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Review

The toxicity of E-cigarettes and children's respiratory health

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Educational aims

The reader will be able to:

- Provide an overview of the use of E-cigarettes among children and potential future parents.
- Outline what is known, and not known of toxicity of E-cigs exposure to the child during pregnancy and early childhood.
- Emphasise the need for precautionary advice to the public, parents and the young adolescent about the risk of nicotine addiction and the additional components of E-cigs.
- Provide a basis for arguments in public debates on regulation of E-cigs, taking the paediatric perspective.

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SUMMARY

Electronic cigarettes (E-cig), also referred to as Electronic Nicotine Delivery System (ENDS), were initially developed in 2003 to reduce the harmful effects of tobacco smoking. Since then, E-cig have become widely available in many countries and are used by many young people who would be unlikely to take up cigarette smoking. However, the adverse effects on child health remain largely unknown. E-cigs are available through regulated sale in many countries, but easily accessible by the internet in others.

Adverse effects may be ascribed to the nicotine itself, to the accompanying substances in the aerosol (often referred to as vapour) or to temperature modifications of the content. There is a lack of human studies to assess respiratory effects of nicotine exposure to the unborn or young child. Also assessing the effects of the vaping content apart from nicotine is challenging, with the huge variety of exposure by frequency, duration and content, but experimental studies are on the way that may indicate the level of harm by such products.

This article will summarize what is currently known about the use of E-cigs in children and in pregnancy, and discuss adverse effects of direct or in utero exposure to E-cig on the respiratory health of children. We thereby hope to provide a background for discussing potential harms to the respiratory system of children by E-cig exposure in pregnancy and early post-natal life, in a setting where an increasing proportion of adolescent and young adults use E-cigs, marketed to be 95% less harmful than conventional cigarettes.

INTRODUCTION

An E-cig is produced to deliver nicotine-containing aerosol by heating a solution often containing glycerol and a battery, a vaporizer and a cartridge with fluid aerosolized through a mouthpiece. With the large variation in content, doses and concentrations of nicotine, flavouring and other substances, often with poor labelling, it will be challenging to determine the effects on children's respiratory wellbeing. Indeed, acute and life-threatening nicotine poisoning due to ingestion of the cartridge contents has been reported [1].

The invention of the electronic cigarette (E-cig) in 2003, or Electronic Nicotine Delivery System (ENDS) (hereafter referred to as E-cig), has been attributed to a Chinese pharmacist (Hon Lik) [2] to reduce the harmful effects of cigarette smoking. Electronic cigarettes became available in the United States of America in

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2007 selling for $20 million in 2008, with sales increasing to $1.7 billion in 2014 and expected to grow about 25 percent a year through 2018 [3]. Rapidly increasing use of E-cigs has been observed also in other countries with increased availability [2] followed by heated public and medical debates [4,5] on potential benefits versus harmful effects of E-cigs. To combat potential harmful effects, regulating the sale of E-cig is currently implemented in 68 countries, often by regulations that have not been developed to embrace ENDS [2]. However, most include a minimum age for purchase and restrictions of indoor use, production, import and marketing [2] of E-cigs, often challenged by how to classify and regulate E-cigs related to content of nicotine and flavoured additions to the aerosols. Arguments against regulations include claims [6,7] or beliefs [3,8] that E-cigs are substantially less harmful than conventional cigarettes or even safe [8]. However, the increasing use of E-cigs among the young and potential future parents and the hitherto unclear harmful effects on the offspring, challenges the overall societal harm-reduction benefits of E-cigs. In line with many countries around the world [2], the European Commission recently concluded that the use of refillable electronic e-cigarettes, and the potential exposure to e-liquids containing nicotine in high concentrations, may pose risks to public health [9].

Potential benefits of E-cigs would be related to cessation or reduced smoking in established smokers, and E-cigs have been claimed to be 95% less harmful than smoking conventional cigarettes. In fact, in the Royal College of Physicians report. "Nicotine without smoke: Harm reduction" from 2016, E-cigs are classified as a Nicotine Replacement Therapy (NRT) [7], with the clear intention of preventing unnecessary deaths in smokers. However, documentation of E-cigs being effective in smoking cessation is controversial [10], and the claimed 95% harm reduction compared to conventional cigarettes [6,7] has not been documented [4,7]. Worryingly, E-cigs have become widely used by young people who were unlikely to take up smoking [11,12,13], and cigarette smoking appears to be more common among adolescents who tried E-cigs than among those who had not [13]. The overall harm-reducing effects of E-cigs to society and to individuals are therefore questionable, as there is no safe or risk free level of nicotine exposure [14]. Also, there are limited human studies to outline potential harmful effects of E-cigs with and without nicotine [15]. The public acceptance of E-cig –use [16] to reduce harm from cigarette smoking, challenges the efforts to prevent tobacco or nicotine use in young people, in a setting where harmful effects of E-cigs are largely unknown. Based upon the known harmful respiratory effects in the offspring by maternal (or grandmother) cigarette smoking, snuff use and nicotine exposure in animal models [17], we need rapid action to prevent avoidable respiratory disease in the child.

The prevalence of E-cig use among women and men of childbearing age is not available in many countries. However, from the United States, current (last 30 days) use of tobacco was reported by 20% of high-school students and 7.2% of middle-school students in 2016. This was most often reported as use of E-cigs in 11.3% of the high-school and 4.3% of the middle-school students [18]. In Finland, reported ever-use of E-cigs increased among 12- to 18-year-old children from 17.4% in 2013 to 25% in 2015, half of them having tried nicotine e-liquids [12]. Weekly use was, however low, at 1.5% [12]. Although males more commonly reported any type of tobacco use as well as E-cigs, 9.5% of American high-school females reported current use of E-cigs, carrying a significant risk of using E-cigs in future pregnancies [19]. Data on the beliefs and use of E-cigs before or during pregnancy is emerging [19,20,21]. In an online survey of 455 pregnant women in the United States, 6.52% reported sole use of E-cigs, 5.6% sole use of conventional cigarettes and 8.45% both E-cigs and conventional cigarettes during pregnancy [19], whereas another anonymous survey of 316 pregnant women showed ever-use in 13%, but current daily use in 0.6% only [21].

Adverse effects on child respiratory health by exposure to tobacco smoking before, during and after pregnancy has been firmly established [17], whereas the effects of exposure to nicotine by other routes are less well documented. Registry studies from Sweden, where snuff has been on sale for many years, have shown that snuff use increases the risk of stillbirths [22], preterm delivery, pre-eclampsia, infant apnoea [23], neonatal mortality [24] with a modest reduction in birth weight [24]. Snuff was subsequently not seen as a safe alternative to smoking in pregnancy [24]. There is however a lack of follow-up studies in children to determine the possible role of pre-natal snuff exposure on respiratory development and consequences for health of the child. Spindel and McEvoy [17] recently concluded that the effects on off-spring pulmonary development by prenatal nicotine exposure in animal models were strikingly similar to those of maternal cigarette smoking in pregnancy. With the current rapid increase in use of E-cigs, there is an urgent need to determine both short-term and long-term potential adverse effects on the growing child, including foetal and post-natal development of the respiratory system.

EXPOSURE BY ELECTRONIC CIGARETTES

An electronic cigarette may include a variety of substances, with and without nicotine of varying doses and concentrations, which are often poorly labelled [25]. The toxicity is therefore likely to be affected by factors including content, doses, concentrations, duration, frequency and age of exposure. A pub-med search using the words Electronic Cigarette and Toxicity gave 120 publications, all since 2015. No doubt, nicotine is the chemical in tobacco with the most pronounced effect on the developing brain on addiction development [26], while other toxic effects are established [27,28,29,30,31,32], particularly from studies in animals. Despite emerging studies [27,28,33], the general lack of human studies assessing pulmonary toxicity of E-cigs, particularly over time and in young subjects who have not smoked cigarettes [15], point to particular areas of concerns, including potential interactions between additives and nicotine on airway toxicity, added to the effects of voltage and higher temperatures that has been shown to increase E-cig aerosol toxicity [27]. The liquid used in E-cigs have (by mass spectrometry and gas chromatography) been shown to include variety of substances besides nicotine, including Glycerol, Propylene glycol, Acetone, acrolein, 1,3-butadiene, cyclohexane, diethylene glycol, ethylene glycol, ethanol, formaldehyde, alkaloids from tobacco (nor nicotine, myosmine, ana basin) [34]. From the emitted aerosol Glycerol, Propylene glycol, Nicotine, Acetaldehyde, Acetone, Acrolein, Formaldehyde, N′-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were identified, along-side metals including cadmium, lead, nickel, tin, copper and toluene [35,36,37]. Compared to conventional cigarettes, similar substances with potential carcinogenic or toxic effects are found in aerosol from electronic cigarettes, but in lower concentrations, whereas emitted reactive oxygen radicals appear comparable [36].

The amount of nicotine found in 13 inhalations from an e-cigarette with fluid containing 18 mg /ml nicotine was estimated to be equivalent to the amount found in a typical tobacco cigarette containing 0.5 mg nicotine [35]. After ten puffs with an interval of 30 s from nicotine containing e-cigarettes, serum nicotine concentration and heart rate increased significantly within five minutes, demonstrating a rapid absorption of nicotine from e-cigarettes [38].

ADVERSE HEALTH EFFECTS OF ELECTRONIC CIGARETTES

Health risks conferred by smoking ordinary tobacco cigarettes include a number of non-communicable diseases, such as chronic obstructive pulmonary disease (COPD), lung cancer and cardiovas-

cular diseases. The first suspicions on the health risk from cigarette smoking evolved from observations of increased mortality in smoking compared to non-smoking British physicians in the early 1960s [39]. Many years, and a large body of evidence has led to the present understanding of the health risk of tobacco cigarette smoking. However, in spite of limited evidence at present, it is a genuine worry that E-cigs may be subjected to a similar process; awaiting future observations from current exposure before evidence is sufficient to make bold health promoting decisions in the future [16]. This must be taken into consideration when assessing harmful effects of e-cigarettes, and a precautionary principle is highly relevant.

Despite the relatively short time of availability for E-cigs and the large variation in contents, use and availability, several harmful effects are already documented, and many studies are ongoing. In general, these studies suggest potentially harmful effects from both the vapour and the nicotine which reach lungs, airways and the cardiovascular system. The effects include inflammatory changes, changes in the organ development and in mucous membrane function as well as risk for cancer development by affecting gene expression in different organs [40]. The harms caused by the vapour content may be related to both nicotine [28] as well as substances other than the content of nicotine [28,41]. Exposure to nicotine per se has been shown in animal studies which suggest reduced fertility, increased risk for adiposities, hypertension, cardiovascular effects, gastric ulcer and gastric cancer, behavioural problems and reduced pulmonary development related to exposure to nicotine. The effect of nicotine exposure during pregnancy is well known from animal studies, but is also known from human studies, especially from studies of mothers using snuff during pregnancy. The nicotine exposure increases the risk for eclampsia, premature birth, still birth, reduced birth weight, reduced lung function at birth, apnoea, cleft lip and palate [42] and probably affects muscle and skeletal development in the new-born child [43,44,22]. This is in line with the effects of maternal and paternal smoking in pregnancy that may lead to lower lung function in the newborn baby [45,46], increased risk of later asthma and reduced lung function up to 14 years of age [47] as well as even the grandmother's smoking during her pregnancy may be linked to asthma in the grand child [48,49], probably through epigenetic mechanisms.

In rats it has been shown that exposure to nicotine in pregnancy changes the lung development with an emphysematous appearance [50]. This may continue into the next generation [51]. A similar effect may by caused by exposure to nicotine through the mother's use of e-cigarettes during pregnancy. Also, in healthy men from Mid-Norway, snuff use was associated with reduced flow mediated dilatation in the left brachial artery, as a sign of vascular changes preceding cardiovascular disease [52].

The impact upon immune function by e-cigarettes has been studied in mice using an inhalation chamber. Mice exposed to vapour from e-cigarettes had similar levels of cotinine compared to those of human e-cigarette users. Exposure to e-cigarettes for two weeks increased significantly oxidative stress and caused moderate macrophage mediated inflammation. Compared to mice that had been exposed to air, only, mice that had been exposed to e-cigarette damp showed significantly lower clearance of bacteria after a nasal infection with *Streptococcus pneumoniae*. This reduced bacterial clearance was caused by reduced macrophage phagocytosis after exposure to e-cigarette aerosol. As a response to Influenza A virus infection, mice who were exposed to aerosol from e-cigarettes showed increased viral titres in the lungs and increased viral induced morbidity and mortality, suggesting inhibition of pulmonary antimicrobial defence mechanisms [53].

Increased use of e-cigarettes should thus be observed closely with respect to increased occurrence of pulmonary infections in particular among groups with chronic lung diseases.

ACUTE POISONING WITH ELECTRONIC CIGARETTES

Acute poisoning with e-cigarettes has been reported from the USA through swallowing, inhaling or absorption through skin or mucous membranes of the fluid contained in replaceable ampullas used in e-cigarettes. Such ampullas contain in most cases 6–24 mg nicotine. Intake of 0.5–1 mg nicotine per kg body weight is stated to be a lethal dose for adult humans, and 0.1 mg/kg for children [54].

In the United States of America 56 centres for poisoning received almost 6000 telephone calls about poisoning from September 2010 through December 2014 concerning intoxication with e-cigarettes [55], with an increase from one per month to 401 per month in this period. Also, the annual E-cig exposure rate increased by 40.3% from 2.0 in 2012 to 4.2 per 100 000 in 2014, mostly in children younger than two years of age [56]. Children exposed to E-cigs were more likely to exhibit more than one clinical effect and effects were more serious, compared to children exposed to cigarettes [56]. Although most toxic effects were mild, and mostly happened in children between 0 and 5 years (58%) or above 20 years of age (34.7%) [55], children exposed to E-cigs were 2.3 times more likely to have a severe outcome than when exposed to cigarettes [56]. Serious toxic effects included cyanosis and respiratory arrest, and nausea, vomiting, convulsions and coma, while two deaths were reported, one in a child below five years of age, and one in an adult above 20 years of age. This underlines the need of safety measures for replaceable ampullas containing nicotine for e-cigarettes [55].

CONCLUSIONS

The evidence that nicotine as well as other substances in tobacco products have or may have health related adverse effects are strong, with increasing documentation also for newer forms of nicotine delivery systems. There is no doubt that smoking, nicotine via snuff or e-cigarettes are not safe for children, and evidence is emerging also for compounds other than nicotine in vaping solutions of E-cigs. Although there is a lack of current evidence that E-cigs are equally detrimental to respiratory and other health measures as is the case for traditional cigarette smoking, there is no safe lower limit for nicotine exposure to children, be it in the womb or later. Also, the short time of availability of E-cigs, the lack of documented smoking cessation with E-cigs and the increased use of such products instead of, or in addition to cigarette smoking among young adults, call for a strong political and health related warning about serious threats to the health of children. These authors believe that the precautionary principle to prevent harm to children by electronic cigarettes is highly relevant.

FUTURE RESEARCH DIRECTIONS

- To determine how to identify and quantify short and long-term exposure to varying contents of E-cigs.
- To identify strategies to obtain zero nicotine exposure the developing child.
- To identify inflammatory, epigenetic and biological mechanisms related to harmful effects of E-cigs, particularly on the developing lungs.
- To determine the effects of E-cig exposure on lung function development, respiratory symptoms, inflammation and general morbidity.

- To untangle effects of nicotine versus other content of aerosols on child morbidity, basal and clinical research.

Practice points

- It is important to influence the attitude of young girls to E-cigarette use in order to prevent harmful effects of nicotine exposure to the child during and after pregnancy.
- E-cigarettes are likely to be less safe than commonly believed, and the precautionary principle is essential to prevent harmful effects on future generations.
- The untoward respiratory and general health effects of E-cig exposure on the fetus, newborn and young child, during and after pregnancy should be discussed with (the pregnant) women.

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