Maternal smoking – a contributor to the obesity epidemic?

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Abstract

The prevalence of obesity is increasing worldwide, and the rising number of obese children and adolescents is of particular concern. In humans, smoking is a predisposing factor for abdominal obesity, glucose intolerance and insulin resistance. Maternal smoking is associated with preterm birth and low birth weight. On the other hand, the incidence of obesity is higher in children and adults born of smoking mothers. Disorders in eating behaviour, reduced physical activity, and increased risk of hypertension and nicotine addiction have been observed in the offspring of smoking mothers. Evidence from animal and human studies suggests that intrauterine smoke exposure may alter peripheral and central mediators involved in the regulation of appetite and energy metabolism. Smoking cessation during pregnancy is desirable to improve health outcomes in offspring.

The obesity epidemic

Obesity occurs when energy intake exceeds energy expenditure [1]. Our evolutionary history led to selection for consumption of high fat, protein rich and calorie dense food in times of plenty to protect against famine. The relatively recent availability of highly palatable, and energy dense food, combined with more sedentary lifestyles, have contributed to the global obesity epidemic. Thus the current increase in rates of obesity may be seen as an ironic outcome of our developed society.

Obesity is a major public health problem, which is closely linked to increased risk of type 2 diabetes and cardiovascular disease. Approximately 85% of people with diabetes have type 2 diabetes, and of those, 90% are obese or overweight [2]. Visceral obesity is thought to be a key contributor to the development of the metabolic syndrome, encompassing abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance, and a proinflammatory and prothrombotic state [3]. Enlarged fat cells demonstrate increased release of free fatty acids (FFA), a major contributor to insulin resistance [4-6].

Increasingly around the world, obesity is no longer restricted to adults. Childhood obesity is currently rising at an alarming rate, with 22 million children under five estimated as overweight [7]. In the USA, the number of overweight children has doubled and the number of overweight adolescents has tripled since 1980 [7], while in Australia 19-23% of children and adolescents were overweight or obese in 1995-1997 [8,9].

Cigarette smoking and weight control

Smoking is linked to lower body weight and reduced appetite [10,11]. Therefore smoking is commonly used as a weight control strategy, especially among the young, and in women [12-14]. This action of smoking on appetite appears to be nicotine mediated [15]. However, cigarette smoking is another major public health problem, leading to chronic obstructive pulmonary disease (eg. emphysema, bronchitis, bronchiolitis), and it is one of the leading preventable causes of death and disability worldwide [16]. Smoking is an addictive behaviour with low cessation rate, and relapse can happen even after repeated treatments [17]. The uncontrolled weight gain upon smoking cessation is another reason preventing people from quitting, as over 75% of former smokers gain weight after quitting [18-20].

In society, smoking *per se* is a predisposing factor for abdominal obesity [21], which was confirmed by our preliminary study in mice using cigarette smoke exposure [22]. Both active and passive smoking contribute to glucose intolerance and insulin resistance, leading to type 2 diabetes, and smoking cessation has been demonstrated to improve insulin sensitivity [23-26]. It has been speculated that the impaired insulin sensitivity among smokers may be directly due to nicotine, carbon monoxide, or other agents in tobacco smoke [25]. Vascular changes due to prolonged smoking may lead to reduced blood flow to skeletal muscles to decrease insulin-mediated glucose uptake [25]. A reduction in skeletal muscle mass due to wasting might also contribute to impaired glucose uptake. Nicotine infusion has been demonstrated to stimulate lipolysis to increase fasting triglyceride levels in both human and animal studies [27-29], further contributing to insulin resistance.

Impact of maternal nutrition on the development of offspring

Apart from the social and environmental factors that influence children's behaviour [30], the prenatal maternal condition is also critical to offspring body composition, and can predispose the fetus to the development of obesity [31]. Maternal obesity and hyperglycemia during pregnancy can lead to large birth weight, increased circulating insulin, glucose, FFA, triglycerides and glucose intolerance, as well as obesity in offspring [32-39].

Malnutrition during pregnancy can result in small birth weight, the classical example of which was children born after the Dutch Famine winter [40]. A number of epidemiological and animal studies have revealed a strong inverse relationship between birth weight and the risk of developing abdominal obesity and the metabolic syndrome in adulthood [40-43]. Barker first proposed the "fetal origins" hypothesis in 1992, which posits that poor fetal nutrition causes adaptations that program a future propensity to obesity, diabetes and cardiovascular disease [44]. Those observations were also interpreted as the "Thrifty Phenotype Hypothesis" [45]. This hypothesis suggests that, in response to undernutrition, a fetus responds physiologically in the short term by selectively distributing nutrients to preserve brain growth at the expense of other organs such as liver, pancreas, and muscle. However, these adaptations have sequelae that are potentially disadvantageous in the long term. The limitations on cell numbers in key organs will alter hormonal regulation, which increases the prevalence of type 2 diabetes and coronary heart disease [45]. The mechanisms underlying the association between intrauterine growth retardation and the appearance of the metabolic syndrome are not completely understood. A resetting of the hypothalamo-pituitary-adrenal axis has also been proposed to participate in the pathophysiology of obesity and the metabolic syndrome associated with intrauterine growth retardation [46,47].

Impact of maternal smoking on mothers

Prevalence studies suggest that 20-50% of women in developed countries report smoking at the onset of pregnancy [48]. About 25 to 29% of women arrive at the end of their pregnancy without stopping smoking and 50% of non-smoking mothers live in an environment polluted by tobacco during pregnancy [49].

Smoking has many impacts on maternal health, manifesting prior to, during and after pregnancy, including fertility difficulties, extrauterine pregnancy, premature labour and early placenta detachment; intrauterine growth retardation; and increased perinatal morbidity [50]. Smoking is known to have anti-oestrogenic effects, caused by smoking-induced alterations in hepatic oestrogen metabolism [51,52]. Women who smoke have significantly more variable menstrual intervals and menses length than non-smokers, with heavy smokers (more than 20 cigarettes per day) running a risk of shorter segment length than non-smokers due almost entirely to the shortening of the follicular phase [53]. Smoking has long-term effects on reproductive function, such as subfertility and malignancy [48]. An animal study using a modest dose of cigarette smoke showed smoke-exposed females had significantly increased interpubic ligament length, elevated serum oestrogen levels, and a reduced progesterone to estradiol-17β ratio compared with air-exposed controls [54]. However, smoke exposure had no significant effects on maternal body weight gain, litter size, or sex ratio in mice [54].

Impact of maternal smoking on offspring

Maternal smoking not only affects the metabolic system of mothers, but can also affect the fetus and its postnatal development. When considering the effects of smoking in pregnancy, there are short-term effects on pregnancy outcome that include miscarriage, low birth weight,

preterm birth and perinatal death [54-58]. Furthermore, there are also long-term effects on the health of children, including congenital abnormalities, childhood respiratory [59-61] and behavioural problems [62-65]. What has to be emphasized here is that some symptoms in later adulthood, such as ischaemic heart disease, hypertension, insulin-dependent diabetes, obesity, obstructive lung disease and cerebrovascular accidents, are also attributed to maternal smoking [48]. In the following discussion we will focus on the metabolic consequences following maternal smoking during pregnancy.

i. Effects on birth weight and growth in offspring

In western countries, maternal smoking during pregnancy (rather than poverty) is a major cause of low birth weight [66]. A poor nutritional status due to the anorexigenic effect of nicotine, carbon monoxide exposure, as well as blood flow restriction to the placenta because of the vasoconstrictive effects of catecholamines released from the adrenals and nerve cells can indirectly affect the fetus [67]. Studies in both human and primate show that maternal smoking or exposure to nicotine can result in lower birth weight [55,68-73]. Intrauterine exposure to tobacco during the third trimester of pregnancy was shown to be the strongest predictor of decreased weight and head circumference at birth [69]. Even maternal obesity cannot counteract the infant growth retardation due to smoking during pregnancy [70]. Using nicotine (the major addictive element of tobacco smoke) in animal models allows an examination of the developmental defects due to intrauterine cigarette smoke exposure. At birth, the brain weight of offspring from nicotine treated primate mothers was similar to those from saline treated mothers [72]. This may be due to the distribution of nutrients to preserve brain growth, therefore, as a result, adrenal and pancreas weights were significantly lower in newborns from nicotine treated mothers [67].

Catch-up growth is normally observed postnatally in children with intrauterine smoke exposure, and there is evidence of a strong link between maternal smoking and childhood obesity in offspring, especially amongst early pregnancy smokers [66,74-77]. At 3 years of age, no association between maternal smoking and central obesity in offspring was observed [75]. However, at this age smoking during early pregnancy is directly associated with increased BMI, although these associations were somewhat attenuated after adjustment for potential confounders [75]. Since there is no difference in height, the influence of maternal smoking on BMI may be mediated by changes in body weight alone [75]. Others reported that children of mothers who smoked during pregnancy started to display increased risk of overweight at 5 years of age [77]. At age 11 for females and 14 to 16 for males, offspring of mothers who smoked had an increased risk of being among the highest decile of BMI [66,76]. At mean age 9.9 years, offspring from mothers smoking at any time during pregnancy have higher total fat mass, but also higher lean mass, after adjustment for age, sex, height, and height squared for total fat mass [78]. However, there is no strong link to central obesity. It is postulated that the increased lean mass is simply a reflection of associations with fat mass. Interestingly, it has also been found that maternal smoking during only the first trimester had a similar impact on offspring as maternal smoking during the whole pregnancy [79], suggesting the first three months of pregnancy might be critical for long term effects on the offspring. Children from former smoking mothers were not as overweight as those from mothers smoking during early pregnancy [75].

ii. Effects on eating behaviour and lifestyle in offspring

Smoking mothers tend to have shorter breastfeeding periods and introduce solid food to children earlier than non-smoking mothers, which may reduce the protective effects of breast milk against eating disorders in offspring [66,79-82]. The British National Child Development Study in 42 year olds born in 1958 suggest the ratio of adults reporting poor diet was higher in the cohort with maternal smoking during pregnancy, and was positively linked with maternal smoking states [74]. However, there was no evidence of a link between maternal smoking and bulimia nervosa in offspring [83]. Lifestyle differences were identified in the offspring of smoking mothers compared with those of non-smoking mothers, reflected in the consumption of more fried food and soft drinks and less fresh fruit/vegetable, and greater inactivity [66,76,79]. Furthermore, maternal smoking has also been shown to increase the risk of nicotine addiction in offspring [66,84]. Nicotine exposed newborns had more signs of stress and dysregulation of the hypothalamic-pituitary-adrenal axis [62]. They had fewer qualifications, however higher social class at year 33 compared with offspring from non-smoking mothers [66]. This may be also an influence from the parental lifestyle, because mothers who smoked in early pregnancy were younger, less educated, less likely to be married, and had lower household income compared with those who had never smoked [75]. Children of smokers are more likely to be exposed to passive smoking. The diets of smokers also differ from those of non-smokers with lower intake of fibre, vitamins and minerals, and higher higher intakes of monounsaturated fatty acids, starch, and sugar-sweetened soft drinks, which could affect children's food preference [85,86]. Physical activity levels may be lower in the children of smokers [87], which may be due to impaired lung function. This could be due to either an adverse effect of in utero smoke exposure on pulmonary development or postnatal passive smoking [88-90].

iii. Effects on blood pressure in offspring

Obesity is a predisposing factor for increased blood pressure. It is of interest to examine the link between maternal smoking and blood pressure changes in offspring. Children from mothers who smoked throughout pregnancy, those with low birth weights, those who were not breast-fed, and those who were obese in childhood or adolescence tend to have higher blood pressure in adulthood [91-93]. These predisposing factors are all observed in offspring from smoking mothers.

Maternal smoking in early pregnancy and even before pregnancy was somewhat associated with higher systolic blood pressure (SBP) at age 3 [75]. SBP of children of early pregnancy smokers was 2.4mmHg higher, and that of former smokers was 1.5mmHg higher than children of non-smokers [75]. These results also suggested smoking may have a persistent influence on offspring blood pressure even if the mother quits months before pregnancy [78]. However, after SBP was adjusted for BMI, the SBP of children from smoking mothers was only 1.5 mmHg higher, suggesting the higher adiposity only partially contributed to the elevated blood pressure [75]. Blake and colleagues demonstrated that smoking during pregnancy and lower birth weight were positively associated with higher childhood blood pressure at age one through to age six [73]. The average SBP of 6 year old children of smoking mothers was higher than that of those of non-smoking mothers, and was associated with the amount of cigarettes the mother smoked. The increase in SBP of children born of heavy smoking mothers (more than 20 cigarettes per day) was 3.4 mmHg compared 1.2 mmHg of light smokers. Nicotine may directly affect the development of fetal renal, cardiovascular, or nervous systems, as well as the maternal vasculature, thereby indirectly affecting placental

formation and blood flow [94]. Therefore evidence from several studies suggests that prenatal smoke exposure predisposes individuals to hypertension.

iv. Effects on peripheral and central appetite mediators in offspring

Nicotine passes rapidly and completely across the placenta, with fetal concentrations generally being 15% above maternal levels [95]. Products of cigarette smoke, such as carbon monoxide and ingredients in tobacco tar, can directly affect the fetal brain [67]. The alteration in neuronal and hormonal pathways involved in feeding regulation and energy metabolism in the offspring of smoking mothers is poorly understood. Studies in humans and primates indicate some hormonal and neuronal abnormalities relevant to feeding regulation due to maternal smoking or exposure to nicotine [55,72].

Leptin, an adipose-derived hormone, is a critical regulator of food intake and metabolism. Exogenous leptin injection decreases fasting-induced hyperphagia, reduces food intake, body weight and fat accumulation [96,97]. The feeding inhibitory effect of leptin is via activating neurons expressing anorexigenic peptides, such as proopiomelanocortin (POMC), and inhibiting neurons expressing orexigenic peptides, such as neuropeptide Y (NPY) in the hypothalamus [98]. NPY, a 36 amino acid member of the pancreatic polypeptide family, is a powerful orexigenic peptide, signaling for periodic eating behavior and the maintenance of body weight [99]. Central administration of NPY was shown to induce hyperphagia even under conditions of satiation, increase fat deposition, decrease energy expenditure, and promote obesity [100,101]. Elevated NPY neuronal activity due to leptin deficiency is linked to obesity as shown in morbidly obese *ob/ob* mice [102,103]. POMC mRNA levels are reduced by fasting and restored by refeeding, or increased by leptin administration [104,105]. Mutations within the

POMC gene or gene product abnormalities result in early-onset obesity, adrenal insufficiency and red hair pigmentation in humans [106].

It has been suggested that smoking might increase the production of catecholamines in infants and lead to lipolysis, which might be followed by a corresponding decrease in leptin levels [55,107]. Lower plasma leptin levels were found in some studies, whereas no differences in breast milk leptin levels was observed between smoking and nonsmoking women [107,108]. Cord blood leptin concentrations in both full-term and preterm newborns from smoking mothers were significantly decreased compared to those from nonsmoking mothers [55]. In newborns from non-smoking mothers, a positive correlation between leptin concentrations and birth weight was observed, which was not obvious in newborns from smoking mothers [55]. Similarly in the primate, although maternal serum leptin levels were not altered by nicotine injection, its level was reduced by 50% in newborns from nicotine treated mothers compared with those from control mothers [72]. In early life, leptin is critical for the development of neurons and pathways between hypothalamic nuclei involved in appetite control [109]. Mutations in either the leptin (ob) gene or its receptor result in disruption of arcuate neuron projections and an obesity phenotype [102,109,110]; supplementation of leptin during the early postnatal period can partially restore the reduced hypothalamic neuron fibre density and projection pathways in *ob/ob* mice and partially reverse the hyperphagic phenotype [109]. Therefore, reduced leptin in newborns from smoking mother may contribute to the disorders in eating behaviour in later adulthood.

Maternal smoking may also affect neuron development. Maternal nicotine exposure significantly reduced NPY expression in the arcuate nucleus of the hypothalamus, whereas a 2-fold increase in POMC gene expression was observed in this area in newborn [72]. The

normal negative correlation between blood leptin and brain NPY and POMC expression was disturbed by maternal smoking. However, it is hard to interpret the inhibition of orexigenic peptide (NPY) and increase in an anorexigenic peptide (POMC) in the newborn primate, and further studies are needed to examine the long term impact of maternal smoking.

The observations on newborn primates with intrauterine nicotine exposure are similar to our previous study on adult mice exposed to cigarette smoke [111,112]. In this study, smoke exposed mice had lower daily caloric intake compared to air sham exposed mice, resulting in lower weight gain, fat loss, and lower plasma leptin concentrations. NPY concentration in the paraventricular nucleus was reduced by smoke exposure, which we interpreted as the probable cause of appetite loss. However, compared to a pair-fed group, we demonstrated that weight loss was not only related to reduced calorie intake, but also altered energy expenditure linked to smoking [113]. The increased risk of obesity in offspring from smoking mothers might be similar to the weight gain observed after smoking cessation or nicotine withdrawal. Smoking cessation typically produces weight gain from a combination of increased caloric intake and decreased energy expenditure [114]. Without the inhibitory effect of nicotine, hypothalamic NPY expression is increased, leading to hyperphagia; while uncoupling protein 3, a marker for energy expenditure, is reduced [115]. Unfortunately, direct data on the impact of maternal smoking on energy turnover in offspring are sparse.

Perspective

As the offspring age, the environment is likely to exert a greater influence on the metabolic outcomes of interest. Without dietary challenge, low body weight due to early postnatal or intrauterine undernutrition in the rodent can be maintained till adulthood [116,117]. When a high

fat diet was introduced, there was catch-up growth [116]. An increased incidence of obesity in offspring of parents who smoke may be also linked to an unhealthy lifestyle modeled by their parents who might be also obesity-prone. Studies that can strictly control the postnatal environment are required to separate the effects of maternal smoking *per se* from postnatal lifestyle influences.

Smoking cessation has been called for not only to reduce the incidence of cancer [118], but also to reduce adverse effects on fetal development [48]. It has been shown that when mothers stopped smoking during pregnancy, body mass index and incidence of overweight and obesity among adolescent offspring were similar to those of non-smoking mothers, even if the mothers smoked at other times in the child's life [76]. It is noteworthy that weight gain upon smoking cessation may contribute to maternal obesity during pregnancy. However, the benefits from smoking cessation might override the impact of maternal weight gain. Future studies could explore strategies for maternal weight control during pregnancy via dietary and physical activity interventions.

In summary, smoking during pregnancy has an important impact on maternal metabolism and significantly influences fetal development and birth weight. In addition, it is associated with increased risks of both childhood and adulthood obesity and elevated blood pressure. Alterations in hypothalamic appetite regulatory peptides have been described in smoke or nicotine exposed animals and these may contribute to changes in appetite. On a positive note, the detrimental effects of maternal smoking were reduced in former smokers and public health messages should promote smoke cessation prior to pregnancy.

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