



Vitamin C against the harmful effects of prenatal passive smoking: when all other options fail?

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Vitamin C administration to severely addicted pregnant smokers may induce a small improvement in lung function of their offspring compared to controls. To assess any clinical relevance, replicate and long-term follow-up studies are needed. <https://bit.ly/2DZoVRT>

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The mortality and morbidity due to cigarette smoking are gigantic. Worldwide, about 7 million people die every year (800 per hour!) due to a smoking-related illness and the morbidity is estimated to be about 30 times as high [1]. And though we all agree that tobacco companies making a product that eventually kills about 50% of its customers should be shut down and the product be banned, producing or selling cigarettes is not illegal yet. The tobacco industry even actively seduces “replacement smokers” to compensate for the loss of customers who died using their products [2] and the youngest, most vulnerable generation is the target of that strategy, including women who become pregnant. Apparently, cigarettes are made so addictive that worldwide about 50% of women who smoke daily even continue to smoke during pregnancy, ranging from about 30% in the European Region to about 80% in the Western Pacific Region [3]. Antenatal exposure to products of tobacco smoke during pregnancy is the most common preventable cause of infant morbidity and mortality [4]. Although exposure comes from many individuals, the most important exposure is maternal smoking. Well known complications associated with antenatal exposure to smoking include prematurity, stillbirth, antenatal growth failure [4], low birth weight [5], congenital anomalies [6] and sudden infant death syndrome [7]. Maternal prenatal smoking has a durable effect on her offspring's wellbeing, and is associated with increased risk for many noncommunicable diseases including asthma [8], increased body mass index [9] and metabolic syndrome [10], reduced lung function [11], serious conduct disorders [12, 13], and according to animal studies, a predisposition to nicotine addiction [14, 15].

Proving that exposure to tobacco smoke causes harm to the unborn child is impossible for ethical reasons, but persuasive evidence of causation comes from the drop in adverse perinatal outcomes immediately after smoke-free legislation is introduced [16]. Plausible mechanisms include *in utero* hypoxia, nicotine-induced nutritional deprivation and reductions in uteroplacental blood flow, placental toxicity, toxic growth restriction from the many toxicants in tobacco smoke, depressed fetal breathing movements and the direct neurotoxic effects of nicotine on the developing brain.

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Clearly all efforts should be made to stop antenatal exposure to products of tobacco smoke, but when the smoking mother is not able to quit, how nice would it be if the harm from exposure could be modified by a safe and simple intervention.

Different aspects of maternal dietary intake during pregnancy have been linked to risk for perinatal outcomes and respiratory outcomes in childhood [17]. One “candidate” beneficial dietary exposure is vitamin C. Vitamin C is an anti-oxidant that helps antagonise the nicotine induced damage [18, 19], or alterations in lung metabolism [20] and there is some indication that it prevents offspring DNA methylation changes associated with maternal smoking in pregnancy [21]. Previous work also suggests that vitamin C can reduce the nicotine exposure induced impaired neurological functioning in rats [22], and reduce the risk of developing sudden infant death syndrome [23]. In other animal experiments vitamin C seems to antagonise the negative effects of prenatal exposure to nicotine on the development of the lungs [24, 25]. Hence, the suggestion that vitamin C might counteract some of the negative effects of prenatal passive smoking in humans was launched.

Published in this issue of the *European Respiratory Journal*, vitamin C was administered in a randomised placebo-controlled trial to smoking pregnant women to assess its effects on airway function of the offspring at the age of 12 months [26]. This paper follows on from an earlier publication from the same cohort based on infant lung function testing at the age of 3 months [27]. The mothers included had very high urinary cotinine concentrations at randomisation, so were not simply occasional smokers. Also of note, the participant’s vitamin C concentration at recruitment were consistent with “normal” values so the intervention achieved above normal vitamin C exposures and did not simply supplement any vitamin C deficiency. The main finding was that the intervention was associated with statistically significant, but small, increases in lung function (as evidenced by forced expiratory volume in 0.5 s (FEV_{0.5})) of approximately 0.2 z-scores at 3 months and of 0.1 z-scores at 12 months of age.

What are the public health implications of these findings?

First, this study provides again a level of evidence that maternal smoking is harmful to unborn children. The offspring of both study groups of smoking pregnant women had a birth weight reduction of –1 Z-score despite vitamin C supplementation. The vitamin C intervention therefore seems unlikely to palliate against the many noncommunicable diseases associated with prenatal passive smoking being small for gestational age and we should not assume that the nicotine-induced brain damage is avoided either.

Second, this provides proof-of-concept that palliation against a reduction of airway function may be possible, but further follow-up is required (ideally with replication) before these findings should be incorporated into policy. At the age of 3 months, the primary lung function end-point was not, but secondary lung function end-points were, statistically significantly different compared to the control population; and also at the age of 12 months, there was a small but statistically significant difference between groups with respect to some expiratory flow measures suggesting that airway function was increased due to the intervention compared to the control population [27]. However, in the current study, this was not associated with a between group difference in the overall incidence of composite wheeze and further follow-up should clarify whether the slightly higher forced expiratory flows are clinically relevant (*i.e.* result in a reduction of wheeze symptoms and/or respiratory disease in later life).

Hence, vitamin C supplementation administered to severely nicotine-addicted pregnant women who cannot quit smoking seems a safe and inexpensive measure that may improve offspring respiratory function, although the clinical relevance of this effect is not clear yet. Therefore, taking vitamin C can never be an excuse to continue smoking. The bigger picture is that smoking remains a social norm in too many communities and contributes to health inequalities within and between countries. The best we, as healthcare professionals, can do is help children and teenagers not to start smoking. At the (inter)national level, all efforts are required to challenge all acceptance, and break family traditions, of smoking and help future generations fight against health inequalities.

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