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Cost-Effectiveness of Vitamin C Supplementation for Pregnant Smokers to Improve Offspring Lung Function at Birth and Reduce Childhood Wheeze/Asthma

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Abstract

Objective: To determine the implications of supplemental vitamin C for pregnant tobacco smokers and its effects on the prevalence of pediatric asthma, asthma-related mortality, and associated costs.

Study Design: A decision-analytic model built via TreeAge compared the outcome of asthma in a theoretical annual cohort of 480,000 children born to pregnant smokers through 18 years of life. Vitamin C supplementation (500 mg/day) with a standard prenatal vitamin was compared to a prenatal vitamin (60 mg/day). Model inputs were derived from the literature. Deterministic and probabilistic sensitivity analyses assessed the impact of assumptions.

Result: Additional vitamin C during pregnancy would prevent 1,637 cases of asthma at age 18 per birth cohort of pregnant smokers. Vitamin C would reduce asthma-related childhood deaths and save \$31,420,800 in societal costs over 18 years per birth cohort.

Conclusion: Vitamin C supplementation in pregnant smokers is a safe and inexpensive intervention that may reduce the economic burden of pediatric asthma.

Introduction

Approximately 12% of pregnant women smoke tobacco in the United States.¹ Smoking during pregnancy is associated with premature birth, low birth weight, sudden infant death syndrome, and childhood wheezing.² Fetuses exposed to in utero smoke are at increased risk of developing asthma, even when controlling for ex utero exposures.³ Animal models have demonstrated that nicotine causes oxidant-antioxidant imbalances and damages the DNA of proliferating cells in the fetal lung, which has low antioxidant capacity during most of pregnancy.⁴ Consequently, disruption during this critical window of development may

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adversely affect lung structure and function postnatally. In a non-human primate model of in utero nicotine exposure, it has been shown that nicotine crosses the placenta, upregulates nicotinic acetylcholine receptors, and alters lung development by increasing collagen expression around airways.⁵ Detrimental changes in postnatal lung function persist into childhood and adolescence as individuals continue to track along their pulmonary function test (PFT) percentiles that are established very early in gestation and early postnatal life.⁶⁻⁷

The overall prevalence of pediatric asthma is 8.4% while those exposed to in utero tobacco smoke are more than three times as likely to develop persistent asthma.⁸⁻⁹ It is currently the fourth largest health condition leading to personal health care spending in childhood.¹⁰ Additionally, maternal smoking during pregnancy is associated with an increased risk of childhood respiratory illnesses, further contributing to increased health care costs.¹¹ Children with asthma utilize more health care services, such as emergency room visits, outpatient visits, hospitalizations, and prescription medications.¹² The burden on families is also significant with school and work absenteeism and decreased productivity.¹³

Thus, interventions to ameliorate the effects of smoking during pregnancy on offspring, in addition to smoking cessation, are critical from a public health perspective. Proskocil et al. demonstrated that prenatal nicotine exposure reduces forced expiratory flows in the offspring of rhesus monkeys, but these harmful effects were prevented if mothers were simultaneously treated with vitamin C.⁵ It is hypothesized that this alteration of airway geometry may be prevented by supplemental vitamin C through blocking formation of reactive oxygen species. Vitamin C also attenuates the effects of nicotine exposure on placental hemodynamics in non-human primates.¹⁴ The association between cigarette smoking and shorter telomere length has been well studied in adult smokers.¹⁵ A recent study demonstrated an association between prenatal tobacco exposure and telomere shortening in children compared to controls who were not exposed in utero.¹⁶ Interestingly, vitamin C may also modify fetal programming by slowing down telomere shortening through suppression of intracellular oxidative stress.¹⁷

Beneficial effects of supplemental vitamin C in human infants of pregnant smokers were recently described by McEvoy et al. In this randomized, double-blind, placebo-controlled trial, pregnant smokers were randomized between 13 and 23 weeks' gestation to either supplemental vitamin C or placebo in the form of a prenatal vitamin containing the minimum daily requirement for vitamin C. All women received the same standard prenatal vitamin. A reference group of pregnant non-smokers and their offspring was also studied. The primary outcome was pulmonary function tests within 72 hours of birth whereas secondary outcomes included clinical respiratory outcomes through one year of age and repeat pulmonary function tests at one year. Smoking cessation counseling was provided at each interval prenatal visit, and medication adherence was assessed with pill counts and fasting plasma ascorbic acid levels. Infants in the supplemental vitamin C group had improved neonatal pulmonary function tests and decreased incidence of wheezing in the first year of life compared to infants whose mothers were randomized to placebo. No serious adverse events occurred in the vitamin C group.¹⁸

Vitamin C may be a simple intervention, alongside cessation counseling, to maximize the respiratory health of infants of pregnant smokers as it is safe to administer during pregnancy. While vitamin C is inexpensive, it has not been studied at a population level, and there may be associated costs with the implementation of a public health campaign that require a full understanding of the benefits. Thus, we undertook an economic model to provide a public health perspective on the utility of empirically prescribing supplemental vitamin C at 500 mg/day for all pregnant smokers in the U.S. and its effects on the prevalence, mortality, and costs associated with pediatric asthma.

Materials and Methods

A decision-analytic model (Figure 1) was designed to estimate costs and outcomes that followed standard guidelines as outlined by the International Society for Pharmacoeconomics and Outcomes and the Panel on Cost-Effectiveness in Health and Medicine.^{19,20} We used TreeAge Pro 2017 software to build a decision-analytic model to compare the outcomes of asthma, asthma-related deaths, and associated costs. The model follows children of pregnant smokers from birth through 18 years of age. The decision model begins with a decision node of the interventions compared: supplemental vitamin C (500 mg/day) and a prenatal vitamin containing the minimum daily requirement for vitamin C versus only a prenatal vitamin (vitamin C dose = 60 mg/day). The next nodes are chance nodes for neonatal pulmonary function tests, specifically the time to reach peak tidal expiratory flow as a proportion of total expiratory time (TPTEF:TE), above or below the normal median.⁶ Newborn pulmonary function studies after in utero smoke exposure have reported this measurement as a potential estimate of expiratory flow restriction in patients who are unable to perform voluntary maneuvers.^{18,21} Other newborn pulmonary function tests include measurements of passive respiratory compliance and resistance and functional residual capacity. TPTEF:TE is a complex measurement that can be obtained in a non-invasive manner on non-sedated infants. It takes into account airway size, mechanical properties of the lung and chest, and respiratory control. Most importantly, it may reflect intrinsic airway obstruction as a low TPTEF:TE at birth is associated with subsequent wheezing later in childhood.^{22,23}

The next level is a chance node for asthma at age 0–9 years, no asthma at age 0–9 years, or death from asthma at age 0–9 years. The next chance node is asthma or no asthma at age 10 followed by asthma or no asthma at age 18. The last chance node is death from asthma at age 10–18 years or survival with asthma. The time points within the decision tree were in part chosen based on the available literature input. In addition, the complexity of the decision tree takes into consideration that wheezing and asthma can have a remitting and relapsing pattern throughout childhood. Asthma can be difficult to diagnose before age six, and a significant proportion of children will eventually outgrow their symptoms.²⁴ Longitudinal studies of prospective birth cohorts, however, have shown that individuals follow along their pulmonary function trajectories established very early after birth into adulthood. Hayatbakhsh et al. followed infants of pregnant smokers until the age of 21 and showed in utero exposure had adverse effects on lung function independent of postnatal smoke exposure.³ In the Tucson Children's Respiratory Study, infants who had diminished forced expiratory flows after birth were more likely to show signs of airflow obstruction at

22 years of age.⁷ Therefore, those exposed to smoke prenatally are at increased risk for developing asthma and likely chronic obstructive pulmonary disease later in life.

Patient population and probabilities

For this analysis, we used a theoretical annual cohort of 480,000 children, which is an estimate of the annual number of offspring of pregnant smokers in the United States. Although smoking prevalence varies geographically within the United States, we based our cohort on an estimated 4 million annual births, 12% of which would be born to pregnant smokers.^{1,25} All probability inputs were derived from the literature (see table in Supplemental Material).

Utilities and quality-adjusted life year

Utilities were derived from an instrument that incorporated levels of physical activity and emotional states of children with pediatric asthma and the parental preference weights for health states using the visual analog scale and standard gamble technique.²⁶ We then applied these utilities to number of years with asthma during the first 18 years of life to generate quality-adjusted life years (QALYs) discounted 3% per year.²⁰

Costs

Costs were examined from the health care and societal perspectives, and all costs were expressed in 2016 U.S. dollars. Costs of medical care services were estimated from Lozano et al. and based off the 1987 National Medical Expenditure Survey.¹² Indirect costs, which include lost lifetime productivity from asthma-related death and lost parental wages from school absenteeism, were derived from the 1996 Medical Expenditure Panel Survey.¹³ We assumed an estimated cost of \$20 for supplemental vitamin C based on present market value. The remaining cost estimates were derived from the literature (see table in Supplemental Material) and converted to 2016 U.S. dollars when necessary using the consumer price index for health care.²⁷ Discounting at a 3% rate per year was applied.²⁰

Analytic methods

Our analysis involved determining the number of children who would be diagnosed with asthma at each chance node, including those whose symptoms would resolve and potentially relapse later in childhood. For each terminal node, we calculated the total costs and QALYs, which consisted of multiplying utilities by number of years with asthma discounted at 3%. To assess the cost-effectiveness of prescribing prenatal supplemental vitamin C, we calculated the incremental cost-effectiveness by dividing the marginal costs of each intervention by the marginal effectiveness gained for preventing asthma cases compared to a standard prenatal vitamin containing the minimum daily requirement of vitamin C. The incremental cost-effectiveness ratio was determined from a societal perspective and considered cost-effective at a threshold of \$100,000 per QALY. Deterministic and probabilistic sensitivity analyses were performed by varying inputs in order to assess the robustness of the model. For deterministic sensitivity analysis, we performed univariate sensitivity analysis whereas for probabilistic sensitivity analysis, a Monte Carlo simulation was performed using 100,000 trials to simultaneously vary all model inputs, including

probabilities, costs, and utilities. This approach helps to evaluate uncertainty as the inputs vary simultaneously across their respected distributions for each of the 100,000 runs. Costs were assumed to have a gamma distribution, which restricts values to non-negative. Probability and utility estimates were assumed to have a beta distribution, which restricts values between 0 and 1.

Results

For the base case analysis, among our hypothetical cohort of 480,000 women, additional vitamin C supplementation at 500 mg/day compared to the minimum daily requirement in the prenatal vitamin for pregnant smokers would prevent 6,936 cases of asthma between ages zero to nine, 1,443 cases of asthma at age ten, and 1,637 cases of asthma at age 18. While the risk of childhood asthma-related death is overall low, vitamin C supplementation also reduced asthma-related deaths in childhood by 0.1 per one million compared to the placebo group. The strategy of additional vitamin C in pregnant smokers would save \$5,947,200 in direct health care costs and \$31,420,800 in societal costs over 18 years per birth cohort. Supplemental vitamin C would increase total QALYs by 19,200 per birth cohort compared to the standard prenatal vitamin (Table 1). Thus, supplemental vitamin C is considered a dominant strategy associated with lower costs and better outcomes.

Sensitivity analyses were performed to help interrogate the robustness of the model. Deterministic one way-sensitivity analysis allowed for a wide range of supplemental vitamin C cost, from a baseline of \$20 up to \$89.60 per pregnancy episode for the breakeven point (Figure 2). Given that the prevalence of smoking varies by geographic region in the United States, supplemental vitamin C would still decrease cases of asthma and associated costs even with the prevalence as low as 1% (Table 2). As the prevalence of pregnant smokers increases, the cost-savings and health benefits of vitamin C increase.

To simultaneously test multiple parameters in the model, we performed Monte Carlo simulations, demonstrating that supplemental vitamin C compared to the minimum dose was the dominant strategy in 96.9% of the 100,000 trials (i.e., supplemental vitamin C is cheaper and more effective compared to the minimum daily requirement).

Discussion

In this study, vitamin C supplementation in pregnant smokers appeared to mitigate the effects of in utero smoke exposure on offspring and decrease the economic burden of pediatric asthma in this population. Vitamin C is a safe and inexpensive intervention that is easy to administer during pregnancy. Furthermore, the use of vitamin C in pregnant smokers is more economically favorable the higher the prevalence of smoking is in a population. This is the first cost-effectiveness study to analyze the public health implications of empiric supplemental vitamin C at 500 mg/day for pregnant smokers at the population level.

The use of decision analysis allows us to model the clinical and financial implications of a therapy at a population level, which is a strength of this study. In addition, our model is comprehensive in that it follows pregnant smokers prenatally and their infants from birth to adolescence. Furthermore, the complexity of the decision tree recognizes the observed

natural history of wheezing and asthma throughout childhood.^{24,28–30} However, such studies have a number of potential limitations as well. One limitation to our study is that probabilities were obtained from the literature, many of which were from the Environment and Childhood Asthma birth cohort study in Norway, which has a relatively homogenous population and universal, single-payer health system. Therefore, our findings may not be generalizable to different populations or in countries with different health care systems, such as the United States. However, we were reassured by the sensitivity analyses, even if the model inputs were overestimates of the effects. The Environmental Influences on Child Health Outcomes program funded by the National Institutes of Health will also help to increase understanding of the natural history of wheeze and subsequent asthma as it will include over 50,000 children from ages 0–18 in diverse areas of the United States.³¹ Furthermore, it is likely that our estimates of neonatal pulmonary function tests below the median were conservative and the number of preventable cases of asthma is much higher. Moreover, the number of pregnant smokers in the U.S. may be underestimated due to self-reported surveys and social stigmas associated with smoking.³² The cost savings for our health care system and society are significant compared to the cost of vitamin C, though implementation of such a public health campaign is not included in the model and should be taken into account by relevant decision makers in addition to other factors affecting decisions on resource allocation in health care.

While the rates of smoking are slowly decreasing in some states, there have been significant increases in other states, such as West Virginia and Mississippi.¹ Nevertheless, as Table 2 demonstrates, vitamin C supplementation would be cost-saving even if the prevalence of pregnant smokers was as low as 1% in a specific region. E-cigarette use has continued to increase in recent years, especially among adolescents, due to perceived safety compared to conventional cigarettes.³³ The primary ingredient, though, is still nicotine, which is the main culprit for adverse effects on fetal lung development.²

Ultimately, the most important prevention goal is smoking cessation, especially when considering other adverse effects of smoking during pregnancy, such as prematurity and low birth weight.³⁴ However, more than 50% of women who smoke prior to becoming pregnant have difficulty quitting during pregnancy despite cessation counseling.³⁵ Nicotine is highly addictive, and little is known about the fetal safety of nicotine replacement therapies. A Cochrane Review that assessed efficacy and safety of nicotine replacement therapy in pregnant smokers concluded there was insufficient evidence for successful smoking cessation.³⁶ Thus, a safe pharmacologic intervention to mitigate the negative fetal effects of smoking is needed in addition to continued smoking cessation counseling. The results of our model suggest that a public health campaign to encourage obstetrical providers to prescribe additional vitamin C to pregnant smokers has merit as a cost-saving intervention in the United States. Important outcome measures should include maternal adherence to vitamin C and offspring respiratory outcomes. Other supplements, such as vitamin D and fish oil, have been studied in pregnant women as possible interventions to decrease the incidence of wheezing and asthma in offspring, but none of these studies have looked specifically at pregnant smokers.^{37,38} Vitamin C, therefore, appears to be a safe and cost-saving option while we continue to search for the best strategy to help pregnant women quit smoking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:**Decision analysis tree**

Branches with triangles represent terminal branches (i.e., endpoints), and branches ending in circles represent collapsed branches to facilitate ease of display and are already represented in the model. The standard prenatal vitamin (placebo group) contains the minimum daily requirement of vitamin C (60 mg).

Sensitivity Analysis with Varied Supplemental Vitamin C Cost

Figure 2:

One-way sensitivity analysis for cost of vitamin C supplementation

X-axis represents discounted cost of vitamin C. Y axis represents total direct and indirect costs per case of asthma in our theoretical birth cohort, so total costs per birth cohort can be determined by multiplying by 480,000.

Incremental Cost-Effectiveness, Standard Prenatal Vitamin with 500 mg Vitamin C vs. Standard Prenatal Vitamin

Figure 3:

Incremental cost-effectiveness plot

The ellipse represents the 95th percentile for women in our model, and each dot represents one pregnant smoker. Most dots are located in quadrant IV, which represents lower cost and increased effectiveness. WTP, Willingness to Pay (\$100,000 per QALY).

Outcomes and Costs

Table 1:

Respiratory Outcomes in Offspring of Pregnant Smokers with and without Additional Vitamin C Supplementation, Single Year Birth Cohort			
	Standard Prenatal Vitamin ¹	500 mg Vitamin C and Standard Prenatal Vitamin	Difference in Outcomes
History of wheezing/asthma at 0–9 years (n)	98,205	91,269	↓6,936
Asthma at 10 years (n)	69,428	67,985	↓1,443
Asthma at 18 years (n)	92,196	90,559	↓1,637
Death from asthma 0–18 years (per 1 million children)	25.7	25.6	↓0.1
Direct health care costs	\$294,816,000	\$288,868,800	↓\$5,947,200
Indirect societal costs	\$641,630,400	\$610,209,600	↓\$31,420,800
Quality-adjusted life years through 18 years of age	6,230,400	6,249,600	↑19,200

This table illustrates the difference in outcomes between the two groups. The input data from birth is based off a randomized, placebo-controlled trial by McEvoy et al. as described in text.¹⁸

¹The standard prenatal vitamin (placebo group) contains the minimum daily requirement of vitamin C (60 mg).

Table 2:

Difference in outcomes with variation in prevalence of smoking

Prevalence of smoking during pregnancy	Cases of asthma at 18 years of age				Total direct and indirect costs				QALYs			
	Standard prenatal vitamin	Supplemental vitamin C and standard prenatal vitamin	Difference in cases of asthma		Standard prenatal vitamin	Supplemental vitamin C and standard prenatal vitamin	Difference in costs		Standard prenatal vitamin	Supplemental vitamin C and standard prenatal vitamin	Difference in QALYs	
1%	7,683	7,547	↓136		\$78,037,200	\$74,923,200	↓3,114,000		519,200	520,800	↑1,600	
5%	38,415	37,733	↓682		\$390,186,000	\$374,616,000	↓15,570,000		2,596,000	2,604,000	↑8,000	
12%	92,196	90,559	↓1,637		\$936,446,400	\$899,078,400	↓37,368,000		6,230,400	6,249,600	↑19,200	
15%	115,245	113,199	↓2,046		\$1,170,558,000	\$1,123,848,000	↓46,710,000		7,788,000	7,812,000	↑24,000	
20%	153,659	150,932	↓2,727		\$1,560,744,000	\$1,498,464,000	↓62,280,000		10,384,000	10,416,000	↑32,000	

This table demonstrates the overall cost-effectiveness of supplemental vitamin C for pregnant smokers if the prevalence of smoking ranges from 1–20%.

¹The standard prenatal vitamin (placebo group) contains the minimum daily requirement of vitamin C (60 mg).