Effect of Maternal and Paternal Nutrition on DNA Methylation in the Offspring: A Systematic Review of Human and Animal Studies

Abstract
Maternal or paternal diet may influence health throughout the life course. This is a systematic review of studies in humans and animals specifically investigating DNA methylation in progeny in relation to diet of the mother or father, or previous generations. There is an overview of the types of diet studied and the metabolic paths affected. Food deprivation in humans and animal models, studies on imprinted genes, hypothalamic pituitary adrenal axis and influence of paternal diet are discussed.

Keywords: Epigenetics; Diet; Health; Disease; Methylation

Abbreviations: CpG sites: Cytosine-Guanine Dinucleotides; Dnmt: DNA Methyltransferase; SAM: S-Adenosylmethionine; ICR: Imprinting Control Region; HPA: Hypothalamic-Pituitary-Adrenal; CRH: Corticotrophin Releasing Hormone

Introduction
Throughout our lives nutrition contributes strongly to our state of health and plays a role in the aetiology of many common diseases. The diet of our mother and father may also influence our life course, affecting our biochemistry during development at a fundamental level. The Barker hypothesis of the developmental origins of health and disease has highlighted the crucial role of prenatal life in influencing our future [1]. The effect of the pregnant mother’s diet on the foetus and life course of the adult has become of particular interest. There is an influence of environmental exposure in utero on the establishment of phenotype but relatively little is known of the mechanism by which in utero exposure causes a change. In the last decade, interest has grown in epigenetic mechanisms altering the DNA’s potential gene expression profile in a heritable way.

This review deals with the most highly characterized epigenetic modification, DNA methylation. The cytosine residue in DNA can be methylated to 5-methyl cytosine, catalysed by DNA methyltransferase enzymes (Dnmt). This occurs mainly at cytosine-guanine dinucleotides (CpG sites). Isolated CpG sites are usually methylated but at the promoter regions there is often a cluster of CpG sites, a CpG island, often unmethylated in promoter regions. Methylation of a CpG island may block access to DNA binding proteins such as transcription factors inhibiting gene expression. Interestingly, on replication of a DNA strand the pattern of methylation may be reproduced.

The donor of the methyl groups for DNA methylation is S-adenosylmethionine (SAM) which is derived from methionine [2]. Loss of the methyl group from SAM forms S-adenosylhomocysteine (SAH) and the plasma SAM: SAH ratio has been used as a marker of DNA methylation capacity. SAH is metabolised to homocysteine, and this is remethylated to methionine. Dietary components, folate, betaine, choline, and vitamin B12 are important cofactors and methyl group donors for this system.

It is epigenetic mechanisms that give each cell of the early embryo a distinct developmental fate. At two stages in development there is removal of the DNA methylation marks and de novo methylation, firstly following formation of the zygote from sperm and oocyte, and secondly days later in the primordial germ cells [3]. Environmental conditions around the time of conception or during gestation may reprogram the developing embryo to follow an altered future path by affecting the epigenetic mark of the genome. Changes in phenotype associated with in utero exposure to a change in nutrition may be heritable to the following generation.

Furthermore, there may be an influence of paternal circumstances, such as diet, on the progeny, in which case epigenetic marking of sperm DNA is postulated [4]. Some genes, many of which are important for foetal development, are imprinted [5]. In an imprinted gene only one allele is expressed depending on the parent of origin. The marker for parent of origin is epigenetic, DNA methylation playing a key role. The promoter region for an individual imprinted gene, or an imprinting control region, which may regulate expression for several imprinted genes, may be differentially methylated for each allele. DNA methylation of imprinted genes usually resists the global de-methylation of the early zygote, but may be reset in the de-methylation and de
novo methylation of the primordial germ cells. Periconception is thought to be a critical time in epigenetic programming and in re-establishment of imprinting in the primordial germ cells. Many researchers investigating the effect of parental nutrition on the offspring have looked in particular at imprinted genes.

Inclusion and exclusion criteria for review

This systematic review is of studies in humans and animals specifically investigating DNA methylation in progeny in relation to diet of the mother or father, or previous generations with the aim of providing a complete overview of the current research topics in the field.

The National Library of Medicine PubMed database was searched in two stages for published studies, firstly using the MeSH terms “nutrition disorders”, or “diet”, or “food” with the MeSH term “DNA methylation”, or using the keyword “nutrition” with the keyword “DNA methylation”. The results were then sorted by title and abstract to include studies on humans or animals investigating an effect of diet on DNA methylation, and then sorted using the abstract and full text to include specifically only studies investigating DNA methylation in progeny in relation to diet of maternal line or paternal line. Also included are studies referenced to in an included study or a relevant review, which met the inclusion criteria. As the described PubMed search was excluding some studies on folate supplementation in pregnancy, a further search was carried out using the keywords “folate” and “pregnancy” and “DNA methylation”. Secondly, from May 2012 the publications to be included were kept up to date by regular searches of the PubMed database with the keyword “DNA methylation” and inclusion on the basis of title and abstract.

Only studies which assessed or intervened with dietary or nutritional supplement intake are included in the systematic analysis. Studies which use a proxy for nutrition such as low birth weight of progeny or plasma/serum folate were excluded. Alterations in profiles or gene expression of DNA methyltransferase enzymes have not been comprehensively considered in this review. Animal studies published before 2009 were excluded.

Results

DNA methylation endpoints investigated have been either a general measure of DNA methylation of CpG across the whole genome by analysis of repetitive element DNA methylation, or examination of specific loci in genes of interest. The locus chosen for investigation may be a candidate because the method of analysis for that locus is available, or because there is thought to be involvement of the gene or protein in cardiovascular or metabolic disease [6].

Although a large number of animal studies satisfied the inclusion criteria, only thirteen published studies in humans, listed in Table 1, looked at the effect of maternal diet on offspring DNA methylation, and all of these involved diet during pregnancy. No human study was found which has yet looked for an effect of paternal diet on offspring DNA methylation. Among the maternal diets observed were very low caloric intake during the Dutch Hunger Winter, an African rainy season diet versus dry season diet, and a Scottish high meat, low carbohydrate diet. Randomised controlled trials compare supplement use or lack of use. The earliest study found which looked at DNA methylation in relation to maternal diet in humans was 2008. The majority of the studies have focused on a possible periconceptional effect of exposure. Offspring have been newborn, young children or mature adults. Most studies have looked at DNA methylation at only one time point but the Gambian supplementation trial has looked at newborn and 9 month old infants, allowing an informative comparison [7,8].

Functionally, the effect of maternal diet in utero in humans on the IGF2/H19 imprinted region has been extensively examined and the hypothalamic-pituitary-adrenal axis has been a focus. Three human studies examined multiple loci with different functionalities and one looked at genome wide repetitive elements, thus moving towards a wider view of how nutrition in pregnancy acts to alter phenotype of the offspring.

The animal studies have spanned a wide range of functional fields of study, involving a number of different dietary regimens. All of the animal studies are presented in Tables 2-8. Many of them directly support or have been a foundation for the human studies and many involve different functional fields of study, diets unlike those tested in humans, and different affected loci. Many of the animal studies that involved methyl donor deficient diets or methyl donor supplementation have investigated tumourigenesis and DNA repair. Ongoing debate over the benefits and mechanism of action of folic acid supplementation programmes is reflected in the large number of animal studies attempting to elucidate the action of folate. In this review, topics of interest covered by the human studies are discussed, with the relevant animal studies being mentioned, while a tabular overview of the areas covered by animal studies alone is provided.

Famine, protein restriction and restricted feeding

A severe famine of six months suffered by an area of Holland during the war (the Dutch Hunger Winter), affected the health of people exposed prenatally. As recently reviewed [79], intrauterine famine exposure affected adult glucose tolerance, lipid profile (in women), may be associated with metabolic syndrome, may lead to higher body weight, BMI, waist circumference (in women), and is associated with increased in incidence of psychiatric disorders.

There are thought to be windows of sensitivity, or time points during development when the germ cell, gamete or developing embryo is more susceptible to environmental influence on the phenotype. The timing of exposure to famine affected the outcome on the health of the adult offspring. Different organs or systems are more sensitive at different stages of development. There were greater effects of periconceptional exposure on glucose metabolism, schizophrenia incidence, incidence of cardiovascular disease [79,80]. Increased adult mortality of cardiovascular disease, cancer, and breast cancer occurred in women exposed in early gestation [81]. Mid-gestational exposure appeared to have an impact on lung health and late gestational exposure affected birth weight [79].
Table 1: Human studies investigating the effect of maternal diet during pregnancy on DNA methylation in the offspring.

| Field of Enquiry                                         | Maternal Diet                                         | Time of Exposure                                      | Time of Measurement of Endpoint in Offspring | DNA Methylation Changes                                                                 | Reference |
|----------------------------------------------------------|-------------------------------------------------------|------------------------------------------------------|---------------------------------------------|----------------------------------------------------------------------------------------|-----------|
| IGF2/H19 region                                          | Dutch famine exposure                                 | Periconception or Late gestation                     | 60 year old adults                          | Lower methylation at IGF2 DMR with periconceptional exposure No effect of late gestational exposure | [9]       |
| Imprinted and non-imprinted loci, candidates for growth and metabolic disease | Dutch famine exposure                                 | Periconception or Late gestation                     | 60 year old adults                          | Periconceptional exposure: lower methylation of INSIGF and higher methylation of IL10, LEP, ABCA1, GNASAS, MEG3 Sex differences Late gestation exposure alteration in methylation of GNASAS and in men, LEP | [6]       |
| Putative metastable epialleles                           | Rainy season (less food abundance, more folate, harder work) or dry season diet at conception, Gambian population | Periconception with seasononal influence during pregnancy | Children 8-9 years                          | Methylation at all 5 putative metastable epialleles higher in rainy-season conceived children No effect on global DNA methylation or at IGF2, GNASAS, IL10 | [10]      |
| Genome-wide effect of famine                             | Dutch famine exposure                                 | Part of the time from conception to birth, analysed as blocks of time: wk 1-10, 11-20, 21-30, 31-birth | 60 year old adults                          | No effect of famine exposure in utero on blood global DNA methylation in white blood cells | [11]      |
| IGF2/H19 region                                          | Dutch famine exposure                                 | Periconception and first part of pregnancy           | 60 year old adults                          | Altered methylation at INSIGF, IGF2 DMR0, IGF2 DMR1, IGF2 DMR2 CTCF locus No effect on H19 DMR Global DNA methylation unchanged | [12]      |
| Search for affected loci and functional associations      | Multinutrient supplementation, Gambian population     | Periconception                                       | Newborn and Baby 9 months                   | Differential methylation of multiple loci at birth and 9 months, associated with eg immune defence, sex differences Δ methylation at imprinted loci: GNAS, MKRN3, SLC22A18 | [8]       |
| Imprinted genes, including IGF2/H19                      | Multinutrient supplementation, Gambian population     | Periconception                                       | Newborn and Baby 9 months                   | Imethylation at IGF2R in newborn girls; 1 methylation at GTL2-2 in newborn boys 1 methylation at PEG1-DMR in infant girls at 9 months; 1methylation at GNASAS-DMR in infant boys at 9 months Methylation at H19 and H19 loci not changed | [7]       |
| Mechanism of action of folic acid                        | Folic acid supplementation                            | During pregnancy                                      | Newborn                                     | No effect of folic acid supplementation on newborn cord blood global DNA methylation    | [913]     |
Effect of Maternal and Paternal Nutrition on DNA Methylation in the Offspring: A Systematic Review of Human and Animal Studies

Table 2: Animal studies investigating DNA methylation in offspring exposed to maternal protein restriction in utero.

| Field of Study                  | Animal | Time of Exposure | Time of Measurement of Endpoint in Offspring | DNA Methylation in progeny Exposed in utero to Maternal Protein Restriction | Reference |
|--------------------------------|--------|-----------------|---------------------------------------------|--------------------------------------------------------------------------|-----------|
| Key hepatic metabolic genes    | Pigs   | Gestation       | Late gestation, birth, weaning, finisher pig | Influence of DNA methylation in transcription of glucocorticoid receptor gene NR3C1 in late gestation and in cytochrome P450 superfamily CYP2C34 in newborns ↑methylation in some sites in peroxisome proliferator-activated receptor PPARα | [19]      |
| Chromosome condensation and segregation | Pigs   | Gestation       | Late gestation, birth, weaning, finisher pig | Hepatic global DNA methylation in late gestation, no change postnatally, no change in skeletal muscle global DNA methylation ↑methylation in sites in NCAPG promoter region of foetal liver, different methylation of sites in NCAPG promoter region in foetal muscle, correlations with transcription | [20]      |
| Topic                                    | Organisms | Stages | Phenotype                                                                 | Reference |
|-----------------------------------------|-----------|--------|---------------------------------------------------------------------------|-----------|
| Mitochondria (dysfunction in malnutrition) | Pigs      | Gestation | Newborn                                                                 | [21]      |
|                                         |           |         | ↓ mean methylation over 47 CpG sites in somatic cytochrome c gene (CYCS) promoter in newborn piglet liver, negative correlation with transcript amount |           |
| Glucose homeostasis                     | Pigs      | Before and during gestation | Newborn                                                                 | [22]      |
|                                         |           |         | Hypomethylation of glucose 6 phosphatase gene promoter in males.         |           |
| Insulin Resistance                      | Rats      | Gestation | Aged adults                                                             | [23]      |
|                                         |           |         | ↑ methylation in the PGC-1α promoter sequence, a key gene in regulation of insulin resistance |           |
| Glucose homeostasis                     | Rats      | Gestation and lactation | Three generations at 70d                                               | [24]      |
|                                         |           |         | ↓ methylation in three of the nine CpG sites in Phosphoenolpyruvate carboxykinase promoter in progeny, in F1, F2 and F3 generations, one CpG site showed similar effect in all three generations |           |
| Lipid metabolism                        | Rats      | Gestation | Offspring weaned onto low fat or high fat diets.                         | [25]      |
|                                         |           |         | Newborn & adult                                                          |           |
|                                         |           |         | ↓ methylation of PPARα promoter in neonatal and adult heart, unaffected by post-weaning diet. Methylation of PPARα promoter in adult heart negatively associated with mRNA level |           |
| Tumour suppressor, mammary gland, cyclin dependent kinase inhibitor 1 (p21) | Rats      | Gestation | 38d pups                                                                 | [26]      |
|                                         |           |         | No change in DNA methylation at the p21 promoter in mammary gland of pups |           |
| Tumour suppressor, mammary gland, p16   | Rats      | Gestation | 38d pups                                                                 | [27]      |
|                                         |           |         | No change in DNA methylation at p16 promoter.                           |           |
| IGF2/H19                                | Rats      | Gestation (from day 2) | Newborn                                                                 | [28]      |
|                                         |           |         | ↑ methylation of imprinting control region at IGF2/H19 locus in liver, attenuated by folate supplementation Global DNA methylation unchanged |           |
| Hypothalamus                             | Rats      | Gestation and/or lactation | 12d pups                                                               | [4]       |
|                                         |           |         | ↑ methylation in hypothalamic neuropeptide gene Pomc promoter with in utero protein restriction, control diet after birth. |           |
| Appetite                                | Rats, also folate supplemented group | Gestation | Foetus day 20                                                            | [29]      |
|                                         |           |         | Liver global DNA methylation unchanged                                 |           |
| Imprinted genes DMRs                    | Mice      | Gestation and/or lactation | 3 weeks & adults                                                        | [30]      |
|                                         |           |         | Mostly unchanged ↑ methylation in some CpG sites in Grb10 and Nespa/Gnas DMRs at 3 weeks, not adulthood, in liver; global DNA methylation unchanged |           |
Effect of Maternal and Paternal Nutrition on DNA Methylation in the Offspring: A Systematic Review of Human and Animal Studies

Table 3: Animal studies investigating DNA methylation in offspring exposed to maternal restricted feeding in utero.

| Field of Study                                | Animal, Maternal Feeding Protocol | Time of Exposure                                                                 | DNA Methylation In Progeny Exposed to Restricted Feeding in Utero                                                                 |
|-----------------------------------------------|----------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Pulmonary vascular dysfunction                | Mice Restricted diet: 65% of ad lib intake | From day 7 of gestation to delivery                                             | ∆ global DNA methylation in lung pulmonary dysfunction                                                                      |
| Gluconeogenesis                               | Baboons Restricted diet: 70% of ad lib intake of controls | Before and during gestation                                                     | ↓Methylation at 6 sites in promoter of foetal liver phosphoenolpyruvate carboxykinase 1 gene (PCK1)                          |
| Organ specific effects                        | Baboons Restricted diet: 70% of ad lib intake of controls | From early gestation (day 30)                                                  | Global DNA methylation per organ in nutrient restriction: ↓methylation in kidney mid gestation, ↑methylation in kidney late gestation, ↑methylation in frontal cortex |
| Energy balance regulation in hypothalamus     | Sheep undernourished            | Before gestation and early gestation only                                      | Hypothalamus: ↓methylation ppropiomelanocortin (POMC) promoter, ↓methylation glucocorticoid receptor (GR) promoter methylation at Oct4 promoter unchanged |
| Energy balance regulation in hypothalamus     | Sheep undernourished            | Before gestation and early gestation only                                      | Hypothalamus: ↓methylation ppropiomelanocortin (POMC) promoter, ↓methylation glucocorticoid receptor (GR) promoter methylation at Oct4 promoter unchanged |
Table 4: Animal studies investigating DNA methylation in offspring exposed to maternal methyl group supplementation or restriction in utero, published since 2009.

| Field of Study          | Animal, Maternal Diet | Time of Exposure                                                                 | Time of Measurement of Endpoint in Offspring | Finding                                                                                           | Reference |
|-------------------------|-----------------------|----------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------------------|-----------|
| DNA repair in brain     | Mouse, Low folate     | Gestation and lactation Offspring high fat from weaning                          | Adult                                       | ∆ in DNA methylation at excision repair genes                                                    | [40]      |
| Behaviour               | rats methyl donor deficiency | Before and during gestation                                                       | Newborn, young adult, aged adult            | ↓global DNA methylation in newborn liver No major difference in DNA methylation at glucocorticoid receptor promoter, 11β-hydroxysteroid dehydrogenase type 2, neuronatin, or reelin gene in hippocampus of young adult or aged adult, but ∆methylation at one Cpg unit in neuronatin gene in young adult female offspring | [41]      |
| Intestinal cancer       | mice WT and Apc(+/- Min), folate deficient diet | Gestation and lactation                                                          | At weaning (32d) and adult                  | ↓DNA methylation of p53 in small intestine. ↑methylation at IGF2 and apc in Apc (+/Min) mice.          | [42]      |
| Intestinal cancer       | Mice low, control, high folate | Gestation and lactation                                                          | adult                                       | ↓ global DNA methylation in low folate exposed adult offspring                                  | [43]      |
| Intestinal cancer       | Mice low, control, high folate | Gestation                                                                       | Foetus 17.5d                                | ↓methylation of Sk:39:4a and no change in methylation of Esr1 or IGF2 DMR1 in foetal gut         | [44]      |
| Atherosclerosis         | Apo E-/- mice Methyl donor supplemented | Before and during gestation and lactation                                          | 17 weeks, 28 weeks                          | ↑ global DNA methylation in T-cells                                                              | [45]      |
| Effect of arsenic, microarray | Mice, folate supplement and arsenic in utero | Gestation                                                                      | Foetus day 18                               | ∆ DNA methylation at 12 genes Increased number of genes ∆ DNA methylation in response to arsenic | [46]      |
| Glucose homeostasis     | Rats folic acid supplementation | Gestation                                                                       | 84 - 90d old                                | ∆ methylation of Phosphoenolpyruvate carboxykinase promotor in females, not males                | [47]      |
| Placenta                | Rats folic acid supplementation, vitamin B12 deficiency, omega 3 fatty acid supplementation | Gestation                                                                      | Placenta day 20 gestation                  | Influence of docosahexaenoic acid on vitamin B12 deficiency-induced ∆ global DNA methylation in the placenta | [48]      |
| Study Type                        | Diet Intervention          | Time Points                                      | Outcomes                                                                 |
|----------------------------------|----------------------------|-------------------------------------------------|--------------------------------------------------------------------------|
| Microarray approach, Heritability | Mice methyl supplemented diet | Before and during gestation, continued for 6 generations | 5 weeks old 1 variation in DNA methylation at multiple loci in liver of supplemented mice, magnified in subsequent generations Unchanged hepatic global DNA methylation | [49] |
| Tumour mammary gland             | Rats folic acid supplementation | Before and during gestation and lactation | 28 weeks ↓ global DNA methylation in mammary gland | [50] |
| Colitis                          | Mice methyl donor supplementation | Before and during gestation and lactation | 30d and 90d Δ Colonic mucosa DNA methylation, including at Ptpn22- associated Smal/Xma1 interval (associated with diseases eg rheumatoid arthritis, diabetes) | [51] |
| Intestinal cancer                | Rats folic acid supplementation | Before and during gestation and lactation | 14 weeks ↑ colorectal global DNA methylation | [52] |
| Multiple effects of fortification | Rats Folic acid supplementation +/- post-weaning supplementation | Gestation and lactation | At weaning and 14 weeks ↓ global DNA methylation, ↓ methylation at Ppar-y, Era, p53, Apc in weaning liver ↑ methylation at Era and Apc in adult liver Influence of post-weaning supplementation | [53] |
| Epigenetics of agouti mouse      | Mice, agouti Methyl donor supplementation | Day 8.5 to day 15.5 gestation only | First generation offspring and unsupplemented next generation offspring | No increase in density of CpG methylation in the silent LTR | [54] |
| HPA axis                         | rats methyl donor supplementation | Gestation | Adult | no change in DNA methylation of GR exon 1(7) promoter | [55] |
| Placenta, 1-carbon metabolism    | rats folic and homocystine supplement | Before and during gestation | Placenta day20 ↑ global methylation in placenta, DNA methylation strongly related to maternal folate levels and hepatic 1-carbon intermediates | [56] |
| Mammary gland cancer             | Rats, choline deficient, control or supplemented | Gestation days 11-17 | Adult | On tumour induction, Δ DNA methylation in tumour suppressor gene, stratifin correlated with choline exposure | [57] |
| Effect of alcohol on developing hypothalamus | Rats, exposed to alcohol + or - choline | Gestation days 7-21 | Adult | ↑ methylation of proopiomelanocortin gene in hypothalamus with alcohol exposure but not with choline + alcohol exposure. | [58] |

**Citation:** Vansant G, Wallace S, Godderis L (2016) Effect of Maternal and Paternal Nutrition on DNA Methylation in the Offspring: A Systematic Review of Human and Animal Studies. Adv Obes Weight Manag Control 4(4): 00093. DOI: 10.15406/aowmc.2016.04.00093
Table 5: Animal studies investigating DNA methylation in offspring exposed to maternal diet of particular fat content in utero.

| Field of Study | Animal, Maternal Feeding Protocol | Time of Exposure | Time of Measurement of Endpoint in Offspring | Epigenetic Outcome | Reference |
|----------------|-----------------------------------|------------------|---------------------------------------------|--------------------|-----------|
| Insulin sensitivity | Rats, Fish oil supplementation | Before and during gestation and lactation for 2 further generations | 75d old | ↓hepatic global DNA methylation in G2, not in G1, no change in muscle global DNA methylation | [59] |
| Fatty acid status | Rats, low fat, adequate fat, high fat, butter vs fish oil | Before and during gestation and lactation | Adult | ↑methylation at hepatic Fads2 promoter with high fat exposure, particularly with fish oil, negative correlation with Fads2 mRNA relationship of methylation at one CpG site in Fads2 promoter with 20:4n-6:22:6n-3 ratio | [60] |
| Fatty acid metabolism | Mice, control (containing soybean oil) and deficient (corn oil) | Before and during gestation. Maternal diet from delivery α-linolenic acid supplementation (ω-3) as flaxseed oil, or continuation on the control or the deficient diet | At weaning | ↑Fads2 promoter methylation in offspring liver only with maternal control diet in gestation and postnatal supplementation. No effect of diet on Fads2 intron 1 methylation in offspring. ∆methylation in Fads2 in maternal liver. methylation status of Fads2 in liver in mothers and offspring associated. | [61] |
| Dopamine and opioid circuitry in the brain | Mice, high fat diet through pregnancy | Before and during gestation and lactation | Adults | ↓global DNA methylation in brain ↓ promoter methylation at dopamine reuptake transporter, µ-opioid receptor and preproenkephalin | [62] |
| Insulin sensitivity | Mice, high fat diet | Before and during gestation and lactation, for two further generations | Adults | ↓methylation at GHSR promoter in second generation offspring brain | [63] |
| Bone | Rats, high fat diet to produce obese dams | Before and during gestation | Foetus 18.5d | ∆methylation IGF2 DMR. Sex difference. HFD led to ↓global DNA methylation in female placenta. | [64] |
| Imprinted genes in placenta | Mice, high fat diet | Gestation | Placenta 15d | progeny fed high fat diet or control diet ↓global DNA methylation in adipose tissue with high fat diet after weaning | [65] |
| Leptin | rats fed various diets, | Gestation and lactation | 10 weeks | methylation at CpG islands in the promoter and at exon hepatic cell cycle inhibitor at 2d post natal, not 27d. | [66] |
| Metabolic disorders | Mice, high fat diet | Gestation and lactation | Pup 2d, 27d | methylation at CpG sites in Npas2 promoter Histone difference | [67] |
| Circadian rhythm | Primates high fat diet | Before and during gestation | Foetus 130d | No difference in DNA methylation at CpG sites in Npas2 promoter Histone difference | [68] |
| Vascular tone | Rats, 7% or 21% fat | Before and during gestation and lactation | 11 weeks | Hypermethylation at aortic Fads2 promoter in high fat group, correlation with expression | [69] |
Table 6: Animal studies investigating DNA methylation in offspring exposed to maternal overfeeding in utero.

| Field of Study                          | Animal, maternal feeding protocol | Time of exposure                                      | Time of measurement of endpoint in offspring | Epigenetic outcome                                                                 | Reference |
|----------------------------------------|----------------------------------|------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------|-----------|
| Methyl donor metabolism, gluconeogenesis | Overfed mice                     | Gestation and lactation, sustained for 4 generations | Adult                                         | Δ methylation at PEPCK, relationship with mRNA hepatic Dnmt methylation of Dnmt promoter | [70]      |
| Chromosome condensation and segregation | Pigs, protein excess             | Gestation                                             | Late gestation, at birth, at weaning, finisher pig | Δ hepatic global DNA methylation; Δ methylation of NCAPG                           | [20]      |
| Triglyceride biosynthesis in liver     | Mice, high fat/high sucrose diet (high calorie lipogenic diet) | Before and during gestation and lactation             | Pups 5d                                       | Methylation of hepatic glycerol-3-phosphate acyltransferase 1 promoter, inversely correlated with mRNA | [71]      |

Table 7: Animal studies investigating DNA methylation in offspring exposed to other maternal dietary regimens in utero.

| Field of Study              | Animal, Maternal Feeding Protocol | Time of Exposure | Time of Measurement of Endpoint in Offspring | Epigenetic Outcome                                                                 | Reference |
|-----------------------------|----------------------------------|-----------------|----------------------------------------------|-----------------------------------------------------------------------------------|-----------|
| Iron metabolism             | Mice, iron-chelating flavonoid quercetin throughout gestation | Before and during gestation | Foetus 14.5d, adult                          | ↑ global DNA methylation                                                         | [72]      |
| Glucocorticoid metabolism   | Rats, magnesium deficient diet    | Before and during gestation and lactation             | Pup 21d                                       | ↑ methylation at the 11beta-hydroxysteroid dehydrogenase-2 promoter              | [73]      |
| Renin angiotensin system    | Rats, high salt diet during pregnancy | Gestation          | Foetus 21d                                   | Mean methylation at five CpG sites linked to AT1b promoter in heart                | [74]      |
| Zinc metabolism             | Mouse, low zinc diet              | From day 7 gestation                                  | 5 weeks                                       | ↑ methylation in two CpG sites of hepatic metallothionein2 promoter region        | [75]      |
| IGF2/H19                    | Sheep, Isoenergetic diets of either alfalfa haylage (high in fibre), corn (high in starch) or dried corn distillers grains (protein, fat, fibre) mid to late gestation | Mid-late gestation | Foetus late gestation (130d) | With fibre and dried corn distillers (protein fat fibre) based diets, increased methylation of CpG islands of IGF2 and H19 compared to corn starch based, low amino acid, ie low methyl group in muscle tissue | [76]      |
| Congenital heart defects    | Rats, Vitamin A deficient diet    | Before gestation ± during gestation                   | Foetus 13.5d                                  | ↑ methylation at CpG loci of GATA-4 gene in embryo heart                          | [77]      |
| Obesity                     | Rats, high multivitamin diet then further diet groups after weaning | Gestation                              | 29 weeks                                      | No change in global DNA methylation in adult offspring                              | [78]      |

Citation: Vansant G, Wallace S, Godderis L (2016) Effect of Maternal and Paternal Nutrition on DNA Methylation in the Offspring: A Systematic Review of Human and Animal Studies. Adv Obes Weight Manag Control 4(4): 00093. DOI: 10.15406/aowmc.2016.04.00093
DNA methylation of several imprinted loci which were candidate genes for metabolic or cardiovascular disease, was different with periconceptional exposure to famine compared to unexposed siblings: DNA methylation of INSIGF (part of the proximal promoter of INS which encodes the insulin precursor) was lower and DNA methylation of GNASAS and MEG3 was higher [6]. These effects were sex dependent for some of the loci. There was also an effect on some of the non-imprinted loci examined: periconceptional exposure led to higher DNA methylation at IL10, LEP, and ABCA1. Nine of the 15 loci examined showed no alteration in DNA methylation with periconceptional famine exposure. With exposure later in gestation there was altered methylation level at GNASAS and in men, LEP. Thus there is a sex dependent change at some loci and the change is also dependent on timing of exposure which the group points out does support epidemiologic findings that exposure to famine has a sex and timing specific effect. The group also observes that the differential response to famine at different loci does not conform to a simple view that lower availability of methyl donors directly causes less DNA methylation at the loci. Famine exposure also affected DNA methylation at the IGF2/H19 region which is a topic discussed later in this review [9,12].

Protein restriction is commonly used as a model of malnutrition or famine. As a result of the search described above, seventeen studies on animals from 2009 onwards were found which have examined protein restriction in the maternal diet during pregnancy and the resulting DNA methylation in the offspring, and are listed in Table 2. Four are on pigs, the rest on rodents. One study continued until the third generation of progeny [24]. A number of functional pathways have been examined, with a rather different focus from that of the human studies.

The diets used in the rodent studies were approximately comparable with regard to protein content. Not only has protein content of the diet decreased in the treatment group, but protein to carbohydrate ratio has altered, there is increased carbohydrate, and in some cases methionine content of the diet is altered. Thus the effect of the diet may not be due solely to a reduction in protein.

Another model for famine or food deprivation is feeding a reduced diet to animals, and the five published studies using this model to examine an effect on DNA methylation are listed in Table 3. Four of these are studying energy or glucose metabolism. One finds an alteration in global DNA methylation in mouse lung [35], interesting as famine impacted lung health in exposed human offspring [79]. A key enzyme in gluconeogenesis [36] and organ specificity of global DNA methylation changes have been investigated in baboons [37]. The hypothalamic pituitary axis was examined in sheep [38,39].

Further to investigation of an effect on DNA methylation of a target gene, researchers often look for a correlation with gene transcription and study whether there is a regulatory role of methylation. For example, correlations of change in DNA methylation with change in gene transcript suggested a regulatory role for DNA methylation on target genes in pigs exposed to maternal protein restriction in utero [19-21]. Liver x-receptor alpha, which regulates cellular lipid homeostasis, was hypermethylated in liver of foetal rats exposed to maternal low protein and there is a relationship between methylation of this gene and transcription, thus this may have been a regulatory factor in the concomitant reduction in mRNA level [34]. PPARα promoter methylation in adult but not foetal heart was negatively associated with transcription [25]. The hypomethylation of ACE-1 promoter with prenatal low protein exposure was related to gene transcription but not to protein levels [33]. The effect of DNA methylation on transcription may influence effect of in utero protein restriction or famine on phenotype.

DNA methylation at imprinted genes

Several of the human studies reviewed have looked at the insulin-like growth factor 2 (IGF2) gene. IGF2 is important for growth and development in utero in humans and thus pertinent to studies of the effect of maternal diet or nutritional challenge on development in utero [82]. The gene IGF2 is in tandem with H19 on chromosome 11 and is imprinted [83]. A differentially methylated control region for both IGF2 and H19 is methylated in the paternal allele and unmethylated in the maternal allele. The mechanism of epigenetic regulation of expression of Igf2 in mice is reviewed in Chao & D’Amore [84]. The H19 promoter is methylated and therefore inactive in the paternal allele, so only maternal mRNA is expressed. A region upstream of H19 promoter, the imprinting control region (ICR) allows binding of a zinc finger protein, CTCF when demethylated, acting as an insulator on the maternal allele. Access to the Igf2 promoter is consequently
blocked in the maternal allele but not in the methylated paternal allele resulting in transcription of Igf2 mRNA. Other elements are involved in the regulation of IGFR transcription. As briefly reviewed by Tobi and others, [12], the nearby insulin promoter INS has an influence and INSIGF is a fusion transcript of INS and IGFR. Loss of imprinting at the IGFR/H19 locus has been associated with disease states. Note that there is some extent normal variation in the methylation of the DMR as shown in monozygous twins [85].

The mechanism of regulation of this IGFR/H19 system and imprinting by DNA methylation is very well characterized therefore, in addition to being associated with growth, this imprinting region has proven to be a useful tool to investigate the effect of parental diet on DNA methylation.

In the Dutch Hunger Winter cohort, adults whose mothers were exposed to famine around the time of conception, had a lower DNA methylation at CpG sites in the IGFR DMR compared to unexposed siblings [9]. This difference was not evident in offspring of mothers exposed to famine later in the pregnancy with adequate nutrition at conception suggesting that the timing of exposure to the nutritional factor is important for DNA methylation of this region. The difference between the experimental and control group is small. 5.2% lower methylation is seen with periconceptional famine exposure.

More recently the IGFR/H19 region was examined in more detail in the Dutch Hunger Winter cohort, drawing on the more sophisticated techniques available and the high level of knowledge at this time on the role of the components of the control region [12]. In adults exposed to famine in utero, there were small differences in methylation at DMRs compared to unexposed same sex siblings. Methylation was lower at the INSIGF locus in the INS promoter, methylation was lower in IGFR DMR0, which is also called IGFR DMR in other papers. Methylation was higher in IGFR DMR1, which is a region that binds CTCF. At the IGFR DMR2 CTCF-binding locus there was lower methylation of three CpG sites with famine exposure but methylation at another locus had no association with exposure. H19 DMR methylation level was not associated with exposure. The magnitude of the effects of exposure was comparable to those found in other studies reported. Interestingly, it has now become possible to find out whether there is an interplay of the gene sequence, in the form of small nucleotide polymorphisms, in the response of the epigenome to nutritional challenge in development. Single nucleotide polymorphisms (SNPs) at the IGFR/H19 region are associated with DNA methylation and the authors suggest that the effect of famine and of SNPs on DNA methylation could be additive at the same locus.

Folic acid supplementation is routinely recommended for pregnant women in many countries and in some countries food is fortified with folic acid as a public health policy. Periconceptional folic acid supplementation increased DNA methylation by 4.6% of the DMR of IGFR2 in the 17 month-old Dutch children [14]. However in an American trial there was no difference in methylation at IGFR DMR in newborn cord blood with folic acid supplementation before pregnancy or during pregnancy [15] Perhaps due to differences in the cohort or study design, the discrepancy may be due to the age of offspring examined. With multinutrient supplementation there was a difference in IGFR2 DMR methylation level of effect between newborns and 9 month babies [8].

Methylation at H19 DMR in newborns exposed to folic acid supplementation before and during pregnancy was lower compared to unexposed newborns [15]. The size of this effect is similar to other studies, and the decrease was greater for male babies than female babies, adding to the evidence of a sex difference in the epigenetic response to intrauterine nutritional factors. In rats prenatally exposed to low protein the ICR at the IGFR/H19 locus was hypermethylated in newborn liver, expression of IGFR2 was increased and this increase was significantly associated with the methylation of the ICR [28]. There was no change in methylation at DMR2.

In a sheep model Lan and co-workers, 2013, investigated a variety of energy sources in the maternal diet and imprinted gene DNA methylation in offspring exposed late in gestation [76]. Different diets did affect gene expression in a number of imprinted genes and DNA methyltransferase genes. There was a higher DNA methylation at CpG islands of IGFR2 and H19 with the fibre-based diet and a diet of fibre, protein and fat, than the starch-based, low amino acid diet. DNA methylation at the CpG island in intron 2 of IGFR2 positively correlated with gene expression.

More recent studies have a more epigenomic approach and also can take advantage of a more detailed knowledge of the molecular systems involved. A randomised controlled trial was carried out in the Gambia [7]. Women who were not yet pregnant took a supplement containing vitamins A, D, E, C, B1, B2, B6, B12, Niacin, folic acid, Iron, Zinc, Copper, Selenium, Iodine, or they took a placebo, until confirmation of pregnancy (average 9.5 weeks gestation), then all subjects were switched to iron and folate supplement only. The group looked at patterns of DNA methylation at 13 imprinted loci: 2 paternally methylated germline DMRs, 3 paternally methylated somatic DMRs, and 7 maternally methylated germline DMRs. Results were adjusted for season of conception as season has been found to have an impact on nutrition in the Gambia. Changes in DNA methylation were found to be gender specific. In maternally supplemented groups there was lower methylation at IGFR2 in newborn girls and lower methylation at GTL2-2 in newborn boys. These changes were not found at the second time of analysis, 9 months, and the authors suggest this may be due to the small sample size. Methylation at the paternally methylated germline DMRs at H19 and IG loci were not changed. At 9 months other changes are found: a lower methylation at PEG1-DMR in girls and a lower methylation at GNASAS-DMR in boys at 9 months.

With the same cohort of Gambian women described above [8], a genome-wide investigation using a microarray chip containing individual CpGs in promoters associated with 14000 genes was able to make powerful comparisons of changes in methylation status of CpG loci in blood from infants at birth and 9 months, finding effects of periconceptional supplementation, age, and gender at multiple loci.

14 genes exhibited changes with periconceptional supplementation in boys and 21 genes in girls. A greater number of genes are differentially methylated with supplementation at

Citation: Vansant G, Wallace S, Godderis L. (2016) Effect of Maternal and Paternal Nutrition on DNA Methylation in the Offspring: A Systematic Review of Human and Animal Studies. Adv Obes Weight Manag Control 4(4):00093. DOI: 10.105466/aowmc.2016.04.00093
9 months. 50% of the changes seen in newborns are present at 9 months. There is little overlap in differentially methylated loci between the sexes, and the group suggests that there are sex-specific developmental paths. The greatest number of changes was between birth and 9 months independent of treatment. An interesting point to note that most of the sites differentially methylated were lone CpG sites outside CpG islands.

By means of databases a functional analysis of the differentially methylated loci showed that a number of them were associated with defence against infection and the immune response. In male newborns, interestingly, affected genes were involved in nervous system development and skeletal development. For female newborns, particular affected genes were involved in immune and non-immune defense against infection, and in cardiovascular function. In 9 month infants, both sexes had changes in immune response genes and genes involved in defence against infection, cancer and development, neurological function and in males, cardiovascular function. In three imprinted genes there is an effect of supplementation: GNAS, involved in intrauterine growth, MKN3, involved in obesity and SLC22A18, associated with various tumours.

Metastable epialleles are regions where epigenotype, such as DNA methylation, is stochastically set in the early embryo to be retained in all differentiated cell lineages. There is thus high variation between individuals in levels of DNA methylation at these regions. Based on what is known of murine metastable epialleles, Waterland and co-workers, 2010, found putative human metastable alleles [10].

They postulate that level of DNA methylation at these loci may affect susceptibility to disease and they describe a study in a rural Gambian population where seasonality dramatically affects the diet. 9 year old children, who had been conceived in the dry season, when food is abundant, were compared with children conceived in the rainy season when there is a short supply of food as well as a greater amount of physical work to be done. Blood folate levels in this population increase during the rainy season. Data was retrospective from years with a strong effect of seasonality on birth weight. Interestingly, DNA methylation of all 5 putative metastable epialleles was significantly higher in children conceived in the time of hardship. There was no change in DNA methylation at IGF2, GNASAS, and IL10 in relation to season of conception. The effect of season of conception in the Gambia on metastable epialleles was larger than the previously discussed effect of conception during famine on DNA methylation in adults [6]. The epigenotype at the metastable epialleles is in tissues from all three germ layers which means it is established before gastrulation. This is consistent with a sensitivity to conditions around the time of conception.

Hypothalamic-pituitary-adrenal axis

Hypothalamic-pituitary-adrenal (HPA) axis is a complex system regulating glucocorticoid production. Alterations in the foetus have been implicated in development of later life disease [86]. Animal models have shown increased maternal glucocorticoids during gestation leads to a metabolic syndrome-type profile in adult offspring. In adult humans high glucocorticoid level is associated with cardiovascular disease and neurobehavioral problems and high maternal cortisol is associated with low birth weight. Glucocorticoids are involved in glucose, protein and fat metabolism and are important in foetal development. The HPA also plays a key role in the response to stress and chronic stress has long since been linked to metabolic disease states.

Retrospective summaries of dietary intake of mothers advised to eat a high meat, low carbohydrate diet during pregnancy were used to investigate the relationship with DNA methylation at candidate genes in blood of the 40 year old offspring [86]. Methylation at the glucocorticoid receptor gene (exon 1F) was increased in offspring whose mothers had higher meat, fish and vegetable intake and lower bread and potato intake in late pregnancy. This exon has a role in control of glucocorticoid receptor expression, which in turn mediates glucocorticoid action. The authors suggest that the increased methylation may impact on transcription factor binding. Methylation increased at a specific site in 11β-hydroxysteroid dehydrogenase enzyme 2 gene (HSD2) region 2 with increased meat and fish intake in late pregnancy. HSD2 modulates access of glucocorticoid to the glucocorticoid receptor. The group has previously found that methylation at this locus increases its gene expression and is associated with hypertension. Thus maternal diet in utero may influence the pathway of glucocorticoid action decades later via DNA methylation changes.

A randomised controlled trial tested the effect of intake of high or moderate choline during the third trimester of pregnancy [18]. With higher choline intake there was a 33% lower plasma cortisol in cord blood. There was higher methylation in the proximal promoter region of corticotrophin releasing hormone (CRH) promoter and in glucocorticoid receptor promoter region including exon1-F in the placenta at birth following higher level of consumption of choline. Transcription of CRH was lower with more choline consumption maybe due to decreased binding of transcription factors because of DNA methylation of the promoter region. In contrast, in cord blood leukocytes DNA methylation of the promoter regions of the same two genes was lower. CRH regulates HPA axis reactivity and cortisol production, thus this study suggests that the quantity of choline in the maternal diet may impact a system which could affect the response to stress over the life course and affect the susceptibility to metabolic disease.

This study also examined the effects of the experiment on DNA methylation at GNAS-AS1, IGF2, IL10 and LEP.Only at one site was a difference found: one CpG unit in GNAS-AS1 in placental tissue was less methylated with high choline intake. The authors suggest that choline supplementation could be given to pregnant mothers where stress might adversely affect the HPA axis reactivity of the foetus.

Sheep have been chosen as an apt animal model because the hypothalamic pituitary axis and placental function are similar to humans [38,39]. Sheep were nutritionally deprived before conception and for early pregnancy, then were fed ad lib. Proopiomelanocortin (POMC) is a neuropeptide involved in energy balance at the hypothalamus, acting to decrease food taken in and increase energy extended. In late gestation foetus where pregnant mothers were food deprived around conception,
Effect of Maternal and Paternal Nutrition on DNA Methylation in the Offspring: A Systematic Review of Human and Animal Studies

Vansant G, Wallace S, Godderis L (2016) Effect of Maternal and Paternal Nutrition on DNA Methylation in the Offspring: A Systematic Review of Human and Animal Studies. Adv Obes Weight Manag Control 4(4): 00093. DOI:

In pigs, global DNA methylation in liver in utero was affected by the maternal low protein diet but after birth there was not a difference between low protein and control groups [20]. No change in global DNA methylation of skeletal muscle was observed but global DNA methylation was found to decrease with age in all treatment groups. In adult mice progeny exposed to low protein in utero, global DNA methylation of white adipose tissue was not different from the control group [32]. Thus there are tissue differences in the response to low protein exposure, and it may be that an early effect is lost by adulthood.

In spite of a high level of folate supplementation, rats exposed to low protein in utero had no change in global DNA methylation, and with their other results this group conclude that any effect of folate on appetite regulation is likely to be gene specific [29]. The relationship of dietary intake of methyl donors to global DNA methylation is not straightforward and may be affected by targeted gene specific methylation changes.

Timing of exposure

The majority of the human studies involve exposure to the dietary factor around the time of conception, as conditions at this time may affect the de novo methylation of the DNA of the embryo or the imprinting of certain genes. In some cases an effect of periconceptional exposure has been found but without an effect of late gestational exposure [89]. In some cases a different pattern of genes are affected by exposure to the dietary factor periconceptionally or at a later time in gestation [6]. Choline supplementation only late in gestation in a human trial affected promoter methylation [18], and for a small period in gestation in an animal study and affected methylation of a tumour suppressor gene [57]. Methyl donor supplementation of the agouti mouse is given for a mid-gestation window only [54]. Feeding sheep different diets late in gestation affected IGF2/H19 methylation [76]. Thus exposure to a maternal dietary factor at periconception or at a later stage of in utero development can affect DNA methylation.

Paternal epigenetics

A fascinating aspect of epigenetics is the ability to transfer a circumstance of the father, adverse or otherwise, to first generation or even subsequent generation offspring. To date there are no published investigations in humans as far as we are aware where the father’s diet has been observed or trialled and epigenetic changes in the offspring analysed. Soubry and co-workers (2013) examined obesity in fathers prior to conception and found an association with hypomethylation at IGF2 DMR [90]. The authors point out that the difference is of a similar magnitude to the effect of the Dutch famine. There was no significant association of obesity with DNA methylation level at H19 DMR. Animal studies have examined paternal diet effect on the DNA methylation in progeny.

Whilst the effect of grandmaternal famine exposure during the Dutch Hunger Winter on the F2 generation was not observed through the paternal F1 generation [91], transgenerational influence of paternal and grandpaternal nutritional exposure has been observed elsewhere, as reviewed by Curley and others, [92]. In an animal study, male mice were fed a protein restricted diet then mated with control-fed dams and the effects of the dietary intervention on the subsequent generation were examined [4].
Hundreds of genes were differentially expressed in the three week old F1 generation. In particular there was upregulation of pathways of DNA replication, and lipid and cholesterol biosynthesis. About 1% of the mouse genome was mapped for differential methylation of cytosines. There was an effect of the paternal low protein diet on methylation of CpG islands, albeit a small one, and the promoters where methylation changed were not correlated with those of altered gene expression. There was a 30% increase in methylation at a likely enhancer locus for Ppara, a key lipid regulator, which did correlate with Ppara gene expression down regulation. Interestingly, preliminary investigations were carried out on a possible epigenetic mechanism of action in sperm. A change in global DNA methylation was not detected.

Braunschweig and co-workers investigated paternal inheritance with respect to methyl donor exposure in pigs [93]. The F0 generation of boars was fed a diet high in methyl donors, their offspring F1 boars and their offspring F2 pigs were fed normally. As well as other effects of grandpaternal methyl donor exposure, there was a change in DNA methylation at IYD gene promoter in liver. This interesting finding suggests that there may be an epigenetic effect of increased methyl donors for generations.

As a rat model of paternal obesity, male rats were fed a high fat diet. Female offspring had impaired glucose homeostasis, and a large number of pancreatic islet genes were differentially expressed, Il13ra2 to the greatest degree. Lower DNA methylation at the Il13ra2 gene suggests that the high fat diet of the father may have affected the progeny by epigenetic means [94].

Conclusion

The study of nutrition and epigenetics in development is a fast moving new field. Up to now human studies are few but the animal model is burgeoning. The areas of biochemistry studied are very diverse and likely to remain so. In pace with progress in techniques more genome wide microarray studies are emerging enabling a picture to be built up of the effect of in utero conditions. Imprinted genes of offspring are affected by exposure to maternal diet in utero, and the IGF2/H19 region has been particularly extensively examined. The hypothalamic pituitary adrenal axis is another area of active study.

Future work is needed to understand any role of paternal diet on DNA methylation, and as obesity and undernutrition remain significant issues an understanding of how a parent’s diet can affect future generations is of great interest.

References

1. Barker DJ (2004) The developmental origins of adult disease. J Am Coll Nutr 23(Suppl 6): 5885-5935.
2. Dominguez-Salas P, Cox SE, Prentice AM, Hennig BJ, Moore SE (2012) Maternal nutritional status, C (1) metabolism and offspring DNA methylation: a review of current evidence in human subjects. Proc Nutr Soc 71(1): 154-165.
3. Seisenberger S, Peat JR, Hore TA, Santos F, Dean W, et al. (2013) Reprogramming DNA methylation in the mammalian life cycle: building and breaking epigenetic barriers. Philos Trans R Soc Lond B Biol Sci 368(1609): 20110330.
4. Carone BR, Fauquier L, Habib N, Shea JM, Hart CE, et al. (2010) Paternally induced transgenerational environmental reprogramming of metabolic gene expression in mammals. Cell 143(7): 1084-1096.
5. Abramowitz LK, Bartolomei MS (2012) Genomic imprinting: recognition and marking of imprinted loci. Curr Opin Genet Dev 22(2): 72-78.
6. Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, et al. (2009) DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. Hum Mol Genet 18(21): 4046-4053.
7. Cooper WN, Khulan B, Owens S, Elks CE, Seidel V, et al. (2012) DNA methylation profiling at imprinted loci after periconceptional micronutrient supplementation in humans: results of a pilot randomized controlled trial. FASEB J 26(5): 1782-1790.
8. Khulan B, Cooper WN, Skinner BM, Bauer J, Owens S, et al. (2012) Periconceptional maternal micronutrient supplementation is associated with widespread gender related changes in the epigenome: a study of a unique resource in the Gambia. Hum Mol Genet 21(9): 2086-2101.
9. Heijmans BT, Tobi EW, Steen AD, Putter H, Blauw GJ, et al. (2008) Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci 105(44): 17046-17049.
10. Waterland RA, Kellermayer R, Laritsky E, Rayco-Solon P, Harris RA, et al. (2010) Season of conception in rural gambia affects DNA methylation at putative human metastable epialleles. PLoS Genetics 6(12): e1001252.
11. Lumey LH, Terry MR, Delgado-Cruzata L, Liao Y, Wang Q, et al. (2012) Adult global DNA methylation in relation to pre-natal nutrition. Int J Epidemiol 41(1): 116-123.
12. Tobi EW, Slagboom PE, van Dongen J, Kremer D, Stein AD, et al. (2012) Prenatal famine and genetic variation are independently and additively associated with DNA methylation at regulatory loci within IGF2/H19, PloS One 7(5): e37933.
13. Fryer AA, Nafee TM, Ismail KM, Carroll WD, Emes RD, et al. (2009) LINE-1 DNA methylation is inversely correlated with cord plasma homocysteine in man: a preliminary study. Epigenetics 4(6): 394-398.
14. Steegers RP, Obermann-Borst SA, Kremer D, Lindemans J, Siebel C, et al. (2009) Periconceptional maternal folic acid use of 400 microg per day is related to increased methylation of the IGF2 gene in the very young child. PloS one 4(11): e7845.
15. Hojo C, Murtha AP, Schildkraut JM, Jirtle RL, Demark-WW, et al. (2011) Methylation variation at IGF2 differentially methylated regions and maternal folic acid use before and during pregnancy. Epigenetics 6(7): 928-936.
16. Boeke CE, Baccarelli A, Kleinman KP, Burris HH, Litojuna AA, et al. (2012) Gestational intake of methyl donors and global LINE-1 DNA methylation in maternal and cord blood: prospective results from a folate-replete population. Epigenetics 7(3): 253-260.
17. Drake AJ, McPherson RC, Godfrey KM, Cooper C, Lilleycrop KA, et al. (2012) An unbalanced maternal diet in pregnancy associates with offspring epigenetic changes in genes controlling glucocorticoid action and fetal growth. Clin Endocrinol 77(6): 808-815.
18. Jiang X, Yan J, West AA, Perry CA, Malyshova OV, et al. (2012) Maternal choline intake alters the epigenetic state of fetal cortisol-regulating genes in humans. PASEB 26(8): 3563-3574.
19. Altmann S, Murani E, Schwerin M, Metges CC, Wimmers K, et al. (2013) Dietary protein restriction and excess of pregnant German Landrace sows induce changes in hepatic gene expression and promoter methylation of key metabolic genes in the offspring. J Nutr Biochem 24(2): 484-495.

20. Altmann S, Murani E, Schwerin M, Metges CC, Wimmers K, et al. (2012) Maternal dietary protein restriction and excess affects offspring gene expression and methylation of non-SMC subunits of condensin I in liver and skeletal muscle. Epigenetics 7(3): 239-252.

21. Altmann S, Murani E, Schwerin M, Metges CC, Wimmers K, et al. (2012) Somatic cytochrome c (CYCS) gene expression and promoter-specific DNA methylation in a porcine model of prenatal exposure to maternal dietary protein excess and restriction. Br J Nutr 107(6): 791-799.

22. Jia Y, Cong R, Li R, Yang X, Sun Q, et al. (2012) Maternal low-protein diet induces gender-dependent changes in epigenetic regulation of the glucose-6-phosphatase gene in newborn piglet liver. J Nutr 142(9): 1659-1665.

23. Zeng Y, Gu P, Liu K, Huang P (2013) Maternal protein restriction in rats leads to reduced PGC-1alpha expression via altered DNA methylation in skeletal muscle. Mol Med Rep 7(1): 306-312.

24. Hoile SP, Lillycrop KA, Thomas NA, Hanson MA, Burgd Ge (2011) Dietary protein restriction during F0 pregnancy in rats induces transgenerational changes in the hepatic transcriptome in female offspring. PLoS One 6(7): e21668.

25. Slater-Jefferies JL, Lillycrop KA, Townsend PA, Torrens C, Hoile SP, et al. (2011) Feeding a protein-restricted diet during pregnancy induces altered epigenetic regulation of peroxisomal proliferator-activated receptor-a in the heart of the offspring. J Dev Orig Health Dis 2(4): 250-255.

26. Zheng S, Rolbet M, Yang K, Pan YX (2012) A gestational low-protein diet represses p21(WAF1/Cip1) expression in the mammary gland of offspring rats through promoter histone modifications. Br J Nutr 108(6): 998-1007.

27. Zheng S, Pan YX (2011) Histone modifications, not DNA methylation, cause transcriptional repression of p16 (CDKN2A) in the mammary glands of offspring of protein-restricted rats. J Nutr Biochem 22(6): 567-573.

28. Gong L, Pan YX, Chen H (2010) Gestational low protein diet in the rat mediates Igf2 gene expression in male offspring via altered hepatic DNA methylation. Epigenetics 5(7): 619-626.

29. Engeham SF, Haase A, Langley ESC (2010) Supplementation of a maternal low-protein diet in rat pregnancy with folic acid ameliorates programming effects upon feeding behaviour in the absence of disturbances to the methionine-homocysteine cycle. Br J Nutr 103(7): 996-1007.

30. Ivanova E, Chen JH, Segonds PA, Ozanne SE, Kelley G (2012) DNA methylation at differentially methylated regions of imprinted genes is resistant to developmental programming by maternal nutrition. Epigenetics 7(10): 1200-1210.

31. Balasa A, Sanchez VA, Sadikovic B, Sangji HH, Bravo J, et al. (2011) Chronic Maternal Protein Deprivation in Mice Is Associated with Overexpression of the Coheresin-Mediator Complex in Liver of Their Offspring. J Nutr 141(12): 2106-2112.

32. Jouss C, Parry L, Lamber -LS, Maurin AC, Averous J, et al. (2011) Perinatal undernutrition affects the methylation and expression of the leptin gene in adults: implication for the understanding of metabolic syndrome. FASEB 25(9): 3271-3278.

33. Goyal R, Goyal D, Leitzke A, Gheorghie CP, Longo LD (2010) Brain renin-angiotensin system: fetal epigenetic programming by maternal protein restriction during pregnancy. Reprod Sci 17(3): 227-238.

34. Van Straten EM, Bloks VW, Huijkm NC, Baller JF, van Meer H, et al. (2010) The liver X-receptor gene promoter is hypermethylated in a mouse model of prenatal protein restriction. Am J Physiol Heart Circ Physiol 298(2): R275-R282.

35. Rentaj E, Bloch J, Jalet PF, Rimoldi SF, Dessen P, et al. (2011) Fetal programming of pulmonary vascular dysfunction in mice: role of epigenetic mechanisms. Am J Physiol Heart Circ Physiol 301(1): H247-H252.

36. Nijland MJ, Mitsuya K, Li C, Ford S, McDonald TJ, et al. (2010) Epigenetic modification of fetal baboon hepatic phosphoenolpyruvate carboxykinase following exposure to moderately reduced nutrient availability. J Physiol 588(8): 1349-1359.

37. Unterberger A, Syf M, Nathanielsz PW, Cox LA (2009) Organ and gestational age effects of maternal nutrient restriction on global DNA methylation in fetal baboons. J Med Primatol 38(4): 219-227.

38. Begum G, Stevens A, Smith EB, Connor K, Challis JR, et al. (2012) Epigenetic changes in fetal hypoxiamic energy regulating pathways are associated with maternal undernutrition and twinning. FASEB 26(4): 1694-1703.

39. Stevens A, Begum G, Cook A, Connor K, Rumball C, et al. (2010) Epigenetic changes in the hypothalamic proopiomelanocortin and glucocorticoid receptor genes in the ovine fetus after periconceptional undernutrition. Endocrinology 151(8): 3652-3664.

40. Langie SA, Achterfold S, Gorniak JP, Halley-Hogg KJ, Oxley D, et al. (2013) Maternal folate depletion and high-fat feeding from weaning affects DNA methylation and DNA repair in brain of adult offspring. FASEB 27(8): 3323-3334.

41. Konycheva G, Dziadek MA, Ferguson LR, Krägeloh CU, Cooen MW, et al. (2011) Dietary methyl donor deficiency during pregnancy in rats shapes learning and anxiety in offspring. Nutr Res 31(10): 790-804.

42. McKay JA, Williams EA, Mathers JC (2011) Effect of maternal and post-weaning folate supply on gene-specific DNA methylation in the small intestine of weaning and adult apc and wild type mice. Front Genet 2:23.

43. McKay JA, Waltham KJ, Williams EA, Mathers JC (2011) Folate depletion during pregnancy and lactation reduces genomic DNA methylation in murine adult offspring. Genes Nutr 6(2): 189-196.

44. McKay JA, Wong YK, Retlon CL, Ford D, Mathers JC (2011) Maternal folate supply and sex influence gene-specific DNA methylation in the fetal gut. Mol Nutr Food Res 55(11): 1717-1723.

45. Delaney C, Garg SK, Fernandes C, Hoeltzel M, Allen RH, et al. (2011) Dietary methyl donor deficiency during pregnancy in rats leads to reduced p21WAF1/Cip1 expression via altered DNA methylation in skeletal muscle. Epigenetics 7(3): 239-252.

46. Tsang V, Fry RC, Nicolescu MD, Rager JE, Saunders J, et al. (2012) The epigenetic effects of a high prenatal folate intake in male mouse fetuses exposed in utero to arsenic. Toxicol Appl Pharmacol 264(3): 439-450.

47. Hoile SP, Lillycrop KA, Grenfell LR, Hanson MA, Burgd Ge (2010) The liver X-receptor gene promoter is hypermethylated in a mouse model of prenatal protein restriction. Am J Physiol Heart Circ Physiol 298(2): R275-R282.

Citation: Vansant G, Wallace S, Godderis L (2016) Effect of Maternal and Paternal Nutrition on DNA Methylation in the Offspring: A Systematic Review of Human and Animal Studies. Adv Obes Weight Manag Control 4(4): 00093. DOI: 10.15406/aowmcc.2016.04.00093
Effect of Maternal and Paternal Nutrition on DNA Methylation in the Offspring: A Systematic Review of Human and Animal Studies

48. Kulkarni A, Dangat K, Kale A, Sable P, Chavan-Gautam P, et al. (2011) Effects of altered maternal folate, citrulline, and vitamin B12 on placental DNA methylation patterns in Wistar rats. PloS One 6(3): e17706.

49. Li CC, Copley JE, Cowley MJ, Preiss T, Martin DI, et al. (2011) A sustained dietary change increases epigenetic variation in isogenic mice. PLoS Genet 7(4): e1001380.

50. Ly A, Lee H, Chen J, Sie KK, Renlund R, et al. (2011) Effect of maternal and postweaning folate acid supplementation on mammary tumor risk in the offspring. Cancer Res 71(3): 988-9897.

51. Schaible TD, Harris RA, Dowd SE, Smith CW, Kellerman R (2011) Maternal methyl-donor supplementation induces prolonged murine offspring coat color susceptibility in association with mucosal epigenetic and microbiomic changes. Hum Mol Genet 20(9): 1687-1696.

52. Sie KK, Medline A, van Weel J, Sohn KJ, Choi SW, et al. (2011) Effect of maternal and postweaning folate acid supplementation on colorectal cancer risk in the offspring. Gut 60(12): 1687-1694.

53. Sie KK, Li J, Ly A, Sohn KJ, Cro福德 R, et al. (2013) Effect of maternal and postweaning folate acid supplementation on global and genespecific DNA methylation in the liver of the rat offspring. Mol Nutr Food Res 57(4): 677-685.

54. Copley JE, Suter CM, Beckman KB, Martin DI (2010) CpG methylation of a silent controlling element in the murine Aryl alcohol is incomplete and unresponsive to methyl donor supplementation. PloS One 5(2): e9055.

55. Herbek Y, Gulevich RG, Amelkina OA, Plyusnina IZ, Oskina N (2010) Conserved methylation of the glucocorticoid receptor gene exon 1(7) promoter in rats subjected to a maternal methyl-supplemented diet. Int J Dev Neurosci 28(1): 9-12.

56. Kim JM, Hong K, Lee JH, Lee S, Chang N (2009) Effect of folate deficiency on placental DNA methylation in hyperhomocysteinemic rats. J Nutr Biochem 20(3): 172-176.

57. Kowachew VP, Davison JM, Melott TJ, Rogers AE, Yang S, et al. (2002) Raising gestational choline intake alters gene expression in DMBA-evoked mammary tumors and prolongs survival. FASEB J 23(4): 1054-1063.

58. Bekdask R, Zhang C, Sarkar DK (2013) Gestational Choline Supplementation Normalized Fetal Alcohol-Induced Alterations in Histone Modifications, DNA Methylation, and Proopiomelanocortin (POMC) Gene Expression in β-Endorphin-Producing POMC Neurons of the Hypothalamus. Alcohol Clin Exp Res 37(7): 1133-1142.

59. Hirabara SM, Fiolador A, Fiamoncini J, Lambertucci RH, Rodrigues CF, et al. (2013) Fish oil supplementation for two generations increases insulin sensitivity in rats. J Nutr Biochem 24(6): 1136-1145.

60. Hoile SP, Irvine NA, Kelsall CJ, Sibbons C, Feunteun A, et al. (2012) Maternal fat intake in rats alters 20:4n-6 and 22:6n-3 status and the epigenetic regulation of Fads2 in offspring liver. J Nutr Biochem 23(7): 1213-1220.

61. Niculescu MD, Lupo DS, Criclunescu CN (2013) Perinatal manipulation of α-linolenic acid intake induces epigenetic changes in maternal and offspring livers. FASEB J 27(1): 350-358.

62. Vucetic Z, Kimmel J, Totoki K, Hollenbeck E, Reyes TM (2010) Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. Endocrinology 151(10): 4756-4764.

63. Dunn GA, Bale TL (2009) Maternal high-fat diet promotes body weight increases and insulin insensitivity in second-generation mice. Endocrinology 150(11): 4999-5009.

64. Chen JR, Zhang J, Lazarenko OP, Kang P, Blackburn ML, et al. (2012) Inhibition of fetal bone development through epigenetic downregulation of FoxA10 in obese rats fed high-fat diet. PASEB 26(3): 1131-1141.

65. Gallou KC, Gabory A, Test J, Karimi M, Mayeur S, et al. (2010) Sex- and diet-specific changes of imprinted gene expression and DNA methylation in mouse placenta under a high-fat diet. PloS one 5(12): e14398.

66. Chmuryzna A, Stachowiak M, Pruszyńska OE (2012) Maternal protein and folate diet intake during gestation does not program leptin transcription or serum concentration in rat progeny. Genes Nutr 7(2): 217-222.

67. Dudley KJ, Skoboda DM, Connor KL, Beltrand J, Vickers MH (2011) Offspring of mothers fed a high fat diet display hepatic cell cycle inhibition and associated changes in gene expression and DNA methylation. PloS one 6(7): e21662.

68. Suter, M, Bocock P, Showalter L, Hu M, Shope C, et al. (2011) Epigenomics: maternal high-fat diet exposure in utero disrupts peripheral circadian gene expression in nonhuman primates 25(2): 714-726.

69. Keskall CJ, Hoile SP, Irvine NA, Masoodi M, Torrens C, et al. (2012) Vascular dysfunction induced in offspring by maternal dietary fat involves altered arterial polynsaturated fatty acid biosynthesis. PloS One 7(4): e43492.

70. Burdge, G. C. et al. Progressive, transgenerational changes in offspring phenotype and epigenotype following nutritional transition. PloS One 6, e28282 (2011).

71. Ehtara T, Kamey H, Takahashi M, Yuan X, Kanai S, et al. (2012) Role of DNA methylation in the regulation of lipogenic glycerol-3-phosphate acyltransferase 1 gene expression in the mouse neonatal liver. Diabetes 61(10): 2442-2450.

72. Vanhees, K, Godschalk RW, Sanders A, Van Schooten FJ, Van Waalwijk VDKSB (2011) Maternal quercetin intake during pregnancy results in an adapted iron homeostasis at adulthood. Toxicology 290(2-3): 350-358.

73. Takaya J, Ibarara A, Okihana H, Kaneko K (2011) Magnesium deficiency in pregnant rats alters methylation of specific cytosines in the hepatic hydroxysteroid dehydrogenase-2 promoter of the offspring. Epigenetics 6(5): 573-578.

74. Ding Y, Lv J, Mao C, Zhang H, Wang A, et al. (2010) High-salt diet during pregnancy and angiotsin-related cardiac changes. J Hypertens 28(6): 1290-1297.

75. Kurita H, Ohsako S, Hashimoto S, Yoshinaga J, Tohyama C (2013) Prenatal zinc deficiency-dependent epigenetic alterations of mouse metallothionein-2 gene. J Nutr Biochem 24(1): 256-266.

76. Lan X, Cretney EC, Krupp J, Kha-teek B, Berg MA, et al. (2013) Maternal Diet During Pregnancy Induces Gene Expression and DNA Methylation Changes in Fetal Tissues in Sheep. Front Genet 4: 49.

77. Feng Y, Zhao LZ, Hong L, Shan C, Shi W, et al. (2013) Alteration in methylation pattern of GATA-4 promoter region in vitamin A-deficient offspring’s heart. J Nutr Biochem 24(7): 1373-1380.

78. Cho CE, Sánchez HD, Reza-López SA, Huot PS, Kim YJ, et al. (2013) Obesogenic phenotype of offspring of dams fed a high multivitamin diet is prevented by a post-weaning high multivitamin or high folate diet. Int J Obes 37(9): 1171-1182.

79. Lumey LH, Stein AD, Susser E (2011) Prenatal famine and adult health. Annu Rev Public Health 32: 237-262.
80. Roseboom T, de Rooij S, Painter R (2006) The Dutch famine and its long-term consequences for adult health. Early Hum Dev 82(8): 485-491.

81. Van Abeelen AF, Veenendaal MV, Painter RC, de Rooij SR, Dijkgraaf MG, et al. (2012) Survival effects of prenatal famine exposure. Am J Clin Nutr 95(1): 179-183.

82. Ong K, Kratzsch J, Kiess W, Costello C, et al. (2000) Size at birth and cord blood levels of insulin, insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-1 (IGFBP-1), IGFBP-3, and the soluble IGF-II/mannose-6-phosphate receptor in term human infants. The ALSYAC Study Team. Avon Longitudinal Stud. J Clin Endocrinol Metab 85(11): 4266-4269.

83. Ratajczak MZ (2012) Igf2-H19, an imprinted tandem gene, is an important regulator of embryonic development, a guardian of proliferation of adult pluripotent stem cells, a regulator of longevity, and a “passkey” to cancerogenesis. Folia histochemica et cytobiologica / Polish Academy of Sciences, Polish Histochemical and Cytochemical Society 50:171-179.

84. Chao W, D’Amore P (2008) IGF2: epigenetic regulation and role in development and disease. Cytokine Growth Factor Rev 19(2): 111-120.

85. Coolen MW, Statham AL, Qu W, Campbell MJ, Henders AK, et al. (2011) Impact of the genome on the epigenome is manifested in DNA methylation patterns of imprinted regions in monozygotic and dizygotic twins. PloS One 6(10): e25590.

86. Reynolds RM (2013) Glucocorticoid excess and the developmental origins of disease: two decades of testing the hypothesis–2012 Curt Richter Award Winner. Psychoneuroendocrinology 38(1): 1-11.

87. Terry MB, Delgado-Cruzat LA, Vin-Raviv N, Wu HC, Santella RM (2011) DNA methylation in white blood cells: Association with risk factors in epidemiologic studies. Epigenetics 6(7): 828-837.

88. Zhang FF, Santella RM, Wolff M, Kapil MA, Markowitz SB, et al. (2012) White blood cell global methylation and IL-6 promoter methylation in association with diet and lifestyle risk factors in a cancer-free population. Epigenetics 7(6): 606-614.

89. McKay JA, Groom A, Potter C, Coneyworth LJ, Ford D, et al. (2012) Genetic and non-genetic influences during pregnancy on infant global and site specific DNA methylation: role for foetal gene variants and vitamin B12. PloS One 7(3): e33290.

90. Soubry A, Schildkraut JM, Murtha A, Wang F, Huang Z, et al. (2013) Paternal obesity is associated with IGFB2 hypomethylation in newborns: results from a Newborn Epigenetics Study (NEST) cohort. BMC Med 11: 29.

91. Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DI, et al. (2008) Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. BJOG 115(10): 1243-1249.

92. Curley JP, Mashoodh R, Champagne FA (2011) Epigenetics and the origins of paternal effects. Horm Behav 59(3): 306-314.

93. Braunshweig M, Jagannathan V, Gutzwiller A, Bee G (2012) Investigations on transgenerational epigenetic response down the male line in f2 pigs. PloS One 7(2): e30583.

94. Ng SF, Lin RC, Laybutt DR, Barres R, Owens JA, et al. (2010) Chronic high-fat diet in fathers programs β-cell dysfunction in female rat offspring. Nature 467(7318): 963-966.