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Review

PARENTAL OBESITY: THE PANDEMIC OF INTERGENERATIONAL PHYSICAL AND MENTAL HEALTH CARNAGE

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Abstract: A review of the maternal and paternal impact of obesity at conception on the subsequent health of the offspring paints a nightmarish future in terms of suffering and out-of-control healthcare spending. Consequences of parental obesity on the offspring include obesity, type 2 diabetes, cardiovascular disease, chronic kidney disease, stroke, and premature death. Children of obese women tend to have high blood pressure, left ventricular thickening, increased abdominal fat mass, hyperlipidemia with reduced high-density lipoprotein levels, increased aortic root diameter, insulin resistance, and elevated inflammatory markers, which culminate in a threefold greater risk of cardiometabolic complications than in children of normal-weight mothers. Babies are at greater risk of developing asthma, autism spectrum disorder, attention deficit hyperactivity disorder, cognitive delays, inflammation, cerebral palsy, epilepsy, and the chronic diseases of obesity (such as insulin resistance, high blood pressure, atherosclerosis, cardiovascular disease, stroke, some cancers, including breast, endometrial, and colon cancer, gall bladder disease, polycystic ovarian syndrome, musculoskeletal problems such as osteoarthritis and back pain, gout, cataracts, stress incontinence, and sleep apnea), as well as psychiatric disorders including substance abuse. All parents desire healthy babies, as does the society, to avoid the health costs and consequences of our obesity pandemic, but significant personal, societal, public policy, economic, and marketplace interventions will be necessary to avert further devastating impacts. We need to publicize the intergenerational harm caused by obesity, offer support to individuals to help change eating habits and produce a healthier food chain for the nation. Interventions fashioned after the twelve-step program of Alcoholics Anonymous and the adoption of a low carbohydrate abstinence model have proven effective. The time has come to spread the obesity and intergenerational obesity research findings, long accepted by the scientific community but scarcely recognized by the public. We must act before another generation is impacted by lifestyles that have continuously worsened since the 1970s.

Keywords: Maternal obesity, pre-natal programming, epigenetic changes, offspring consequences, obesity interventions, Twelve-Step programs, food addiction

INTRODUCTION Animal and human studies suggest that obesity and food addiction (FA) are plaguing our society with an intergenerational syndrome of obesity. Babies born to obese mothers who eat sugar, high fructose corn syrup (HFCS), and ultra-processed substances (U-PS) and those who have active FA at conception and during pregnancy produce babies with the syndrome of intergenerational obesity- (IGO) and a propensity for obesity and the chronic diseases that accompany obesity.

The prevalence of overweight and obesity in reproductive-aged women has been increasing significantly in recent decades. The percentage of women with pre-pregnancy obesity rose from 13% in 1993 to 26.1% in 2016 to 29.0% in 2019 [1,2]. In high- and middle-income countries, over 50% of women enter pregnancy either overweight or obese [2-7]. Compared with normal-weight mothers, these women are less likely to get pregnant. Still, if

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successful, they are at increased risk of adverse outcomes such as miscarriage, stillbirth, preterm birth, pre-eclampsia, induction, instrumental delivery, gestational diabetes (GDM), hypertension, postpartum hemorrhage, and postpartum depression [8-11]. Infants of women who are overweight or obese are more likely to be born large for gestational age (LGA), and these mothers are less likely to maintain breastfeeding [12-15]. If labor is induced, the risks of cesarean section and low APGAR scores are increased [16].

Excessive maternal body weight during pregnancy predisposes an increase in adiposity of the fetus and neonate, increases the likelihood of childhood and adolescent obesity, and produces a 2-3-fold increased risk of obesity, type 2 diabetes (T2DM), cardiovascular disease, chronic kidney disease, stroke, and even premature death in adulthood [17]. Children of obese mothers tend to have high blood pressure, left ventricular thickening, macrosomia, increased abdominal fat mass, increased aortic root diameter, hyperlipidemia with reduced high-density lipoprotein levels, insulin resistance, and elevated inflammatory markers, which culminate in a threefold greater risk of cardiometabolic complications than in children of normal-weight mothers [16,17-25].

In 1992, David Barker, an epidemiologist, introduced in his book, Fetal and Infant Origins of Adult Disease, the hypothesis that sub-optimal nutrition in early life was responsible for increased birth weight, susceptibility to adult diseases, like metabolic syndrome, and risk for coronary artery disease and stroke [26]. The deleterious influence of poor nourishment during pregnancy on the long-term health consequences for the offspring was hypothesized to be due to fetal programming that takes place when the optimal environment in which a fetus grows is disrupted by hostile factors, especially during critical periods of development of essential organs. The fetal origins hypothesis suggests that adequate nutrition during fetal development is critical. Over-nutrition has increased in the United States over the past several decades and is a form of malnutrition in which nutrients are oversupplied relative to the amounts required for optimal growth, development, and metabolism. The overnutrition hypothesis claims that high maternal glucose, free fatty acid, and amino acid concentrations produce permanent changes in appetite control, neuroendocrine functioning and/or energy metabolism in the developing fetus. Evidence for the effects of maternal obesity and overnutrition on metabolic programming were reviewed by Gomes and Şanlı, who concluded that neonatal overnutrition during any phase (prenatal, perinatal, or postnatal) of the reproductive period could lead to metabolic imprinting in the offspring [20-21].

ANIMAL STUDIES Animal models provide a useful tool to study offspring outcomes in studies of maternal obesity. Animal studies are able to address causality, assess cardiometabolic outcomes across a lifespan, and investigate sex differences and critical windows of vulnerability of programming effects [27]. Studies in rats have shown that eating an energy-dense diet, high in fat, during pregnancy affects the development of neural pathways in the developing fetus, permanently altering the offspring's responses to foods rich in fat and sugar [28]. Gugusheff reported that mRNA expression of the μ-opioid receptor in the ventral tegmental area at weaning was 1.4-fold (males) and 1.9-fold (females) lower in offspring of junk-food-fed rat dams than in offspring of dams fed a standard rodent diet (control) [29]. Similar findings were observed for total energy intake. Naloxone treatment did not affect intake of standard rodent feed in control or junk-food-fed offspring. These findings suggest that exposure to a maternal junk-food diet results in early desensitization of the opioid system, which may explain the increased preference for junk food among these offspring.

Muhlhausler and Ong went on to study the effect of consumption of a low-fat diet on the offspring in this study and discovered that the perinatal junk-food exposure on food preferences and fat mass could be reversed by consuming a low-fat diet from weaning to adulthood in males, but females retained a higher propensity for diet-induced obesity [30].

Shalev conducted a similar study in rats and found that post-weaning exposure to a highly palatable diet increased body weight, body fat, plasma leptin levels, and plasma glucose response to a glucose challenge [31]. Sertie agreed that alterations in the leptin set point around which leptin regulates body weight in offspring persisted into adulthood and contributed to obesity [32].

Gali Ramamoorthy wrote in her review, *Developmental Programming of Hypothalamic Neuronal Circuits: Impact on Energy Balance Control* that the pro-opiomelanocortin

(Pomc) gene played an important role in the regulation of the hypothalamic–pituitary–adrenal-axis and adrenal development, as well as in obesity [27]. Overnutrition in the dams predisposed offspring to metabolic challenges as they matured. She reported that with the maternal high fat diet, the offspring had greater adiposity, hyperleptinemia, and rapid early weight gain at weaning. In another study, Gali Ramamoorthy fed weanling rats a high-fat or low-fat diet for six weeks before mating, and throughout gestation and lactation. On postnatal day 21, samples were collected from 1/3 of the offspring [28]. The remainder of the pups were weaned onto low-fat or high-fat diets for an additional 12 weeks. When the mothers were fed a high-fat diet, the offspring had rapid early weight gain, increased adiposity, and hyperlipidemia. The programmed offspring subsequently fed a low-fat diet retained increased body weight. The maternal high-fat diet and continuation of a high-fat diet produced even greater obesity and insulin resistance among the pups. Sullivan supported Gali Ramamoorthy's conclusions in his review of the topic [25].

Šeda reviewed studies chronicling excess carbohydrate intake in animals and concluded that carbohydrate consumption is a main driving force of obesity and the development of metabolic syndrome [33]. His review summarized the evidence for the effects of maternal carbohydrate (fructose, sucrose, glucose) overnutrition on the modulation of metabolic syndrome in the offspring. Hales cited the *Thrifty Phenotype Hypothesis* where adults with a history of fetal malnutrition had adopted predictive-adaptive strategies, while a fetus, to maximize chances of postnatal survival [34].

In a disturbing report on this subject, Bocarsley fed rat dams a control diet or a high-fat diet (HFD), and female offspring were cross-fostered to dams consuming the control diet [34]. The HFD-exposed offspring were heavier in body weight, had increased circulating triglyceride levels, and consumed more alcohol and HFD in adulthood compared to controls. In a second experiment, dams were fed standard chow alone or standard chow plus a 16% HFCS, or 10% sucrose solution. Offspring from each group were cross fostered to dams in the other groups. The offspring exposed to HFCS or sucrose in utero had greater body weights in adulthood and exhibited increased alcohol intake among female offspring and increased antihistamine-induced locomotor activity in males. Exposure to HFCS or sucrose only during the pre-weaning period had a similar effect of increasing amphetamine-induced locomotor activity in males but produced no change in circulating triglycerides or alcohol intake. Bocarsley's data suggest that prenatal and pre-weaning exposure to fat- and sugar-rich diets, increases body weight and affects responses to drugs of abuse.

A grim finding observed in animals was that the effect of maternal obesity on the offspring can last over multiple generations [36]. In fact, the severity increased through generations (F2 > F1 > F0) and was accompanied by a gradual increase of histological scoring of steatosis in male mice with transgenerational high-fat feeding [37].

HUMAN STUDIES Catalano and Shankar reviewed the literature and the adverse consequences for children born to obese mothers [38]. Neonates of obese women had increased body fat at birth, which increased their risk of childhood obesity. The authors believe increased pre-pregnancy maternal insulin resistance and accompanying hyperinsulinemia, inflammation, and oxidative stress contribute to early placental and fetal dysfunction. According to Pereira-Miranda, diet and lifestyle during pregnancy affect critical stages of development and contribute to the development of chronic disease in adult offspring [39]. Through physiological and/or epigenetic mechanisms, fetal programming of metabolic function also has an intergenerational effect, and the result may perpetuate metabolic disorders in the next generation and thereby increase disease prevalence over time [40,41].

This could be the reason for our obesity pandemic in the United States.

Data from 597 children (505 unexposed to maternal GDM) and 92 exposed to GDM who participated in the longitudinal *Exploring Perinatal Outcomes among Children (EPOCH) Study* in Colorado were collected at two research visits when the participants were, on average, 10.4 and 16.7 years old [42]. BMI, waist/height ratio, and visceral and subcutaneous adipose tissue (as determined by MRI) were measured. Compared with unexposed participants, those exposed to maternal GDM had higher BMIs, waist/height ratios, visceral adipose tissue, and subcutaneous adipose tissue. The magnitude of these differences was stable between measurements and the associations could not be explained by postnatal behaviors. These data provide evidence that intrauterine

exposure to maternal GDM is associated with increased adiposity in the next generation, an effect that appears early in life and tracks throughout adolescence and beyond. Efforts to prevent childhood obesity following intrauterine exposure to maternal GDM may be doomed by fetal programming.

In another study of offspring of 254 obese mothers, elevated hepatic fat fractions, independent of childhood and adolescent adiposity, were observed [43].

Gomes strove to assess the impact of late-pregnancy dysglycemia on obese pregnancies with negative testing for GDM on long-term mother-child outcomes [20]. The prospective cohort study, *Programming of Enhanced Adiposity Risk in Childhood-Early Screening (PEACHES)*, (n = 1,671) enrolled obese and normal weight mothers with trimester-specific data on glucose metabolism, including GDM status at the end of the second trimester and maternal glycated hemoglobin (HbA1c) at delivery, as a marker for late-pregnancy dysglycemia (HbA1c ≥ 5.7%). She assessed offspring's short- and long-term outcomes up to 4 years and maternal glucose metabolism for 3.5 years, postpartum. In all, 898 mother-child pairs were included in her analysis. Among obese mothers with negative testing for GDM (n = 448), those with late-pregnancy dysglycemia (n = 135, 30.1%) had higher proportions of excessive total gestational weight gain, excessive third trimester gestational weight gain, and offspring with LGA birth weights and higher cord-blood C-peptide concentrations than those without. Offspring of these women had greater weight gain during early childhood and higher BMI z-scores at 4 years than offspring of the obese, GDM-negative mothers with normal HbA1c values at delivery. Late-pregnancy dysglycemia in GDM-negative mothers accounted for about one-quarter of the association of maternal obesity with offspring BMI at age 4 years (n = 151). In contrast, childhood BMI z-scores were not affected by a diagnosis of GDM in obese pregnancies versus GDM-negative pregnancies. These findings suggest that offspring of obese mothers treated because of a diagnosis of GDM appeared to have a better BMI outcome in their children's childhoods than those of obese mothers who, following negative GDM testing, remained untreated in the last trimester but developed dysglycemia.

Gomes continued her study of subjects enrolled in the *PEACHES* study among 1671 mothers with or without pre-conception obesity and their offspring [44]. She observed that 20% of the children displayed a higher-than-normal BMI growth pattern preceding overweight (defined as BMI z-score >1 SD) between age 6 months and 5 years.

The articles and studies cited above indicate the deleterious effects of maternal obesity at conception and during pregnancy on the offspring. Many more studies and reviews in the literature support these findings [45-49].

Fathers also play a role in IGO. In one study, fathers and sperm donors, were responsible for a sex-specific risk of excess weight programming in the offspring, with paternal BMI correlating with infant parameters such as birth weight, biparietal diameter, head circumference, abdominal diameter, abdominal circumference, and pectoral diameter, but only in male newborns [50]. This differential programming of the hypothalamic-pituitary-adrenal-axis in male fetuses was postulated because of an association between paternal BMI and cortisol concentrations in the male neonates studied [51].

Other authors have observed that paternal obesity affects the methylation pattern of insulin-like growth factor-2 in blood obtained from the umbilical cords of newborns. This suggests that excess weight in the father could have a preconception epigenetic effect on spermatogenesis [52]. In a study of 1,494 parents followed since the early 1980s, both paternal and maternal BMI were strong predictors, not only of BMI in the offspring, but also of the offspring's BMI increases from childhood to adulthood. As the offspring's age rose from 5 to 21 years, so did the percentage of subjects with increased BMI (from 14.7% to 22.8%) when either parent had presented with pregestational overweight or obesity, with the effect being most pronounced when excess weight was present in both parents [53]. Fathers' role in IGO cannot be minimized [54-57].

In a retrospective trial of 800 children around 10 years of age, obesity in either parent determined the severity of obesity and the altered carbohydrate metabolism in the offspring, with the impact being greater when the obesity was maternal and when it affected both parents. [9] Moreover, a preliminary study has described that the effect of antenatal lifestyle therapy in overweight and obese women on neonatal anthropometric measurements

is significantly modified when the father has a high BMI; when the father's BMI was ≥ 35 kg/m^2, the reduction of skinfolds in the triceps, thighs, and supra-iliac areas and the percentage of neonatal fat mass were significantly higher than when the father's BMI was lower, thus demonstrating that the body weight of both parents has an effect on that of the newborn [58].

Research on the maternal and paternal preconception-effects on first- and second-generation offspring clearly demonstrates that parental obesity and prenatal over-nutrition are causal. In addition to childhood obesity and all its implications, IGO may promote the plague of diseases associated with a lifetime of obesity, i.e., T2DM, metabolic syndrome, cardiovascular disease, mental disorders, and some cancers. Proper treatment of these obese parental food addicts could break the chain of IGO and consequent health problems.

MECHANISMS OF ACTION The mechanisms responsible for the observation that maternal obesity can predispose the offspring to chronic diseases may involve alterations in the uterine immune cell environment. St-Germain and Segovia see an important role for inflammation [59,60]. Gamete epigenetic modifications are believed to be responsible for this transfer to offspring. The presence of obesity and diabetes change DNA and histone methylation levels, as well as noncoding RNAs in both oocytes and sperm. One study showed that 76 CpGs sites (where cytosine lies next to guanine in a DNA sequence) were significantly and differentially methylated in peripheral blood of infants born to overweight mothers compared to normal weight mothers [61]. Another study found 56 CpGs changes in placental tissues [62]. Ou explained that recent studies indicated that both obesity and diabetes change DNA and histone methylation levels, histone acetylation, and noncoding RNAs in oocytes and sperm [63]. Lasting effects on the prevalence of metabolic diseases in the next generation are exerted by maternal obesity or overnutrition during pregnancy or lactation. These include non-alcoholic fatty liver disease (also called metabolic-associated fatty liver disease), non-alcoholic steatohepatitis, obesity, diabetes, chronic kidney disease, hypertension, and cardiovascular disease [21, 64-70]. Peng demonstrated that offspring born to mothers who had consumed high fat diets displayed a disruption of lipid homeostasis, which was accompanied by altered methionine and abnormal one-carbon metabolism in the livers of offspring [71]. Peng claims that this would lead to DNA hyper-methylation and L-carnitine depletion associated with deactivation of AMP-activated protein kinase (AMPK) signaling and decreased expression of PPAR-α in genes for fatty acid oxidation. Different methy-lation patterns have been described in thousands of genes related to glucose metabolism and inflammation in siblings conceived before and after successful maternal bariatric surgery for weight reduction [72].

Modulation of DNA methylation of different genes involved in energy metabolism, glucose homeostasis, insulin signaling, and fat deposition are responsible for an increased risk of non-alcoholic fatty liver disease, obesity, diabetes, and chronic kidney disease [71,72].

In conclusion, prenatal exposure to maternal obesity disrupts hepatic metabolic programming, altering fatty acid oxidation, the tricarboxylic acid cycle, and lipid metabolism and can increase insulin and leptin resistance, dyslipidemia, hepatic inflammation, and steatosis in the subsequent generation. The effect of maternal obesity on the offspring can last over generations and includes cardiometabolic morbidity in the offspring.

ADDITIONAL OFFSPRING HEALTH CONSEQUENCES Obesity, FA, T2DM, and other chronic diseases are not the only intergenerational consequences attributed to parental obesity. A link to both pre-pregnancy BMI and weight gain during pregnancy has been established with asthma in the offspring. In a cohort of 4,656 children aged 1-4 years, Leermakers observed that children born to women with pre-pregnancy obesity and a history of asthma or atopy presented a 47% increased risk of wheezing at preschool age [73]. Excessive weight gain during pregnancy increased this risk, independently from the mother's pre-pregnancy weight, and was unrelated to the presence or absence of a history of maternal asthma or atopy. Forno performed a meta-analysis involving 108,321 mother-infant pairs to evaluate the influence of maternal obesity or excessive weight gain during pregnancy on the risk of childhood asthma [74]. Maternal obesity was associated with an increase in asthma, independent from the child's BMI. Excessive weight gain was associated with an increase in occasional asthma. A history of asthma in the mother did not modify this risk, nor was any relationship detected with lifestyle,

socioeconomic level, characteristics of child-birth, or BMI of the child at the time of evaluation of their asthma. In a more recent study population of 6,450 children (followed 0-4 years), Polinski found a 60% increase in the risk for asthma when the mother was obese. The greater her BMI, the greater the odds of her children having asthma [75].

Different theories suggest that low-grade chronic inflammation associated with obesity, the negative influence of poor maternal dietary habits, alterations in the digestive microbiome, and other factors that induce epigenetic modifications can potentiate the underlying risk of asthma in offspring [9].

Studies have characterized the effect of maternal obesity on the development of the neonatal immune system. Children born to obese mothers have a 16-fold higher risk of having detectable C-reactive protein levels at 12 years of age after adjusting for BMI, Tanner stages (scale of physical development), and gender, compared with children born to lean mothers. C-reactive protein is a marker for inflammation [76]. Pantham argues that maternal obesity and gestational diabetes are associated with a state of chronic, low-grade inflammation termed metainflammation, as opposed to an acute inflammatory response [77]. This inflammatory environment may be part of the prenatal milieu in which offspring of obese women are programmed to develop disorders later in life. Pantham proposes that the placenta 'senses' and adapts to the maternal inflammatory environment and plays a central role as both a target and producer of inflammatory mediators. In this way, maternal obesity and gestational diabetes could indirectly program the fetus for later disease by influencing placental function.

Epidemiological studies have found an increased risk of intellectual deficits, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), cerebral palsy (CP), and epilepsy in children born to women who were overweight or obese during pregnancy [9]. In a systematic review of 12 studies, as well as a 10-year Finnish nationwide registry of 649,043 live births, an increased risk of cognitive, emotional, and behavioral problems was observed in the offspring (children and adults) of women with pregestational and gestational overweight and obesity compared with those of normal-weight women [78,79]. These problems included reduced intelligence quotient, ADHD or conduct disorder, eating disorders, and psychotic pathologies, including schizophrenia and mood-related disorders [80].

Among a group of 574 mother-child pairs studied by Pugh from birth to 14 years, both pregestational obesity and excessive weight gain during pregnancy were statistically related to lower academic performance among the offspring in mathematics, reading, and spelling at the ages of 6, 10, and 14 years [81]. Maternal obesity appears to affect the mental health of offspring throughout their lives because of a relationship between low intelligence quotient and a higher risk of developing psychiatric disorders in adulthood [82].

School teachers assessed the presence of ADHD symptoms in 12,556 children in prospective gestational cohorts from Sweden, Denmark, and Finlan [83]. After adjusting for multiple medical, educational, and social confounding factors, they observed that pregestational BMI and weight gain during pregnancy were significantly associated with the presence of ADHD in a dose-response manner. Children of mothers with high BMIs during pregnancy or excessive weight gain during pregnancy had double the risk of developing ADHD compared with mothers of normal weight. Subsequent studies have confirmed this increased risk of ADHD in the children of obese women. Paternal obesity has also been implicated with risk for offspring, but the association remains controversial [84-86].

A review of population studies of maternal pre-pregnancy BMI and schizophrenia, totaling 305 cases of schizophrenia and 24,442 control cases in the United States and Japan presented a threefold increased risk of schizophrenia in the children of mothers with BMI > 30 kg/m^2 com-pared with those of women with BMIs in the normal range (20.0-26.9 kg/m^2 in the United States cohort [88].

Excessive maternal weight is also associated with an increased risk of CP [8]. A dose-response relationship exists between maternal obesity and CP, with the risk tripling in the case of morbid obesity (BMI > 40). A CP incidence of 2.1 per 10,000 live births was observed in a recent population study of 188,788 children in two Norwegian and Danish patient cohorts [89] .Risk of CP in the offspring was 60% higher in both overweight and obese women compared with lean and normal weight women [9].

Epilepsy is one of the most frequent neurologic disorders in childhood. A large study (1,441,623 newborns) in Sweden found an average epilepsy incidence of 6.79 per 10,000 from the age of 28 days to 16 years [90]. Risk increased in a dose-dependent manner in relation to maternal body weight at conception. Over-weight women (BMI 25 to <30) had an 11% higher risk of epilepsy in their offspring compared to normal weight mothers [91]. The risk was 20% higher in pregnant women with BMIs 30 to < 35, 30% higher in those with BMIs 35 to < 40, and 82% higher in those with BMIs ≥ 40. Excess maternal body weight plays a critical role in fetal neurodevelopment.

A California case-control study of children 2-5 years of age, determined that maternal obesity was related to an increased risk of neurodevelopmental delay compared with normal-weight control subjects [9]. A case-control study in Utah analyzed two populations without differences in mean prepregnancy maternal BMIs, but in which weight gain varied, and found that excessive weight gain during pregnancy was associated with a higher risk of ASD among the offspring [92]. Dodds analyzed a database of children born in Nova Scotia and observed that when prepregnancy weight exceeded 90 kg (198 pounds) or weight increase during pregnancy exceeded 17 kg (37 pounds), the risk of ASD increased significantly (60% and 20%, respectively) [93]. In China, an analysis of 705 Han Chinese children with ASD and 2,236 unrelated children with normal development, revealed that the risk of ASD increased with gestational weight gain in overweight and obese mothers rather than with maternal prepregnancy BMI [95]. Krakowiak studied children aged 2 to 5 years enrolled in the CHARGE (Childhood Autism Risks from Genetics and the Environment) study, a population-based, case-control investigation between 2003 and 2010 [95]. Diabetes, hypertension, and obesity were more common among mothers of children with ASD and developmental delays compared with controls. A meta-analysis of six cohorts of overweight and obese women and one case-control study (total of 8,403 cases and 509,167 controls found it was paternal obesity that was related to an increased risk of ASD and Asperger syndrome [96,97].

Although the mechanisms responsible for these increased risks are unknown, exposure of the fetal nervous system to inductor factors of epigenetic alterations, such as chronic low-grade inflammation and low-grade endotoxemia induced by increased intestinal permeability, endothelial dysfunction, oxidative stress, signals in milk, changes in the microbiome conferred by the mother, nutrient imbalance with elevation of fatty acids and glucose, and even the hormonal misbalance (of insulin or leptin) associated with obesity during critical periods of fetal development have been discussed [24,32,50,51]. These explanations for brain damage are made more credible by the observation that the risk of major malformations of the central nervous system, especially neural tube defects, doubles in the children of obese women. [98,99] Many postnatal mechanisms may also be implicated, such as obstetrical complications, excess childhood weight gain, and psychological or social characteristics of obese mothers (maladaptive personality traits, increased risk of postpartum depression, breastfeeding problems, increased stress levels, social discrimination, and altered home environments).

A variety of metabolic and endocrine derangements accompany obesity [32]. Underlying these characteristics are a host of genetic, epigenetic, and lifestyle differences that directly or indirectly impinge on weight gain, adiposity, and metabolism. Some specific themes have been put forward as mechanisms that potentially link maternal obesity to offspring outcomes. No unifying mechanism appears responsible for all the adverse perinatal outcomes of maternal obesity, but increased prepregnancy maternal insulin resistance and accompanying hyperinsulinemia, inflammation, and oxidative stress seem to contribute to early placental and fetal dysfunction [32]. Drake proposed that additional potential mechanisms might include effects on the development and function of adipose tissue, pancreas, muscle, liver, the vasculature, and the brain. Further studies are required to elucidate the mechanisms underpinning the programming of disease risk in the offspring as a consequence of maternal obesity [100].

Increased risk for obesity, dyslipidemia, hormone imbalances, asthma, ADHD, cognitive deficits, inflammation, CP, epilepsy, and the chronic diseases of obesity (such as insulin resistance, high blood pressure, cardiovascular disease, stroke, some cancers, including breast, endometrial, and colon cancer, T2DM, gall bladder disease, polycystic ovarian syndrome, musculoskeletal problems such as osteoarthritis and back pain, gout, cataracts, stress incontinence, and sleep apnea), as well as psychiatric disorders, including

substance abuse, round out the picture for offspring of overweight and obese parents. Add to this the emotional, societal, and environmental factors that influence overweight and obese people in our society and you have a picture of the pandemic plaguing the United States [101,102]. Due to the intergenerational characteristics of obesity the trend continues to rise.

What can we do to slow or halt the impact of this intergenerational calamity?

INTERVENTIONS TO REDUCE INTERGENERATIONAL OBESITY OBESITY David Barker (1938–2013), the proponent of the fetal origins of adult disease hypothesis, lived to see his theory widely accepted. Just before his death in 2013, he gave an address to the United Kingdom Medical Research Council and said, "The greatest gift we could give to the next generation is to improve the nutrition and growth of girls and young women [103,104]. The next generation does not have to suffer from heart disease, osteoporosis, or breast cancer. They are unnecessary diseases, which did not exist a hundred years ago. We could readily prevent them had we the will to do so." Interventions to prevent maternal obesity before conception and lifetimes of normal body weight are crucial parts of such a gift.

Research has recognized the preconception period as a critical time to intervene to improve health outcomes at a multigenerational level for women and their offspring [9, 18,21,100]. Fathers also impact the lifetime health of their offspring [54-57]. The significance of this period has been acknowledged globally by the World Health Organization Commission on Ending Childhood Obesity [105]. The WHO proposed that the preconception health of parents and donors is a key priority in the prevention of future childhood and adolescent obesity. WHO acknowledged that the risk of obesity can be passed from one generation to the next, that maternal health can influence fetal development, and that the risk of a child becoming obese is increased by having an obese parent. WHO claims that the care that women receive before, during, and after pregnancy has profound implications for the later health and development of their children. They promote interventions to tackle childhood obesity risk factors and prevent other adverse pregnancy outcomes. Based on the above, losing weight is important to reduce the risk of obesity-related reproductive dysfunction in couples seeking to get pregnant. In one of several clinical studies involving Interventions among infertile couples, patients who successfully realized a ''meaningful'' weight loss goal of 10% had significantly higher conception (88% vs. 54%) and live birth rates (71% vs. 37%) than those who did not [106-108].

Gortmaker proposed that high level political leaders (prime ministers, presidents, etc.) should demonstrate leadership by supporting actions to reduce obesity and protect their citizenry by providing treatment services, education, and health promotion foundations funded through taxes on tobacco, alcohol, or unhealthy foods and beverages [109].

Weight loss before pregnancy is the most effective way to reduce maternal and fetal risks. Preconception counseling for overweight and obese women should address the health risks associated with parental obesity at conception and during pregnancy. Healthy diet and exercise are the mainstays of weight management. Clinicians can offer nutritional counseling or enlist help from a dietitian or behavioral health counselor to set up individual diet recommendations.

Weight-control interventions, including drug treatments, in pregnant women have not been widely instituted nor have treatments had sufficient impact on pregnancy and birth to attenuate the obesity problem [110]. With regard to pharmacological interventions, Wen was not specifically considering maternal obesity when he and his colleagues concluded that lifestyle interventions are not sufficient to achieve long-term, meaningful weight loss in many/most cases [111]. Thus, they believe pharmacotherapy is appropriate after failure at attempts of lifestyle modification and recommended drugs as an adjunct to individuals with BMIs ≥30 kg/m^2 or BMIs ≥27 kg/m^2 with obesity-associated comorbidities. Four anti-obesity medications (AOMs) that curb appetite (phentermine, phendimetrazine, diethylpropion, and benzphetamine) for short-term use (≤12 weeks) and five AOMs (orlistat, phentermine-topiramate, naltrexone-bupropion, liraglutide, and semaglutide) for long-term use and another drug, setmelanotide, for people with obesity due to three specific rare genetic conditions, are currently approved by the Food and Drug Administration for sales in the United States. Liraglutide (Saxenda) and semaglutide (Wegovy) are glucagon-like peptide-1 receptor (GLP-1R)

agonists, which help with weight loss by reducing food intake. They reduce appetite and inhibit gastric emptying. Compared with an average of about 5–10% of body weight loss achieved with other currently FDA-approved drugs, semaglutide reaches an approximately 15% average weight loss. This drug could be a game-changer for our obese nation.

Semaglutide is not to be taken during pregnancy. Available data are insufficient to evaluate the drug-associated risk of major birth defects, miscarriage, or other maternal or fetal outcomes, but based on animal data, there may be potential risks to the fetus from exposure during pregnancy. Women of childbearing potential should be encouraged to use contraception during semaglutide therapy. Due to its long washout period both men and women should stop using semaglutide at least 2 months before attempts at conception.

In 2017, Hanson attempted to raise awareness about the importance of good health in the period before pregnancy. He contended that interventions to reduce or prevent obesity before conception and excessive weight-gain during pregnancy could contribute substantially to the health, wellbeing, and productivity of current and future generations. He also stated that a strong new social movement would be required to accomplish the goal. Hanson offered "an integrated approach for pregnancy prevention, planning, and preparation" to reduce common risks to mothers and their babies [112]. He envisioned a bottom-up organization of individuals and communities with the support of policy initiatives, in an attempt to reduce obesity before conception and diminish the overwhelming costs to individuals, their offspring, and subsequent generations, and reduce the ruinous costs for public health. Unfortunately, none of his interventions have been realized.

Various behavioral and lifestyle interventions have been employed to reduce the risk of complications for women who are overweight or obese in pregnancy. These interventions have primarily focused on changes in diet (restricting caloric intake) and physical activity (increasing movement) and targeted the prevention of excessive weight gain during pregnancy. Unfortunately, in our obesogenic environment they have proven largely ineffective on pregnancy outcomes, infant birth weight, and risk of obesity in the offspring.

A recent Cochrane Review found that compared to usual care, lifestyle interventions can modestly reduce mean gestational weight gain (0.89 kg less than control group), but such reduction has no effect on rates of adverse pregnancy outcomes including gestational diabetes, hypertensive disorders of pregnancy, or cesarean section [113].

Behnam conducted a systematic review and meta-analysis of randomized controlled trials that examined diet, exercise, combined interventions or associated behavioral therapy to compare their impact on overweight and obese pregnant women [114]. Among the primary outcomes from the 28 trials selected for inclusion, only hypertensive disorders were significantly reduced by exercise in the total group. When behavioral therapy supported combined interventions, maternal weight gain and neonatal birthweight were significantly reduced. Higher frequencies of physical activity improved the results. Benham concluded that future studies should focus on increased intensities and frequencies of physical activity when combined with other lifestyle interventions. Babu conducted a systematic review and concluded that exercise without significant weight loss had a beneficial effect on MAFLD and was associated with significant reductions in the intrahepatic lipid content, transaminase levels, low-density lipoprotein cholesterol levels, and triglyceride levels [115]. In another systematic review and meta-analysis, the possible impact of preconception-care for adolescents, women, and couples of reproductive age on maternal, newborn, and child health outcomes was conducted by Bellver [9]. Women who received preconception-care in either a healthcare center or the community showed improved outcomes, such as smoking cessation, increased use of folic acid, breastfeeding, greater odds of obtaining antenatal care, and lower rates of neonatal mortality.

Bariatric surgery is considered to be the most effective method of inducing long-term weight loss in obese individuals [116]. The ACOG Guidelines on Pregnancy After Bariatric Surgery recommend that after bariatric surgery, a woman wait 12 to 24 months before conceiving so that the fetus is not affected by rapid maternal weight loss and so that the patient can achieve her weight-loss goals [117].

Al-Nimr conducted a systematic review that focused on the effects of bariatric surgery on maternal and infant

outcomes of pregnancy [118]. He found that bariatric surgery was related to a reduced rate of maternal GDM, pre-eclampsia, and emergency C-section deliveries. Lower infant birth weights and incidences of macrosomia and LGA infants may be reduced by bariatric surgery compared to infants born to obese mothers without surgery. Bariatric surgery did not seem to affect the risk for miscarriage, pregnancy loss, stillbirth, maternal postpartum hemorrhage, rates of preterm births, perinatal deaths, admission to NICUs, congenital malformation rates, or low APGAR scores in infants. While Al-Nimr recommended that pregnant women with a history of bariatric surgery should be closely monitored by a multidisciplinary, maternal/fetal medical team, the authors concluded that bariatric surgery is an effective treatment for severe maternal obesity. Data on long-term outcomes, such as the effects of surgery on metabolic risk in offspring into childhood and adulthood, were lacking in this study.

Bariatric surgery could play a role in dealing with our obesity problem. BMI decreases between pregnancies have been related to a lower risk of overweight in offspring compared with older siblings. [119]

The better scenario would be to address lifestyle changes prior to conception and put FA into remission, to enhance consumption of healthy food, to avoid U-PS, and to increase movement, and thus avoid the potential negative outcomes associated with excessive weight at conception and during pregnancy or with bariatric surgery.

In a Cochrane Report, John Kelly, lauded the efficacy of the abstinence-from-alcohol-based-program of Alcoholics Anonymous for those with alcohol use disorder. [120] Substance Abuse and Mental Health Services Administration (SAMHSA) resources could be augmented with data regarding obesity and IGO to provide abstinence-type interventions and support to prospective parents in an attempt to reduce or eliminate the impacts of IGO. [121]

In 1956, Rinkel and Randolph identified FA as a health problem with mental and physical outcomes [122]. Since then, outcomes have worsened, in part because of HFCS (introduced in the 70s) [123] and now incorporated in U-PS in our diets [124,125]. Energy-rich, highly palatable, cheap 'foods' are abundant in our obesogenic culture, and they support and augment obesity, FA, and IGO [126].

Today we can diagnose FA using the Yale Food Addiction Scale and prescribe effective treatments for food addicts [126]. FA was found in 12% parents and 22.7% of the children in a study population of children ages 5-12 years of age [127].

Voluntary mutual support programs structured after Alcoholics Anonymous that include abstinence are effective in treating many food addicts (GreySheeters Anonymous, Food Addicts in Recovery, Food Addicts Anonymous, etc.). There are literally thousands of self-descriptions of recovery every day within Twelve Step meetings. These programs show that the addiction model can work as effectively for food addicts as for alcoholics and drug addicts. This evidence convinces many self-assessed food addicts and their professional allies to take the disease seriously and protect their progeny by adopting eating plans that can eliminate cravings and reduce maladaptive behaviors by completely abstaining from the foods with addictive properties for each food addict. This is a model that could be adapted to ob/gyn clinics to assist parents.

Using systematic review and meta-analysis, Dean determined the possible impact of preconception care for parents of reproductive age on maternal, newborn, and child health outcomes [129]. She confirmed earlier evidence that promoting improvement in diet and exercise through sustained, daily changes, with the help of a support system resulted in weight loss and higher levels of physical activity.

Preconception counseling should be introduced and embedded in our culture. Children need this information prior to menarche. Counselors could advise prospective sexually active individuals to eliminate alcohol, nicotine, added sugar, HFCS, UP-S, cannabis, vaping, and other substances and behaviors which initiate cravings, withdrawal, tolerance, or hyperkatifeia (signs of addiction).

Better diets/lifestyles are needed during pregnancy according to the authors of *Maternal Obesity, Maternal Overnutrition and Fetal Programming: Effects of Epigenetic Mechanisms on the Development of Metabolic Disorders* [21]. Preconception weight loss interventions for overweight and obese women should incorporate accurate knowledge about the stakes in obese pregnancies

with practical, affordable methods to support healthy behaviors. Regular contact with support networks can enhance accountability and motivation with the goal of facilitating healthy habit formation and maintenance.

The World Health Organization, the American Psychiatric Association, the American Pediatric Society, the American Gynecological and Obstetrical Society, the Centers for Disease Control, the National Institute of Health, Federal, State, and local governments, along with every health professional serving the nation collectively have a responsibility to publicize the facts related to fetal development issues of overweight and obese people to add to the already recognized fetal alcohol syndrome (FASD) and spina bifida health information promotions. The time has come to spread the research findings concerning obesity and IGO that are long-accepted by the scientific community, but still not recognized by the public-at-large, so that another generation is not impacted by lifestyles that have continuously worsened since the 1970s.

PREVIOUS SUCCESSES WITH PROGRAMS TO INFORMA THE PUBLIC Drinking alcohol during any stage of pregnancy is today considered ill-advised because of its proven harm to the fetus. Prior to 1970, the condition of fetal alcohol syndrome (FAS) was not widely known or publicized. Today we know that some babies born with FAS are born with small eyes, thin upper lips, short, upturned noses, and smooth skin between their noses and lips. More importantly, depression, attention deficit hyperactivity disorder (ADHD), conduct disorder (aggression towards others and disregard of social norms and rules), and alcohol and drug dependence are common mental problems associated with FAS later in life. While only 1% of US babies have fetal alcohol spectrum disorders (FASD), a group of conditions including FAS that can occur in people who were exposed to alcohol before birth, the percentage in other parts of the globe may be as high as 20%. This is a preventable disease, but it is still the largest cause of mental retardation in United States neonates, and ironically, FAS is entirely preventable. FASD arises from a complex interplay of genetic and epigenetic factors involving hypothalamic–pituitary–adrenal axis dysfunction [130]. Transgenerational inheritance in FASD is now being studied [131].

Since the designation of FAS and widespread acceptance of FAS and later FASD, the incidence of the condition has fallen, and research continues which provides the hope of even better therapeutic interventions [132]. However, these statistics still leave 1 to 5.5% of 1st graders in sample cities with a diagnosis of FASD [133].

Another treatable success has been seen with neural tube defects (NTDs), including spina bifida and anencephaly which are major birth defects of the brain and spine that occur early in pregnancy as a result of improper closure of the embryonic neural tube. In 1992, the United States Public Health Service recommended that all women of child-bearing age consume 400 μg of folic acid daily to prevent these birth defects. Beginning in 1998, the United States mandated fortification of enriched cereal grain products with 140 μg of folic acid per 100 g. [134] Immediately after mandatory fortification, the birth prevalence of NTD cases declined. Fortification was estimated to avert approximately 1,000 NTD-affected pregnancies annually in the United States [135,136] In 2014, a total of 19 population-based birth defects surveillance programs in the United States reported that the number of cases of spina bifida and anencephaly among deliveries occurring during 1995–2011 was reduced by 28%. An updated estimate of approximately 1,300 NTD-affected births were averted annually during the post-fortification period. The lifetime direct costs for a child with spina bifida are estimated at $560,000, and for anencephaly (a uniformly fatal condition), the estimate is $5,415; multiplying these costs by the NTD case estimates translates to an annual saving in total direct costs of approximately $508 million for the NTD-affected births that were prevented. (Since low carbohydrate eating plans exclude cereals, folate supplements must be used in mothers who abstain from grains).

It is time for us to determine if we will continue this nightmare of inter-generational suicide or awaken from the nightmare and find workable solutions for our obese culture. We have the models of FAS and NTD and Alcoholics Anonymous to guide changes. The choice is ours.

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