The Relationship between Caesarean Delivery and Increased Risk of Developing Asthma in Childhood

Nicole Ankenbrandt

Recommended Citation
Ankenbrandt, Nicole, "The Relationship between Caesarean Delivery and Increased Risk of Developing Asthma in Childhood" (2017). School of Physician Assistant Studies. 626.
https://commons.pacificu.edu/pa/626
The Relationship between Caesarean Delivery and Increased Risk of Developing Asthma in Childhood

Abstract

Background: Asthma prevalence nationwide is increasing. In 2011, an estimated 39.5 million individuals, or 12.9% of the population, had a diagnosis of asthma, and 14% of those were children. Rate of caesarean delivery (CD) has concurrently increased over the past few decades and comprised 32.2% of all deliveries in 2014. Recent research has begun to explore for possible association between CD and later asthma development. Studies may even suggest differences in the gastrointestinal microbiome of neonates after CD and that of neonates after vaginal delivery (VD); this microbiome has been shown to affect development of a properly functioning immune system. This review aims to investigate whether there is increased risk of asthma development in childhood after CD.

Methods: An extensive literature search of Web of Science, CINAHL, and MEDLINE via PubMed and Ovid databases was performed using the following search terms: caesarean or cesarean, asthma, and intestinal flora or gastrointestinal microbiome. Articles were screened for relevance and eligibility criteria. An assessment of quality was performed for the resulting included studies using the GRADE system.

Results: The literature search yielded a total of 3 qualifying studies: 2 were retrospective cohort studies while the other was a prospective cohort study. The overall quality of those included was low; however, one study was upgraded to high quality with reasons. Results were consistent between the three studies when comparing asthma development after CD to that after VD. These studies support that children have an increased risk of asthma if delivered via CD, particularly female and first-born children.

Conclusion: Based on recent studies, there appears to be an increased risk of asthma development in children delivered via CD compared to those spontaneously vaginally delivered (SVD). This trend is significant only in female and first-born children. Further research is needed in order to advance current knowledge and understanding of which bacteria colonize the gut in asthmatic versus non-asthmatic children and how this difference in introduction of organisms results in abnormal immune system development. Future conclusive evidence may foster advancements in asthma therapy and prevention.

Degree Type
Thesis

Degree Name
Master of Science in Physician Assistant Studies

Keywords
caesarean, cesarean, delivery, asthma, intestinal flora, gastrointestinal microbiome, allergy

Subject Categories
Medicine and Health Sciences

This thesis is available at CommonKnowledge: https://commons.pacificu.edu/pa/626
The Relationship between Caesarean Delivery and Increased Risk of Developing Asthma in Childhood

Nicole Ankenbrandt

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 12, 2017

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
|| Biography ||

[Redacted for privacy]
Abstract

Background: Asthma prevalence nationwide is increasing. In 2011, an estimated 39.5 million individuals, or 12.9% of the population, had a diagnosis of asthma, and 14% of those were children. Rate of caesarean delivery (CD) has concurrently increased over the past few decades and comprised 32.2% of all deliveries in 2014. Recent research has begun to explore for possible association between CD and later asthma development. Studies may even suggest differences in the gastrointestinal microbiome of neonates after CD and that of neonates after vaginal delivery (VD); this microbiome has been shown to affect development of a properly functioning immune system. This review aims to investigate whether there is increased risk of asthma development in childhood after CD.

Methods: An extensive literature search of Web of Science, CINAHL, and MEDLINE via PubMed and Ovid databases was performed using the following search terms: caesarean or cesarean, asthma, and intestinal flora or gastrointestinal microbiome. Articles were screened for relevance and eligibility criteria. An assessment of quality was performed for the resulting included studies using the GRADE system.

Results: The literature search yielded a total of 3 qualifying studies: 2 were retrospective cohort studies while the other was a prospective cohort study. The overall quality of those included was low; however, one study was upgraded to high quality with reasons. Results were consistent between the three studies when comparing asthma development after CD to that after VD. These studies support that children have an increased risk of asthma if delivered via CD, particularly female and first-born children.

Conclusion: Based on recent studies, there appears to be an increased risk of asthma development in children delivered via CD compared to those spontaneously vaginally delivered (SVD). This trend is significant only in female and first-born children. Further research is needed in order to advance current knowledge and understanding of which bacteria colonize the gut in asthmatic versus non-asthmatic children and how this difference in introduction of organisms results in abnormal immune system development. Future conclusive evidence may foster advancements in asthma therapy and prevention.

Keywords: caesarean, delivery, asthma, intestinal flora, gastrointestinal microbiome
Acknowledgements

[Redacted for privacy]
List of Tables
Table I. Quality Assessment of Reviewed Articles

List of Figures
Figure I. Study Search and Selection

List of Abbreviations
- CD: Caesarean Delivery
- CDC: Centers for Disease Control
- ECD: Emergency Caesarean Delivery
- GRADE: Grading of Recommendations Assessment, Development and Evaluation
- HR: Hazard Ratio
- IgE: Immunoglobulin E
- IVD: Instrumental Vaginal Delivery
- MBRN: Medical Birth Registry of Norway
- NIS: Norwegian National Insurance Schema
- NTR: Netherlands Twin Register
- OR: Odds Ratio
- PCD: Planned Caesarean Delivery
- PFT: Pulmonary Function Testing
- PROM: Premature Rupture of Membranes
- SVD: Spontaneous Vaginal Delivery
- VD: Vaginal Delivery
- WHO: World Health Organization
The Relationship between Caesarean Delivery and Increased Risk of Asthma Development in Childhood

BACKGROUND

Asthma has become a common and chronic disorder in the United States, leading to increased morbidity and mortality nationwide. Based on a survey\(^1\) in 2011 of the US population, approximately 39.5 million people, or a total of 12.9% of the population, have had a diagnosis of asthma in their lifetime. Of those 39.5 million, nearly 10.5 million were children, or 14%, diagnosed with asthma. Moreover, 18.9 million or 8.2% of adults and 7.1 million or 9.5% of children still suffer from asthma. The study\(^1\) estimated that asthma prevalence in the United States increased 28% from 2001 to 2011.

The burden of this disorder impacts the individual in multiple ways, including quality of life, limited productivity in terms of work and school absence, financial expense, and earlier death. The healthcare system as well incurs the cost of this chronic disorder, as number of hospitalizations, emergency department visits, and clinic visits for routine and urgent reasons continue to increase due to asthma complications.\(^1\)

The rate of caesarean delivery (CD) both globally and in the United States has risen as well. Since 1985, the World Health Organization (WHO)\(^2\) has established that the ideal CD rate in any country should fall between 10% and 15%. As the rate of CD increases up to 15%, the rate of newborn and maternal fatality decreases; yet when procedures for CD increase above this ideal, the fatality rates do not improve. However, CD has become increasingly common in both developed and underdeveloped nations.\(^2\) Particularly in the United States, the rate of CD was 32.2% in 2014, according to the Centers for Disease Control (CDC).\(^3\)
Based on these data\textsuperscript{2,3} provided by the WHO and CDC, CD are an effective way to preserve the life of mothers and their newborns, yet only when required for medically indicated reasons. At a rate above 10-15\%, there is no reduction in mortality with CD, and CD carries risk associated with significant complications, including disability and death. Although CD are necessary procedures, benefit has not been shown in performing them in mothers whose situations do not require the procedure.\textsuperscript{2} It is essential for healthcare professionals to provide CD for women in need, undoubtedly. Yet it is also necessary to provide full education in terms of benefit versus risk posed to both mother and child for those whose preference is and request, rather than need, the procedure.

Further, disability after CD has been observed and recent studies have explored the possible association between CD and asthma development in childhood, as trends for both have concurrently increased over the past few decades.\textsuperscript{1,2,3} This is an idea that perhaps has not been included in the discussion between expectant mothers and healthcare providers regarding delivery options.

There has been a quandary in determining by what mechanism interplay exists between CD and asthma as well as other allergic and autoimmune disorders. According to an article published in 2011 by Neu and Rushing,\textsuperscript{4} hypotheses include the famous, or infamous, hygiene hypothesis, which has been gaining popularity in terms of studies with supportive evidence. Neu and Rushing\textsuperscript{4} report that development of the immune system is heavily dependent on bacteria that colonize the intestinal tract in infancy. These microbes are involved in training the immune system to recognize self and non-self. According to Rook,\textsuperscript{5} as the immune system becomes familiar with what pathogens and allergens coexist in the intestinal tract, it learns to tolerate this microbiome over time. One of the functions of this gut microbiome is to stimulate lymphoid tissue to produce antibodies and regulate other immune cells such as T-helper cells when presented with
unfamiliar pathogens. In this way, the bacteria that colonize the intestinal tract promote development of the immune system. This development can be either normal or abnormal depending on which bacteria are present early in life. However, still very little is known about this mechanism.4,5

Interestingly, contemporary research4,6,7 suggests that the gastrointestinal tract of a normal fetus is not yet colonized by microbes and that mode of delivery has a critical role in the primary establishment of neonatal intestinal flora. In 2008, Biasucci et al6 published a study exploring potential differences in bacterial colonization of the neonatal intestine after CD compared to that after VD. Results determined that the gastrointestinal flora of neonates after CD is less diverse than the flora of their VD counterparts. Specifically, the infants who were born via VD had fecal cultures of numerous Bifidobacterium species, Klebsiella oxytoca, and Escherichia coli. Of these, Bifidobacterium species were the most prominent in VD children and of the greatest difference when compared to children delivered via CD. In CD infants, no or few Bifidobacterium species were cultured.6

Dominguez-Bello et al7 as well reports differences in gastrointestinal microbiota between neonates after CD and those after VD. Specifically, fecal cultures of newborns delivered by CD grew bacteria found on skin and in hospitals, including Staphylococcus and Acinetobacter. However, Lactobacillus, a common bacterium found in the vaginal canal, colonized the neonatal intestinal tract after VD. Ultimately, current research appears to suggest that bacterial intestinal colonization is altered by mode of delivery.4,6,7

While CD are effective and necessary procedures, they may alter a child’s ability to develop a properly functioning immune system4,5 and predispose him or her to chronic and limiting disorders. The objective of this review is to explore for a possible association between CD and risk of development of childhood asthma.
METHODS

An extensive literature search of Web of Science, CINAHL, and MEDLINE via PubMed and Ovid databases was performed using the following search terms: caesarean or cesarean, asthma, and intestinal flora or gastrointestinal microbiome. Yielded articles were then screened for relevance and eligibility criteria. Inclusion criteria included studies of pediatric patients, emergent or elective CD, spontaneous VD, and clinically diagnosed asthmatic children. Exclusion criteria included non-English language studies, studies published prior to the year 2000, non-human studies, studies of pre-term or low birth weight infants, studies using non-clinical diagnosis of asthma, and studies that did not adjust for atopic parent confounders. Finally, an assessment of quality was performed for the resulting studies using the GRADE system.

RESULTS

The literature search initially yielded 74 articles for review. After eliminating duplicates and screening for relevant articles using the eligibility criteria, a total of 3 qualifying studies remained. The articles included 2 retrospective cohort studies\(^9,10\) and 1 prospective cohort study\(^12\) (Figure I). The quality of those included was low due to their inherent nature of being observational studies. However, the study by Tollånes et al\(^9\) was able to be upgraded to high quality for a large magnitude of effect and plausible confounding (Table I).

| Tollånes et al |

This retrospective observational study\(^9\) was published in 2008 and aimed to explore the possible relationship between caesarean delivery (CD) and development of asthma. The authors gathered data from the Medical Birth Registry of Norway (MBRN), selecting births from 1967 through 1998. The MBRN lists birth data including year of birth, mode of delivery, infant gestational age, sex, medical condition, and maternal age
and marital status. As it is required to list all births after 16 weeks gestation in this registry in Norway, there were a total number of 1 869 380 births between the set years. After applying exclusion criteria (death prior to 1 year, any birth defect except congenital hip dislocation, and children in a multiple pregnancy), 1 756 700 children remained eligible for the study.9

In order to determine which children from this population later developed asthma, the researchers used the Norwegian National Insurance Schema (NIS). The NIS registers individuals who receive cash benefits for asthma. Qualifying for enrollment in this registry requires documented physician diagnosis of moderate to severe asthma, based on ICD9 and ICD10 codes used in electronic health records. Enrollment in the NIS is irrespective of income.9

Analysis of the children was performed by Cox proportional hazard models which assessed mode of delivery versus benefit received for asthma. Two models were analyzed: CD and instrumental vaginal delivery (IVD) (ie. with the use of forceps) were contrasted against spontaneous vaginal delivery (SVD) from 1967 through 1998; and emergency caesarean delivery (ECD), planned caesarean delivery (PCD), and IVD were contrasted against SVD from 1988 through 1998, as CD was further classified as emergent or planned from 1988 onward. Children became ineligible and their data were no longer included in analysis at the age of 18 years or in December of 2002, whichever came sooner. The authors adjusted for confounding including birth year, the child’s sex, birth order, maternal age, maternal education, and maternal asthma. According to the researchers, year of birth was the only important confounder that altered the hazard ratios (HR).9

The authors found that the rate of CD increased over the study period, from 1.7% in 1967 to between 11% and 12% from 1985 to 1998. Interestingly, the rate of diagnosed asthma also increased during the study period, until 1992. The authors attribute the
plateau or decrease in rate of asthma diagnosis after 1992 to the young age of the remaining children in the study, suggesting that they had not yet developed asthma or had not yet applied for the NIS registry by 2002.9

Based on the analysis of this study, there was a 52% increased risk of developing asthma after CD from 1967 through 1998 (HR 1.52 when adjusted for all confounders including year of birth). (Note: researchers also included the HR when adjusted for all confounders except year of birth: HR 2.17.) During this timeframe, 3.6 per 1000 VD children developed asthma while 7.7 per 1000 CD children developed asthma. Further, children born by ECD and PCD from 1988 through 1998 were at 59% and 42% increased risk of developing asthma, respectively (HR 1.42 and HR 1.59, respectively). During this timeframe, 7.3 per 1000 VD children developed asthma while 10.8 per 1000 ECD children and 10.1 per 1000 PCD developed asthma.9

Renz-Polster et al

This was a retrospective observational study10 published in 2005. The authors sought to evaluate for differences in risk of allergic disorders including asthma, allergic rhinitis, atopic dermatitis, and food allergy between children born by CD and those born by VD. Researchers utilized the electronic medical records of Kaiser Permanente Northwest to gather data on children born between January 1, 1990 and December 31, 1992. Exclusion criteria were premature infants, individuals without Kaiser Permanente Northwest healthcare coverage during the follow-up period, and records without mode of delivery information. After linking the resulting 8953 births with health data from the birth registry of the state of Oregon as well as with that from the mothers, a total of 7872 children were ultimately included in this study. Age of the children ranged from 3 years to 10 years old during the follow-up period from 1996 to 2000.10

In order to determine asthma development, the authors searched the children’s health records for an asthma diagnosis from outpatient visits from 1996 to 2000 and
additionally watched for prescription patterns. Authors defined asthma development as having at least one diagnosis at the age of 6 years old or older during the study period. Their reasoning for selecting this age minimum was to reduce the number of children with early onset asthma and transient wheeze as other research,\textsuperscript{11} the authors note, has suggested that wheezing is common in young children prior to age 6 and not likely to be associated with allergic sensitization. Taking this information into account, researchers also determined potential confounders including the child’s sex, multiple gestation, and exposure to antibiotics in the immediate postnatal period. The mothers’ health records were screened for medications commonly prescribed to treat asthma. Lastly, the Oregon Birth Registry identified maternal education, marital status, and smoking during pregnancy, as well as the child’s ethnicity, birth weight, and birth order.\textsuperscript{10}

Authors then examined the association of asthma diagnosis with CD versus VD and also with contaminated versus uncontaminated delivery. Contaminated delivery was defined as any VD or CD after premature rupture of membranes (PROM); uncontaminated delivery was defined as CD or repeat CD. Statistical analysis was completed using logistic regression to establish the effect of CD on subsequent diagnosis of asthma. Of the total number of births included in this study, 1286 were via CD. Results were adjusted for the child’s sex, age at diagnosis, birth weight, birth order, exposure to antibiotics in the postpartum period, and multiple gestation as well as for maternal age, ethnicity, education, marital status, smoking status during pregnancy, and use of asthma and/or allergic rhinitis medications.\textsuperscript{10}

Through their research, the authors concluded that the risk of asthma diagnosis significantly increased after any CD (initial, repeat, or contaminated), but only when the data was stratified by sex. Interestingly, females were at higher risk of asthma diagnosis after any CD (OR 1.53, p=0.009) whereas males had no statistically significant increased risk after any CD (OR 1.08, p=0.62), according to this study. Overall, for both sexes
together, data showed that children of any CD had a higher likelihood of diagnosis of asthma at 6 years up to 10 years of age (OR 1.24, p=0.04). Furthermore, females born by an uncontaminated delivery were also at increased risk (OR 1.83, p=0.01) whereas without sex stratification and for males alone, there was no statistically significant result of asthma diagnosis after uncontaminated delivery.  

van Beijsterveldt and Boomsma

This was a prospective observational study published in 2008 that explored for a relationship between CD and asthma as well as other allergic disease. This study was different from the other two, other than being longitudinal, in that it focused on twins, hoping to capture both genetic and environmental effects on the development of asthma. In order to find their population of interest, researchers used the Netherlands Twin Register (NTR), which is composed of families with twins who voluntarily include themselves in the database. The NTR reportedly contains data on 40% of all multiple births in the Netherlands. Specifically, children included in this study were born after the year 1990.

Utilizing the information provided in the NTR, the researchers of this study mailed surveys to the parents of twins at 1, 2 and 5 years after the births. By the first year of each child’s life, information was received by the researchers via returned surveys regarding mode of delivery, maternal age at birth, gestational age, birth weight, birth order, sex of twins, and smoking behavior of both parents during pregnancy. At the second year, breastfeeding information was collected via a mailed survey. Finally, at the fifth year, mailed surveys were again sent to parents asking yes/no whether each child had received a physician diagnosis of asthma. Children were excluded from the final sample population if born via a vacuum or forceps delivery, born via VD in breech presentation (twins in breech presentation requiring CD were included in the study), or
missing any information required for analysis. The total number of children ultimately was 6330 first-born twins and 5438 second-born twins born between 1991 and 2000.\textsuperscript{11}

Analysis was carried out using chi squared tests and logistic regression. Results were determined after adjusting for the effects of maternal age at birth, smoking during pregnancy, current smoking behavior, breastfeeding, child’s sex, incubator time, and birth weight. Researchers performed a comparison of asthma prevalence between first-born and second-born twins and, because gestational age significantly interacted with mode of delivery, a comparison between infants born at 37 weeks and older and those born earlier than 37 weeks. However, the data prior to 37 weeks was excluded from this systematic review solely for meeting the inclusion and exclusion criteria and for streamlining purposes.\textsuperscript{11}

According to the data, among the 37 weeks and older gestational age group, there was increased risk of asthma in first-born CD children when compared to first-born VD children (OR 1.59, $p<0.01$). The authors concluded that 10.6\% of first-born CD children, 37 weeks gestational age or older, developed asthma by 5 years of age versus 7.5\% of first-born VD children by the same age. Additionally, when comparing the second-born twins, there was no significant difference for asthma development delivered at any gestational age in the CD children: 9.1\% asthma development in those delivered via CD compared to 8.4\% in those via VD (OR 0.91). Lastly, there was no significant difference in asthma development between first- and second-born VD co-twins, but in the CD group, first-born twins had a higher risk of asthma than their second-born co-twins.\textsuperscript{11}

**DISCUSSION**

With the rate of CD increasing concurrently with the rate of asthma diagnoses, contemporary research seeks to determine any relationship between the two phenomena. One of the hypotheses gaining support through this research is the hygiene
hypothesis, which suggests an environmental role in the development of allergic and autoimmune disease, and specifically asthma. Current studies\textsuperscript{4,6,7} have evaluated the neonatal gastrointestinal microbiome and which organisms colonize the intestinal tract after CD as compared to those after VD, and the organisms appear to be distinct. Furthermore, it has been shown that the microbiota of the intestinal tract plays a major role in development of the immune system, suggesting that mode of delivery may alter the risk of developing asthma later in childhood.\textsuperscript{4,5}

After synthesis of the included articles\textsuperscript{9,10,12} in this review, several conclusions can be drawn. Each study first determined that the rate of CD increased with each passing year for the duration of study. Results were consistent between the 3 studies as well, with similar odds ratios (OR) or hazard ratios (HR) when comparing asthma development after CD versus that after VD. It was shown that children born by CD had a statistically significant higher risk of developing asthma than children born by VD. Of interest, one study\textsuperscript{10} showed statistical significance of asthma diagnosis after CD only in females and another\textsuperscript{12} only in first-born children, particularly first-born twins.

The significance of asthma development specifically in females in the study completed by Renz-Polster et al\textsuperscript{10} was not able to be explained. However, the significance of asthma development in first-borns, as shown by van Beinsterveldt and Boomsma\textsuperscript{12} may plausibly be explained by the idea that there could be more microbial exposure to each child. In other words, as the number of siblings increases, the risk of allergic disorders decreases due to greater probability of bacterial load, spread, and contamination or transfer.

Other considerations for each of the studies\textsuperscript{9,10,12} include potential confounding. Although each study adjusted for multiple confounders, there still exists the potential for other interaction with the data. While a maternal history of asthma was adjusted for in each study, it is plausible that a mother with a medical history of asthma is more likely to
undergo a CD. Additionally a maternal history of atopy could genetically predispose the neonate(s) to asthma. Moreover, none of the studies accounted for total number of people or pets living in the home of each of the participants; however, birth order was accounted for in each of the studies, which could very reasonably be used as a surrogate for number of siblings. As mentioned earlier, number of siblings and, more significantly, number of persons in the household may alter the likelihood of asthma development.\textsuperscript{12}

Limitations of the studies include reliance on parental report\textsuperscript{12} of asthma diagnosis, diagnosis by documentation in electronic health records,\textsuperscript{10} or by documented inclusion in a national registry.\textsuperscript{9} Conclusions could have been strengthened by researchers of the studies personally performing or acquiring help in clinical diagnostics for asthma, such as pulmonary function testing (PFT), immunoglobulin E (IgE) staining, etc.

An additional limitation may be that older children are more likely to develop asthma. Although Tollånes et al\textsuperscript{9} analyzed data of many children until age 18, other children were much younger at the conclusion of the study in 2002 and perhaps had not yet developed asthma. Similarly, Renz-Polster et al\textsuperscript{10} analyzed data of children who, by the conclusion of the study, were 6 to 10 years of age. While asthma diagnosis appears to be more likely in this age group,\textsuperscript{11} it is possible that some children were diagnosed with asthma after that timeframe. Again, van Beijsterveldt and Boomsma\textsuperscript{12} only studied children until 5 years of age, missing those who would perhaps later develop asthma, thus reducing any potentially stronger association between asthma development and mode of delivery.

Other limitations of the studies were by nature of their design. Tollånes et al\textsuperscript{9} excluded children diagnosed with mild asthma as the authors based asthma diagnosis on inclusion in the NIS; and in order to be eligible for inclusion in the NIS, an asthma
diagnosis must be at minimum moderate in severity. By a similar design, Renz-Polster et al\textsuperscript{10} excluded participants who did not have healthcare coverage by Kaiser Pacific Northwest, although they had been born at Kaiser Permanente Northwest hospital, where the population of study was gathered. This effectively limited their sample population and may have introduced socioeconomic bias. Further, van Beijsterveldt and Boomsma\textsuperscript{12} selected their participants based on the Netherlands Twin Register which included only voluntary reporters of birth. A registry with mandatory birth report such as that used by Tollånes et al\textsuperscript{9} and Renz-Polster et al\textsuperscript{10} would have been more optimal. Moreover, van Beijsterveldt and Boomsma\textsuperscript{12} relied heavily on surveys for their data outcomes where there is a risk of recall bias. Each of the above described limitations could have diminished the association between asthma development and mode of delivery.

Ultimately, studies performed in the future exploring the relationship between CD and asthma development would benefit from analyzing data for a longer follow-up period in each participant, from birth through 17 years of age, in order to better capture any asthma diagnosis. Also beneficial would be for future researchers to define asthma diagnosis clinically and personally, rather than to rely on parental report, accurate ICD9 or ICD10 code in an electronic health record, or inclusion in a registry also based on others' data.

While the underlying mechanism for the likely association between asthma and CD remains unclear, there is evidence suggesting that contact with vaginal flora stimulates neonatal intestinal colonization with different microbes which in turn promotes functional immune system development.\textsuperscript{4,6,7} Future studies might additionally explore the gastrointestinal microbiome of children who have developed asthma versus that of healthy children and further compare whether or not those children were born via CD or VD. From a clinical perspective, should future data find conclusive and comparable
evidence of distinct intestinal flora in non-asthmatic children, perhaps therapeutic options can be explored. The future may see the intestinal microbiota of healthy individuals transplanted into an asthmatic or other allergic-type individual, similar to fecal transplants used for recurrent diarrhea from *Clostridium difficile* infection. Finally, the use of probiotics and other modulation of gastrointestinal flora of CD neonates may be on the horizon in order to prevent or delay development of asthma and other allergic and autoimmune disorders.

**CONCLUSION**

Rates of asthma diagnosis as well as CD procedures have been climbing. The mechanism behind the positive association between asthma development and CD remains a question for researchers, though hypotheses suggest a difference in bacterial colonization of a child’s gut as determined by mode of delivery. Because neonates are exposed to different bacteria during a CD than during a VD, their immune systems learn to tolerate different intestinal flora and therefore create a dissimilar labeling of self and non-self. This variance promotes distinct antibody production and altered regulation of other immune cells, leading to a difference in recognition of allergens and pathogens.

The reviewed studies demonstrate an association with CD and asthma development. Of interest from this review, there appears to be between a 42% and 59% increased potential risk of developing asthma after CD, either emergent or planned, as compared to that after VD. Additionally, female and first-born children are more likely to develop asthma after CD versus VD, whereas male and second-born children have no statistically significant increased risk.

This research may lead toward a wider array of therapeutic solutions to asthma prevention, delay, or treatment. These options may include the use of healthy intestinal microbiota in an introduction pathway such as fecal transplant or probiotics. With the increase of asthma development nationwide and more than double the ideal rate of CD
procedures, this area has become a lucrative and powerful field of study. Ultimately, healthcare providers should present expectant mothers with this information to create an open discussion and allow for more informed decision-making regarding the upcoming delivery of their child.
References


Figure I. Study Search and Selection

Identification
- Records identified through Ovid (n = 1)
- Records identified through PubMed (n = 12)
- Records identified through CINAHL (n = 25)
- Records identified through Web of Science (n = 36)

Duplicate records removed (n = 28)

Screening
- Records screened (n = 46)
- Records excluded (n = 36)

Eligibility
- Full-text articles assessed for eligibility (n = 10)
- Full-text articles excluded (n = 7)

Included
- Studies included in qualitative synthesis (n = 3)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tollánés et al(^9)</td>
<td>Retrospective Cohort</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not likely</td>
<td>None</td>
<td>High</td>
</tr>
<tr>
<td>Renz-Polster et al(^10)</td>
<td>Retrospective Cohort</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not likely</td>
<td>None</td>
<td>Low</td>
</tr>
<tr>
<td>van Beijsterveldt and Boomsma(^12)</td>
<td>Prospective Cohort</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not likely</td>
<td>None</td>
<td>Low</td>
</tr>
</tbody>
</table>

\(^a\) HR is greater than 2 (crude HR = 2.20, adjusted HR = 2.17)

\(^b\) When Tollánés et al\(^8\) adjusts for confounding variables, HR decreases with each adjustment (crude HR = 2.20, adjusted HR = 2.17, secondary adjusted HR = 1.52)