Gamete/Embryo-Fetal Origins of Obesity

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Abstract

Obesity is defined as abnormal or accumulation of excessive fat accumulation. More than 1.4 billion adults were overweight in 2008, of these over 200 million men and nearly 300 million women were obese. Obesity has become one of the most important risk factors contributing to the overall burden of diseases worldwide, so much so that the World Health Organization (WHO) has called obesity an epidemic.

Origins of obesity and metabolic dysfunction can be traced back to the embryonic and fetal stages of life, when the developing fetus is acted upon by, and responds to, sub-optimal, intrauterine environments during critical periods of cellular proliferation, differentiation, and maturation. It produces structural and functional changes in cells, tissues and organ systems. These changes may have long-term consequences increasing an individual's risk for developing complex common disorders including obesity, diabetes, cardiovascular disease and tumours. In this chapter, we will discuss the evidence related to embryo-fetal origins of obesity.

7.1 Risks of Obesity

7.1.1 Birthweight and Later Obesity

Birthweight is an indicator of fetal growth and long-term health. High birth weights are associated with increased risks of adverse adult health outcomes, such as obesity [1, 2] and type 1 diabetes [3], which are important determinants of adult

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mortality [4, 5]. High birthweights are also associated with higher risks of some adult cancers [6, 7].

Individuals with intrauterine growth retardation (IUGR) are at higher risk of neonatal morbidity and of developing metabolic diseases later in life, including type-2 diabetes, obesity and hypertension [8, 9]. Both human epidemiological and experimental evidence indicate that IUGR contributes to low birthweight, and, higher incidence of obesity in adults [10].

7.1.2 Maternal Undernutrition and Later Obesity

Nutrition during the intrauterine phase may be particularly important for the development of obesity. In October 2012, 868 million people worldwide including a large proportion of women of reproductive age were reported by the United Nations Food and Agriculture Organization to suffer from hunger; nearly all of the undernourished reside in low- and middle-income countries [11]. Deficiencies of protein, vitamin A, iron, zinc, folate, and other micronutrients remain major nutritional problems in poor regions of the world [11].

The Dutch Famine studies have demonstrated that there are different consequences of exposure to undernutrition in different trimesters of pregnancy [12]. Exposure in early pregnancy can increase the risks of adult obesity significantly [13]. Much epidemiological evidence shows that fetal exposure to maternal undernutrition is associated with increased risks of adult obesity. Vignini et al. put forward the viewpoint that maternal undernutrition during pregnancy may permanently change or 'programme' the offspring [14]. Barker concluded that coronary heart disease, and, other associated conditions, such as hypertension, stroke, and, non-insulin dependent diabetes, may be the results of 'programming' [15–17]. At a critical, sensitive period of early life, a stimulus or insult promotes long-term changes in physiology or metabolism in offspring's later life. Some studies showed that nutrient restriction during the first half of pregnancy in humans, mice and rats is associated with postnatal metabolic and endocrine disorders, as well as cardiovascular disorders [17–19].

7.1.3 Animal Studies

Mouse models of low birthweight produced by maternal caloric undernutrition during late gestation found reduced birth weight, IGT, and obesity in both first- and second-generation offspring [18]. Ikenasio-Thorpe et al., used a model of nutrient-restricted rats were randomly assigned to receive 30 % of the ad libitum amount during gestation exhibited fetal growth retardation compared with controls [19]. When these offspring were fed a high-fat diet (45 % kcal as fat) for 20 weeks from weaning, there were significant alterations in POMC, NPY, AgRP and OBRb gene expression together with elevations in circulating levels of both plasma leptin and

insulin [19]. There appeared to be interactions between prenatal undernutrition and postnatal high-fat nutrition on the development of postnatal obesity [19].

Long et al. offered cows 70 % of a control diet during early and mid gestation to evaluate effects of maternal nutrient restriction on the morphology of offspring adipose tissue at standard production endpoints [20]. In nutritionally-restricted offspring adipocyte size altered, showing that nutritional restriction during gestation increased adipose tissue depots in finished calves [20]. Multiparous ewes fed 50 % (nutrient-restricted) of their nutrient requirements between 28 and 78 days of gestation demonstrated that maternal undernutrition during early to midgestation increased body weight and fat deposition during adolescence [21].

7.1.4 The 'Thrifty Phenotype' Hypothesis

The "thrifty phenotype" hypothesis proposes that undernutrition during development leads to reallocation of nutrients to favour development of organs; these organs then go on to break down and fail in adulthood [22]. Human epidemiological studies have associated maternal undernutrition and fetal growth restriction during gestation with development of a "thrifty phenotype" in the later lives of offspring. As an extension of this hypothesis, the DOHaD hypothesis describes the origins of adult disease in terms of fetal developmental 'plasticity', or, the ability of the fetus to respond to poor in-utero conditions.

Inappropriate hyperphagia in adult life induced by fetal undernutrition is an example of an adaptive response, where postnatal hypercaloric nutrition can further amplify the metabolic abnormalities [23]. Similarly, rats undernourished in utero exhibit rapid catch-up growth and are more susceptible to developing obesity [24].

Lifestyle choices that exacerbate obesity, may also have a prenatal origin. Offspring of mothers who were undernourished in pregnancy, are significantly more sedentary in postnatal life compared to those born to well-fed mothers [25]. Postnatal hypercaloric nutrition may exacerbate this sedentary behavior, implying that "programmed" adults may be more resistant to public health policies and interventions aimed at increasing physical exercise and reducing food intake.

7.1.5 Neural Plasticity

Neural plasticity may be another important contributor to the continuation of obesity between early development and adulthood. Early pre- and postnatal metabolic conditions such as undernutrition may lead genetically-predisposed offspring to become even more obese as adults. Maternal metabolic consequences of prenatal undernutrition may modify the developing neural systems that control energy homeostasis in the fetus [26].

Increased hypothalamus-pituitary-adrenal axis activity and decreased sympatho-adrenal system activity in adult male rats [27] was induced by 50 % food restriction

during the last third of pregnancy and lactation. Another rat model fed half of the daily intake during the last week of gestation until weaning, produced similar effects on the hypothalamo-pituitary-adrenal (HPA) axis of offspring [28]. These data suggest that there may be chronic hyperactivity of the HPA axis leading to high glucocorticoid levels in adulthood.

7.1.6 Epigenetic Modifications

Epigenetic mechanisms, such as DNA methylation and nucleoprotein acetylation or methylation, are important to the physiological development of several tissues in mammals, and, they involve several mechanisms to guarantee fluctuations of enzymes and other proteins that regulate metabolism [29–31]. Alterations in nutrition during development can alter epigenetic marks, including DNA methylation and histone modifications in rodents [32–35]. Epidemiological and controlled studies in humans and animals demonstrate that undernutrition can result in DNA hypomethylation in offspring, implicating epigenetics as a potential mechanism through which maternal diet may affect the health of offspring [36, 37]. In humans, emerging data suggests that severe maternal undernutrition may result in persistent epigenetic changes in the offspring [38]. Recent data suggests that gene methylation changes in DNA extracted from umbilical cord tissue are associated with later childhood obesity [39]. Hypomethylation of glucocorticoid receptor (GR) promoter in fetal sheep leads to increasing GR expression in the undernourished group which may, in turn, contribute to fetal programming of a predisposition to obesity [40]. Another animal study showing similar results suggests that hypomethylation of GR promoter associated hypothalamic neuropeptide mRNA expression may lead to obesity in the next generation [41].

7.1.7 Leptin Resistance

Offspring of undernourished mothers have higher concentrations of fasting plasma leptin and insulin which decrease appetite. On the other hand, exposure to a postnatal hypercaloric diet will increase hyperphagia, suggesting an inappropriate response due to insulin and leptin resistance induced by early programming. Ikenasio-Thorpe et al. showed significant alterations in POMC, NPY, AgRP and OBRb gene expression together with elevations in circulating levels of both plasma leptin and insulin when exposed to prenatal undernutrition, suggesting that central leptin resistance possibly increased food intake, and, results in adult dysregulation of appetite homeostasis and reduced AgRP mRNA expression [19]. Leptin-deficient ob/ob mouse offspring exposed to intrauterine undernutrition show that premature leptin surges during neonatal growth promoted lifelong changes in energy-regulating circuitry in the hypothalamus on a high-fat diet, thus playing an important role in accelerating obesity [42].

7.1.8 Hyperinsulinemia and Peripheral Insulin Resistance

Restricting the supply of food to fetus and infant may cause obesity, hyperinsulinemia and peripheral insulin resistance in adult life [43]. This insulin resistance occurs in conjunction with altered glucose uptake in adipose tissue but not in skeletal muscle, and, there is an accompanying increase in adipose tissue insulin receptors in nutrient-restricted offspring [43]. Circulating hormones, including IGF-I and leptin, are important in the regulation of fetal adipose tissue development. Maternal nutrient restriction during this period results in increased expression of both IGF-I and IGF-II receptors, in conjunction with enhanced adipose tissue deposition [44]. A study demonstrated that offspring of sheep mothers who were nutrient-restricted in late gestation went on to have greater adiposity as young adults, along with glucose intolerance and insulin resistance [45]. Adipose tissue deposition in offspring can also be reduced by manipulating the maternal metabolic and hormonal environment by increasing food intake in late gestation [46].

7.1.9 Abnormal Response of Glucose Transporter

Increased glucose transporter 1 (GLUT1) in nutrient-restricted fetuses may enhance responsiveness to IGF and promote the anabolic effects of glucose on fetal adipose tissue growth [47]. Therefore, maternal nutrient restriction in mid-gestation, results in enhanced fetal fat deposition combined with increased numbers of IGF receptors and glucose supply, that may exacerbate the deposition of fat following the restoration of the maternal diet [48]. GLUT4 decreased significantly in adipose tissue of offspring from nutrient-restricted mothers suggesting that impaired glucose tolerance may be related to the ability of adipose tissue to take up glucose in an insulin-responsive manner with reductions closely associated with insulin resistance [49].

7.1.10 Maternal Overnutrition and Later Obesity

Traditionally, the increasing prevalence of childhood obesity is related to life styles with less physical activity and changing dietary habits. Predisposition to obesity may be “programmed” in utero [50]. Studies in rodents show that exposure to maternal obesity or overnutrition during both pregnancy and lactation is associated with development of obesity in the offspring [51, 52]. LaCoursiere et al. demonstrated that the incidence of women being overweight or obese at the start of pregnancy increased from 25 to 35 % between 1991 and 2001, and that the incidence of maternal obesity at delivery increased from 29 to 39 % across the same period [8]. A high maternal BMI increases the risk of developing hypertension, preeclampsia and gestational diabetes mellitus, and, giving birth to a macrosomic infant [53]. These findings may suggest that fetal undernutrition may increase susceptibility to diseases

that occur later in life. Evidence from animal studies suggests that the fetus may adapt to an adverse intrauterine environment by slowing growth and metabolism [18, 20, 21]. This adaptive strategy appears to increase short-term survival, but perhaps with adverse long-term consequences on health [18, 21]. Alternatively, common genetic factors may influence birth size and adult disease or a combination of genetic, and non-genetic, factors may interact throughout the life course to determine disease susceptibility [19].

7.1.11 Animal Studies

Rodent dams, fed a fat-rich or cholesterol-rich diets during the preconception period, pregnancy, or lactation, confirm that maternal peripartum overnutrition can program lifelong offspring with excess adiposity and being overweight [54–56]. Similar results are also observed in sheep experiments [57]. Interestingly, a fat-rich diet during pregnancy may program offspring' obesity even though the mothers themselves are not overweight, indicating that maternal diet may program offspring phenotype even without the relevant maternal phenotype [58]. Maternal fat-rich diets before conception or during lactation only, do not confer similar risks, suggesting that pregnancy itself is the critical time for exposure [59].

Maternal overnutrition during pregnancy in rodents results in offspring phenotypes that almost resemble the metabolic syndrome in humans, such as abnormal glucose homeostasis and serum lipid profiles, increased blood pressure and adiposity [56, 60, 61]. Overweight offspring of overfed mothers had higher glucose, insulin, leptin, and triglyceride levels, and demonstrated the increase in fat mass, reduced muscle mass, and, lower adiponectin secretion [62–65].

7.1.12 The Regulation of Appetite In Utero

The fetus obtains its nutrition entirely from the maternal circulation through transplacental transfer and so it has a limited capacity to respond to alterations in nutrient supply by altering nutrient intake [66]. However appetite-regulating neural networks appear before birth in humans [67] and higher-order mammals, such as sheep [68].

Control areas for appetite and energy balance are expressed principally in the arcuate nucleus (ARC) of the hypothalamus (Fig. 7.1). The hypothalamic neural network integrates pathways relating to energy supply, utilization and total energy reserves, in order to appropriately regulate food intake and energy expenditure to maintain energy balance [69]. Several studies have identified numbers of appetite-stimulating (and suppressing) hormones and neurotransmitters, which bind and activate their CNS receptors, triggering downstream pathways or regulators, resulting in appropriate changes in behaviour of ingestion. Appetite-stimulating neurohormones include neuropeptide Y (NPY), melanin concentrating hormone (MCH),

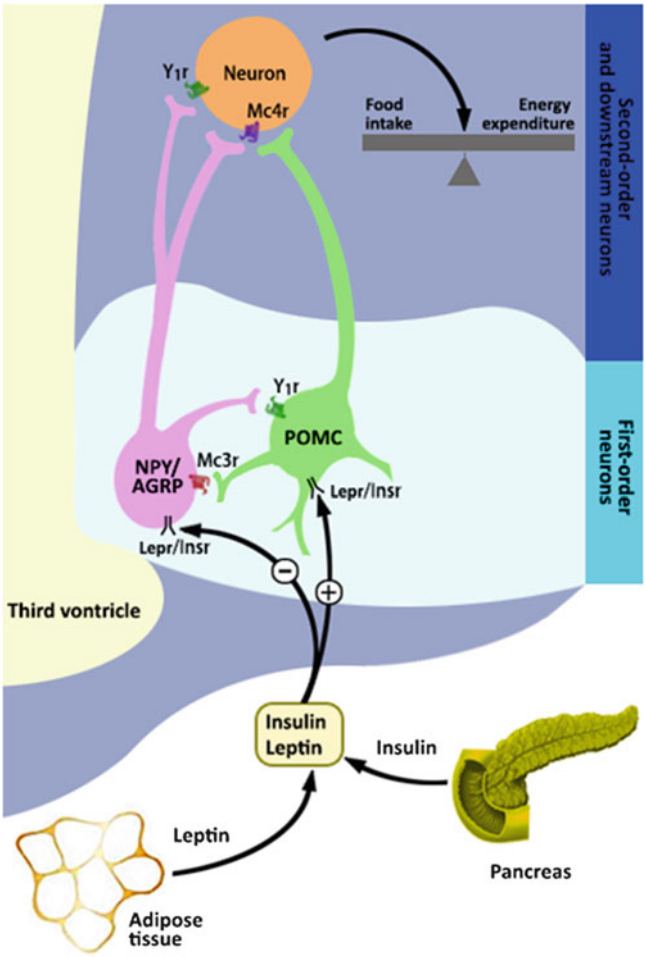

Fig. 7.1 A schematic overview of the appetite regulatory pathways in the adult hypothalamus

the orexins, endorphins, galanin, glucocorticoids, γ-amino butyric acid (GABA), and agouti gene-related protein (AGRP). Negative regulators of appetite include leptin, bombesin, glucagon-like peptide-1 (GLP-1), corticotropin releasing hormone (CRH), cholecystokinin (CCK), cocaine and amphetamine-regulated transcript (CART), and α-melanocyte-stimulating hormone (α-MSH).

Many animal studies suggest that overnutrition before birth may cause reduced enhance sensitivity to satiety signals, or, an exaggerated response to signals of hunger and negative energy balance, in the early postnatal period [70, 71]. The disturbance of appropriately-upregulated, appetite-inhibitory pathways may result in the development of obese phenotypes in animal experiments (Fig. 7.2).

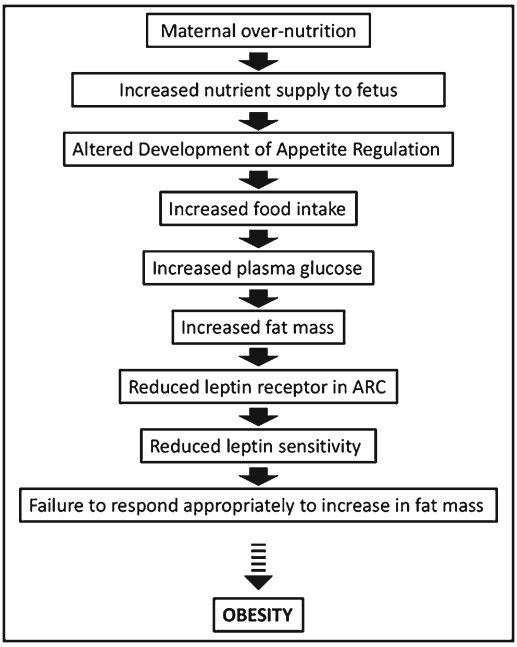

Fig. 7.2 Overview of our current working hypothesis on the pathway through which maternal overnutrition results in the programming of obesity in postnatal life

7.1.13 Altered Glucose Intolerance and Glucose/Insulin Homeostasis

Animal studies support the view that maternal overnutrition can cause later obesity and glucose intolerance of offspring in humans [55]. Offspring of obese women are more likely to be overweight, and may develop insulin resistance in later life [72]. Besides, it is also related with the development of metabolic dysfunction in offspring, including hyperglycaemia, hyperinsulinaemia, and increased plasma levels of triglycerides, cholesterol and leptin [56, 60–65].

7.1.14 Altered Adiposity and Adipocyte Metabolism

Adipogenesis is important in the developmental programming which begins in utero and accelerates in neonatal life. For humans, it will accelerate rapidly again at about age of 6 years old [73]. Premature onset of such adipose tissue mass (before 5.5 years of age) in childhood may be related to adult obesity [73]. It is still unclear how maternal overnutrition influences adipogenesis in offspring, and, how it may determine the critical timing of the 'adiposity rebound'. Unlike many tissues, adipose tissue has potential for unlimited growth, and, diet-induced increases in fat cell number are normally irreversible [74]. Maternal over-nutrition has a direct influence on adipocyte hypertrophy in offspring because glucose is the primary metabolic precursor in lipid synthesis. Increased glucose supply

may increase fat mass in ovine fetus [75]. Altered expression of proteins which influence adipocyte metabolism, such as peroxisome proliferator-activated receptor- γ (PPAR-γ), may have a permanent influence on adipocyte proliferation and hypertrophy [76].

7.1.15 Altered Methylation Status

The methylation status of nuclear DNA (nDNA) has effects on persistent epigenetic changes. Dolinoy et al. suggested that considering the critical roles that genomically imprinted genes play in mammalian growth and development, early nutritional influences on these genomic components may have a substantial impact on human health [32]. The genome of the pre-implantation mammalian embryo undergoes extensive demethylation, and appropriate patterns of cytosine methylation are reestablished after implantation [77, 78]. These DNA methylation patterns must then be maintained over many rounds of rapid cellular proliferation during fetal and early postnatal development. Availability of dietary methyl donors and cofactors during critical ontogenic periods may therefore influence DNA methylation patterns [77, 78]. Dietary methionine and choline are the most important sources for one-carbon units, and folic acid, vitamin B12, pyridoxal phosphate are major cofactors in methyl metabolism. Early methyl donor malnutrition (i.e., overnutrition) could effectively lead to premature "epigenetic aging," [79], thereby contributing to enhanced susceptibility to chronic disease in later life. Besides, the function of leptin, which may primarily programme appetite regulatory centres in the developing hypothalamus may be changed by the alteration in methylation [80]. Altered methylation status in very early embryonic development can contribute to the obese phenotype through embryo transfer and cloning [81].

7.1.16 Parental Factors

Offspring with two obese parents may have higher risks of being overweight in childhood, and, also reveal a stronger pattern of tracking from childhood to adulthood [82]. A cohort study in Washington State found that without obese parents, obese children under 3 years of age were at low risk of becoming obese in adulthood [83]. In this study parental obesity doubled the risk of adult obesity among children less than 10 years of age irrespective of whether the child was obese or not [83]. In another cohort study, they quantified the individual and combined effects of maternal and paternal obesity on childhood obesity [84]. They found that the association between parental weight status and risk of childhood obesity was strong and graded, and, significantly stronger for maternal weight [84].

It has been shown that there is no strong difference between the maternal-offspring and paternal-offspring associations of BMI [82–84]. A large population-based study showed similar parental-offspring BMI associations when the offspring were 3 years old, which indicates that the maternal-offspring association may be explained

by shared familial risk factors including environmental and genetic risk factors rather than by the intrauterine environment [83].

Can obesity be "transmitted" to subsequent generations by fathers? Sperm transmit solely genetic and epigenetic factors. In order to separate environmental from genetic factors, Perez-Pastor et al. extended the analysis of BMI relationships to gender-assorted pairings of mother-daughter and father-son, comparing them with mother-son and father-daughter [85]. They succeeded in finding a same-sex association of body mass index (BMI), which might imply shared environment rather than shared genes because selective mother-daughter and father-son gene transmission is not a common Mendelian trait [85]. However, in 2010, a large UK birth cohort found no evidence of significant differences in mother-daughter and father-son body mass index concordance [86].

To explore the contribution of obese fathers to adiposity and metabolism in offspring, Ng and his colleagues established paternal high-fat-diet (HFD) rat model and found that chronic HFD consumption in Sprague-Dawley fathers induced increased body weight, adiposity, impaired glucose tolerance and insulin sensitivity in female offspring [87]. Carone et al. fed male rats with reduced-protein diets and bred them with chow-fed females and found that both male and female offspring had increased hepatic expression of lipid and cholesterol synthesis genes [88]. Overall DNA methylation in offspring was found unchanged; however, the methylation in an intergenic CpG island between PPAR-α and Wnt7-β modestly increased. These data strongly support the idea that what fathers eat affects the metabolism of their offspring.

7.1.17 Endocrine-Disrupting Chemicals

Over the years, humans have evolved to tolerate and metabolize natural products encountered in diet, however, they may be unable to handle the molecules not usually found in nature. There are a subset of synthetic chemicals referred to as endocrine-disrupting chemicals (EDC), which are environmental pollutants with hormone-like activity that may disrupt programming of endocrine signaling pathways during development and result in adverse effects including obesity, diabetes etc.

Recent epidemiology reports suggest links between exposure to EDCs during development, and, overweight or obesity later in life. If exposed to polychlorinated bisphenyl (PCB) in prenatal and early life, both boys and girls will be heavier at puberty [89]. Children with higher levels of hexachlorobenzene (HCB) in their cord blood weighed more, and, had higher BMI at the age of 6.5 years [90]. Also, children in the higher exposure group of HCB were more likely to be overweight and obese [90].

Numerous animal studies also demonstrate the association between obesity and exposure to various environmental chemicals during development [91]. For example, mice treated with a low dose of diethylstilbestrol (DES) on days 1–5 of neonatal life did not affect body weight during treatment but was associated with a significant increase in body weight at 4–6 months of age [92]. High prenatal DES

doses caused lower birthweight compared to controls, followed by a catch-up growth at puberty, and then resulted in obesity in the DES-treated mice after 2 months of age [92]. In both mouse and rat, there are associations between low doses of BPA during prenatal and neonatal periods and increased body weight [91, 92].

These toxic chemicals can initiate or exacerbate the development of obesity by targeting nuclear hormone receptor, including sex steroid receptor, glucocorticoid receptor, and RXR-PPARγ (retinoic X receptor-peroxisome proliferate activated receptor gamma) [91, 92]. By perturbing these signaling pathways, EDCs alter adipocyte proliferation, differentiation or mediate systemic homeostatic controls and result in long-term consequences. The fetus and newborn, whose detoxification and metabolic mechanisms are still immature, are particularly vulnerable to the effects of EDCs. These adverse effects may be magnified if perturbation occurs during fetal or early childhood development [91, 92]. Newbold and his colleagues analyzed gene expression in uterine samples from DES-treated mice and found alteration in genes involved in fat distribution, including down-regulation of Thbd and Nr2f1 and up-regulation of Sfrp2 [91, 92]. These findings suggest that EDCs may modulate the development of obesity by regulating expression of these genes.

7.1.18 Effect of Prenatal Smoking

A series of studies suggest an association between prenatal maternal smoking and offspring's obesity. Oken and his colleagues performed a meta-analysis of results of 84,563 children reported in 14 studies, and, concluded that offspring of mothers who smoked during pregnancy had higher risk for overweight at ages 3–33 years [93]. A meta-analyses of the effects of maternal environmental tobacco smoke exposure (ETS) during pregnancy on birth outcomes found a small reduction in mean birth weight, and, an increased pooled risk of babies being small for gestational age at birth [94]. A systemic review further demonstrated that exposure of non-smoking pregnant women to ETS reduces mean birth weight by 33 g or more and increases the risk of higher morbidity, low birth weight births by 22 % [95].

In a Spanish cohort study, the authors used longitudinal ultrasound measurements to assess the effects of in utero tobacco exposure on fetal growth. They found that active smoking during pregnancy was associated with a reduction in abdominal circumference, femur length and estimated fetal weight from mid-gestation, and, environmental tobacco smoke adversely affected biparietal diameter from early pregnancy [96]. How maternal smoking programs affect child weight is not well understood. In both humans and animals, nicotine acts both centrally and peripherally to reduce appetite and body weight, and nicotine withdrawal results in hyperphagia and weight gain [97, 98]. In animal studies, exposure of pregnant mothers to nicotine resulted in offspring that were smaller at birth but had increased body fat, and, rats prenatally exposed to low doses of nicotine were normal sizes at birth but became heavier by 5–10 weeks of age [99, 100]. Maternal smoking throughout

pregnancy may be associated with lower cord blood leptin [101]. However, Helland et al. could not confirm that lower birthweights of neonates among smoking mothers is not due to altered plasma leptin concentrations [102].

7.1.19 Maternal PCOS

Polycystic ovary syndrome (PCOS) is characterized by irregular menses, chronic anovulation, hyperandrogenism and infertility and is strongly associated with obesity, increased risk of developing type 2 diabetes (T2D), and cardiovascular disease [103]. Forty to eighty percent of women with PCOS are overweight or obese, implicating BMI as an important determinant in the manifestation of the syndrome [104, 105]. These observations suggest that obesity and PCOS are linked co-morbidities, and, PCOS may be one of the most important causes of obesity in women and their offspring.

7.1.20 Genes Determining the Obesity in Offspring of PCOS Patients

Family-based studies suggest that brothers of PCOS women have decreased insulin sensitivity and glucose tolerance, as well as hypercoagulability, that is independent of obesity [106]. Therefore, brothers of PCOS women may have inherited the speculative genotype for insulin resistance and metabolic syndrome that is characteristic of PCOS [106]. Possible candidate genes predisposing to PCOS include those involved in the regulation of ovarian steroidogenesis but also those genes that influence BMI and adiposity. A likely explanation for the mechanisms underlying the development of obesity in women with PCOS is the combined effect of a genetic predisposition in the context of an obesogenic environment [107]. Recent technological and computational advances in genome-wide association studies (GWAS) have identified variations in or near FTO, INSIG2, GNPDA2, MC4R, NEGR1, SH2B1 MTCH2, KCTD15, and TMEM18 as susceptibility loci for obesity [108–112]. PCOS patients carrying these obesity-susceptible genes, and, may pass on these pathogenic genes to their offspring through oocytes. However, few genetic studies on PCOS have focused on obesity to date, consequently, the contribution of genes that influence body composition in PCOS remains to be clarified.

7.1.21 Insulin Resistance

Abnormal insulin action influences both the ovarian production of androgens by theca cells and their bioavailability by reducing hepatic SHBG production [113–115]. Up to 50 % of PCOS women are obese that additionally contributes to insulin resistance, which, in turn, increases the risk for development of glucose intolerance, T2D, as well as dyslipidemia and hypertension [116]. The D19S884 allele 8 (A8)

which is the susceptibility locus of PCOS is associated with insulin resistance, β-cell dysfunction, and other metabolic phenotypes in PCOS families [117]. D19S884 maps to chromosome 19p13.2 within the FBN3 gene. FBN3 encodes fibrillin-3, one of the three members of the fibrillin family of extracellular matrix proteins [118]. Fibrillins provide structural integrity to connective tissues and regulate the activity of members of the TGF-β superfamily [119], which have been implicated in PCOS, insulin resistance, T2D, and glucose homeostasis [120, 121]. If members of the TGF-β pathway are implicated in various states of insulin resistance, then FBN3, a potential extracellular regulator of this pathway, may also play a role in regulating maternal glycemia [122, 123].

GYS2 gene is a new susceptibility gene that significantly impacts the risk for PCOS through obesity-related conditions [124]. The human GYS2 is located at 12p12.2. It is an enzyme responsible for the synthesis of 1, 4-linked glucose chains in glycogen, and, encodes for rate-limiting liver glycogen synthesis. Its activity is highly regulated through phosphorylation at multiple sites and by allosteric effectors, mainly glucose 6-phosphate. Some studies report that defects in the GYS2 gene cause inherited monogenic disease glycogen storage disease [125, 126]. In addition, GYS2 gene is one of the adipose tissue-enriched genes contributing to obesity from a stratified transcriptomics analysis [127]. GYS2 gene on chromosome 12p12.2 was identified in a PCOS GWAS for obesity-related conditions, and confirmed further associations in an independent childhood obesity study and a gestational diabetes study [124].

7.1.22 Genes for Adiposity

Accumulating evidence suggests a role for the blood coagulation factor gene F13A1 in obesity [128]. Schweighofer et al. found an association of the G allele of F13A1 SNP rs7766109 in PCOS patients with higher BMI, raised FAI, decreased levels of SHBG, and HDL, elevated levels of free testosterone and TG, and higher systolic blood pressure [128]. Some of the associations were more pronounced in obese PCOS women including FAI, free testosterone, SHBG, AUCins, while some in lean PCOS women included BMI, TG, HDL. F13A1 SNP rs7766109 did not contribute to PCOS susceptibility. They also found an association of the G allele of the F13A1 SNP rs7766109 with lower HDL levels in PCOS women [128]. These findings are of particular interest because dyslipidemia is a common feature of PCOS, and, HDL levels are inversely correlated with androgen levels and body fat. Billings et al. investigated the association between F13A1 SNPs and HDL cholesterol levels in a Finnish EUFAM population, and, identified 10 SNPs within the introns 3–5 that were associated with serum lipid levels [129].

Expression of 11β-hydroxysteroid dehydrogenase type 1(11β-HSD1) in visceral and subcutaneous adipose tissues of patients with PCOS is associated with adiposity. PCOS is not associated with increased 11β-HSD1 expression. Increased expression of this gene correlates with markers of adiposity, and, predicts insulin resistance and an unfavorable metabolic profile, independently of PCOS [130]. In the development

of insulin resistance increased cortisol activity in adipose tissue may be important [131]. The enzyme 11β-HSD1 interconverts glucocorticoids cortisone and cortisol in adipose and other tissues [131]. In vivo, the reductase activity prevails, generating cortisol by both autocrine and paracrine functions [131]. Various studies report increased expression of 11β-HSD1 gene (HSD11B1) [130, 131] and activity of this enzyme in subcutaneous adipose tissue of obese people [132]. Several studies demonstrate a positive correlation between HSD11B1 expression with obesity [133, 134], while others found exclusive associations of subcutaneous adipose HSD11B1 expression with obesity and IR [135, 136].

PCOS of women has profound effects on their offspring, and obesity is one of the most important influences. Although the mechanisms responsible are not clearly elucidated, there is consistent evidence that parents may influence the risk of adiposity in their offspring through genetics, the intrauterine environment, and behavioral and environmental factors. The prevalence of PCOS is likely to increase in parallel with the obesity epidemic. The complex aetiology of PCOS is influenced by genetic and environmental – particularly dietary factors. Both factors contribute to adiposity, which in turn influences the severity and expression of PCOS. Given the complexity of adipocyte physiology and pathophysiology, it is likely that we have only just begun to understand the mechanisms linking PCOS with adiposity, and, obesity of their offspring.

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