulthood⁹⁰ while their female counterparts on the other hand show decreased estrogen sensitivity in the medial preoptic area of the hypothalamus resulting to a reduced level of care to their offspring later in life.⁸⁹

In human, it was discovered that maternal separation facilitates increases in arginine vasopressin in the parvocellular neurons of the paraventricular hypothalamus and within the arginine vasopressin gene; four regions are rich in CpG Island that can control gene expression through DNA methylation. DNA methylation is greatly reduced in one of these regions (CGI3) at ages 6weeks, 3 months and a year among male offsprings experiencing maternal separation.⁹¹ Maternal abuse studied in rat in which offsprings were exposed to non-biological mother, there was a decrease in brain derived neurotrophic factor (BDNF), mRNA level within the prefrontal cortex at

adulthood in both male and female offspring which is also linked with increased CpG methylation⁹² Communally reared offsprings have increased hippocampal histone H3 acetylation at the BDNF 1, IV, VI and VII promoter regions⁹³ which leads to changes in neurobiology and behavioral outcomes⁸⁵ Taken together, it is clear that early childhood social experiences have strong influence on epigenetics that may alter how the infant develops physiologically, socially and psychologically. These changes tend to have strong implication for the development or otherwise of some chronic medical conditions in adult life.

CONCLUSION

The challenges of studying epigenomic regulation *in utero*, for example, during gametogenesis and embryogenesis in humans, have been largely hampered due to ethical issues, technical limitations and scarcity of human embryos. Overtime, these limitations have been overcome through advancement in genomic and epigenetic sequencing technologies. These developments have further broadened our understanding of epigenetic regulation in normal development in both humans and rat models, and will play a critical role in shaping fetal development and programming for future health outcomes.

Disease susceptibility due to environmental factors should be studied further and treatment tailored towards discovering molecular biomarkers that can be targeted in the prevention of epigenetic susceptibility from environmental hazards. In other words, there is a need for more studies to ensure better understanding of the complex interplay between diets, maternal health, early childhood social experiences and epigenetics, with a view to mitigating the impacts of these environmental factors on health.

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