Prenatal Cigarette Smoking and Its Association With Childhood Asthma

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Abstract
Background: Cigarette smoking during pregnancy is a common practice and its impact on the development of the lungs of the ensuing child has proven to be detrimental. Recent studies have been done to determine whether prenatal smoking is associated with asthma in the resultant child. Five of the most pertinent studies on this topic will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) in this systematic review.

Method: An exhaustive search of the medical literature was conducted through EBM Reviews, Medline, CINAHL, and PubMed databases which yielded five studies for final review.

Results: Three cohort studies and two case control studies were reviewed. All studies obtained data by parental questionnaires or health registries but data was gathered either prospectively or retrospectively depending on study design. Smoking during pregnancy was associated with childhood asthma, current asthma, and wheezing as compared with children who had a prenatal environment free from cigarette smoke.

Conclusion: Smoking during pregnancy is associated with childhood asthma and current asthma and there is a direct correlation between the amount of cigarettes smoked and the degree of damage. Combining the evidence for the outcomes of asthma and asthma-like symptoms via the GRADE criterion yielded a moderate quality of evidence, showing that the studies are of good quality and of value, but further research must be done to be confident in the magnitude of effect estimates and the accuracy of the results.

Keywords: asthma, pregnancy, cigarette, smoking
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Prenatal Cigarette Smoking and Its Association With Childhood Asthma

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Biography

Jesse Szafarz is a native of Andover, Massachusetts. She went to Connecticut College where she got her undergraduate degree in psychology. After completion of this degree, she moved to Boston, Massachusetts where she became certified as an EMT-B. She worked on an ambulance for the next year and a half while deciding that she wanted to play a larger role in the care of her patients. She decided to become a Physician Assistant and moved to Oregon to attend Pacific University. She enjoys Emergency Medicine and Women’s Health and hopes to return to Boston and begin working in one of these fields.

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To my family, thank you for supporting me through this endeavor and for being there for me when I got a flat tire in the middle of Kansas, when I found a mouse in one of the rented houses I lived in, for helping with the drive from Oregon to Michigan over that weekend, and for everything else in between.

To my friends near and far, thank you for picking up the phone when I needed you, regardless of what time it was in your time zone. Thank you for helping me maintain my sanity.

To Matty, thank you for sticking with me through this thing, for going on adventures and exploring with me wherever chance happened to plant me for 6 weeks, and for keeping your calm when my clutch went out in the middle of the wild animal park surrounded by reindeer.
ABSTRACT

Background: Cigarette smoking during pregnancy is a common practice and its impact on the development of the lungs of the ensuing child has proven to be detrimental. Recent studies have been done to determine whether prenatal smoking is associated with asthma in the resultant child. Five of the most pertinent studies on this topic will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) in this systematic review.

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INTRODUCTION

Background

There is considerable evidence linking maternal cigarette smoking during the prenatal and postnatal periods with various childhood diseases- one such disease is asthma. Asthma is defined as chronic inflammation of the bronchial tubes that causes swelling, constriction, and bronchial hyperreactivity of the airways which results in difficulty breathing, coughing, and wheezing (Szeftel & Schiffman, 2010). Asthma currently affects over 7 million children and it is the most common chronic disease of childhood (Sawicki & Haver, 2010). If there is an association between maternal smoking in the prenatal period and a predisposition toward childhood asthma, making this correlation clear may help motivate women to cease smoking before becoming pregnant.

Although there is a social stigma toward smoking during pregnancy, a number of women continue to smoke while pregnant predisposing their children to serious health risks. The Pregnancy Risk Assessment Monitoring System Survey reported that in 2005 14% of women smoked during pregnancy in the United States (Rodriguez-Thompson, 2010). Since it is socially unacceptable to smoke cigarettes during pregnancy, and because this study relied upon the self-reports of pregnant women, it is thought that the number of pregnant smokers is under-reported. In fact, a study at the University of Alabama noted that while 25% of patients reported being smokers, 43% had cotinine levels that were indicative of active smoking (Rodriguez-Thompson, 2010). Thus, despite the risks to the fetus and resultant child, a large percentage of women continue to smoke during pregnancy.
It has been hypothesized that smoking during pregnancy may lead to asthma by mechanisms that operate both independently and synergistically resulting in hampered lung development. Nicotine and other substances in cigarettes readily pass through the placenta exposing the fetus to nicotine levels consistent with the nicotine levels of the actively smoking mother (Lanner, Wickman, Pershagen, & Nordvall, 2006). Fetuses are exposed to this degree of nicotine each and every time the mother smokes a cigarette. Theories suggest that this exposure causes damage to the fetus and the fetal lung. Damage may develop due to abnormal gaseous exchange across the placenta, through direct toxicity from the 2500 substances in cigarettes, as a result of impaired fetal nutrition, or it may occur as a consequence of impaired clearance of carboxyhemoglobin in fetal circulation resulting in decreased tissue oxygenation (Rodriguez-Thompson, 2010). Damage to the fetal lung is of particular concern, because the pulmonary system is responsible for gaseous exchange and oxygenation of the body. Cigarette smoking may cause damage to the fetal lung by way of different methods, but regardless of the mechanism, a more poorly developed fetal lung may result.

If the fetal lung does not develop as completely as expected due to these mechanisms, it is hypothesized that fetal lungs may be hampered in their development. If the prenatal environment inherently hinders the development of the lungs of the fetus, it would be expected that the asthma encountered by these children will be more severe than the asthma of children exposed to environmental tobacco smoke after birth only. Whether prenatal smoking and the predisposition toward childhood asthma are associated, and the magnitude of effect of this association will be determined in this
paper by reviewing five studies on the topic and critically assessing the level of evidence of each study.

Purpose of the Study

The purpose of this paper is to perform a systematic review of the literature to determine whether smoking during pregnancy is associated with a predisposition toward asthma in the resultant child using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group (Guyatt et al., 2008).

METHOD

An extensive literature search was performed using EBM Reviews, Medline, CINAHL, and PubMed databases which were accessed through the Pacific University Library system. The following keywords were searched individually and in combination: “asthma”, “pregnancy”, “cigarette”, and “smoking”. The search was limited to human subjects, the English language, and to articles published between 2000 and 2011. Initially, this search resulted in seventeen articles to review. Articles that included maternal smoking in pregnancy as well as childhood asthma were included. Articles that included confounding variables such as mental health disorders, low birth weight, or young maternal age that were not separated statistically from prenatal smoking were excluded. Additionally, articles regarding environmental tobacco smoke exposure alone, passive smoking of pregnancy, and different biological alleles and genotypes of children were excluded as these factors were not the focus of this systematic review. This resulted
in five studies for final review. Of the five included studies, 3 studies consisted of cohort studies and 2 studies were case-control studies.

RESULTS

The first of the three cohort studies reviewed was performed by Lannero et al. (2006) who intended to determine whether prenatal smoking increased the risk of recurrent wheezing and doctors diagnosed asthma in a sample of children up to 2 years of age. The population studied was a birth cohort of 4,089 newborn infants born between February 1994 and November 1996 in predefined areas of Stockholm and recruited at their first visit to the Child Health Center. Patients were excluded if they were planning to move from Sweden within the year, if they had insufficient knowledge of Swedish, if they had already enrolled an older sibling, or if the neonate had a serious disease. Neonates consisted of 2,024 girls and 2,065 boys and they were followed by means of parental questionnaires at birth, at two months of age, at one year, and at two years. Questionnaires assessed various lifestyle factors including maternal smoking both during pregnancy and postnatally, as well as other exposure to environmental tobacco smoke, breast feeding duration, other childhood respiratory diseases, eczema, allergic rhinoconjunctivitis, or allergies.

The intervention for this group in the study conducted by Lannero et al. (2006) was exposure to prenatal maternal cigarette smoking versus the comparison group that was comprised of infants that had not been exposed to cigarette smoke in utero. Prenatal cigarette smoking was defined as maternal daily smoking of one cigarette or more during any trimester of pregnancy, and postnatal smoking was defined as exposure to maternal
smoking of one cigarette or more daily during the first months of life and/or maternal smoking at one year of age of the child. Recurrent wheezing was defined as three or more episodes of wheezing after three months of age in combination with the use of inhaled glucocorticoids and/or signs of bronchial hyperreactivity. Asthma must have been diagnosed by a doctor in the first and/or second year of life of the child to be included in the “asthma” group in the study. The outcome of interest was recurrent wheezing or doctor diagnosed asthma at or before the age of 2. The sample of this study was constituted by the 93% of parents who responded to all required questionnaires.

Authors of this study concluded that both prenatal smoking and exposure to environmental tobacco smoke did increase the rate of recurrent wheezing and doctors diagnosed asthma in the infant. For this study, p<0.05 was used to determine statistical significance and 95% confidence intervals were used. Adjusting for a number of confounding variables, the authors concluded that children exposed to maternal smoking during pregnancy but who thereafter had no exposure to environmental tobacco smoke had a 2.2-fold increase in the risk of developing recurrent wheezing up to two years of age. Infants who were exposed to environmental tobacco smoke with or without smoking during pregnancy had a 1.6-fold increased risk of developing recurrent wheezing up to two years of age. Regarding doctors diagnosed asthma, children exposed to maternal smoking during pregnancy but subsequently without exposure to postnatal smoking had a 2.1-fold increased risk of developing asthma by two years of age. There was no reported association regarding infants who were exposed to environmental tobacco smoke with or without smoking during pregnancy due to the confidence interval traversing 1 (0.95-2.1).
In the second study reviewed, Jaakkola et al. (2006) performed a case-control study by means of parental questionnaire to determine whether Russian children between the ages of 8 and 12 who were exposed to prenatal or postnatal smoke were more likely to develop asthma either “ever” or “current”. “Ever” asthma was defined by ever being told by a doctor that the child had asthma. “Current” asthma was asthma that was diagnosed by a doctor within the past 12 months. Finally, “asthma-like symptoms” were defined by asthma symptoms, asthma medication use, awakening by asthma, wheezing upon exercise, or hospital care for wheezing within the past 12 months without an asthma diagnosis. The population of interest were 5951 2nd through 5th graders aged 8 to 12 years that were recruited through primary schools located in 9 Russian cities. The intervention was prenatal exposure to cigarette smoke compared with a prenatal environment free from cigarette smoke. For the purposes of this study, a questionnaire was given to the parents of these school children which was designed to include questions relating to prenatal and postnatal smoking habits. Exposure to cigarettes was determined in the prenatal environment, exposure to tobacco smoke during the first two years of life constituted early-life exposure, exposure after the age of two represented later life exposure, and smoking at the time of the survey comprised current exposure. The outcome of interest was asthma and asthma-like symptoms. Authors used a statistical significance level of p<0.05 and confidence intervals of 95%.

Jaakkola et al. (2006) concluded that prenatal exposure to cigarettes conferred a 2.46-fold increase in the risk of the resultant child ever developing asthma, as well as a 2.64-fold increase in the risk of that child currently having asthma. However, children with in utero exposure did not have an increased risk of developing asthma-like
symptoms, as the confidence interval traversed 1 (0.93-2.08). For children with early life exposure to cigarette smoke there was no association with asthma as the confidence interval crossed 1 (0.93-2.06 “ever”; 0.86-2.15 “current”), but these children were 1.26-fold more likely to develop asthma-like symptoms. For those with later life exposure, there was no association with asthma as the confidence interval passed through 1 (0.96-2.18 “ever”; 0.90-2.32 “current”) but these children were 1.22-fold more likely to develop asthma-like symptoms. For those with current exposure, there was no association with any asthma or asthma-like symptoms as the confidence interval travelled across 1 in all groups (0.70-1.58 “ever”; 0.68-1.74 “current”; 0.90-1.30 “asthma-like symptoms”). By combining all postnatal exposure versus prenatal and postnatal exposure, additional tests were run that showed that those with postnatal exposure alone had no association with asthma, or asthma-like symptoms as the confidence intervals all crossed 1 (0.77-1.87 “ever”; 0.79-2.23 “current”; 1.03-1.54 “asthma-like symptoms”). However, the study reported that those with prenatal and postnatal exposure had a 2.96-fold increase in the risk of asthma diagnosis, a 3.48-fold increase in the risk of having current asthma, and a 1.64-fold increase in the risk of having asthma-like symptoms without a diagnosis of asthma. Analyses regarding prenatal exposure alone could not be run due to the small number of cases who had prenatal exposure without having postnatal exposure as well.

The next cohort study reviewed followed 58,841 Finnish neonates from 1987 through 1994 by means of nationwide registries (Jaakkola & Gissler, 2004). The authors compared childhood asthma data with prenatal smoking to determine whether an increase in risk existed for those exposed in utero to smoking. Through the Finnish Medical Birth Registry, information on smoking habits during pregnancy, birth weight, and gestational
age were obtained. The population of interest were Finnish children born in 1987 through 1994. The intervention was maternal smoking prenatally versus a prenatal environment that was free from cigarette smoke. Pregnant women were classified into the following groups: nonsmoking, less than 10 cigarettes per day, and greater than 10 cigarettes per day. The presence of asthma by the age of 7 was the outcome of interest. Asthma was defined by a child being hospitalized due to asthma before the age of 7, by a child getting free medication for asthma before the age of 7, or by a family requesting special care support due to their child developing asthma before the age of 7. Authors used a p value of <0.05 to determine statistical significance and 95% confidence intervals. Confounders including low birth weight and preterm delivery were taken into account by statistical methods.

The authors of this study concluded that smoking prenatally did increase the likelihood of developing asthma by the age of 7. Women who smoked less than 10 cigarettes per day put their children at a 1.20-fold increase in the risk of developing asthma, and women who smoked more than 10 cigarettes per day put their children at a 1.31-fold increase in the risk of developing asthma when the core covariates, low birth weight and small gestational age, were taken into account.

The final cohort study reviewed was conducted in Brisbane, Australia by Alati, Mamun, O’Callaghan, Najman, and Williams (2006) and used questionnaires both prenatally and postnatally to correlate prenatal smoking with asthma in the ensuing child. Pregnant women were recruited to participate in this study after visiting Mater Misericordiae Hospital for their first prenatal visit between the years of 1981 and 1984. Participants completed a questionnaire at this time that measured maternal smoking and
put mothers into one of three categories: no smoking, 1-19 cigarettes per day, or 20 or more cigarettes per day. Mothers completed similar questionnaires at 3-5 days after delivery, 6 months after delivery, 5 years after delivery, and 14 years after delivery. The questionnaire at 14 years included questions about childhood asthma as well. Thus, the population studied were children 0 to 14 born in Australia between 1981 and 1984. The intervention was prenatal smoking versus a prenatal environment free from cigarette smoke. The outcome was asthma, as determined by maternal report.

The authors of this study concluded that pre-pregnancy smoking did not confer an increased risk of asthma to 14 year old girls or boys. Results showed that there was no association between prenatal or postnatal smoking alone or in combination and an increased risk of 14 year old boys developing asthma. However, smoking both during pregnancy and after pregnancy was associated with an increased rate of asthma in 14 year old girls, with the highest risk coinciding with smoking early in pregnancy. Girls born to mothers who smoked more than 20 cigarettes per day were 1.76-fold more likely to develop asthma if their mothers smoked in early pregnancy, 1.66-fold more likely to develop asthma if their mothers smoked in late pregnancy, 1.53-fold more likely to develop asthma if their mothers smoked postnatally during the first 6 months after delivery, and 1.24-fold more likely to develop asthma if their mothers smoked postnatally 5 years after delivery. Girls born to mothers who smoked less than 20 cigarettes per day were not more likely to develop asthma by the age of 14 than those born to mothers who did not smoke prenatally.

The second case-control study reviewed was performed by Gilliland, Li, and Peters (2001), who administered questionnaires to the parents of 5,762 4th, 7th, and 10th
grade students in 12 public schools in Southern California communities to determine the prevalence of physician diagnosed asthma and its association with prenatal and postnatal exposure to cigarette smoke. Accordingly, the population of interest was the Californian $4^{th}$, $7^{th}$, and $10^{th}$ grade students, the intervention was exposure to prenatal cigarette smoke versus no exposure to cigarette smoke in utero, and the outcome was physician diagnosed asthma or wheezing. In this case-control study, questionnaires were used to determine whether children had ever been diagnosed with asthma, and whether they currently had asthma. Current asthma was defined by asthma diagnosis in the past 12 months. Postnatal smoking was subcategorized as none, past exposure, or current exposure. Many other confounding variables were taken into account in this study including grade, age, sex, ethnicity, maternal education, socio-economic status, family history of asthma, family history of atopy, gestational age, history of hay fever in the child, pets in the house, indoor air conditioning, gas stove usage, water damage in the house, and humidifier use. Prenatal exposure was defined as any smoking while pregnant. The authors used a $p<0.05$ level to determine statistical significance and 95% confidence intervals.

The authors of this study concluded that there was no association between asthma and postnatal smoking, as the confidence interval crossed 1 (0.9-1.3). This trend of no association held true for both boys and girls individually (0.8-1.3 “boys”; 0.8-1.4 “girls”). However, boys exposed to smoking in utero were 1.7-fold more likely to have developed asthma before the time of the survey, while girls exposed to smoking in utero were 1.9-fold more likely to have developed asthma. Boys and girls in combination were 1.8-fold more likely to develop asthma than children whose prenatal environment did not include cigarette smoke. Regarding current asthma, girls and boys exposed postnatally only were
not more likely to develop asthma than those children who had never been exposed to cigarette smoke. However, girls and boys exposed in utero only, were 2.3-fold more likely to have current asthma than those who had not been exposed to cigarette smoke in utero.

DISCUSSION

Study Limitations

The first study reviewed is a cohort study performed by Lannero et al. (2006) to determine whether children born to mothers who smoked prenatally were more likely to develop asthma than children who had not been exposed to cigarette smoke in utero. Results of this study illustrated that by two years of age, children born to mothers who smoked prenatally were over two times more likely to develop asthma and recurrent wheezing than the cohort of children whose mothers did not smoke while pregnant. This result was maintained in the absence of postnatal smoking. This work provided evidence that there is an association between smoking while pregnant and childhood asthma.

Although the results of the study seem clear, the evidence is marked by several limitations. Firstly, this study relies on the willingness of parents to join a study that focuses on smoking while pregnant and to be honest reporting prenatal smoking behaviors. Smoking mothers may have underreported their behaviors on the questionnaire because smoking during pregnancy is not socially acceptable which may have led to some degree of reporting bias. The questionnaire itself had limitations, as it did not collect information regarding second-hand smoke exposure during the in utero period. Environmental exposure to smoking may have influenced the fetus if smoking
was done in the house on a consistent basis exposing the fetus to second-hand smoke via his or her mother. Thus, limitations regarding a potential bias of participants, possible inaccuracies of reporting smoking behavior, and a confounding variable not accounted for were the most conspicuous problems in this study.

The study by Jaakkola et al. (2006) had similar results regarding the prevalence of asthma in children exposed to prenatal smoking. This study used a case-control design thereby distributing parental questionnaires to report prenatal smoking habits as well as to determine the presence of asthma in their 8 to 12 year old children. The authors concluded that children who were exposed to prenatal smoking were nearly two and a half times more likely to have been diagnosed with asthma in the past, and were more than two and a half times more likely to currently have asthma than their cohort of peers not exposed to cigarette smoke in utero. If their mothers smoked prenatally and postnatally, they were approximately three times more likely to have asthma than those children without mothers that smoked cigarettes. Interestingly, it was noted that children only exposed to smoking after birth were no more likely to develop asthma than the control group. In answer to the clinical question, this study further supports the association between prenatal smoking and childhood asthma.

Although the results of this study confirm the results of the study by Lannero et al. (2006), it is hindered by its own limitations. Authors noted that maternal smoking during pregnancy was reported to be 4% compared to the 12% rate of maternal smoking after delivery. This discrepancy may be explained by mothers quitting smoking based on cultural beliefs about cigarette smoking during pregnancy, or it may be explained again by reporting bias. This observational study is reliant on parents telling the truth, so
reporting error may have also significantly impacted the results. Parents were expected to remember behaviors during pregnancy up to 12 years prior. This retrospective analysis could lead to innocent errors in memory or systematic distortions. Finally, this study could not separate prenatal smoking from postnatal smoking without statistical means, as there were only 10 participants who smoked prenatally without subsequent postnatal smoking. Thus, the large magnitude of effect of childhood asthma may be synergistic due to prenatal and postnatal smoking, or it may have occurred as a result of postnatal smoking exposure alone, as opposed to being an isolated effect of prenatal smoking. Finally, second-hand smoke exposure was not addressed as a confounding variable in this study either. In this study, limitations inherent to a case-control study design, the inability to isolate prenatal smoking, and a confounder not taken into account were the most evident limitations noted.

In contrast to the two studies reviewed above which used questionnaires to obtain information on participants, the third study to be reviewed used national administrative health registries to determine whether children born to mothers that smoked while pregnant were more likely to develop asthma than those whose prenatal environment did not include cigarette smoke (Jaakkola & Gissler, 2004). The study had a large sample size, using information from 58,841 Finnish children to generate its results. It was concluded by the authors, that children of mothers who smoked less than 10 cigarettes per day were at a 20% increased risk of developing asthma by the age of 7; children of mothers who smoked more than 10 cigarettes per day were at a 30% increased risk of developing asthma. In addition to supporting the idea that prenatal smoking is associated
with childhood asthma, this study provides evidence of a dose-response relationship between increased prenatal smoking and increased risk of asthma.

However, this study also has limitations comparable to the studies evaluated above based on its method of data collection. Information was amassed via registries instead of questionnaires and is therefore reliant on obstetricians’ relationships with the pregnant women and the doctors’ ability to elicit the truth from their patients regarding prenatal smoking behavior. Physicians are often seen as authority figures and a patient’s desire to please her physician may result in an underestimation of prenatal smoking figures. Furthermore, there is no level of anonymity in the physician’s office which may augment behaviors by patients to diminish their smoking behaviors in the office. Finally, the last striking limitation was the lack of information contained in the registries themselves. Information on maternal age, parity, marital status, and maternal occupation was obtained, but information on maternal or paternal asthma, second-hand smoke exposure in utero, or smoking in the home after birth could not be obtained. Likewise, confounding variables such as the presence in the home of furry or feathery pets, pests, presence of mold or other allergens, or living in an older house could not be statistically separated from the asthma diagnosis, as they were unknowns. Confounding variables due to limited data on the parts of both mother and child constituted the major limitation of this study.

The fourth study reviewed was conducted by Alati et al. (2006) by recruiting participants at their first prenatal visit and following them with questionnaires at designated times for the next 14 years to assess prenatal and postnatal smoking and its association with childhood asthma. This study concluded that pre-pregnancy smoking
was not associated with asthma. Additionally, it provided evidence that earlier exposure to cigarette smoke in utero was associated with a higher prevalence of asthma than a later exposure to cigarette smoke in utero in a dose dependent manner. Specifically, it was demonstrated that by the age of 14, girls who were born to mothers that smoked greater than 20 cigarettes per day in early pregnancy were 76% more likely to develop asthma than girls who were not exposed to cigarette smoke in utero. Girls who were born to mothers that smoked greater than 20 cigarettes per day in late pregnancy were 66% more likely to develop asthma than girls who were not exposed to cigarette smoke in utero. Girls who were born to mothers that smoked greater than 20 cigarettes daily postnatally 6 months after delivery were 53% more likely to develop asthma than girls who were not exposed to cigarette smoke postnatally. Finally, girls who were born to mothers that smoked greater than 20 cigarettes per day 5 years after delivery were 24% more likely to develop asthma than girls who were not exposed to cigarette smoke postnatally.

Remarkably, girls whose mothers smoked less than 20 cigarettes per day prenatally were not more likely to get asthma than their cohort of peers who lacked exposure to cigarette smoke in their in utero environment. Also of interest, this study found that 14 year old boys whose mothers smoked any amount of cigarettes prenatally or postnatally were not more likely to develop asthma than boys born to mothers that did not smoke in the prenatal or postnatal period. Results of this study are notable because they provide evidence of a dose dependent relationship, and because they provide insight into the harmful effects of smoking earlier in pregnancy.

This study provides evidence to support the hypothesis that prenatal smoking is associated with childhood asthma, but analogous to other studies it has a set of
limitations. The most notable was that information was obtained by questionnaire in the confines of a doctor’s office. Again, the problem of patients trying to please their providers arises as does the possibility of dishonesty and reporting bias. No objective measures, like measuring cotinine levels to substantiate claims made by pregnant women, were included to corroborate subjective assertions. Additionally, asthma in the child was determined by parental report alone, and was not verified by doctor’s report. Thus, this questionnaire was a subjective measure of prenatal smoking and asthma diagnosis in the child. Also of note, this study did not take second-hand smoke exposure in utero into account, which might be a confounding variable that influenced the results of the study. The subjective nature of the questionnaire and the confounding variable not taken into account were the major problems encountered by this study.

The final piece of evidence reviewed was a case-control study by Gilliland, Li, and Peters (2001) where parents of 4th, 7th, and 10th grade students filled out questionnaires that assessed prenatal smoking, postnatal smoking, and physician diagnosed childhood asthma. Results of this study illustrated that women who smoked prenatally conferred a 70% increased risk of developing asthma to their male offspring, and a 90% increased risk of developing asthma to their female offspring. Children of mothers who smoked in utero were also over twice as likely to currently have asthma as their cohort of peers who had not been exposed to cigarette smoke in utero. Postnatal smoking was not found to be associated with asthma. This study echoes the findings that prenatal smoking does confer an increased risk of developing asthma in the resulting child.
This study lends further support to the association between prenatal smoking and childhood asthma but has limitations of its own. The population was homogenous, and described as mostly “10 years of age or younger, white, and from households with health insurance and high educational attainment” (Gilliland et al., 2001). Beyond this statement, a table of participants’ races was not included. For this reason, the sample may not be generalizable to the population because the interplay between smoking and genetics may be limited. Also, since research has shown that people with lower educational status are more likely to smoke, this population may have smoked less than the general population. Finally, the problem of retrospective analyses and inaccuracies of memory inherent to case-control designs also plague this study. The notion that this evidence may not be as generalizable to the population as other studies included in this review constitutes its main limitation.

GRADE Outcomes

To assess the level of evidence of each outcome independently, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) standard will be applied. This tool was created to minimize bias among interpretation of articles and to create a standard for the reader of scholarly articles. Articles start with an inherent grade based on study type and can be upgraded or downgraded based on a variety of factors related to study design. Specifically, randomized controlled trials start with a grade of “high” and observational studies including case-control studies and cohort studies begin with a grade of “low”. In view of the fact that this clinical question regards harming a child, randomized controlled trials on the subject would be unacceptable. Accordingly,
cohort studies and case-control studies constituted the highest grade of evidence available to answer this clinical question. “High” grade evidence can be reduced if there is a serious limitation to study quality, important inconsistency, uncertainty about directness of effect, imprecise data, or a high probability of reporting bias (Guyatt et al., 2008).

“Low” grade evidence can be increased if there is strong substantiation of association as defined as “a significant relative risk of >2 based on consistent evidence from two or more observational studies with no plausible confounders”, evidence of a dose dependent response, or if all plausible confounders that would have reduced the effect have been taken into account (Guyatt et al., 2008, 926). With usage of this grading scheme evidence can be upgraded or downgraded for final review.

Based on these criteria, a final grade will be awarded for each outcome and an overall grade provided across all outcomes. Grades range from very low quality evidence through high quality evidence with the following definitions for each gradation of evidence:

“High quality evidence- Further research is very unlikely to change our confidence in the estimate of effect or accuracy. Moderate quality evidence- Further research is likely to have an important impact on our confidence in the estimate of effect or accuracy and may change the estimate. Low quality evidence- Further research is very likely to have an important impact on our confidence in the estimate of effect of accuracy and is likely to change the estimate. Very low quality evidence- Any estimate of effect or accuracy is very uncertain” (Guyatt et al., 2008, 926).
Each study will be graded by this criterion both in text and in the appendix and a final grade of the evidence will be ascertained.

Lannero et al. (2006) completed a study that provided evidence for the outcomes regarding both asthma and asthma-like symptoms. Based on study design an initial grade of “low” was given to this data. Evidence was upgraded for magnitude of effect, as the relative risk of developing childhood asthma was greater than 2. However, a dose-response relationship was not elicited, and the list of confounding variables was not exhaustive due to the lack of information on second-hand smoke exposure in utero, so upgrades were not given for these reasons.

The study completed by Jaakkola et al. (2006) provided evidence for the outcomes regarding both asthma and asthma-like symptoms. Based on study design an initial grade of “low” was given to this data set. This evidence was also upgraded for magnitude of effect, as the relative risk of developing childhood asthma was greater than 2. However, a dose-response relationship was not elicited, and the list of confounding variables was not exhaustive due to the lack of information regarding second-hand smoke exposure in utero, so upgrades were not given for these reasons.

Jaakkola and Gissler (2004) completed a study that provided evidence for the outcome of asthma. Based on study design an initial grade of “low” was given to this set of evidence. This was upgraded for noting a dose-response relationship between more prenatal cigarettes being correlated with an increased risk of asthma. However, there was not a large magnitude of effect, and the list of confounding variables was not exhaustive due to limited data in the registries so upgrades were not given on these grounds.
The study completed by Alati et al. (2006) provided evidence for the outcome of asthma. Based on study design an initial grade of “low” was given. The list of confounding variables was not exhaustive due to the lack of information on second-hand smoke exposure, so an upgrade was not given here. However, evidence was upgraded for noting a dose-response relationship between more prenatal cigarettes being correlated with an increased risk of asthma and for providing evidence that smoking prenatally provided a large magnitude of effect for its association with childhood asthma.

Gilliland, Li, and Peters (2001) completed a study that provided evidence for the outcome of asthma. Based on study design an initial grade of “low” was given. A dose dependent relationship between smoking prenatally and childhood asthma was not sought, so the evidence could not be upgraded for this. However, evidence was upgraded for noting all identifiable confounders that may have impacted the results and for providing evidence that smoking prenatally provided a large magnitude of effect for its association with childhood asthma.

Combining GRADE scores for each outcome, the quality of evidence could be assessed in another way. Five studies provided evidence for the outcome of asthma. Three of the studies were upgraded once from their “low” ranking and two of the studies were upgraded twice from their “low” ranking. Based on these results, the overall grade of this evidence was assigned moderate quality evidence.

Two studies provided evidence for the outcome of asthma-like symptoms. Both of the studies were upgraded once from their “low” ranking for magnitude of effect and thus the overall grade was assigned a ranking of moderate quality evidence.
Consequently, combining the evidence for the outcomes of asthma and asthma-like symptoms yielded a moderate quality of evidence as well, meaning that “further research is likely to have an important impact on our confidence in the estimate of effect or accuracy and may change the estimate” (Guyatt et al., 2008, 926). This rating shows that the studies are of good quality and of value, but further research must be done to be confident in the magnitude of effect estimates and the accuracy of the results.

Conclusions and Clinical Implications

Smoking during pregnancy is known to predispose the ensuing infant to a multitude of risks, both in utero and after birth. However, despite these risks, a number of women continue to smoke in the prenatal period. Synthesizing the results of these five studies, it becomes evident that the prenatal environment does have an effect on the respiratory health of the child. All studies have provided evidence that smoking prenatally does increase the risk of the resultant child developing asthma. Congruent results are also shown when comparing prenatal smoking and postnatal smoking—prenatal smoking increases the risk of asthma more in the resultant child than postnatal smoking does. This seems to support the hypothesis that prenatal smoking hinders the development of the fetal lungs. Lastly, studies that inquired about a dose response relationship between the number of cigarettes smoked prenatally and the resultant prevalence of asthma seem to concur that there is a direct correlation between more cigarettes smoked and a greater risk of asthma in the ensuing child. Amalgamating this evidence, it appears that is more harmful to smoke more cigarettes earlier in the pregnancy than fewer cigarettes later in the pregnancy or in the postnatal period alone.
These studies appear valid in a number of respects. Since all studies used questionnaires or birth registries to obtain information on prenatal smoking and childhood asthma, and because one would assume this methodology would answer the clinical question at hand, the face validity of these studies appears legitimate. A stronger measurement of validity is criterion validity which appears to be authenticated by the high correlation in findings throughout studies. Construct validity is present if studies are accurately measuring what they intend to measure. Since studies explicitly asked about prenatal smoking, generally used physician-diagnosed asthma as the outcome, and tried to statistically extract information from confounding variables, construct validity appears to be present as well. Finally, with collective studies using populations from a variety of countries, external validity appears to be present because individual studies maintain similar findings regardless of population. The fact that two year old children in Sweden demonstrate the same effect and propensities as eight year old children throughout Russia indicates that there is an internal integrity to the studies. This makes the work generalizable to many different populations and settings. The ability of these studies to meet the criteria for a number of different types of validity lends credence to the idea that these studies are compelling evidence on the subject at hand.

Naturally, there are areas of discrepancy in the studies. Alati et al. (2006) noted that there was no predisposition toward asthma in 14 year old boys, regardless of whether their mothers smoked prenatally or postnatally. This evidence directly conflicts with evidence from Gilliland, Li, and Peters (2001) where 4th, 7th, and 10th grade boys were noted to have a 70% increased prevalence of asthma if their mother’s smoked prenatally. Whether this result is due to an ungeneralizable population or a flaw in study design
remains uncertain. Or, whether at the age of 14 puberty influences or tempers asthma also remains unknown. Whether the predisposition toward asthma is diminished in adolescent boys remains a question of discrepancy.

Likewise, Alati et al. (2006) noted that girls born to mothers who smoked less than 20 cigarettes per day prenatally had no predisposition toward asthma. This conflicts with findings from Jaakkola and Gissler (2001), who noted a dose dependent response with the prenatal smoking of 10 cigarettes per day. This discrepancy could be due to the category of smoking 1-20 cigarettes per day being too broad. Combining results of women who smoked 1 cigarette per day with women who smoked 20 cigarettes per day might have influenced the results toward the null hypothesis.

Areas of discrepancy can provide insight as to where future research should be focused. Whether childhood asthma goes into remission in adolescent boys remains a query. Another interesting topic would measure smoking behavior each trimester and quantify the degree of asthma experienced by the ensuing children. Are children born to prenatal smokers more likely to develop mild asthma treated by rescue inhaler alone, or are they more likely to need additional medications to control the asthma? Synthesizing this information with fetal development during each trimester could provide insight as to what physiologically has developed abnormally, and where the predisposition toward asthma arises from. There are many avenues for future research on this topic.

Implications for clinicians and patients need to be aimed at developing smoking cessation programs before pregnancy. Asthma is the most common disease of childhood, and for most, it is a life-long disease. Alerting pregnant women to this correlation may be enough encouragement to stop smoking prenatally. And, decreasing the incidence of
asthma among children would be life-changing for those not affected by the shortness of
breath, coughing, trouble exercising, and the future cost of medications that comes with
the disease. Preventing this modifiable risk factor during pregnancy may provide fetuses
with the greatest opportunity to develop normal healthy lungs, and to decrease the
prevalence of childhood asthma simultaneously.
REFERENCES


# APPENDIX A

## GRADE Table

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Type of Evidence</th>
<th>Findings</th>
<th>Starting grade</th>
<th>Magnitude</th>
<th>Dose response</th>
<th>Confounders</th>
<th>Grade of evidence for outcome</th>
<th>Overall grade of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal smoking exposure vs. Smoke-free prenatal environment</td>
<td>Development of asthma</td>
<td>3 cohort studies and 2 case-control studies</td>
<td>Positive association</td>
<td>low</td>
<td>+1</td>
<td>+1</td>
<td>0</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Development of asthma-like symptoms</td>
<td>1 cohort study and 1 case-control study</td>
<td>Positive association</td>
<td>low</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>