

Review Article

The Molecular Mechanisms of Offspring Effects from Obese Pregnancy

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Key Words

Maternal obesity · Epigenetics · Reactive oxygen species

Abstract

The incidence of obesity, increased weight gain and the popularity of high-fat / high-sugar diets are seriously impacting upon the global population. Billions of individuals are affected, and although diet and lifestyle are of paramount importance to the development of adult obesity, compelling evidence is emerging which suggests that maternal obesity and related disorders may be passed on to the next generation by non-genetic means. The processes acting within the uteri of obese mothers may permanently predispose offspring to a diverse plethora of diseases ranging from obesity and diabetes to psychiatric disorders. This review aims to summarise some of the molecular mechanisms and active processes currently known about maternal obesity and its effect on foetal and neonatal physiology and metabolism. Complex and multifactorial networks of molecules are intertwined and culminate in a pathologically synergistic manner to cause disruption and disorganisation of foetal physiology. This altered phenotype may potentiate the cycle of intergenerational transmission of obesity and related disorders.

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Introduction

Following conception, embryos are exposed to a myriad of heterogeneous and multifactorial conditions which impact upon the complex processes of foetal growth and development. Genetics, maternal factors, uterine environment and maternal and foetal hormonal status are

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all interlinked and are responsible for the progression of embryo to full term foetus [1]. The sequential and continued involvement of these factors must be tightly regulated to ensure optimal intrauterine homeostasis for the delicate architecture of the developing foetus and to promote healthy pregnancy outcome. Any alteration or variation away from optimal growing conditions can have deleterious and long lasting effects [2]. Maternal obesity, significant weight gain or high dietary fat and sugar intake during pregnancy can be characterised by altered glucose metabolism in which various maternal factors are pathologically altered in such a way that may induce changes in foetal growth and developmental trajectories. Human studies have shown that this may predispose offspring to develop obesity, diabetes, cardiovascular abnormalities, adult schizophrenia and asthma [3–9]. Concurrently, studies in animals have found evidence that offspring from obese and high calorific pregnancy may be predisposed to hypertension, renal disorders, non-alcoholic fatty pancreas and liver disease, metabolic disease as well as possible links to psychiatric disorders such as hyperactivity in ADHD [10–15]. In comparison, a study by Smith et al. [9] has shown that offspring born after significant maternal weight loss as a result of biliopancreatic diversion bariatric surgery show improvements in cardiometabolic markers sustained into adolescence, attributable to an improved intrauterine environment. Increasing maternal BMI also increases obstetric complications for the mother and offspring (congenital malformations, macrosomia) [2, 16, 17]. The Barker hypothesis states that environmental influences acting in foetal life are reflected in impaired growth and development which permanently affect structure and metabolism, leading to increased risk of metabolic disease later in life [3]. Indeed during obese pregnancy, the altered nutrient supply present during sensitive periods of gestation may lead to a response by the foetus to ‘program’ its organs and tissues in a way that results in long-term alterations to their function [18].

Global obesity rates have been increasing logarithmically over recent decades, indeed doubling since 1980, and in 2008 1.5 billion adults were overweight and 500 million obese. Of concern are the 43 million children under the age of 5 who were overweight in 2010. Furthermore obesity rates are higher in woman then in men, and consequently young woman are increasingly likely to be obese before pregnancy [5, 19]. If current trends continue unchallenged, projected figures for overweight and obese individuals will be more than 2.16 billion and 1.12 billion respectively by 2030 [20]. The metabolic phenotype associated with obesity involves several of those factors associated with diabetes, namely insulin resistance and glucose intolerance. These factors are crucial to the development of the metabolic syndrome and concurrently increase the risk of developing type 2 diabetes mellitus (T2DM). Other studies have shown evidence that obesity and rapid linear growth in early childhood significantly increases the risk of developing type 1 diabetes [21]. This ‘diabesity’ phenotype is a chronic self-perpetuating cycle. Emerging evidence, including substantial evidence from experimental animals, suggests that overweight and obese mothers may predispose their offspring to similar fates later in life, while mothers who undergo weight loss before pregnancy produce healthier offspring with significant improvements in many cardiometabolic markers [9, 16, 22, 23].

Mechanisms Involved

Epidemiological data and experimental studies in animal models have elucidated several mechanisms which may explain, at least in part, the aetiology of the offspring effects arising from maternal obesity. During development of multicellular organisms, cells become differentiated from one another by changing their genetic programme in response to transient stimuli [2]. Long after the stimulus is removed, ‘cellular memory’ processes allow cells to

remember their chosen fate over many cell divisions [24]. Consequently, the obese maternal intrauterine environment constitutes an unfavourable combination of pathogenic factors that appear to interfere with developmental processes during critical time windows causing obstetric complications and lifelong epigenetic malprogramming in offspring. Foetal malprogramming of certain hypothalamic feeding circuits, among other pathways, by means of processes that will be discussed hereafter have been shown in various experimental animal models to be capable of causing persistent effects on the metabolic and feeding activity of offspring and can even be transmitted to the next generation [2, 13]. This can predispose these offspring to a host of downstream disorders and pathologies previously mentioned. This review will summarise some of these mechanisms in a temporal manner beginning with mechanisms affecting the early embryo and progressing from there. Topics including:

- Maternal and foetal hyperglycaemia is a primary influencing agent on various downstream molecules and processes vital for the development of key organs and systems such as the heart, placenta, and the hypothalamic-neuroendocrine system.
- The arachidonic acid-prostaglandin, nitric oxide, and inflammatory pathways, in addition to foetal hyperinsulinaemia and insulin resistance have been shown to play important roles in embryo development, cardiovascular and placental function.
- Reactive oxygen species and lipotoxicity are also discussed as aggravators of foetal inflammation and negatively affect foetal development.
- And finally, the nature of permanent metabolic alteration and predisposition to later age onset of disease in offspring is discussed.

Hyperglycaemia

Glucose is the primary fuel source used by embryos, but fluctuations in maternal blood glucose constitute an unfavourable environment for embryonic and foetoplacental development [22, 25]. Maternal glucose levels correlate with foetal size and adiposity [26]. Excessive blood glucose or hyperglycaemia is believed to be the primary teratogen associated with obese pregnancy and responsible for a wide array of developmental abnormalities [16, 17, 27]. Several mechanisms have been proposed to explain how maternal hyperglycaemia and insulin resistance may alter the intrauterine milieu.

Arachidonic Acid-Prostaglandin and Nitric Oxide Pathways

Synthesis of prostaglandins and related molecules depends on the availability of arachidonic acid and the activity of cyclooxygenases (COX-1, COX-2). Cyclooxygenases convert arachidonate to many different active prostaglandins in response to a variety of stimuli and have a diverse range of actions [28]. Alterations in prostanoid production as a result of insulin resistance and hyperglycaemia in different tissues depend upon several factors. These include, whether good glycaemic control is adhered to or not, regulation of COX-1 and COX-2 gene expression, and levels and responses to ROS and non-esterified fatty acids (NEFAs) [28, 29].

Nitric oxide (NO) is an important player in the arachidonic acid-prostaglandin pathway. NO is constitutively expressed in vascular endothelium by endothelial NO synthase (eNOS) and inducibly expressed in immune cells by inducible NO synthase (iNOS) after stimulation by cytokines, lipopolysaccharides and other immunogenic agents [28]. NO activates haeme-containing enzymes such as COX, which stimulates the production of prostaglandins in different tissues [30]. Thus NO seems to act as a positive regulator of prostaglandin production.

During normal embryonic development, prostaglandins and NO play crucial roles in various key stages. However too much or too little of either can lead to deleterious effects downstream. Obesity presents increased concentrations of oxidised low-density lipoprotein (oxLDL) [31] and inflammatory molecules such as TNF- α [32], which both cause the down-regulation of eNOS expression, via a reduction in its mRNA half-life [29]. Protein kinase C $_{\beta}$ (PKC $_{\beta}$) has been shown to be activated in insulin-resistant states and capable of inhibiting phosphatidylinositol-3 kinase (PI3k) and eNOS activity and expression [29, 33]. As a result, decreased NO production negatively impacts prostaglandin function. Prostaglandins, and in particular PGE $_2$, have shown to be essential in follicular maturation and ovulation. NO is also involved in oocyte maturation, ovulation, fertilization and implantation [34]. During this time period there is an increase in both PGE $_2$ and COX-2 in the ovaries [28]. Studies have shown that impaired meiotic maturation, impaired ovulation, insensitivity to exogenous gonadotropin therapy and depressed ovarian steroidogenesis may occur in association with the hyperglycaemic state [35, 36]. Indeed maternal hyperglycaemia in mice has shown to adversely affect pre-implantation progression from a one-cell to blastocyst stage. Mouse blastocyst cells were effectively starved as a result of the down-regulation of facilitative glucose transporters. This reduction in available glucose is sufficient to induce apoptosis in the embryo and along with altered NO and prostaglandin production may account for impaired growth and development [37–40]. Insulin treatment early in gestation normalises glycaemia and concurrently improves embryo development and restores normal cell number in both the inner cell mass and trophectoderm of blastocysts [41].

Reactive Oxygen Species

NO is no more reactive than oxygen, but its toxicity is vastly enhanced when it reacts with superoxide to form peroxynitrite. NO is the only biological molecule produced at sufficiently high concentrations to out-compete the anti-oxidant superoxide dismutase for superoxide binding [42]. Peroxynitrite inflicts significant cellular damage by inducing lipid peroxidation, oxidation of sulfhydryl groups in proteins, and nitrate amino acids (e.g. tyrosine) which can affect many signalling transduction pathways [42]. Peroxynitrite also causes DNA strand breakage and mutagenesis, and subsequently results in the activation of nuclear enzyme poly(ADP-ribose)synthetase (PARS), which causes cellular energy depletion (decreased mitochondrial respiration) and cellular injury [43]. Both prostaglandins and NO have been found to play a role in the destruction of β -cells in pancreatic islets of Langerhans. However NO seems to play a biphasic role in reproduction, in that a narrow range of NO concentrations, usually low, will stimulate and enhance important early events in reproduction, whereas a lack of NO or too much NO has negative consequences [34]. Chronic increases in ROS production in mitochondria in response to hyperglycaemia, plus damage inflicted during embryogenesis can lead to a catastrophic cycle of mitochondrial DNA damage, functional decline, further ROS generation, cellular injury and apoptosis [44, 45]. For example; ROS can directly impair contractile function by modifying proteins central to excitation-contraction coupling, such as the critical thiol groups on ryanodine receptors, thereby enhancing their open probability, suppression of L-type calcium channels and inhibition of Ca $^{2+}$ uptake in the sarcoplasmic reticulum by means of oxidative interaction with Ca $^{2+}$ ATPase [46]. ROS can also affect myocardial development and function by means of activating many downstream signalling pathways involved in myocardial growth [44, 45], matrix remodelling, and cellular dysfunction. A broad range of hypertrophic signalling kinases and transcription factors can be stimulated by ROS, including Src (tyrosine kinase), Ras (GTP-binding protein), PKC, mitogen-activated protein kinase, and Jun-nuclear kinase (JNK). Low levels of ROS are asso-

ciated with protein synthesis, whereas higher levels of ROS induce mitochondrial and DNA damage and apoptosis [44, 47].

ROS can also indirectly impact myocardial development/function. For example, in adult hearts, inflammatory mediators can be stimulated by ROS to subsequently activate myocardial matrix metalloproteinases which promote the progression of cardiac remodelling [44]. Furthermore, Eriksson et al. [48] found that the addition of reactive oxygen scavenging enzyme superoxide dismutase to cultured rat embryos protected against the teratogenic effects of hyperglycaemia. Secondly, the cytoprotective role of NO on cardiac physiology (which includes coronary vasodilation, inhibition of platelet and neutrophil adhesion and activation and modulation of cardiac contractile function) can be reversed when it forms peroxynitrite [49]. ROS have also been shown to stimulate cardiac fibroblast proliferation and cardiomyocyte hypertrophy directly [50]. Once activated, embryonic fibroblasts stimulate embryonic cardiomyocyte proliferation in utero [51]. Cardiac fibroblasts account for up to two thirds of cells in the adult heart [52] and unlike adult cardiomyocytes, adult cardiac fibroblasts can proliferate and increase deposition of extracellular matrix (ECM) proteins such as fibronectin and collagen, which induce interstitial fibrosis and increased passive stiffness of the myocardium that leads to cardiac dysfunction [53]. Angiotensin-II, the main effector peptide of the renin-angiotensin system, can induce cardiomyocyte hypertrophy and cardiac fibroblast proliferation via the AT₁ receptor by means of intracellular ROS intermediates. [54]. Accordingly, cardiac fibroblast proliferation and cardiomyocyte hypertrophy, combined with increased synthesis of ECM proteins such as collagen and fibronectin, may lead to ventricular remodelling and cardiovascular disease. Human and animal studies have shown a higher prevalence of cardiovascular disorders in offspring from obese pregnancy compared to normal pregnancy [55–57].

Lipotoxicity and Placental Function

Studies have shown that obese woman accumulate more upper-body fat, whereas lean woman accumulate fat in the lower-body compartment during pregnancy [58, 59]. This is important as visceral fat is associated with an abnormal metabolic and adipokine profile [60]. Upper-body fat is more prone to lipolysis and produces approximately 60% of circulating NEFAs compared to only 15–20% circulating NEFAs produced by lower-body fat stores [60]. Hypertrophic obesity or the enlargement of adipose cells in the upper-body causes an inhibition of fatty acid uptake with increased lipolysis, inflammatory cell infiltration and adipokine secretion [61]. This causes lipotoxicity, which involves the release of excess NEFAs into circulation which accumulate in organs and tissues (heart, liver, muscle) [62]. When intracellular levels of fatty acids become too much for the cell to cope with, cellular disturbances occur, including excessive oxidation of fatty acids causing ROS production, disruption in cell membrane and phospholipid composition as well as changes in ceramide signalling and cholesterol content [63]. This hypertrophic obesity with lipotoxicity, inflammation and cellular dysfunction can cause local insulin resistance with decreased insulin receptor substrate-1 (IRS-1) and GLUT4 protein content [62]. Elevated lipid levels and oxidative stress lead to the production of three harmful oxidised lipid products: lipid peroxides, oxidised lipoproteins and oxysterols [60]. High NEFA levels can produce NO radical formation in smooth muscle and endothelial cells [60], and like ROS, NEFAs can also directly inhibit NO bioavailability [29] and activate NADPH oxidase and the electron transport chain to generate superoxide [64] which damages cell structures such as mitochondria. Oxysterol production during lipotoxic conditions may impact on placental development and function [60]. oxLDLs containing high amounts of oxysterols and phosphatidylcholine hydroperoxide derivatives

provide ligands for liver X receptor α and β (LXR α and β) and peroxisomal proliferator-activated receptor γ (PPAR γ) expressed on human placenta, and may alter lipid transport and metabolism. Furthermore the interaction between oxLDL and LXR β is involved in the inhibition of human trophoblast invasion in vitro in a concentration-dependent manner [65]. Studies in sheep found maternal obesity increases placental fatty acid transporter expression, foetal blood triglycerides, inflammatory signalling pathways (PPAR γ) and enhances cytokine expression in mid-gestation [66]. Zhu et al. [67] found that maternal and foetal blood concentrations of cholesterol and triglycerides were significantly higher in obese pregnancy. Triglycerides cannot cross the placenta; instead, placental lipases free NEFAs from triglycerides, and these cross over to the foetus where they are transported to the foetal liver via albumin, red blood cells and α -fetoprotein, where they are re-assembled into triglycerides. Therefore excess NEFAs and lipotoxicity in the foetus may induce detrimental cascades which impact on many developmental pathways and cellular memory processes.

Hyperinsulinaemia

Early gestational hyperglycaemic conditions can induce significant deleterious effects on embryonic physiology by causing the death of crucially important progenitor cells and inflicting potentially irreversible damage to others. In mid to late gestation however embryos begin producing their own insulin to regulate glycaemia and growth. Unfortunately this process quickly changes from a helpful mechanism needed for ameliorating high levels of circulating blood glucose to one of a pathogenic accomplice to hyperglycaemia. Insulin decreases blood glucose by triggering liver, muscles and adipose tissue to absorb glucose from circulation and storing it as glycogen or fatty acids [68]. High amounts of insulin are produced in response to overwhelming concentrations of foetal blood glucose. Consequently, high glucose levels combined with high insulin levels cause rapid foetal growth and offspring born large for gestational age or macrosomic. Secondary to macrosomia, foetal hyperinsulinaemia has also been associated with the development of hypertrophic cardiomyopathy [69, 70]. Cardiomyopathy can be characterised by increased passive tension of embryonic myocytes and delayed relaxation time which impair diastolic function and exacerbate foetal hypoxia. Passive stiffness of the myocardium is determined by collagen-based stiffness of the ECM, and titin-based stiffness of the myofilaments [71]. Isoform switching of the giant elastic protein titin is one of the main mechanisms involved in altering passive myocardial stiffness in perinatal heart development and chronic heart disease. In the mammalian heart, titin exists in two main isoforms, both expressed in sarcomeres – the longer more compliant N2BA isoform and the shorter, stiffer N2B isoform [71]. Krüger et al. [71] described how insulin can regulate titin isoform expression with a preference towards increased N2B expression. Furthermore they elucidated that titin isoform shift towards the stiff N2B was reliant on PI3k/Akt signalling pathway and that activation of PI3k increased phosphorylation of Akt at serine 473 by a factor of 4.6 in response to insulin treatment. The authors also discovered that the PI3k activation of mTOR (mammalian target of rapamycin) was important in N2B expression. Moreover, titin stiffness can be altered without any changes in titin-isoform expression. The activation of the mTOR/rictor complex by insulin enhances (PKC α) activity. Phosphorylated PKC α and oxidative stress-related disulphide bridge formation in the cardiac specific N2B-titin domain increase myocardial stiffness, whereas protein kinase G-mediated titin phosphorylation can soften both cardiac titin isoforms [72–74]. Consequently, the multifactorial nature of the obese intrauterine environment may contribute to altered function in cardiomyopathy. Studies using adult rats found that this was a result of increased myocardial fibrosis and collagen volume fraction, higher intra-myocardial vascular

advanced glycation end product deposition, and higher cardiomyocyte resting tension which may be related to insulin-induced increase in stiff N2B-titin isoform [71, 75]. Because many of these processes persist throughout the life of obese/overweight individuals, these factors may contribute to heart disease and dysfunction and may account for the increased risk of later life cardiovascular disease in offspring of obese pregnancy [55–57].

Insulin Resistance

Insulin secretion doubles between the first and third trimester, followed by progressive insulin resistance. This seems to be a natural process that restricts maternal glucose uptake to ensure adequate glucose availability for the growing foetus [23]. However obese mothers have an overproduction of insulin combined with insulin resistance (T2DM), which results in maternal and foetal hyperglycaemia [76]. Diets rich in saturated fatty acids have been shown to play important roles in the onset of obesity-induced insulin resistance. Free fatty acids (FFA) bind to the innate immune receptor TLR4 on adipocytes and macrophages [77]. This leads to production of pro-inflammatory cytokines such as TNF- α . Adipose tissue macrophages were shown to be the source of almost all adipose tissue TNF- α expression and significant amounts of iNOS and IL-6 expression [78]. It is thought that this process is initiated by adipocytes producing low levels of TNF- α in response to FFA. This in turn stimulates pre-adipocytes, endothelial monocyte chemotactic protein-1, adipocytokine expression (IL-6, TNF- α , TGF- β 1), iNOS, C-reactive protein, soluble ICAM and NEFA release. All of which further promote pro-inflammatory and pro-oxidative state [78, 79]. Pro-inflammatory signals induce insulin resistance by inhibiting insulin signalling. TNF- α directly decreases insulin sensitivity in adipocytes by promoting serine phosphorylation of IRS-1 and by impairing tyrosine phosphorylation of insulin receptor. TNF- α also stimulates lipolysis in differentiated human adipocytes through the activation of mitogen-activated protein kinase and extracellular signal-related kinase, and by elevating intracellular cAMP [80]. The activation of other pro-inflammatory pathways such as JNK1, IKK α , IKK β , and PKC are also critical regulators of insulin action [77]. This ultimately leads to hyperglycaemia, glucose intolerance and increased risk of developing the metabolic syndrome and possible onset of T2DM [79]. Furthermore adipose tissue, being an active endocrine organ, secretes a wide range of adipogenic and angiogenic factors such as VEGF, bFGF, IL-6, adiponectin, angiogenin, leptin, IGF-1 and various others. These factors not only play a role in inflammation and oxidative stress resulting in insulin resistance but are also critical factors involved in growth of new vasculature [81]. This enhanced adipose vascular system supplies increased levels of FFA, cytokines and monocytes available to adipose tissue, ultimately perpetuating the progression of obesity, insulin resistance and hyperglycaemia.

Pre-Disposition of Offspring to Later Onset Disease

There are many long-term pathogenic adaptations that the obese intrauterine environment imparts on offspring. The Barker hypothesis initially focussed on the impact of perinatal under nutrition on later life cardiovascular disease [3] and it has been shown in sheep studies that under nutrition at the time of conception can affect offspring glucose-insulin homeostasis [82]. However recently there has been considerable interest on the foetal programming effects of maternal ‘over-nutrition’ or obesity. The most important of these are the increased risk of developing lifelong disorders similar to that present in the mother, namely diabetes and obesity, alongside the multitude of associated disorders. These lifelong maladaptation’s fuel the perpetual cycle of ‘diabesity’ which is of great concern.

Hypothalamic Reprogramming and Epigenetic Modification

Well documented animal studies have shown that maternal obesity and high-fat diet can cause important alterations in the foetal neuroendocrine system which controls appetite, metabolism and energy expenditure. These processes are tightly regulated by a complex neuronal network of the arcuate nucleus of the hypothalamus (ARH) and the paraventricular nucleus of the hypothalamus (PVH). The most important components are the neurons in the ARH which produce proopiomelanocortin (POMC) and neuropeptide-Y (NPY) and co-expressed agouti-related peptide (AgRP) [76]. These neurons provide overlapping projections to the PVH (among other areas) and have opposing effects on appetite, metabolism and energy expenditure. POMC neurons are potent anorectic regulators that suppress appetite by producing α -melanocyte-stimulating hormone (α -MSH). In contrast, the NPY/AgRP neurons act as major orexigenic regulators that stimulate appetite and feeding [83]. Foetal exposure to maternal obesity results in increased expression of orexigenic NPY/AgRP neurons and decreased expression of anorexigenic α -MSH. This leads to a lifelong imbalance in the hypothalamic feeding circuitry and persistent hyperphagia. Studies have shown that the adipokine leptin plays a central role in this programming [84].

Leptin is primarily produced by adipose tissue but is also produced by human placenta, the mammary gland (especially in the early stages of lactation), and in gastric peptic cells. Leptin is involved in many diverse biological functions, but for our purposes we will focus on its effect on the hypothalamus where it plays a crucial role in appetite and food intake. Leptin inhibits the activity of orexigenic NPY/AgRP neurons and stimulates the activity of the anorexigenic POMC neurons to suppress hunger [84]. However studies have shown that offspring of obese mothers develop a central leptin resistance in the hypothalamus [85], possibly due to an early leptin surge. Recently we have found that lambs born to ewes given late pregnancy propylene glycol had significantly heavier birth weights, ponderal index and plasma glucose levels, and they reached the same carcass weight at an earlier age compared to lambs born to control ewes [86]. This study demonstrated that even transient high glycaemic intakes in the third trimester of pregnancy increased the birth weight of offspring and resulted in faster growth rate in early postnatal life. Kirk et al. [85] found that offspring from obese rats display an amplified and prolonged neonatal leptin surge, and this can lead to central leptin resistance and permanently affect hypothalamic functions involving the ARH and PVH. This may be sufficient to program hyperphagia and obesity in offspring.

Another alternative mechanism of epigenetic programming involves the permanent alteration of DNA expression via changes in methylation status, histone acetylation and phosphorylation [2]. Plagemann et al. [87] reported that pre- and neonatal rat pups exposed to overnutrition developed a permanent disposition to obesity, insulin resistance, and cardiac disorders in adulthood. The authors discovered that this was due to altered DNA methylation patterns in hypothalamic promoter regions of genes critically involved in the lifelong regulation of food intake and body weight. The Plagemann group discovered that the promoter of the main orexigenic neurohormone – NPY – was methylated at low levels, but the hypothalamic gene promoter of the anorexigenic neurohormone – POMC – was hypermethylated at CpG dinucleotides within the two Sp1-related binding sequences (Sp1, NFkB) which are essential for the mediation of leptin and insulin effects on POMC expression [87]. Furthermore, Dunn and Bale [88] showed that alterations in methylation status induced by maternal high-fat diet can be passed to at least two subsequent generations in mice. The authors showed that the methylation status of the growth hormone secretagogue receptor was decreased in the ARH and was present in the following two generations of offspring from obese and insulin-resistant mice. This was associated with an increased expression of secretagogue growth hormone and led to an increase in body length and insulin resistance in offspring [88, 89].

Concluding Remarks

Obesity in pregnancy represents a real and tangible risk both to mothers and their children. Although adult diet and lifestyle are of paramount importance to the development of adult obesity, emerging evidence supports the theory that the origin of adult obesity and related disorders may occur during foetal development and early postnatal life. In this review we have summarised mechanisms by which this can occur, namely maternal body type (apple vs. pear), lipotoxicity, hyperglycaemia, hyperinsulinaemia, insulin resistance, generation of ROS and release of NEFAs, damage to mitochondria and the interference of NO and prostaglandin function. These and many other processes create an unfavourable and arduous environment for the foetus to develop. Placental, cardiovascular, musculoskeletal, neurological and metabolic systems can all suffer as a result. Permanent disorganisation of key hypothalamic regulatory elements and hormonal responses burden the offspring of obese mothers with a predisposition to a plethora of childhood and adult diseases which may potentiate the pathogenic cycle once more. Epigenetic studies of maternal obesity and offspring effects have largely been undertaken in animal models, as investigating humans presents ethical and practical difficulties. In time, more detailed longitudinal human studies should provide a comprehensive analysis of the impact of the obesigenic environment on foetal development. The data available to us at the present time shows that reducing the exposure of foetuses to the obesigenic in utero environment can significantly decrease the risk of obesity and associated metabolic disorders in children and adult offspring [9]. Consequently, obese woman planning a pregnancy should be encouraged to lose weight before conception and during pregnancy should be advised on a suitable diet and weight gain. Continued research into the various intertwined molecular systems will further enable us to focus on effective therapeutic and behavioural interventions. Effectively tackling these issues will help alleviate suffering of future generations and help prevent the intergenerational cycle of obesity and related disorders.

Disclosure Statement

The authors declare no conflict of interest.

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