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Fetal Programming of Renal Development–Influence of Maternal Smoking

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Abstract

Smoking is a known risk factor for non-communicable illness including pulmonary disease, cardiovascular disease, and Type 2 diabetes. Smoking also contributes significantly to the rising 'epidemic' of chronic kidney disease. It is increasingly recognised that maternal programming of fetal development during pregnancy predisposes offspring to future disease. Maternal smoking, particularly in the first trimester, imposes a significant adverse impact on fetal renal development that determines the future risk of chronic kidney disease. Several mechanisms may contribute. Firstly, epigenetic modification of fetal nuclear or mitochondrial DNA, induced by intrauterine exposure to chemicals within the cigarette smoke, may result in an increased risk for metabolic and renal disorders. Secondly, nicotine and other chemicals within the cigarette smoke can cross the blood placental barrier concentrate in the fetus and result in direct toxicity. Thirdly, malnutrition due to the anorexigenic effect of smoking results in nutritional deficits in the fetus and impairs organ growth and development. 10-45% of pregnant women from diverse populations smoke during pregnancy. Hence it is considered a major and significant public health issue that imposes adverse health consequences not only to the pregnant women, but also inherited by their offspring, and potentially affecting future generations.

Keywords: Maternal smoking; Fetal programming; Renal development

Introduction

There is increasing attention paid to the contribution ofthe intrauterine environment to disease in adulthood. It has been suggested when maternal factors impact on foetal and/or infant growth and development, this predisposes individuals to subsequent environmental insults, rendering them more susceptible to developing various metabolic disorders, such as type 2 diabetes, hyperlipidemia, and hypertension [1-5]. As such, maternal smoking has been recognized as a significant intrauterine factor contributing to the onset of these diseases in offspring. However this review will focus on a less studied area, the link between maternal smoking and renal disorders in offspring.

Smoking and passive smoking during pregnancy are unfortunately still common in both developed and developing countries [6,7]. Maternal smoking has been recognized as an important perinatal factor that predispose offspring to not only metabolic disorders, but also respiratory and behaviour disorders (reviewed in [8-11]). Although smoking itself has been linked to increased risks of renal dysfunction and chronic renal disorders for many years [12], research on the direct impact of maternal smoking on renal disorders in offspring are scarce.

Maternal smoking, particularly in the first trimester, imposes a significant adverse impact on fetal renal development that determines the future risk of chronic kidney disease. The functional unit of the kidney is the nephron: a structure that contains vascular loops of the glomerulus at the site of blood filtration and a tubular segment that reabsorbs and excretes components of the filtrate and ultimately connects to the collecting system. The number of glomeruli in the kidney significantly correlates with birth weight, in addition to non-modifiable factors, such as sex (men 17% higher than women), age (adults have significant less than children), and race [13-15]. Alterations in the intrauterine environment may affect renal development, including maternal malnutrition, infectious diseases, and toxins (including medication) can all lead to intrauterine growth retardation (IUGR) and low birth weight [1,16,17].

Therefore, renal developmental disorders due to intrauterine growth retardation may hold the key to the later onset of renal disorders in offspring of smoking mothers. Several mechanisms are proposed that may predict the susceptibility to future renal disease (Figure 1), including 1) epigenetic modification of fetal nuclear/mitochondrial DNA, 2) changes in fetal renal growth factors and 3) direct toxicity from the chemicals in the cigarette smoke. In addition, malnutrition due to the anorexigenic effect of smoking results in nutritional deficits in the fetus and impairs organ growth and development. Inherited genetic modification or epigenetic induced by environment may also promote the development of metabolic and renal disease later in life. Several studies have suggested potential candidate genes predisposing to a susceptibility to renal disease among particular ethnic groups [2]. It has long been suspected that many putative genetic variants only influence kidney disease progression in the presence of specific environmental factors. However, whether these genetic variants can also be affected by epigenetic mechanisms that predispose individuals to the development of kidney disease has not been confirmed. Family members are normally exposed to similar environmental conditions, which can interact with genetic factors to promote what has previously been considered as 'polygenic inheritance [2]. The current review will discuss the detrimental impact of maternal smoking on fetal renal development and the known mechanisms involved.

Maternal Cigarette Smoking and Renal Development in Offspring

Despite the disadvantages of smoking due to the risk of various

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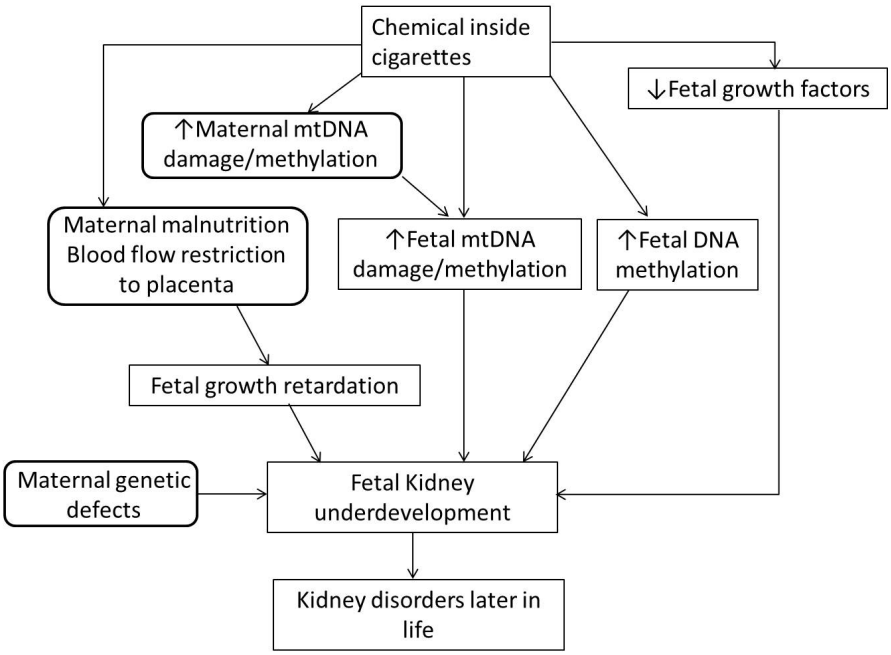

Figure 1: A flow-chart showing effects of maternal smoking related factors on fetal kidney development. Maternal smoking causes fetal growth retardation and underdeveloped kidney through multiple mechanisms, including fetal DNA modifications, direct impacts of chemicals in the cigarette smoke, changes in growth factors in the fetus and reduced fetal nutrition supply due to maternal under nutrition and placental blood flow restriction induced by cigarette smoke. Maternal genetic defects can also have a direct impact on fetal kidney development and the predisposition of kidney disorders later in life.

diseases including cancer, respiratory, and cardiovascular diseases, in the USA, UK and Australia, 19-25% adult woman smoke, and many are of childbearing age [18,19]. Despite the general education on the risks of smoking in pregnancy, smoking during pregnancy remains a major and significant public health issue. Socioeconomic status is known to affect attitudes towards smoking among pregnant mothers. Those with lower social status are more likely to smoke during pregnancy [20]. Passive smoking also has a significant impact on the health of the mothers and fetus (reviewed in [8]), as concentrations of harmful chemicals in second-hand smoke are potentially higher than those in the original smoke inhaled from the cigarettes [21,22].

A strong relationship between birth weight and renal size, nephron number, albuminuria, and systolic blood pressure has been shown in several racial groups [1,6,13,23]. It has been reported that newborns with low birth weight have 30% less nephron numbers compared with those with normal birth weight [1]. Additionally, low birth weight is also associated with large glomerular size (glomerulomegaly) [1] and retarded kidney growth during the first 18 months of life [24]. The decrease in nephron number is then associated with susceptibility to developing hypertension and chronic renal failure [25,26]. Approximately, 20% of babies with low birth weight arise from mothers who smoked during pregnancy [27,28]. A recent retrospective cohort study among 1,072 children confirmed that maternal smoking was associated with a reduction of fetal and infant kidney volumes [29]. The impact of low birth weight caused by maternal smoking on health outcomes is amplified if a rapid increase in body weight occurs after 2 years of age [30]. In the offspring of smoking mothers, an accelerated increase in body mass index (BMI) has been observed after birth [31].

However, studies to date have not addressed renal disorders caused by maternal smoking, where the pathogenesis may be independent or additive to the known renal risks of IUGR and low birth weight [32]. In this study, a dose-dependent association between the number of cigarettes smoked during pregnancy and kidney volume in fetal life was reported. Smoking less than five cigarettes per day was associated with larger fetal kidney volume, considered be an adaptation to reduced kidney function [29]. Smoking more than ten cigarettes per day tended to be associated with smaller fetal kidney volume [29]. However, these correlations disappeared by age 2 [29]. Hence it is suggested that maternal smoking may directly lead to impaired renal function, due to a multiplicity of factors, including low numbers of nephrons, secondary hyperfiltration, and ultimately glomulosclerosis [29]. However, studies directly addressing the link between maternal smoking and renal dysfunction in offspring are scarce.

Maternal cigarette smoking is associated with congenital renal abnormalities in offspring, such as urinary organ malformation, bilateral renal agenesis and renal hypoplasia [33-35]. There is a twofold increased risk of congenital urinary tract anomalies in offspring from smoking mothers [35,36]. However, there remains a lack of studies investigating the underlying molecular and epigenetic mechanisms within the kidney, leading to future renal dysfunction.

Epigenetic and DNA Modifications

DNA methylation is an important regulator of gene expression and occurs primarily on cytosine residues in CpGdinucleotides [37]. About half of human genes contain CpG-rich regions (CpG islands). The majority of CpG islands are unmethylated, whilst individual CpGs are mostly methylated [38]. DNA methylation is established *in utero,* with the traditional view that this is mainly influenced by maternal genotype change induced by smoking even prior to gestation [39,40], with the methylation pattern being largely preserved during development. Hence smoking prior to pregnancy may influence the fetus even if cessation at gestation regardless of lifestyle after birth. However, environmental

and metabolic factors during the intrauterine period may also affect the establishment of cytosine and lysine methylation [41]. Indeed, it has been increasingly recognized that during development, DNA can be modified epigenetically to alter gene expression and transcription without a change in DNA sequence, primarily by DNA methylation and/or histone acetylation [42]. Thus, DNA modification may be the fundamental mechanism that drives the programming of fetal development by environmental factors, including intrauterine cigarette smoke exposure as a consequence of maternal smoking.

In humans, nephrogenesis starts at gestational week 6-8 [43], and most nephrons are formed by the third trimester, gestational week 28-40 [2]. Nephrogenesis ends by 36 weeks of gestation in humans, therefore the final number of nephrons in each kidney is established at birth [44]. After birth the nephrons still undergo maturation until the age of 12 years [2]. In rodents, nephrogenesis continues after birth for a short period of time [45]. Therefore, any changes in renal DNA methylation *in utero* may not only significantly affect nephrogenesis and nephron numbers at birth, but also disturb final nephron maturation.

The earliest recognition of nicotine induced DNA methylation was shown inhuman oesophageal cancer [24]. Differential methylation across the genome in relation to maternal smoking during pregnancy only addressed the genes that are methylated without linking to any specific adult diseases [46]. In the study by Joubert et al. the most frequent CpG sites methylation in the cord blood of babies from smoking mothers were found in the coding region of arylhydrocarbon receptor repressor (AHRR), coding region of growth factor independent 1 transcription repressor (GFI1), the upstream region of cytochrome P450 isoform CYP1A1, and within the coding region of myosin 1G (MYO1G) [46]. AHRR and CYP1A1 play a key role in the detoxification of tobacco smoke via the AhR signalling pathway; while GFI1 is involved in diverse developmental processes, which may affect renal development [46]. Other genes that were methylated on one CpGs cite include HLA-DPB2, ENSG00000225718, CNTNAP2, EXT1, TTC7B, and RUNX1 [46]. The impacts of gene methylation on renal developmental and functional change, as well as their contributions to the predisposition to renal disease in the future, are still unknown.

The Long Interspersed Nuclear Elements-1 (LINE-1s or L1 elements) are active members of an autonomous family of non-LTR retrotransposons and occupy nearly 17% of the human genome. The LINE-1 (L1) gene products possess mRNA binding, endonuclease, and reverse transcriptase activity that enables retrotransposition. There is strong evidence suggesting that increasedLINE-1 activity is strongly linked to the development of cancer and aging process [47,48]. Normally LINE-1 methylation decreases with age and reduced LINE-1 methylation is also linked to various cancer types, possibly due to chromosomal instability. Thus LINE-1 has been considered as an early indicator of disease [49,50]. Innewborns with low birth weight, there were significantly lower Long Interspersed Nuclear Elements (LINE)-1 methylation levels in the cord blood compared to normal weight infants [51], suggesting increased susceptibility to diseases. However, the link between LINE-1 hypomethylation and the risk of developing renal functional disorders has not yet been reported. Maternal smoking commonly leads to low birth weight [32,52]. However direct measurement of renal DNA methylation in offspring from smoking mothers has not been reported to date.

Mitochondrial damage by maternal smoking may play a role in renal developmental disorder and determine future renal disease. Mitochondrion has been suggested as a regulator of DNA methylation, as cells deplete in mitochondrial DNA (mtDNA) showed altered DNA methylation of the nuclear genome, which was rescued upon the repletion of mtDNA [53]. The limited understanding of the contribution of mtDNA damage to human disease arises from cancer research. *In vivo* and *in vitro* evidence suggests that nicotine can induce oxidative stress and mtDNA damage in human tissue [54,55]. An increase in reactive oxygen species (ROS)has been shown to decrease mtDNA methylation, which has been suggested as a compensatory response to mtDNA damage [56]. However, the contribution of maternal mtDNA damage to renal dysfunction in offspring is unknown. Interestingly, nicotine can accumulate in the kidney [57]; whereas mtDNA functional damage following maternal administration of nicotine has to date only been reported in fetal pancreas [58]. Nevertheless, mtDNA dysfunction can result in reduced capacity of the mitochondria to regulate growth, tissue maintenance, and cellular metabolism, which are dysregulated in kidney disesase [59]. Indeed, mtDNA damage and deletion have been found in the kidneys of rats with type 1 diabetes [60]; yet the contribution to fetal renal development or it response to intrauterine cigarette smoke exposure remain unclear.

Therefore, heritage of mtDNA damage and further DNA modification by epigenetic methylation due to intrauterine cigarette smoke exposure is likely to significantly increase the risk of kidney disease in susceptible populations.

Direct Damage from Chemicals in the Cigarette Smoke

Studies have shown that smoking is a key cause of renal dysfunction in adults, due to the detrimental impact of smoking on renal hemodynamics, water diuresis, and electrolyte excretion [61,62]. As such, smoking is closely related to proximal tubular damage, kidney cancer, and end-stage kidney disease [12]. Tobacco smoke is a mixture of more than 4000 chemical substances [63]. Nicotine alone can cause renal dysfunction in humans and animal models [29,64], attributed to the vasoconstrictive effect of nicotine [29,64], increased activity of the renin-angiotensin-aldosterone (RAAS) system [65], and an increased ratio of the angiotensin type 1 receptor AT1 versus AT2 receptor density [29,64].

The chemicals in cigarette smoke inhaled by the pregnant mothers, such as nicotine, pass rapidly and completely across the placenta, with fetal concentrations generally being 15% higher than maternal levels [66-68]. It has been shown that nicotine infusion in rat dams lead to smaller kidneys in offspring compared to those from non-smoke exposed mothers [4,69]. An increase in glomerular size in response to reduced number is considered to compensate for low nephron numbers, in order to restore the total filtration surface and excretory homeostasis [70]. However, this adaptation can lead to adverse consequences in the long term. If glomeruli are overly enlarged, glomerular hypertension and hyperfiltration ensues, resulting in accelerated nephron loss [71]. Glomerulosclerosis ultimately ensues, further reducing the functional nephron capacity [72]. Further enlargement of remaining nephrons will occur, leading to a vicious cycle of nephron loss and renal dysfunction. As such, hypertension, and albuminuria will develop [29,64,73].

In humans, maternal blood cadmium during pregnancy is positively correlated with the risk of fetal growth restriction [74,75]. Tobacco smoking is the most important single source of cadmium exposure in the general population. It has been estimated that about 10% of the cadmium content of a cigarette is inhaled through smoking [76]. However, on average, smokers have 4–5 times higher blood cadmium concentrations and 2–3 times higher kidney cadmium concentrations than non-smokers [77]. It has been shown that environmental exposure to cadmium may cause kidney damage and tubular proteinuria, and end-stage renal disease [78,79].

Polycyclic aromatic hydrocarbons are another group of chemicals in the cigarette smoke that has been suggested to be able to cause IUGR [80,81]. They bind to aryl hydrocarbon receptor, which is a ubiquitous transcription factor involved in renal development [82,83].

However, none of these human and animal studies on cadmium and polycyclic aromatic hydrocarbons have directly measured kidney weights in the new born, nor have renal structural and functional changes been measured in the short or long term.

Growth Factors

Maternal smoking is implicated in IUGR; while IUGR results in reduced nephron number in the offspring, partially due to the alteration of signalling gene expression involved in fetal nephrogenesis. Glial-cell-Derived Neurotrophic Factor (GDNF) is an important growth factor at the initiation of adult kidney formation, which determines the location and number of ureteric bud [84]. In a rat model of IUGR, GDNF and its downstream signalling pathway are significantly deregulated in the fetal and newborn kidneys, leading to underdeveloped kidneys [85,86]. However, the effect of smoking on GDNF and its downstream signalling pathway is unknown.

Notch homolog protein (Notch) 2 is a growth factor required for normal development of the proximal nephron (epithelia of glomeruli and proximal tubules) [29,87]. In fetuses with IUGR, the co-activators and downstream target of Notch2 are also down-regulated [85]. The direct impact of smoking on Notch expression in the kidney is not clear. However, It has been shown that nicotine can significantly increase the expression of Hes1, the downstream effector of Notch, in human embryonic stem cells [88]. Increased Hes1 can lead to epithelial to mesenchymal transition in renal tubular epithelial cells [89]. In addition, the renal growth hormone (GH)–insulin-like growth factor (IGF) axis is critical for renal organogenesis, which is also low in the fetus and newborn with IUGR [90,91]. The binding affinity of growth hormone to its receptor was also significantly lower in babies with IUGR [92,93]. It has been shown that deregulated GH, IGFs and vascular endothelial growth factors are closely associated with diabetic kidney diseases [94]. Cigarette smoke exposed mice displayed a phenotype of increased albumin excretion in the urine, which was associated with a moderately increased glomerular collagen type IV deposition compared with the control mice [95]. They also had a two-fold increase in glomerular IGF-I receptor mRNA expression compared with the control mice [95]. In addition, the cord blood level of IGF-I was also shown to be 3-fold lower compared to that in newborns from non-smoking mothers [96]. It will be interesting to investigate whether abnormal IGF-I receptor expression can affect renal genesis in the offspring of cigarette smoke exposed mothers. Indeed, changes in growth factors may be a critical contributor linked to renal underdevelopment and later renal functional disorders by intrauterine smoke exposure.

Leptin, encoded by the *ob* gene, is an important growth hormone in the developing fetus and new born, which plays a critical role in growth and maturation [97,98]. Leptin in the fetus is mainly sourced from the maternal circulation, placenta, and foetal organs. It is involved in the induction of mitosis in different cells through regulating growth hormone production [98,99] and affecting mitochondrial proteins synthesis and function [97]. Low blood leptin levels have been shown to lead to foetal growth retardation [97]. Human studies have shown that leptin concentrations in the cord blood of the newborns from smoking mothers are significantly decreased compared to those from non-smoking mothers [100]. Similarly in the primate, serum leptin levels are reduced by 50% in newborns by intrauterine nicotine exposure [101].

Clearly this data does not suggest causation but rather an association between smoking, which is known to result in IUGR and a reduction in factors known to regulate normal fetal nephrogenesis. Similarly the direct modification of maternal smoking on these growth factors in offspring developing kidneys remains unknown.

Nutritional Factors

Maternal smoking is related to a poor nutritional status in the mothers [102]. This was proposed to be due to the anorexigenic effect of chemicals in the cigarette smoke, such as nicotine and carbon monoxide (reviewed in [8,9]). Nicotine can also directly reduce the nutrition supply to the fetus by causing blood vessel constriction that limits blood flow to the placenta and fetus (reviewed in [8,9]). Foetal development is thus affected, leading to IUGR and low body weight as reviewed previously [8].

Substantial intrauterine protein or caloric restriction has been shown to be linked to reduced glomerular number, glomerular enlargement, increased blood urea and urinary albumin excretion in resulting offspring [103-106]. Hence developmental abnormalities induced by altered maternal nutrition can predispose newborns to kidney diseases and hypertension at adulthood [17,107]. In addition, it has been further shown that protein supply is also important to support fetal renal development. Renin-angiotensin-aldosterone system (RAAS) is up-regulated during renal development and in the perinatal period. It has been suggested that angiotensin (Ang) II, signalling through both AT1 and AT2 receptors, are involved in the development of the nephron [108]. It has been well demonstrated that suppression of the RAAS in neonatal rats significantly affects renal maturation leading to renal malformation [109]. Protein restriction inhibits the renal renin and AngII expression in offspring, leading to renal underdevelopment [110]. Unfortunately, changes in Ang II and AT1/2 in rodents exposed to nicotine during perinatal periods have only been measured at mature age or in the brain and aorta [64,111], but not in the fetal or new born kidneys.

Conclusion

Although it is already known that maternal smoking or nicotine treatment during pregnancy is linked to kidney underdevelopment in offspring, the renal functional change and underlying mechanism is not fully understood. Currently available data suggests a link between smoking-induced dysregulation of growth factors that are critical for renal development. In addition to the direct impact of cigarette smoke to modify fetal genome at DNA level, smoking can also change maternal methylation prior to gestation, which is inheritable by the fetus. The consequence of maternally derived epigenetic changes on the development of chronic kidney disease in progeny is yet to be determined, Smoking cessation prior to or at early stage of pregnancy is critical to promote not only a healthy start to life, but also to prevent potential epigenetic modifications of genome that lead to chronic disease in adulthood, an objective shared by all communities.

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