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Supplements

Caesarean Section (C-Section) Delivery Mode and Health Risks on Children

Supplementary Paper:

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Wisma Nugraha Building, Suite 501, 5th Floor
Jl. Raden Saleh No. 6 Jakarta Pusat
Website : www.worldnutrijournal.org
Phone: +622131905330 Email : worldnutritionjournal@gmail.com
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Supplementary Paper

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LITERATURE REVIEW

Rising trends and indication of Caesarean section in Indonesia

Ali Sungkar[1], Ray Wagiu Basrowi[2,3]

1. *Department of Obstetric Gynecology, Medical Faculty, Universitas Indonesia*
2. *Occupational Medicine Division, Department of Community Medicine, Medical Faculty, Universitas Indonesia*
3. *Danone SN Indonesia*

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Abstract

The rate of Caesarean delivery is rising dramatically worldwide, and also nationally. The number of Caesarean births exceeds the WHO recommended rate. This study aims to provide an overview of current increasing trend of Caesarean section, including elective procedure, and its risk. A review was conducted using online database, surveillance reports, and national surveys to identify studies with topics of prevalence, trend, indications, and risks of Caesarean delivery. Overall, there is an increase of Caesarean section in global, Asia, and Indonesia setting. We found an increase of 8% from 2013 to 2018 based on population survey, and increase of elective Caesarean surgery, particularly in tertiary care. We listed the possible health risks in short term, long term among mothers and child. Advanced maternal age, higher socio-economic status, higher educational level, residing in urban area, and ownership of health insurance were found to be factors associated with maternal choice on Caesarean delivery. The information presented is important to raise awareness among policy makers aimed to develop a national strategy in reducing the rate of Caesarean delivery.

Keywords: Caesarean section, prevalence, C-section indication, gut dysbiosis, synbiotic

Introduction

Caesarean section (C-section) is a life-saving surgical procedure for both mother and the baby when pregnancy and birth complications occur. It has been recorded in the history as a procedure to save the fetus from a dying mother, even before the introduction of anesthesia.[1] However, in the modern era, the use of C-section is no longer limited to emergency indications. It is a popular alternative to vaginal delivery. The rate has been increased progressively worldwide in the last decades, including those in the middle-lower income countries.[2,3] The World Health Organization (WHO) has suggested that a national C-section rates should not exceed 10-15% as the higher rate would not reduce maternal and neonatal mortality rates.[4] Nevertheless, recent evidences have shown that most countries have higher C-section rates than the WHO recommended rate, e.g. 40.5% in Latin America and the Caribbean region, 32.3% in Northern America, 25% in Europe, and 19.2% in Asia. In Indonesia, the trend is similar, with increasing C-section rate from 2% in 1986 to 16% in 2012.[5]

Nowadays, with the increased attention to patient's autonomy and shared decision making, women could express their preference for C-section, even without any medical indications. Fear of labor

Corresponding author:
Dr. dr. Ray Wagiu Basrowi, MKK
Science and Medical Affairs Department
Danone SN Indonesia
Email: ray.basrowi1@danone.com

pain is the most common reason for elective surgical delivery.[6-8] Other determinants include previous negative birth experiences, maternal age, economic, social and cultural factors. It has been estimated about 3.6% of about 18.5 million C-section around the world are carried out without any medical indications.[9]

Even with the advanced surgical technic, C-section procedure is not without complications. A multi-country survey had been carried out and found increased risks of C-section without indications for severe maternal outcome.[10] There has been debate about the short-term and long-term risks of C-section, such as risk of miscarriage and stillbirth, placenta previa, placenta accreta in the subsequent pregnancy, and risk of childhood asthma.[11]

Early interventions are proposed during pregnancy to reduce unnecessary C-section. WHO recommends various support programs, e.g. childbirth training workshop, psychosocial couple-based prevention program, nurse-led applied relaxation training program, and psychoeducation for women with fear of labor. Educational interventions identified to be effective in reducing C-section and increasing vaginal delivery.[12]

With the implementation of national health insurance in Indonesia, there has been concern towards the increase of C-section. Basic Health Research (*Riset Kesehatan Dasar*/*Riskesdas*) in 2018 recorded about 17.6% of all births were delivered through C-section, higher than the WHO recommended rate at population level.[13] The high number of C-section delivery also contributing to the financial burden to BPJS, as the national insurance agency.[14] Nevertheless, there has been any studies that summarized the evidences in this This study aims to provide a review on the trend of C-section in Indonesia, factors contributing to elective C-section, and the risks of C-section.

Methods

We identified articles through multiple channels, including surveillance reports or national surveys, United Nations report, and articles from electronic search database, e.g. PubMed, Cochrane, and Google Scholar. We also include those national publication from relevant institutions, e.g. Ministry of Health, Healthcare and Social Security Agency (*Badan Penyelenggara Jaminan Sosial-Kesehatan*/*BPJS-Kesehatan*), Health Research and Development Agency (*Badan Penelitian dan Pengembangan Kesehatan*/*Balitbangkes*), and other national-based data from non-profit organizations. Literatures reported C-section rate in single institution or single area were excluded. We considered studies that provide nation-wide estimates, regional or multi-country estimates.

We reviewed all articles which included the following topics of prevalence, trend, indications, and risks of C-section, particularly in Indonesian setting. Articles were either in English or Indonesian language, and not limited to publication year. Studies included prospective, retrospective, trials, observational study, systematic review, and meta-analysis.

Results and Discussion

The result of this review is classified into three main topics: 1) Prevalence and trend of C-section; 2) Indications of C-section; and 3) Risks and intervention to reduce risks of C-section.

Prevalence and trend of C-section

Data presented in **Table 1** are C-section in global, regional, and national estimates. At global level, Bertrán identified the lowest rate in Africa (7.3%) and highest in Latin America and the Carribeans (40.5%). Nevertheless, the study found that the average increase rate was the highest in Asia (6.4% per year), compared to other regions, e.g. Africa (4.0%), Europe (3.4%), Latin America and the Carribeans (2.6%), and North America (1.6%).[2]

Study by Festin et al[15] estimated the C-section rate from four countries in South East Asia and collected the data from hospital. While Verma et al obtained the data from 9 countries in South and South East Asia countries. The lowest C-section rate was found in Timor Leste, i.e. 1.51%. Meanwhile, the highest was found in Bangladesh (58.54%) for institutional birth, and Maldives (31.78%) for both institutional and non-institutional birth.[16]

We obtained the data for national estimate from research articles and nation-based population survey. Basic Health Research in 2010, 2013, and

2018 estimated the C-section rate between 9.8% to 17.6%, lowest in 2013, but then increased almost double in 2018. This number was higher than study done by Festin et al,[15] whom collected the data from hospital. Overall, we observed an increasing trend of C-section use in national, regional, and global level.

Indications of C-section

The decision to perform a C-section should be based on what is best for the mother and child. We should consider the risks and benefit for the mothers, including previous experience of C-section or complicated pregnancy. The standard and globally accepted C-section offering pathway available through a recommendation from NICE and RCOG. In RCOG guideline (2015), planned vaginal birth after C-section (VBAC) has success rate of 72-75%.[20] Hence, clinician and patients should be aware that there is higher risk of uterine rupture for mothers with two or more previous surgical delivery. Additionally, VBAC is contraindicated in women with placental localization, previous uterine rupture or classical caesarean scar. RCOG also noted breech presentation as primary indication for 10% of all C-section, placenta previa for 3% and multiple pregnancy for 1%. The guideline also recommended women with HIV-positive and women with Herpes Simplex Virus infection to be offered with C-section to prevent mother-to-child transmission of maternal infection.[21]

WHO proposed the use of Robson classification system to assess, monitor, and compare C-section rate between health facilities.[22] Using Robson, health providers would be able to identify the groups of women which contribute the most and least for C-section. Vogel et al[23] had identified that group 1 and 3 of Robson classification contributed the most to C-section rate among moderate human development index groups. Women in term gestation (≥ 37 weeks), nulliparous, with singleton and cephalic pregnancy in spontaneous labor is considered as group 1. While group 5 has similar characteristics, except that women are multiparous and had experienced C-section. The overall C-section rate was 28.4% in 2004-2008 to 32.4% in 2010-2011.

While in Indonesia, a national survey has not been performed using Robson classification. Nevertheless, Sungkar et al[24] had performed it in tertiary health center in Indonesia, and found that group 10 contributed the most. Group 10 (women with single cephalic, < 37 weeks' gestation and previous scar) hold the largest group (28.1%), followed with group 1 (17.6%) and 3 (15.2%). A study held in public hospital in Indonesia assessed the indication of C-section between 2017 and 2018. The study reported having previous C-section as the main maternal indication (25.2%) and fetal distress among fetal indication (54.1%). When maternal and fetal indications are combined, severe preeclampsia and fetal distress were found to be the most common indications.[25] Other study conducted in one public hospital and one private hospital in 2011 obtained similar result for fetal indication, with fetal distress as the main indication.[26] While for maternal indication, premature rupture of membrane and preeclampsia were found to be significant factor related to C-section. Beside those indications, failed induction of labor also found to be one of the contributors.[27]

This Robson classification can be used to understand which group contribute the most to C-section; however, we could not identify the underlying indication for performing C-section. A hospital-based analysis in South-east Asia, as part of SEA-ORCHID project, identified the reasons for C-section, with the most common indications were malpresentation, previous C-section, and cephalopelvic disproportion.[15] Nevertheless, in that study, it was noted that maternal request was also the main reason found merely in Indonesia, and not in the other three countries, i.e. The Philippines, Malaysia, and Thailand.

C-section by maternal request

The American College of Obstetricians and Gynecologists stated that C-sections performed in the absence of medical indications are considered as maternal request.[28] Women who voluntarily choose this delivery method should understand its potential risks and benefits. The risks might not be apparent in the first delivery, but would increase in the subsequent delivery. For instance, repeated C-sections would increase the likelihood of placenta accreta, placenta previa, and other risks related to maternal mortality and morbidity.[28,29] International

data estimates roughly about 4 to 18% of all C-sections were performed on demand.[30] No specific prevalence data on C-section by maternal request in Indonesia. Nevertheless, National Health and Demographic Survey revealed an increasing trend of C-section from 1991 to 2007. We have not obtained specific data regarding C-section by maternal request in Indonesia. Nonetheless, Festin et al found that it was commonly performed in tertiary hospital in Indonesia.[15]

Factors affecting women's choice on C-section

Evidences found several factors related with women's choice on C-section. A cohort study in Sweden among 357 mothers mentioned fear of childbirth as the main reason (64%), followed with anxiety for the infant's health (28%) and complex pregnancy condition among their relatives (20%).[31] A systematic review has also been conducted to understand the reasons for elective C-section. Similar reasons were found in the result, such as fear of labor pain, fear of child birth, anxiety of their children's health, urinary incontinence, vaginal trauma, previous traumatic experience in birth delivery, lack of emotional support, etc.[32]

We also looked at the characteristics of women who choose C-section. Jenabie et al[32] found the following factors to be significant, e.g. advanced maternal age, education level, parity, maternal obesity, household income, number of children and marital age. An analysis among Indonesian women also considered the socio-economic status, educational level, area of residence (urban versus rural), employment, and ownership of health insurance, to be the factors of maternal choice for C-section. Verma et al[16] analysed the determinants of C-section in Indonesia and found urban residence (adjusted OR: 2.78; 95% CI: 2.53-3.07), maternal age (adjusted OR: 1.07; 95% CI: 1.06-1.08), and educational level (adjusted OR: 3.95; 95% CI: 2.03-7.69) as significant factors. This result also aligned with study done by Sihombing et al.[33] Additionally, Sihombing et al[33] also considered that women with maternal gestation age ≥42 weeks, multiple pregnancy and maternal height < 145 cm were more likely to have C-section.

Risks of C-section

The risks associated with C-section can be divided into short-term, long-term, and future risk; and whether it affects the mother and/or the child. The **Table 2** summarized the potential health risks that occur in C-section procedures.

There are limitations to this review. The articles were not identified through a systematic searching strategy. Useful information and unpublished studies might have been missed. The role of medical staff as birth attendant also need to be reviewed as the decision making of C-section also part of the role of medical practitioner.[37] Nevertheless, we try to include information from trustworthy and reliable sources, including those published from government website. We aim for studies which have best methodology, i.e. systematic review and meta-analysis. Nevertheless, we did not perform critical appraisal for the included articles.

Conclusion

This literature review pointed out the increasing trend of C-section all over the world, and particularly in Indonesia. There have not been any studies in Indonesia that monitor the utilization of C-section using national data, and therefore, we could not conclude which group contributed the most to C-section based on Robson classification system. There are wide range of health risks associated with C-section procedure towards mother and child.
Research should be conducted in the future to explore the main drivers that influence Indonesian women's decision making for childbirth. The process of coming to a decision for C-section is not easy, and the role of husband and family might be important in Indonesian context. Moreover, further exploration on C-section pattern in Indonesia using Robson classification system would give a comparable situation regarding C-section trend to international audience. It would also provide an audit and feedback system to the government of Indonesia in understanding the current maternal healthcare services.

Table 1. C-section estimate rate at global, regional, and national level

Year of data collection	n of countries	Global estimate (%)	Regional estimate (%)	National estimate (%)	Source
1990-2014	150	18.6 (6.0–27.2)	Asia: 19.2 (1.7–47.5) South-eastern: 14.8 (1.7–32.0)	N/A	(2)
2000-2015	169	2000: 12.1 (10.9–13.3) 2015: 21.1 (19.9–22.4)	2000: 13.4 (11.0–15.9) 2015: 28.8 (26.3–31.2)	N/A	(17)
2002-2016	9	N/A	11.8 (1.51–31.8)	11.6[a] 21.1[b]	(16)
2005	4	N/A	26.6 (19.1–34.8)	29.6[b]	(15)
2010	1	N/A	N/A	15.3[a]	(18)
2013	1	N/A	N/A	9.8[a]	(19)
2018	1	N/A	N/A	17.6[a]	(14)

Table 2. Risks of C-section

Risks	OR (95% CI)	Reference
Short-term*		
Post-partum infection	2.83 (1.58-5.06)	(34)
Hemorrhage	0.52 (0.48-0.57)	(34)
Maternal death	3.10 (1.92 – 5.00)	(34)
Thromboembolism	3.7 (3.0-4.6)	(35)
Long-term		
Urinary incontinence	0.56 (0.47-0.66)	(11)
Pelvic organ	0.29 (0.17-0.51)	(11)
Fecal incontinence	1.04 (0.73-1.48)	(11)
Child		
Childhood asthma	1.20 (1.15-1.25)	(36)
Subsequent pregnancy		
Uterine rupture	25.81 (10.96-60.76)	(11)
Hysterectomy	3.85 (1.04-14.02)	(11)
Placenta accreta	2.95 (1.32-6.60)	(11)
Placenta previa	1.74 (1.62-1.87)	(11)
Placental abruption	1.38 (1.27-1.49)	(11)
Antepartum hemorrhage	2.43 (0.81-7.34)	(11)
Postpartum hemorrhage	0.72 (0.55-0.95)	(11)

Note: Short-term risk was assessed for cesarean section without indication.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Caesarean section and gut microbiota in children

Ariani D Widodo[1], Mohammad Juffrie[2]

1. *Pediatric Gastrohepatology Working Group, Harapan Kita National Center for Woman and Child Health Care, Jakarta, Indonesia*
2. *Pediatric Department, Medical Faculty, Gadjah Mada University-Sardjito Hospital, Yogyakarta, Indonesia*

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Abstract

Over the last two decades, the C-section rate has increased worldwide. It is understood that colonization patterns of intestinal microbiota in infant delivery in C-section vary from those that were delivered vaginally. These different microbial pattern and diversity will impact and respond to immune and dysbiosis-related diseases. This article examined the effect of C-section on gut microbiota in children.

Recent findings: Newborns are influenced by various factors, including mode of delivery, feeding, nutrition, hospitalization, antibiotic and host gene. Several studies have shown that infants with C-section have lower *Bifidobacterium* while others have shown lower abundance of *Enterobactericeae* and *Bacteroides* in infants with C-section compared to infants born vaginally. Although the mode of delivery is only one factor that influences infant microbiota composition, studies conclude that reduced microbial exposure during the C-section is important because it can affect dysbiosis several years after birth. Good microbiota is a key source of microbial-driven immune regulation, changes in normal patterns of bacterial colonization can alter the immune development outcome and may predispose to certain immune-related disorders later in life.

Summary: The composition and concentrations of intestinal microbiota between vaginally and C-section born infants are significantly different. Among C-section infants, gut microbiota is associated with lower diversity and therefore induces dysbiosis, which can affect immune development and may predispose to some immune disorders, i.e. allergies in particular. Nutritional approach with pre-, probiotics, and/or synbiotics can have a promising effect early in life in preventing gut dysbiosis.

Keywords: Caesarean section, children, gut microbiota, dysbiosis, synbiotic, probiotic, prebiotic

Introduction

The term 'microbiota' refers to the number of all microbial colonies living in or on the human body. The human gut, primarily the large intestine, contains 10^{14} bacteria, the body's largest numbers of microbiota compared to certain human bodies such as skin, vagina, mouth and ears. Gut microbiota coexists with host in a homeostatic relationship and has bidirectional interaction with the immune system. In the first year of life, the production of gut microbiota is a complex process and an important process in the human life cycle as it plays a key role in immunological and metabolic processes, thereby affecting human health and diseases.[1]

The pioneering bacteria colonizing infant intestine and its shift towards a stable ecosystem are crucial to the development of optimal interaction

Corresponding author:
Dr. dr. Ariani D. Widodo, SpA(K)
Pediatric Gastrohepatology Working Group, Harapan Kita National Center for Woman and Child Health Care, Jakara, Indonesia
Email: dr.ariani@gmail.com

(symbiosis).[2] Tissier published the idea in 1900 that fetuses are sterile *in utero* and microbial colonization begins later during and after birth, this is recognized for centuries. In comparison, studies have shown that uterine microbiota is associated with healthy term pregnancies and there is potential for placental barrier bacterial transmission. Recent studies have detected bacteria from healthy newborns in placenta tissue, umbilical cord blood, amniotic fluid, meconium and fetal membranes with no sign of infection or inflammation.[2,3]

The human bowel is easily colonized by a large variety of microbes and is distinctive in composition, but over 95% can be allocated to four main phylas: Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria.[3] The formation of microbiota starts at birth and plays an important role in host immune system maturation, defending against pathogens and providing nutrients.[4] Influenced by many factors, the diversity and colonization patterns of infant gut microbiota include pregnancy, mode of delivery (vaginal vs Caesarean section), diet (breast milk vs formula), sanitation, and antibiotic treatment.[5]

The newborns' first big exposure to microbes happens during birth and significantly influenced by delivery methods.[3] The skin, gut, oral and nasopharyngeal cavities of the vaginally-born neonates are initially seeded by *Lactobacillus* spp, which resembles maternal vaginal microbiota. The absence of *Lactobacillus* spp and dominance of specific skin and environmental microbes such as *Staphylococcus, Streptococcus* or *Propionibacteria* is found in infants delivered by Caesarean section (C-section).[6,7] These initial microbiota evolve over time and are adapting to the body and formed by the availability of different nutrients. Recent study showed that although the difference between delivery modes gradually decreased at 4 months and 12 months of age, C-section-born infants remained have more heterogeneous gut microbiota compared to the vaginally-born.[3]

The rate of C-section has been increasing worldwide over the last two decades. It is observed that intestinal colonization patterns of infant delivery in C-section vary from those that were vaginally delivered. However, the relationship between these trends and delivery mode is still unclear. Various colonization patterns and diversity of the intestinal microbiota can impact and respond to immune development and also with several illnesses associated with changes of the intestinal microbiota (dysbiosis).[8] Thus, this article analyzes the relationship of Caesarean section (C-section) delivery and its effect on the gut microbiota of children.

Methods

This article reviewed how C-Section affect gut microbiota and its effect on children. We focus on gut microbiota, the difference between different delivery method on gut microbiota, and how it affect children's health. Articles included in this review are from several electronic database i.e Pubmed, Medline and Google Scholar with the key words "mode of delivey", "ceasarean section", "gut microbiota", "dybiosis", "prebiotics", "probiotics" and "synbiotics". Articles included are the one in English or Indonesia language and published from April 2010 until April 2020.

Results and Discussion

Gut microbiota within the first 100 days of life

The sterility of uterus and microbial colonization of newborn is generally recognized since 1900. This view is based on the fact that microbial analyses in pregnancy-related samples were conducted only in cases of suspected infection. It is also discussed as culture studies have shown that microbes are found in placenta, amniotic fluid, fetal membrane, umbilical cord blood and meconium.[2]

Nearly half of the umbilical cord samples and all of the meconium samples contain bacteria from cultivable sources such as *Enterococcus, Streptococcus, Staphylococcus* and *Propionibacterium*, as well as human placental bacteria *Bifidobacterium* and *Lactobacillus*.[4] The mechanism by which gut bacteria enter human uterus is not fully understood. Several studies have shown that certain bacteria from the maternal digestive tract can spread in healthy host to extra digestive locations. The mechanism consists of dendritic cells and $CD18^{+}$ cells that may take non-pathogenic bacteria from the intestinal lumen and transport them to other locations.[9] However,

dendritic cells may open tight intersections between intestinal epithelial cells, send dendrites out of the epithelium and directly sample bacteria without damaging the epithelial barrier. It has also been shown that small numbers of dendritic intestinal cells can maintain live commensal bacteria in mesenteric lymph nodes for several days. Dendritic cells and/or macrophages, once within the lymph nodes, can spread elsewhere because lymphocytes circulate in the associated lymphoid system.[9,10] This hypothesis is confirmed by a study which found *Enterococcus faecium* in amniotic fluid and meconium following sterile C-section of pregnant mice previously inoculated with the bacteria.[2] This could be transferred to the fetus via the bloodstream. A recent research has also found that microbiota is present in human placenta and has shown that it can be the route for maternal oral bacteria to be given to fetus like microbiota in the oral cavity.[11] The microbial interaction in prenatal life is thus seen, but previous studies have not used techniques to quantify the number of bacterial cells and to differentiate accurately between DNA, dead cells, living cells and active cells that make it difficult to identify placental microbiota or pregnancy risk factors.[11] It requires further research to validate the presence, amount and effect of intrauterine microbiota on the health of children.

Post-natal microbial interaction is higher and extensive during birth and breastfeeding than in prenatal life. Newborns' first exposure to microbes happens during the birth process and may differ according to delivery method. *Lactobacillus* spp is dominant in vaginally-delivered newborns but different species are present in each newborn because of various motherly vaginal microbiota. Newborns therefore continue to live exposed to various bacterial species, depending on interaction with vaginal flora. In comparison, C-section born children showed various *Staphylococcus*, *Streptococcus*, *Clostridium* or Propionibacterium colonization. This indicates that early colonization benefits bacterial communities associated with each mode of delivery.[6,12]

In newborns, gut microbiota has a low diversity and characterized by the relative prevalence of the phyla *Proteobacteria* and *Actinobacteria*. The colonization begins first with optional anaerobic species, followed by the creation of compulsory anaerobes organisms such as *Bifidobacterium*, *Bacteroides* and *Clostridium*. Full-term breast-fed infants show dominance of compulsory anaerobic bacteria, such as *Bifidobacteria* in the gut, while premature infants show lower bacteria but lower facultative anaerobes such as *Enterobacteriaceae* and *Enterococcaceae.* In addition, the proliferation and dominance of other bacteria, such as *Firmicutes* and *Bacteroidetes* diversify the microbiota. Finally, by the end of the first year of life, children microbial profile start to resemble that in adult, and by 2-3 years of life have developed their signature microbial profile.[3,13]

Newborn microbiota is a complex ecosystem that is influenced by various factors such as delivery mode, feeding/dieting, medication, hospitalization and host gene. Demographic factors such as gender, gestational age and postnatal age also contribute in the development of gut microbiota. These contributing factors have been identified in several studies, and most have shown that interaction between host-microbial products and their different factors play an important role in infant health and immune development processes.[13,14]

Impact of C-section and gut dysbiosis in children

There are many factors influencing the production of gut microbiota such as delivery mode, diet, genetics, health status, gestational age, etc. Breast milk encourages intestinal microbiota production by adding probiotics and prebiotics and providing protection to pathogens. *Lactobacillus*, *Bifidobacterium, Staphylococcus*, *Bacteroides*, *Enterococcus, Streptococcus* and *Clostridium* are several examples of breast milk bacteria. These bacteria are evident in breast milk and neonatal feces, which indicate vertical transmission of bacteria through breastfeeding. Full-term infants that are exclusively breastfed tend to have more *Bifidobacterium,* but less diverse gut microbiota compared to formula-fed infants. When children are exposed to solid food, the gut microbiota pattern shifts towards adult microbiota pattern at around 12 months of age.[13]

The use of antibiotics will alter the microbial diversity and affect the health of children. Short-term use of antibiotics will significantly affect the colonization and diversity of gut microbiota. Good

microbiota diversity has been shown to decrease significantly in the first three weeks of life in infants with longer-term antibiotics treatment, compared with infants exposed to short-term antibiotics. In infants, it is shown that after antibiotic treatment, the colonization pattern of *Bifidobacterium* decreases while *Proteobacteria* increases. Preterm infants are often delivered through C-section and the use of antibiotics in this situation is common. In this case, the evolving pattern of microbiota may be associated with a serious intestinal disorder, such as neonatal necrotizing enterocolitis (NEC).[15]

Initial microbial exposure occurs during and shortly after birth, as described. The newborn's first high exposure to microbes occurs during childbirth and relies heavily on mode of delivery.[13] In infants born vaginally and via the C-section, different bacterial colonization occurs. Vaginal bacteria are transmitted from mother to child during vaginal birth, primarily Lactobacilli, while infants born with C-section have microbial pattern resembling environmental microbes.[6,8,12] It is known that in infants born with C-section, the gut microbiota in the first week of life is less diversed compared with those delivered vaginally. Nevertheless, the pattern of colonization of its phylum is not affected by the mode of delivery. Some studies have shown lower *Bifidobacterium* and *Enterobactericeae* in C-section infants compared with those delivered vaginally. Meanwhile, *Clostridium* genus is more common in C-section delivered infants. Four studies have indicated that the *Bacteroides* phylum was less diversed among infants delivered in C-section within the first week, and two studies have shown that there is no significant difference within the *Firmicute* phylum between C-section and vaginally-delivered infants.[8]

C-section has saved many lives but has become overperformed, often with no or weak indications, over the last decades. In creating "good" gut microbiota profile, the existence of healthy/abundant diversity plays a decisive role. Increased C-section rate, prematurity, antibiotics usage, improvements in feeding and the environment, may have affected gut microbiota. The transformation of microbial communities at risk of dysbiosis (microbial imbalance). Microbiota plays a key role via symbiosis in humans (controllable benefits), which may lead to short-term inflammation that leads to children's gastrointestinal disorders. Several studies have shown that dysbiosis of children coincides with emerging immune changes (asthma), inflammatory bowel disease and metabolic (obesity) disorders.[16]

A balanced relationship between the host microbiota and the immune system is essential for a homeostatic toward pathogenic attack and avoid inflammation. Infants with dysbiosis gut foster a strong T-helper (Th)-1 bias, which makes the immune system susceptible to inflammation hence secreting cytokines Interleukin (IL)-12 and Interferon (IFN)-γ. This inflammation affects tissue and tissue repair, disturbing the normal immune system, potentially leading to long-term consequences such as inflammatory bowel disease (IBD), allergy and autoimmune disease.[3]

C-section born infants have a lower diversity of microbiota compared with vaginally born infants, especially on *Bacteroides* colonization. *B. fragilis* which significantly higher in infants born vaginally, has been shown to have an anti-inflammatory role by acting on T cells. *B. fragilis* produces surface polysaccharide A (PSA), a microorganism-associated molecular pattern (MAMP) that is recognized by toll-like receptor 2 (TLR 2) on T cells. Engagement of TLR2 and PSA leads to T cell induction and limits Th-17 response which will promote tolerance and immunosuppression in the gut.[3] Appropriate microbial stimulation during infancy is required to develop Th1-like and T-cell response. Difference in infants gut microbiota could shape later immune responsiveness, influencing Th1 maturation may impact on immune mediated disease.[17] Lower microbial diversity might explain why infants born by C-section are associated with the development of allergy and asthma, type-1 diabetes, and obesity.[3,14,17]

Gut dysbiosis and its impact on health

Inadequate transfer of maternal microbiome to infants born through C-section may lead to impaired immunological development. Although mode of delivery is only one factor that influences the composition of infant microbiota, studies conclude that reduced microbial exposure during C-section is important because it may cause dysbiosis several years after birth. Gut microbiota is an important key

source of microbial-driven immune regulation. Alterations of the normal bacterial colonization patterns may change the outcome of immune development and may predispose to certain immune-related disorders later in life, such as allergy, obesity or diabetes.[18]

The development of the newborn immune system depends on the gut microbiota composition in early life. Hypothesis on microbial deprivation syndrome in economically-developed countries and its association with high incidence of multiple sclerosis, type-1 diabetes and Crohn's disease has been proposed.[19] Low-diversity microbiota leads to insufficient T-cell induction with regulatory and/or Th1-like properties to counteract Th2 response in induced allergies. Early exposure to diverse gut microbiota is important as the distribution of specific microbial species in immune maturation. Repeated exposure to new microbial antigens may enhance the development of immune response through Th1-like responses.[17] A study using culture-independent bacterial molecular techniques concludes low gut microbiota diversity during childhood in children with eczema or sensitization.[14] Indeed, a number of cross-sectional epidemiological studies showed differences in the composition and activity of gut microbiota among healthy and atopic children. Asthma incidence was also linked to abnormal microbiota in pediatric populations.[19] A study reported that gut microbiota depletion at 3 months of age was found in subjects with atopy and wheeze. In this group, biosynthesis of lipo-polysaccharides and short-chain fatty acid (SCFA) acetate is also reduced.[3]

Gut microbiota also contributes to the production of SCFA in fat tissues to the formation of triglycerides block through fermentation of indigestible polysaccharide-derived plants. Kalliomaki[20] found lower intestinal *Bifidobacterium* and higher concentration of *Staphylococcus aureus* at 6 and 12 months in obese children compared to children with normal weight. Alterations in early exposures to microbiota (such as C-section delivery), lack of breastfeeding, maternal pregnancy BMI, and infants antibiotics, may alter the diversity of microbiota and may influence the risk of overweight in later childhood.

Aberrant gut microbiota colonization can affect the immune system in adulthood, making it more susceptible to certain diseases. Persistent increases in natural killer cells can only be prevented by neonatal colonization of the microbiota, and microbiota also drives the generation of T cell that control inflammation. IgA secretion and inflammatory cytokine profiles are also influenced by gut microbiota. This conclude that immune disturbance may be caused by altered gut microbiota, which explains the increased risk of autoimmune disorders in adulthood.[18]

C-section, gut dysbiosis and allergies

The most common chronic disease in childhood is allergic diseases. Allergic disease is an immune-mediated disease that has increased considerably over the past decades with a high increase in C-section deliveries. [2] There are reports that there is a risk of developing allergic disease, allergic rhinitis, asthma and asthma-related hospitalization, and food allergy, whereas there was no association with inhalant atopy and eczema/atopic dermatitis.[21,22] As already mentioned, gut microbiota plays an important role in improving immune system development and maturation. Gut dysbiosis has been shown to be associated with atopic children in several studies. Allergic infants have been found to have less *Bifidobacterium* colonization than in non-allergic infants. [23] Reduced exposure to microbial antigens to the gut explain immune system dysregulation. To develop a more balanced immune phenotype, appropriate microbial stimulation during childhood, including maturation of Th1-like responses and appropriate development of regulatory T-cell response is required. The imbalance in gut microbiota has affected the Th1 ripening pathway showing that children born through C-section have lower levels of Th-1 chemokines CXCL 10 and CXCL 11.[17] A study by Kalliomaki first showed the difference between *Bifidobacteria* and *Clostridia* in newborns. Diversed and balanced gut microbiota are important for normal functioning of the immune system.[23] Other study also showed that in term of gut microbiota composition, nutritional intervention might also play a role on gut microbiota development and showed specific benefit including economic effectiveness.[24]

C-Section delivery is a risk factor for the development of allergies and has been linked to reduced relative abundance and diversity of *Bacteroides* in first year of life.[17,25,26] High Bifidobacterium content is considered to lead to better immune system development and maturation.[2] A meta-analysis shows that C-section delivery has a lower diversity of gut microbiota during the first 3 months of life. At the colonization level, *Bifidobacterium* and *Bacteriodes* genera in vaginally delivered infants seem to be significantly more frequent compared to C-section delivered infants.[8] The presence of *Bacteroides* was associated with high levels of chemokines associated with Th1 in infancy at 1 month. C-section is associated with lower bacterial diversity as described above and lower circulating levels of chemokines are associated with Th1 in infancy.[17] Moreover, Ly *et al.* showed that C-Section delivered infants are characterized by increased cytokine IL-13 production from stimulated cord blood cells.[26] This suggests higher incidence and severity of asthma and atopy caused by gut dysbiosis in these C-section infants.

Intervention of gut dysbiosis with synbiotics

The importance of intestinal composition in health, especially during early life, suggests that microbial interventions may be an effective strategy for potential adverse health outcomes. Some possible strategies have been employed in the effort to achieve a healthy balance of good intestinal microbiota such as vaginal seeding, environmental exposure, and supplementation.[27] The supplementation of prebiotics and/or probiotics is widely studied. Probiotics are live microorganisms that provide hosts with sufficient health benefits when administered. The mechanism of these probiotics' positive effects remains unclear. Prebiotics is a non-digestible nutritional fiber, which has a positive physiological effect for the host by selectively stimulating a small number of indigenous bacteria to increase their growth or activity. Prebiotics is known to boost the growth of beneficial bacteria *Lactobacillus* and *Bifidobacteria* in the upper gastrointestinal tract. Prebiotics produce short fatty acids, lactic acids and acetic acids in such bacteria, which improve host metabolism, the immune system and the gastrointestinal function. The immune and metabolic systems combined with special prebiotics and probiotics (called synbiotics) supplements is thought to have synergistic beneficial effects.[28]

Breast milk, as the gold standard for infant nutrition, not only provides nutrients to the infant but is also a source of probiotics (microbiota) and prebiotics (HMOs) contributing to the establishment of the ideal infant gut microbiota.[29] While breastfeeding, each milliliter of human milk introduces about 10^3 to 10^6 bacterial cells into the body.[30,31] Breast milk microbiota is dominated by *Staphylococcus, Streptococcus, Propionibacterium* and *Bifidobacterium*. The transfer of these microorganisms into the neonatal gut is thought to protect against infections and contribute to the maturation of the immune system.[30-32] Human milk also contains up to 15 g/L of oligosaccharides, whereas only trace amounts are usually found in cow's milk. These human milk oligosaccharides (HMO) act as growth substrates for beneficial gut microbiota such as *Bifidobacteria*.[33]

Nutritional intervention with pre-, probiotics and/or synbiotics may be a cost-effective approach to early life dysbiosis and its correlation with allergic conditions. Evidence of prebiotic supplementation of infant formula with a specific mixture of short-chain galacto-oligosaccharides (scGOS) and long-chain fructo-oligosaccharides (lcFOS) resulting in an intestinal microbiota enriched with *Bifidobacterium*.[27] Knol et al[34] research has shown that adding 0.8g/100ml of prebiotic scGOS/lcFOS in the infant formula enhances the bifidobacterial growth and changes in small, breast-fed infant fatty acids, lactate and pH. Moreover, a randomized clinical trial demonstrated that administration of this specific prebiotic mixture early in life continues to be protective against eczema development at 6 months and even against allergic events up to 5 years, in healthy high-risk infants based on family history of allergy.[35-37]

Existing publications show that intestinal microbiota is typically low in *Bifidobacteria* and *Lactobacilla* compared to healthy infants in infants with allergic conditions.[27] Several studies have shown conflicting results of the presence of *Bifidobacteria* and their relationship to lower risk for developing allergic diseases. Ismail and

colleagues assessed the association between various species of Bifidobacterium and subsequent eczema and atopic sensitization. *Bifidobacterium breve* at 1 week and 3 months of age were shown to be associated with a lower risk of eczema development and sensitization at 12 months of age.[38] Probiotics supplementation intervention together with extensively hydrolyzed casein formula resulted in cow's milk protein tolerance that reduced incidence of allergic manifestations, including eczema and asthma, in children with cow's milk allergy. In other research synbiotics provide supporting evidence in reducing the risk of symptoms of asthma and the use of asthma medication in children who receive synbiotics with extensively hydrolyzed formula (eHF). These infants also have higher *Bifidobacterium* and lower *Clostridium* levels.[27]

Research shows the retarded colonization of *Bifidobacterium spp* in infants born through C-section by modifying gut microbiota with synbiotics supplement. Early supplementation with scGOS/lcFOS and *Bifidobacterium breve* (*B. breve*) M-16V (synbiotics) led to immediate *Bifidobacterium* colonization, which suggests that the first three months of the life represent an opportunity for quick recovery.[27] One study showed protective effect in dysbiosis of mice with food allergy treated with *B. breve* M16-V.[39] A recent study has shown that *B. breve* abundance was correlated with protection from development of eczema and childhood immune sensitivity.[38] Chua et al's[25] pioneering evidence has shown that supplementation with scGOS/lcFOS and *B. breve* M16-V in C-section-born infants allows rapid colonization of *bifidobacteria* from the first days of life and offers promising nutritional intervention in dysbiosis. In this study, synbiotic mixture was able to re-establish the delayed colonization in elective C-section delivered infants from the first days of life, and remained significant until 2 months of age. Synbiotics created a favorable gut ecosystem milieu that contributes in preventing colonization of fast-growing opportunistic pathogens and potentially reduce the development of skin disorders, especially eczema in early life in C-section delivered infants.
World Allergy Organization (WAO) recommends using probiotics to children at high risk of developing allergy, and also provided conditional recommendation for prebiotic supplementation in non-exclusively breastfed infants regardless of their allergic risk.[25,40,41] Although it wasn't supported with a strong certainty of evidence, prebiotic supplementation may place a relatively higher value on possible prevention of allergies and a relatively lower value on additional cost of prebiotic supplementation in not exclusively breastfed infants.[41] The benefits of human milk oligosacharides (HMOs) intervention were also widely studied and considered safe for infant nutrition, including for gut microflora development of C-section born babies.[42] Thus the use of prebiotics on top of probiotics, or in a form of synbiotics, in early life may be beneficial to compensate for intestinal microbiota disorders, but more study is needed on the benefits of patient outcomes, particularly in terms of allergic outcomes.

Conclusion

The intestinal microbiota is a very complex entity and there are a lot more to learn about the underlying processes that shapes microbiota development, interactions with the host, and the role of specific microbes in health and disease. The first major infant exposure that affects gut microbiota is during and shortly after birth, especially related to mode of delivery and breastfeeding. There is a significant difference in the diversity and quantities of gut microbiota between infants born through vaginal and C-section delivery. Gut microbiota in C-section infants is less diversed, and therefore causing dysbiosis. Gut microbiota is the main source of microbial control by T lymphocytes and gut dysbiosis can alter immune developments and predispose to some immune disorders later in life including allergy, atopy, obesity, diabetes, inflammatory bowel diseases and other autoimmune diseases. The use of pre- and probiotics, or in the form of synbiotics, offers a promising benefit for gut dysbiosis especially in C-section born infants as a cost-effective strategy to prevent metabolism and immune disorders.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Immune development of children born from Caesarean section

Zakiudin Munasir[1], Levina Chandra Khoe[2]

1. *Department of Pediatric, Medical Faculty, Universitas Indonesia-Cipto Mangunkusumo National Hospital, Indonesia*
2. *Department of Community Medicine, Medical Faculty, Universitas Indonesia*

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Abstract

Several studies results have shown that mode of delivery affects the health of children, and recent studies showed that elective Caesarean section (CS) is associated with aberrant short-term immune responses in the newborn infant and an increased risk of developing immune disorders. This article focused on the effect and role of the C-section on the immune development in children. Begin at pregnancy, the infant's immune system is activated and develops years after birth. In this article we find that cesarean delivery mode will influence the offspring's immune system by disrupting the intestinal tract's bacterial colonization, different levels of birth adaptive stress, and altering gene expression epigenetic regulation. Some studies have found that gut microbiome composition plays a significant role in the development of immune system along with other factors such as diet/lifestyle, antibiotic use, formula feeding, vaccination with life vaccine, and pathogen exposure. In early life, disrupted colonization induced dysbiosis that was associated with lower *Bifidobacteria* and higher counts of *C. difficile.* These findings are related to infant immune disease and allergy. Dysbiosis following C-section has a huge effect of developing altered immune system, and this microbiome imbalance can be controlled by nutritional support such as maternal breast milk or the use of different combinations of prebiotics and probiotics (synbiotic) which could be beneficial for the immune and metabolic system.

Keywords: Caesarean section, gut dysbiosis, allergy, immunity, synbiotic

Introduction

Caesarean section (C-section) is a surgical procedure developed to prevent or treat life-threatening maternal or fetal complications such as antepartum hemorrhage, fetal distress, abnormal fetal presentation, and hypertensive disease.[1] The number of C-section in the US has risen by up to 48% since 1996.[2] The WHO recommends that in up to 15% of deliveries, C-section may be indicated. However, 37 of 60 developed countries currently surpassing this guideline and taking women undergoing pre-labor, elective C-section without a clear medical indication may present risks to the child.[2,3] Simultaneously with the increase of rising C-section levels, there has been an increasing number of autoimmune and allergic diseases.[4] Possible mechanisms for these associations may include lower and untimely activation of the fetal immune system due to lack of stress response caused by contraction of the uterus and fetal hypoxia,[3] and alteration of the bacterial colonization of the infant's gut after C-section.[2]

Dysbiosis occurs when there is irregular colonization of the body intestine, also considered to be a mismatch between commensal and pathogenic

Corresponding author:
Prof. Dr. dr. Zakiudin Munasir, SpA(K)
Cipto Mangunkusumo National Hospital
Jakarta, Indonesia
Email: zakiudin.munasir@gmail.com

microbes.[5] Intestinal bacterial flora is critical for immune growth, and children with atopic diseases have been shown to have lower gut levels of *Bacteroides* and *Bifidobacterium* species than children without atopic disease. *Bifidobacteria* are associated with reduced risk of atopic disease in children. C-section has been shown to disrupt and change the development of bacterial intestinal flora in infants. This may, in turn, alter development of the immune system and increase the risk of atopic disease in children.[6]

Uterus contraction and fetal hypoxia during childbirth cause a stress response in both the mother and the fetus, raising the substantial levels of cortisol and catecholamine in newborns. Multiple studies show a low level of cortisol and catecholamine in the absence of contraction in the C-section delivery, variations in levels of stress hormones at birth may alter the immune responses and influence the immune system later in life.[3,7] Cortisol may remove uterine preleukemic clones.[7] There is also evidence of altered DNA methylation patterns that are important to immune regulation after C-section.[7, 8]

Methods

This article focused on how the delivery mode affects the neonate's immune system. This analysis was prepared by conducting a search to identify related journals and articles published in 2010 until before April 2020 in several electronic databases, i.e. Pubmed and Medline. The search terms included variants of "delivery mode," "cesarean section," "immune system," "allergy," "asthma," "diabetes," "celiac disease," "allergy to food," "prebiotic" and "probiotic" Additional articles were found by manual search, either in English or Indonesian, from manual references cited in relevant reviews.

Results and Discussion

Immune development in early life

Immune activation starts from insemination as the first immune system exposure to paternal alloantigens. Likewise, it contains paternal immune cells and substances, such as estrogen and testosterone, prostaglandins and various signaling molecules, including IL-8, TGF-b, and IFN-C. It also promotes the transfer and expansion of regulatory T cells (Treg) and promotes the activation and proliferation of dendritic cells (DCs) in responsive cells. Treg is probably involved in T-cells suppression of the mother's effector that promote the success of pregnancy. B cells secrete antibodies that once shield paternal antigens found in the trophoblast on the fetal-maternal interface. The phenotypes of immune cell function, i.e. DC, turning or remaining unchanged and thus tolerant, are modulated by a wide range of molecules formed or secreted by the trophoblast itself, such as the human chorionic gonadotropin (hCG), Heme Oxygenase-1 (HO-1), Regulated on activation, normal T cell expressed and secreted (RANTES), and pregnancy-specific glycoprotein (PSG).[9] Additionally, cell-secreted molecules such as Gal-1 secreted by uterine Natural Killer cells (uNKs) and uterine Mast Cells (uMCs) can have a positive effect on trophoblast physiology while making maternal T cells become receptive or remain to the fetus. These findings suggest that seminal plasma plays an important role in the uterine system preparation for the embryo implantation.[9,10]

A labor will stimulate immune response within the uterine cavity which will be absent in the case of elective C-sections. The production of proinflammatory cytokines in the uterine environment such as interleukin (IL)-1β, IL-6, IL-8 and tumour necrosis factor-α (TNF-α) is thought to be responsible for an activation of the fetal immune system during labor. This reflects the increased of leukocytes in neonates' circulation.[11]

As in all mammals, fetal immune production has been observed at 3-4 weeks of gestation, where the pluripotent erythroid and granulomacrophage progenitors can be found in human embryo's yolk sac. These primitive cells migrate to the liver, which becomes the main haemopoiesis site at 5±6 weeks of gestation, thereby increasing the size of the liver and increasing the number of nucleated cells. A discrete granulocyte/macrophage population is growing at this time.[12] Nevertheless, the neutrophil will not be noticed until the end of the third trimester. As a result, newborn and, in particular, premature infants have impaired neutrophil activity, putting the child at risk of bacterial infections.[13]

In the uterus, the fetus has an immune system that is tolerant to maternal alloantigens. The

mother's uterine natural killer (uNKs) cells, immature dendritic cells (iDCs), T cells and macrophages help to modulate the uterine environment in order to support successful pregnancy.[14] This system will continue after birth when the enormous exposure to environmental antigens, many of which are derived from intestinal commensal bacteria, calls for a rapid change in order establish distinct immune responses that are appropriate for the infant in early life.[13]

The immune system is not fully functioning at birth and therefore infants are at an elevated risk of infection. After birth, infants are moving from the sterile environment of the womb to the wider world, exposed to a wide range of diseases they have never experienced and have no protection against. The 'hygiene hypothesis' theory postulates that early life preparation of the immune system arising from essential immune modulatory exposures helps to stimulate regulatory mechanisms that protect against infectious diseases and allergy.[15]

The definition of allergy has also evolved over the years, and currently, it is considered an umbrella term for an immune defect resulting in the lack of tolerance to usually harmless antigens.[16] Tolerance is antigen-specific and the loss of tolerance in allergies seems to be related to the timing, rate and context of environmental exposures in early life, including bacterial colonization of the infant gut. [17] Specific early microbial intestinal exposure is thought to significantly reduce the incidence of inflammatory, autoimmune and atopic diseases further fuel the scientific view that microbial colonization plays an important role in regulating and fine-tuning the immune system throughout life.[12,18] As a major part of the mucosal immune system, the gut-associated lymphoid tissue (GALT) has M cells that collect small particles and effectively transport them from the intestine to organized lymphoid tissue and cause mucosal immune reaction.[18]

The innate and adaptive immune system

Microorganisms that successfully enter the body will be immediately recognized by the cells and mechanisms of the innate immune system within hours of an antigen-specific response being developed by the adaptive immune system a few days later.[18,19]. Innate immune cells are commonly located along with physical barriers such as skin and mucous membranes, where they release defensive biomolecules such as defensins and complements. Upon pathogen identification, dendritic cells and macrophages (often known as antigen-presenting cells, APCs) are activated to phagocytose the invader, digest, and process pieces (antigens) on the cell surface in the form of major histocompatibility complex (MHC) molecules.[20] Adaptive cells include T-cells that primarily target intracellular microbes, along with B-cells that produce antibodies, most of which target extracellular pathogens. Innate immunity is primarily involved in the initial control of microbes. Adaptive defense is mainly concerned with the final clearance of the invader. Adaptive immunity also maintains certain cells as immune memory cells; these antigen-experienced memory cells do not need the same degree of innate immune support for secondary infection with the same (or similar) pathogen and react much faster and more efficiently.[19]

Impact of C-section on child's immune development

For the postnatal development of the immune system, it is important to microbially colonize the infant gut gastrointestinal tract. C-Section delivered infants, either lacked or displayed a slow colonization of one of the main intestinal phylums, the *Bacteroidetes*, because the infant does not enter the mother's birth canal. Therefore, the delayed colonization leads to low-diversity of the intestinal microbiota, which leads to a lack of regulatory T cell and/or Th1-like responses to avoid Th2 domination. In addition, the dysbiosis in the C-section children is associated with lower circulation of CXCL10 and CXCL11 chemokines related to Th-1 when the risk of allergies increases.[6]

The "hygiene hypothesis" was introduced in 1989 when researchers argued that the increase in allergic diseases was due to a lack in microbial exposure due to improved sanitization practices following a low incidence of early childhood allergy infection.[21] Modern medicines and changes in sanitation and public health have led to an era of unprecedented cleanliness and the near eradication

of previously common pathogens. However, these improvements coincided with the rise of autoimmune diseases and other immune disorders. Strachan and others indicated that a certain amount of microbial stimulation is required to prevent disease.[5] Microbiome includes both pathogens and commensals, which play a role in immune development.

In addition to exposure to parasites outside the body, as many as 100 trillion microbes colonize barrier sites within our body, most of which are in the intestine, indicating how the gut serves as one of the major organ in which the immune system is developed. The composition of the microbiome is dynamic and strongly affected by external factors such as mode of birth, diet/lifestyle, antibiotic usage, vaccination, formula feeding and pathogen exposure. This process is necessary to educate the immune system on how to respond to a wide range of stimuli encountered. Given the intricate communication between the gut microbiota and immune system, which plays a role in the development of tolerance and immune programming, disruption of the diversity and/or the function of the microbiota referred to as dysbiosis may increase risk of immune disorders such as allergy.[21]

There are significant shifts in the makeup of the intestinal microbiota during early life. The intestines are sterile at birth. Within a few hours, the bacteria will begin to appear in the feces. The bacteria colonizing the infant intestine during the first days of childhood derive mainly from the mother and the environment. The mode of transmission is therefore the key determinant of intestinal microbiota.[22] Vaginal infant microbiota (<24 h postpartum) resembles the vaginal microbiota of the mother and is common across various body habitats (skin, oral, nasopharynx, birth canal, and feces), whereas in neonates born by C-section is identical to the skin microbiota of the mother.[6,22,25] The C-section was correlated with lower *Bifidobacteria* counts, lower colonization rates and counts of *B. fragilis* species, and higher counts of *C. difficile*.[22] Infants with a higher number of *Bifidobacteria* species at 1 month of age have higher rates of salivary IgA, which also correlates with allergic symptoms defense.[5] The additional prophylactic antibiotic given in C-section may also lead to aberrant microbial colonization in the infant intestine and may increase susceptibility to metabolic disease in later life.[26] *C. difficile* was also the single gut microbe investigated that was associated with an increased risk for asthma, but this association was restricted to those children with atopic parents.[25]

Another research stated that there is a lack of stress hormones in the infant born by the C-section. Contraction and oxygen hypoxia during vaginal delivery are known to promote the development of stress hormones such as catecholamine and cortisol.[3,27] Cortisol elevation at birth is a predictor of hypothalamic-pituitary-adrenal axis activation of the immune system, lung and organ maturation, and neurogenesis. Vaginal delivery and its effects on elevating glucocorticoids have been associated with increased maturation of the organs, including the intestine. These two stress hormones, on the other hand, are less present in infants born by C-section before labor.[3] Another experimental study showed that the use of synthetic oxytocin, antibiotics or infants delivered by the C-section had higher global DNA methylation in the cord blood cells, and this neonatal epigenetic modification has implications for the wellbeing of the offspring.[28] Higher global DNA methylation could be involved in silencing the pathway that controls the balance between T-helper type 1 and 2 cells, which could lead to a higher risk of developing immune diseases.[29] Further studies on this hypothesis are needed.

Health risks associated with altered immune development on child born by C-section

Recent studies have shown that C-section delivery has been associated with short-term aberrant immune responses in newborn infants and a higher risk of developing immune diseases such as asthma, allergies, neonatal respiratory disease, type 1 diabetes, celiac disease and malignancy.[3,26,30] As mentioned, C-section delivery may alter immune development by three means: (1) disrupting bacterial colonization of the intestines; (2) mounting poor and inadequate stress response; and (3) altering epigenetic regulation of gene expression through DNA methylation.[3]

Respiratory system

The risk of respiratory morbidity after elective CS is mainly related to gestational age in terms of neonates, but it also shows that the lack of work in elective CS may explain reduced production of catecholamines (also in preterm infants).[3,27] This lack of hormones altered the lung adaptation and the associated clinical symptoms such as benign intermittent tachypnea, chronic neonate pulmonary hypertension, pulmonary air leakage and hypoxemia.[27]

Asthma, allergic rhinitis and food allergy

There are reports that there is a risk of developing allergic disease, allergic rhinitis, asthma and asthma hospitalization and food allergy, whereas there was no association with inhalant atopy and eczema/atopic dermatitis.[25,31] Almqvist et al[32] reported the outcome of a cohort study in 2012 in which there was an increased risk of asthma and asthma diagnosis during the follow-up year in children born with a C-section. Increased risk of asthma medication in the emergency-born, but not elective, category suggests that there is no causal effect due to vaginal microflora. A more likely explanation should be sought in the emergency C-section. Changed immune function in infants delivered by C-section compared to vaginal delivery is documented by reduced production of cytokines involved in neonatal immunity, in this respect increased levels of IL-13 and IFN-supposed associated with atopy.[27] The frequent presence of C. difficile in the feces at 1 month post-partum by C-section delivery has an association with the development of wheeze, eczema, and sensitization to food allergens in the first 2 years of life.[25]

A recent cohort study from Mitselou N *et al*[33] using a large population database, shown an increased risk of food allergy in children born through elective or emergency Caesarean delivery compared to those delivered vaginally. This positive association aligned with the theory that exposure to vaginal microflora might reduce the risk of offspring atopic manifestations. The altered composition of the intestinal flora involves these improvements to the immune response to a more atopic profile. The colonization of intestinal microbes appears to stimulate a non-allergic Th1 reaction of the immune system while IgE synthesis seems to be downregulating. C-Sectional children are seemed to have weak immune recognition, especially when born to an allergic mother to foods that are supposed to be tolerated.[34]

Type-1 diabetes mellitus

Recent studies have shown that children born in the C-section are at more than 20% higher risk of childhood-onset type 1 diabetes mellitus relative to those born per-vaginam.[3] Other studies have shown that increased type 1 diabetes mellitus is associated with altered development of the immune system.[27,35,36] In addition, it has been previously suggested that children with decreased early-life exposure to microorganisms may be at increased risk for type 1 diabetes.[27]

Gastrointestinal disease

Bacterial flora of the newborns plays a role in the development of celiac disease. Studies showed a positive association between elective C-section and development of celiac disease, but not for an emergency C-section.[35,37] However, the incidence of inflammatory bowel disease has not been affected by the mode of delivery.[3] Maternal microbial and immune status, infant nutrition and antibiotic exposure affect the development of the intestinal microbiome and therefore the development of the immune system. Dysbiosis can lead to immune-mediated diseases, including allergies and necrotizing enterocolitis (NEC).[5]

Malignancy

There are indications of an increased risk of cancer (leukemia,[3,7] neuroblastoma, testicular cancer) in children born by elective C-section compared to vaginal delivery. Although these correlations have not been verified or refuted in other studies.[3]

Impact of C-section on risk of developing allergy

In this study, mode of delivery was correlated with early childhood asthma and allergy. Children born in the C-section were at an increased risk of developing

childhood asthma, food allergy perhaps associated with risk for allergic rhinitis and atopic dermatitis. Although the mechanisms are not fully understood, it could involve the confounder such as maternal smoking, socioeconomic status or family history of asthma.[32] Microflora plays a number of critical roles in the intestinal colonization and production and homeostasis of the immune system. Some of the strongest data linking dysbiosis and allergies are epidemiological associations with conditions that cause dysbiosis— particularly C-section.[38]

The predominant sources of microbes for the initial colonization of GIT after birth are maternal microbiota, especially during birth delivery, and infant diet (breast versus formula feeding).[22] The mode of delivery is a key factor that shapes the developing infant microbiota and, in this regard, infants delivered by the C-section have been reported to have an enteric microbiota that differs from infants delivered by the vagina, both in time of colonization and in composition. The modified microbiota may have an immunomodulatory effect that increases the child's susceptibility to poor immune recognition of foods that should be tolerated by food-specific IgE found in infants delivered by C-section.[34]

Nutrition intervention to reduce risk of developing allergy

Nutritional measures are key to early-life immune functioning by impacting the gut barrier through strengthening the intestinal microbiota and immune tolerance.[39] Breast milk promotes the colonization and maturation of the infant gut microbiome, as it contains beneficial bacteria such as *Staphylococcus, Streptococcus, Serratia, Pseudomonas, Corynebacterium, Ralstonia, Propionibacterium, Sphingomonas* and *Bradyrhizobiaceae*. Breast milk definitely contributes to stimulate the growth of the microbiota strain specific to the gut *Bifidobacterium* found in the intestines of nursing infants along with *Bacteroides* and it can have an important effect on the development of immune tolerance and genomic capacity for metabolizing the human milk oligosaccharides (HMOs).[24,40] As a prebiotic, HMOs have effects and benefits in the alteration of the intestinal microbiota, pathogens' counter-adhesive effects, epithelial cell response modulation and immune system growth. HMOs are therefore beneficial in the treatment of dysbiosis in breastfeeding children. Moreover, some studies have shown that the role of nutrition intervention could also play in gut microbiota production for un-breastfed babies.[41,42]

Some clinical and preclinical studies demonstrate that synbiotics can prevent certain allergic diseases. This contributed to the use of synbiotic to compensate for early microbial bowel disruptions.[43] World Allergy Organization (WAO) recommended using probiotics to avoid food allergy in pregnant women at high risk of having an allergic infant, women who breastfeed infants with high risk of developing allergy and infants with high risk of developing allergy.[44] Prebiotic supplementation also recommended by WAO panel to prevent allergy in not-exclusively breastfed infants regardless of their allergic risk. However for the prebiotic recommendation is conditional and need a further strong certainty of evidences.[45]

In the JULIUS study conducted by Chua et al,[46] the effect synbiotics on the gut microbiota has been determined in infants born by C-section.The result has shown that supplementation with specific synbiotic mixture (a mixture of short-chain galacto-oligosaccharides (scGOS) and long-chain fructo-oligosaccharides (lcFOS) and *B.Breve M16-V* in C-section-born infants allows rapid colonization of *Bifidobacteria* from the first days of life and offers promising nutritional intervention in dysbiosis. Furthermore, safety follow-up showed a significantly lower incidence of reported skin-related disorders and atopic dermatitis among those treated with this synbiotic compared to the control group.

A randomized study of 90 exclusively atopic dermatitis (AD) at large-formula (eHF) plus synbiotic (a mixture of scGOS and LcFOS and *Bifidobacterium breve* M-16 V) showed significant modulation of the intestinal microbiota, with high percentages of *bifidobacteria* and lower percentages of *Clostridium litusebrense/Clostridium histolyticum* and *Eubacterium rectale/Eubacterium*. The synbiotic impact was sustained for one year following and the incidence of symptoms such as asthma and the use of asthma medications was significantly reduced.[47] Potential role of synthesized human milk oligosaccharides (HMOs) has been

studied recently and are considered safe for infant nutrition to support microflora development.[48]

In addition to this, future approach that provide combination of synbiotic and hydrolyzed formula might be modulate immune system in infants to support tolerance development. Hydrolyzed formula still contains certain protein fractions of different sizes. Some of them may have a role in inducing oral tolerance as recently shown in a study in combination of prebiotic mixture of scGOS and lcFOS lowering sensitization against cow's milk-specific IgG1 and higher level of dendritic and Treg cell, demonstrating its immune tolerance-inducing capacity.[49] This indicates that the use of synbiotic in early life may be beneficial to compensate for gut microbiota dysbiosis, but more study is needed on the benefits of patient outcomes, particularly in terms of allergic outcomes.

Conclusion

Birth process can be a critical time point that decides the immune function of the offspring in later life. The mode of delivery has been associated with several infant conditions. Studies have shown that C-section has been associated with immune and allergic diseases caused by altered immune development compared to vaginal delivery. The potential mechanism for the C-section affecting the development of the immune system may be the alteration of bacterial colonization that causes dysbiosis or may be associated with adverse birth stress reactions and epigenetic modification of gene expression in the immune system. Moreover, dysbiosis causes immune imbalances and is thought to cause allergy, and synbiotic use may improve the immune condition of children.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Caesarean delivery mode and its impact on children's growth and cognitive development

Rini Sekartini[1], Levina Chandra Khoe[2]

1. *Department of Pediatric, Medical Faculty, Universitas Indonesia-Cipto Mangunkusumo National Hospital, Indonesia*
2. *Department of Community Medicine, Medical Faculty, Universitas Indonesia*

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Abstract

There is an increasing concern on the potential risk of Caesarean birth on child health outcomes. This study aims to present the current available evidences on the effect of Caesarean section on child's growth and development. Literature searching were done on several online databases to identify articles which discussed the effect of Caesarean birth on child's body weight, length, nutritional status, cognitive development, memory, learning ability, and intelligence quotient. Several studies showed positive association between Caesarean and risk of overweight and obesity in childhood, adolescence, and adulthood. While, there has not been sufficient evidences to confirm the association between C-section and child's cognitive outcomes.

Keywords: Caesarean section, children, cognitive, growth and development

Introduction

Concerns have been raised due to increasing number of Caesarean deliveries towards the health of mother and baby. There are evidences that linked Caesarean section (C-section) with child health outcomes.[1,2] Data from 150 countries from year 1990 to 2014 recorded the rate of global C-section was 18.6%. In Indonesia, the Basic Health Research (2018) found about 17.6% of all births were delivered by C-section.[3] This number exceeds the standards of the World Health Organization, as increase in C-section rate above 10% had no association with the reduction of maternal, neonatal, and infant mortality rates.[4,5]

Corresponding author:
dr. Levina Chandra Khoe, MPH
Department of Community Medicine
Medical Faculty, Universitas Indonesia
Email: levina.chandra01@ui.ac.id

Initially, C-section was introduced to save mothers and infant's lives. This surgical delivery is important and necessary if used according to medical indications. Unfortunately, many C-sections were performed no longer on the basis of medical indications. Maternal request contributed the most to the rising trend of C-section.[6] The most common reason was fear of birth. Hence, medical indications for maternal and infants were not the top priority reasons. Mothers should be informed with all possible risks and benefits of C-section before making decision on birth mode.

The difference birth mechanism between vaginal delivery and C-section could possibly affect child's health. C-section is considered an unnatural birth mode, in which it lack the birth canal compression and involves surgical procedures that might reduce the early mother-child interaction.[7] In recent years, researchers have done many investigations to understand the possible adverse effect of C-section on child growth and development.

This article is part of Series on Caesarean Section. We aimed to describe the potential health risks of C-section on child growth and cognitive development. In regards to child behavior, it will be discussed in a separate article.

Methods

We identified articles through various sources, such as online database (PubMed/Cochrane), surveys and reports from international organization or national institutions. We searched for the effect of C-section on child growth (body weight, length, nutritional status), and development (cognitive, memory, learning ability, intelligence quotient). We aim for studies with best methodology, i.e. systematic review and meta-analysis.

Results and Discussion

C-section and child growth

It has been hypothesized that Caesarean birth mode is associated with the changes in gut flora of infants. The pattern of gut microbiota in early life affects the composition of microbiota in the long run.[8] Shao et al conducted a cross-sectional study testing 596 healthy babies and assessed the composition of gut microbiota between those vaginally delivered and C-section. The study found that birth mode is a significant factor in the difference of infant's gut flora.[9] Gut microbiota samples from babies delivered vaginally were dominated with Bifidobacterium species; while these were found much less in Caesarean babies. Enterococcus species and other bacteria associated with hospital environment were found in substantially high amount in those born through C-section. The differences are significant in the first three months of life, and slowly disappear after 6 months.[10] Nonetheless, the early microbial colonization could have long-life implications in which it increases the risk of developing allergic diseases and disrupts the development pathway.[11,12] The birth mode is not the only factor, breastfeeding, the introduction of solid food, and the use of antibiotics are other confounders affecting the infant's gut colonization in the first year of life.[13,14]

Gut microbiota have an important role in maintaining human health. The alteration of microbial gut colonization in the early life could lead to various immunologic diseases, neurodevelopmental disorders, and also obesity. An animal study revealed that microbiota increase nutrient uptake, including degradation of indigestible diet, and promotes fat storage, a possible mechanism leading to energy storage and obesity.[15] The pattern of early microbial gut colonization could affect the risk of overweight and obesity in later childhood. A healthy human gut colonization is characterized by high amount of *Bacteroides* species and higher bacterial diversity.[16] While an obese human gut microbiome has more *Clostridium* and *Lactobacillus* species.[17] Caesarean babies have an altered gut microbiome with domination of bacteria found in hospital environment (e.g. *Enterobacter, Haemophilus, Staphylococcus* species), and less of *Bacteroides* species, *Lactobacillus, Bifidobacterium* species (which commonly found in vaginally delivered babies).[18] This altered microbiome is associated with the risk of overweight and obesity in Caesarean babies. **Table 1** summarized some evidences (systematic review/meta-analysis) related to risk of overweight and obesity in childhood and later life.

Overall, the studies showed positive association between Caesarean birth mode and risk of overweight and obesity in childhood, adolescence, and adulthood. The pooled ORs showed in general increased odds of overweight and obesity among children above 2 years old. Nevertheless, we should be aware that risk of obesity is not merely induced by birth mode, but also influenced by genetic and environmental factors, e.g. diet pattern, lack of physical activities, and socio-economic condition.

C-section and child's cognitive development

The intestinal microbiome affects not only the immune system and nutritional status of human, but also the neurodevelopment. A growing body of evidences demonstrates the importance of gut-brain-axis, a bi-directional communication between gastrointestinal tract and central nervous system. The interaction is facilitated through immunological, neural, and endocrine pathway. Studies linked the development of neurological

disorders due to alteration in gut microbiota.[23] Several mechanisms in which microbiota plays role in neurological disorders have been proposed. The alteration of gut microbiota affects the level of cytokine and stimulate inflammatory response. Microbiota could also elicit signals to the vagal nerve directly, which link to the brain. In addition, gut microbiota can activate hormone response which provides communication pathway to the brain.[24] These indicate the initial gut colonization holds important process in infant's brain development.

As explained in the previous section, the delivery mode contributes to the variation in infant's gut microbiota. Caesarean babies have less diversity of microbes and less exposed to maternal microbes.[25] The birth mode, aside from other factors (e.g. gestational age, fetal distress, use of antibiotics in utero) accounts for the alteration of gut microbiota in Caesarean babies. **Table 2** showed a summary of evidences linking C-section and child's cognitive development (memory, IQ, linguistic). Nonetheless, we could not find the highest level of evidence, i.e. systematic review/meta-analysis. Hence, we presented several observational studies in Table 2.

Studies compared between planned C-section or maternal request with vaginal delivery and assessed the outcome, i.e. cognitive ability, learning ability, intelligence quotient, in preschool or school-aged children. One study found significant negative association between C-section and child's cognitive ability (numeracy, reading, grammar at age 8-9). The study also found the significant relationship between breastfeeding, obesity, and autism spectrum disorder with cognitive outcomes. A review also mentioned that the role of breastfeeding even in the specific working mothers' population should be empowered as the benefits of exclusive breastfeeding to support growth and development of babies were well established.[26] Hence, even though the study adjusted these confounding factors, there were still unexplained factors that could influence child's cognitive ability. Other studies did not able to show any clear relationship between C-section and cognitive outcomes. Therefore, we cannot support the notion that Caesarean babies had delayed cognitive development compared with vaginal delivered babies.

Conclusion

Our review identified evidences that assessed the potential risks of C-section on child growth and especially on cognitive development. Based on the current available evidences, positive association was found between Caesarean birth and risk of overweight/obesity in childhood, and continued to adolescence, and adulthood. While, in terms of cognitive ability, there has not been sufficient evidences to confirm the association between C-section and child's cognitive outcomes.

Table 1. Risk of overweight/obesity in childhood and beyond

Author	Year	n included studies	Risk in children	Risk in adolescents	Risk in adults
Li HT et al[19]	2013	9	3–8 years old: 1.32 (1.15–1.51)	9-18 years old: 1.24 (1.00–1.54)	>18 years old: 1.50 (1.02–2.20)
Sutharsan R et al[20]	2015	14	≤5 years old: 1.15 (0.94–1.40)	5–18 years old: 1.09 (0.91–1.30)	>18 years old: 1.28 (1.02-1.34)
Kuhle S et al[21]	2015	28	2–18 years old: 1.34 (1.18-1.51)	N/A	N/A
Keag OE et al[22]	2018	6	Overweight at 3–13 years old: 1.22 (1.06–1.41) Obesity at 5 years old: 1.59 (1.33–1.90)	Obesity at 6-15 years old: 1.45 (1.15–1.83)	Obesity at 20-28 years old: 1.34 (1.25–1.44)

Note: all studies assessed in the systematic review/meta-analysis were observational/longitudinal studies.

Table 2. Summary of evidences linking C-Section and children's cognitive development (memory, IQ, linguistic)

Author	Publication Year	Study Design	n of participants	Location	Groups	Age group	Outcomes
Hanrahan M et al[27]	2019	Cohort	8,845	UK	Normal delivery vs planned CS	3–11 years old for verbal cognitive ability 5–11 years old for visual-spatial cognitive ability	Delay in verbal cognitive ability: 0.65 (0.45–0.94) Delay in visual-spatial cognitive ability: 1.55 (1.07–2.25)
Polidano C et al[28]	2017	Cohort	3,666	Australia	Vaginal delivery vs CS	4 to 9 years old	Difference in numeracy ability: -0.095 (0.034)*
Fox NS et al[29]	2017	Cohort	354	US	Planned vaginal delivery vs planned CS	2 years old	Learning disability: -0.5% (p=0.902)
Khadem N et al30	2010	Cross-sectional	372	Iran	Vaginal delivery vs CS	6–7 years old	Intelligence quotient: -0.61 (p=0.46)
Li HT et al[31]	2011	Cohort	4,144	China	Spontaneous vaginal delivery vs CS on maternal request	Preschool children	Full scale IQ: 1.6 (-1.3–4.5) Verbal IQ: 2.3 (-0.8–5.5) Performance IQ: 0.6 (-2.0–3.3)

Note: *statistically significant ($p<0.05$)

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

The impact of Caesarean delivery mode towards brain and neurodevelopment among children

Tjhin Wiguna[1], Levina Chandra Khoe[2]

1. *Department of Psychiatry, Medical Faculty, Universitas Indonesia-Cipto Mangunkusumo General Hospital, Jakarta, Indonesia*
2. *Department of Community Medicine, Medical Faculty, Universitas Indonesia*

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Abstract

In regards to the rising rate of Caesarean birth globally, there is concern about the risk of Caesarean birth in children. However, the effect of Caesarean delivery towards the child brain and neurodevelopment is not well understood. We reviewed articles from online database with topics related to the relation between Caesarean delivery mode and brain development or neurodevelopment or behavior and emotional development. Several studies discussed how birth mode could affect brain structural connectivity through neural and hormone changes. Some studies also assessed possible effect on child's psychological development. The result showed differences in child's brain development between caesarean and natural delivery in the early life, but not in the long run. Additionally, there was no significant association between birth mode and emotional problem.

Keywords: Caesarean section, children, brain development, neurodevelopment, behavior and emotional

Introduction

In general, birth delivery can be divided into three categories: natural unassisted delivery, assisted delivery, and caesarean delivery. It is commonly known that Caesarean section (C-section) holds important role in saving lives of mothers and infants under certain medical conditions, e.g. labor dystocia, fetal malpresentation, fetal distress, etc. Therefore, the use of C-section for birth delivery is inevitable. However, in present times, mothers could request for C-section, even without any medical indications. And apparently, it becomes increasingly popular. It was estimated that 21.1% of the world's births were occurred through C-section in 2015, increased almost double from 12.1% in 2000.[1] The rate of C-section on maternal request is also growing. Analysis based on the WHO Global Survey on Maternal and Perinatal Health (2004-2008) identified the rate of C-section was 25.7%, and about 1% of them were without medical indications.[2] In Norway population-based study, 5% of the deliveries were occurred through elective C-section.[3] Another study using Swedish Registry also identified a three-fold increase of C-section on maternal request in 10-year period.[4] Similar situation was found in Indonesia, where about 3.7% of Caesarean deliveries in tertiary hospitals were by maternal request.[5]

Even though C-section delivery is sometimes necessary and lifesaving, it can also bring negative consequences for mothers and infants. The short-

Corresponding author:
dr. Levina Chandra Khoe, MPH
Department of Community Medicine
Medical Faculty, Universitas Indonesia
Email: levina.chandra01@ui.ac.id

term health risk includes post-partum infection, hemorrhage, venous thromboembolism, or even maternal death.[6-8] There are also long-term risks for the mothers, child, and subsequent pregnancies.[9] The World Health Organization (WHO) gave statement on C-section delivery rate and acknowledging that the effect of C-section on pediatric outcomes are still unclear.[10] Castillo-Ruiz reported an unexpected effect on neonatal brain development and behavior in mice delivered through C-section.[11] The rates of cell death in the brain were either unchanged or increased at C-section delivery, contrary to vaginal delivered mice, which exhibited an abrupt, transient decrease in cell death. Some human studies also suggested the possible effect of Caesarean birth method on child's cognitive, emotions, and behaviour.[12-13]

Nevertheless, there is no doubt that we also found healthy children born through C-section delivery. It is also important to note that various factors influenced children's growth and development, not merely the birth mode. Little is known about the effect of birth mode on child's neurodevelopment and cognitive behavior. This review aims to provide an overview on the available evidences, exploring how C-section mode could affect brain development in short- and long-term.

Methods

We focus on the effects of C-section delivery mode on children's brain development, neurodevelopment, cognitive, and behavior. Studies on the effects of C-section on children's health, such as obesity, allergy, asthma, were excluded. We only included articles that were published in a peer-reviewed scientific journal. Articles were identified from electronic database, i.e. PubMed, Cochrane, and Google Scholar. The searching strategies included terms related to Caesarean, brain development, neurodevelopment, behavior and emotional development. Articles were either in English or Indonesian language, and not limited to publication year.

Results and Discussion

C-section delivery mode and brain development

There are clearly differences between vaginal delivery and C-section delivery, but the question is how do these differences affect health outcomes in infants? Natural born infant experienced hormonal surge through labor process. Mother's body is naturally prepared for delivering infant, with increasing level of estrogen, oxytocin, prostaglandin activity, beta-endorphins, and prolactin receptors. The infant's body also experiences changes to be fully matured. Buckley[14] noted some possible impacts of planned birth on the infant's brain, e.g. reduced brain maturity and brain-hormone. It is well understood that premature infant has higher risk for brain injury because of the lack of oxygen. About 5 to 10% of infants born before 32-weeks had significant brain impairment, e.g. cerebral palsy, and more than half developed cognitive or behavior disorders.[15-18] Nevertheless, there still lack of evidence on how elective C-section delivery which commonly occurs between the gestation age of 37 to 39 weeks could have impact on the infant's brain. Clinical guidelines recommended C-section delivery on maternal request to be performed after 39 weeks due to risk of respiratory complications, however, no sufficient evidences related to risk of brain immaturity before the gestation age of 39 weeks.[19]

Neonates delivered through C-section have lower concentration of stress hormone that may affect the hypothalamic-pituitary-adrenal (HPA) axis, which latter could have implications on neonatal cardiovascular and autonomic nervous system development. Castillo-Ruiz identified a surge in vasopressin among mice with vaginal delivery, and a relatively small increase among those delivered through C-section. The concentration of circulating vasopressin is almost 100-fold higher in infants born by vaginal delivery compared to C-section.[20] It is assumed that these high concentration of vasopressin acts as natural analgesia in infants born by vaginal delivery. The circulating levels of vasopressin is generally link with concentrations in the central nervous system, and it is reported to decrease neuronal apoptosis in cell culture.

Aside from hormonal effects, Deoni et al[21] performed a cohort study towards two-week-old neonates, three-months to 5-year old, and 8-year old children to observe their brain structural and functional connectivity. The result indicated

significant differences in the first three years, then it was gradually decreased and became unobservable beyond the age of three. The two-week-old infants born by vaginal delivery had higher 4-10% of mean fractional anisotropy, compared to those by C-section. Infant at three-month-old born by vaginal delivery also had better myelination in the frontal, temporal, parietal, and occipital white matter, compared to those delivered by C-section. Hence, the study found no significant differences brain structural connectivity between vaginal and C-section delivery in the older children (7.5 to 8.5 years old). There are possibility that breastfeeding and other environmental exposures, e.g. nutrition, sleep duration, screen-time, contribute to children neurodevelopment.

C-section and its relation to behavior and emotional development

There are theoretical assumptions that Caesarean delivery disrupts the normal change in infant's life and potentially cause traumatic experience that latter affect the child's psychology. The child might be prone to the issue of separation and abandonment.[22] Nonetheless, these were all assumptions and not based on clinical evidence. Kelmanson et al[12] did a case control study comparing 5-year old children born through C-section on maternal request with those vaginal delivery. He found significant difference in terms of anxiety/depression, sleep problems, and internalizing problems. Another study by Huang et al[23] confirmed these potential risk of emotional and behavioral problems among children born via C-section delivery. He compared children born through C-section on maternal request, C-section with medical indications, emergency C-section, and vaginal delivery. Those delivered prior to 39-weeks on maternal request had the highest risk for emotional problems (RR: 3.48; 95% CI: 1.68–7.22) and total difficult problems (RR: 2.17; 95% CI: 1.18–4.02). Nevertheless, study by Rutayisire et al[24] showed different result. He conducted a cross-sectional study among 8,900 pre-schoolers in China and found no significant association between emotional problems and mode of delivery (RR: 1.06; 95% CI: 0.90–1.24).

In regards to its impact on cognitive and behavioral outcome, C-section delivery could have been linked with the alteration of infant's gut microbiota which could affect the memory, mood, and cognition.[25,26] It has been hypothesized that the central and enteric nervous system has bidirectional communications, known as gut-brain-axis. Different gut microbiota has been found in children born through C-section compared with vaginal delivery, not only in the early life, but also beyond infancy. Study by Salminen et al[27] found significantly higher *Clostridium* species in normally delivered children than Caesarean born. The study observed about 60 children aged 7 year old. Animal studies showed that gut microbial colonization affects brain development, particularly in stress reactivity, anxiety-like behavior[28], and brain memory dysfunction. Possible mechanisms include changes in neurotransmitter and brain-derived neurotropic factors, modulation of enteric sensory afferents, and mucosal immune activation.[29-32]

Even though the direct causation between disturbed gut microbiota and child's behavioral development has not been established, there are assumptions that it influences children's cognitive disorder, such as autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD). Study by Rutayisire et al[24] found no differences in emotional problems, but significant result in behavioral problems, i.e. higher risk for total strength and difficulties questionnaire (OR: 1.27; 95% CI: 1.10–1.46) and pro-social behavior (OR: 1.27; 95% CI:1.12–1.45). Another study by Mackay et al[33] also found the risk of special education needs in children with Caesarean delivery. Specifically, he observed a dose-dependent relationship between risk of SEN with younger gestation age. Higher risk was found at preterm delivery i.e. the adjusted odds ratio for SEN at 37-39 weeks was 1.16 (95% CI: 1.12–1.20), at 33-36 weeks was 1.53 (95% CI: 1.43–1.63), at 28-32 weeks was 2.66 (95% CI: 2.38–2.97), and at 24-27 weeks was 6.92 (95% CI: 5.58–8.58). Nonetheless, the association between Caesarean delivery and behavioral disorders are still in debate. Curran et al[34] analyzed a large cohort study in UK and found no association between planned C-section and ASD (aOR: 0.58; 95% CI: 0.19–1.79) or ADHD (aOR: 0.54, 95% CI: 0.18-1.64). He also did a systematic review and calculated a pooled odds ratio of 1.23 (95% CI: 1.07–1.40) for ASD and OR of 1.07 (95%

CI: 0.86–-1.33) for ADHD.[35] A recent systematic review on the association of C-section with risk of neuro-developmental and psychiatric disorders also obtained similar result.[36] The findings revealed a significant association with increased odds for ASD (OR: 1.33; 95% CI: 1.24–1.41) and ADHD (OR: 1.17; 95% CI: 1.07–1.26) among Caesarean infants. However, the study did not find significant association with depression, tic disorders or affective and non-affective psychoses. Even though the associations were significant, the numbers were relatively small, considering the prevalence of ASD was about 1% and ADHD was 7%. In addition, the statistical heterogeneity was high, i.e. I^2=69.5% for ASD and I^2=79.2% for ADHD. Possible confounders, such as genetics, environmental factor, indication for C-section may contribute to this heterogeneity. It is also importantly to consider future reviews and researches related to economic burden on specific child's neurodevelopment condition and its link with nutritional intervention.[37,38] The role and knowledge of health care practitioners also point that need to be taking into consideration in order to keep the management of infants born with C-section will get the proper nutritional intervention and management in the early life. The knowledge update in this particular subject is required.[39,40]

Conclusion

Our review found a growing body of evidences that support the association between C-section delivery and child's neurodevelopmental. The short-term effects were observed in the difference of brain development in the early life. Nevertheless, the long-term effects on child's emotional and behavioral problems were not yet conclusive. Future research should consider the genetic and environmental factors that could influence the emotional and behavioral development of a child. In addition, better understanding on how C-section affects the gut-brain-axis and whether the effect would last in the long run should be explored.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Benefit of synbiotic intervention in Caesarean section born infants and children: A nutritional perspective

Saptawati Bardosono[1], Dian Novita Chandra[1]

1. *Department of Nutrition, Medical Faculty, Universitas Indonesia-Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia*

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Abstract

The benefit to have infants being delivered physiologically through vagina is amongst others to get maternal microbes transmission that will affect host immunity and metabolic development. However this mode of delivery is not always the choice to infants for several reasons. Therefore, it raises questions whether there is a need to give specific intervention to the caesarean section (C-section) born infants and children for their optimal growth and development, i.e. provision of nutrients with or without pre-, pro- or synbiotics. Nutritional intervention is certainly important to support growth and development of all children, especially those born by C-section. However, in addition, to anticipate perturbation in the gut microbiota there is a need to prepare the C-section born infant through translocation from the mother's intestinal microbiota, early initiation of breastfeeding and/or synbiotic supplementation formula. The superiority of synbiotic compare to prebiotic or probiotic alone is that synbiotic thought to have synergistic beneficial effects on the immune and metabolic systems in which it can compensates the delayed *Bifidobacterium* colonization modulates the production of acetate and the acidification of the gut in C-section born infants. However, we still need to find consistent evidence & recommendation in the world on synbiotic for children in general and specifically for the C-section born infant & children.

Keywords: Caesarean section, children, gut microbiota, synbiotic

Introduction

Pregnancy is triggering maternal inflammation due to several physiological changes which results in prenatal stress. In addition, the absence of vaginal microbiota caused by Caesarean section (C-section) delivery mode will alter infant's gut microbiota, or so called dysbiosis. There are several theoretical outcomes of dysbiosis, in which through the increase of blood brain barrier will result to neuroinflammation and will cause abnormal neuronal/brain development. On the other hand, dysbiosis will result to gastro-intestinal dysfuntion or leaky gut that will impair the parasympathetic system function (i.e. vagus nerve) and will cause cognitive and behavioral deficits. While through metabolic disorder caused by dysbiosis, there will be disturbed cross-talk innate immune system and dysregulation of systemic (adaptive) immune system that will result to allergy and autoimmunity.[1]

How could mode of delivery increase the risk of poor child growth and development? Although there is limited evidence on the association between C-section birth and linear growth and/or brain development, a retrospective cohort study among mothers having children aged 6–24 months old in

Corresponding author:
Dian Novita Chandra
Department of Nutrition, Medical Faculty
Universitas Indonesia – Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia
Email: diannovitach@yahoo.com

Ghana found that compared to the C-section infants, vaginally delivered infants were 1.8 times more likely to receive adequate neonatal feeding, and after controlling for potential confounding factors, there's a significant increment by 0.121 standard units on linear growth as measured by height-for-age (HAZ).[2] On the other hand, a cross-sectional study done in East China found that 67.3% were born by C-section, in which 15.7% of those preschool children aged 3–6 years old were obese. And, after adjusted for parental factors, child characteristics and family income, the odd of overweight and obesity was 1.35 and 1.25 respectively.[3]

Furthermore, in relation to brain development, a retrospective study in Arkansas Children's Hospital and Brown University USA found that by using diffusion tensor imaging, myelin water fraction imaging, voxel-based morphometry, and/or resting-state functional magnetic resonance imaging (fMRI), C-section delivery may influence infant brain development. [4] To evaluate the relation between C-section birth and child cognitive development, a longitudinal study of Australian children aged 4 to 9 years revealed that C-section-born children perform significantly below by up to a tenth of a standard deviation in national numeracy test score at age 8–9 years compared to vaginally-born children.[5] To explore the mechanism on how C-section delivery could affect child growth and development in relation to gut microbiota, there is an impact of external factors on the intestinal microbiota of the infant that might explain the mechanism from prenatal to adult-like microbiota through delivery mode at birth, type of feeding especially at the first week and first months. [6] Finally, this article aims to find an appropriate solution or intervention to promote optimal growth and development of the C-section-born infants and children in the perspective of nutrition and gut microbiota balance.

Nutritional intervention to support growth and development of children born by C-section

It is widely agreed that human breastmilk is the gold standard as the first and main food for infants since born to be exclusively provided during the first six months and being continued up to 24 months of age. Breast milk provides complete nutrients to support child growth and development, regardless of difference in the route of delivery. Besides having all essential nutrients, breastmilk also consists of immune-components, hormones, HMOs (human milk oligo-saccharides, and microbiota. The HMOs as prebiotic and microbiota as probiotic, or synbiotic in breastmilk are important on their function to influence on the infant gut microbiota for its long-term health benefits, e.g. lung health. **Figure 1** shows the hypothetical pathway on the association of HMOs as prebiotics and microbiota as probiotic to affect infants' gut microbiota and lung health.[7]

However, not all infants are being fortunate for having the breast milk, but instead will have its substitute, i.e. milk formula. To be updated, the milk formula is continued to be designed to mimic the breast milk, i.e. by 1) decreasing its protein content without changing plasma amino acid profile in preventing obesity; 2) supplemented with cow's milk lactoferrin; 3) having long-chain PUFA (omega-3 and pmega-6) to promote insulin sensitivity, prevention of obesity and dyslipidemia; 4) addition of milk fat globule membrane (MFGM) from cow's milk to add on to the plant oil; 5) supplementation of prebiotic (FOS and GOS) to have a bifidogenic effect; and/or 6) supplemented with probiotic in which there is no report on its harmful effects.[8]

The use of pre-, pro- and synbiotic in infant formula is done through research and innovation by using technological advances along with the development of knowledge about the component of breast milk. However, the evidence about its clinical efficacy is limited to recommend as a routine use in infant formula. Therefore, further research is needed to be able to establish their benefits for health.[9] This recommendation is also considered to the inconsistency evidence, i.e. from 1) the negative finding of a prospective, randomized, double-blind controlled study among full term infants with diagnosed cow's mild allergy (CMA) who received synbiotic supplemented amino acid-based formula (AAF) that showed similar growth to the AAF without synbiotics;[10] to the positive finding from a randomized, double-blind, multicenter study on the effect of synbiotic on the microbiota of caesarean delivery infants in which supplementation with short-chain galacto-oligosaccharides/long-chain fructo-oligosaccharides and *Bifidobacterium*

*breve*M-16V compensates the delay *Bifidobacterium* colonization in C-section-delivered infants and modulates the production of acetate and the acidification of the gut. Physiologically, it reveals as indicator of gut health, emulate those observed in vaginally born infants.[11]

Superiority of synbiotic compare to prebiotic or probiotic intervention alone on C-section born children

There are things to consider regarding to the needs to provide synbiotic intervention. Several studies showed the effects of antibiotic treatment in the pre-natal period and early post-natal life in the gut microbiota, as well as on the risk of wheeze and asthma. While it also evidence that there are maternal factors influencing the composition of breast milk microbiota, and among others is C-section. All of those will induce dysbiosis condition and increase the risk of allergy.[12]

The dysbiosis in children born by C-section is influenced by several factors, i.e. extremes of maternal body mass index (BMI), preterm birth, extremes of infants' size, infection, and gestational diabetes. The impact of microbial dysbiosis caused by C-section delivery is linked with an increased risk of inflammatory bowel disease (IBD) and a wide range of autoimmune, allergic and metabolic condition, as shown in **Figure 2**.[13]

What are the potential for pre-, pro- or synbiotics in the management of infants at risk of dysbiosis? The use of prebiotic is due to its potential effect in selectively utilized by host microorganisms conferring a health benefit. While probiotic as live organisms has it potential when administered in adequate amount confer a health benefit on the host. Furthermore, synbiotic as a mixture of pre- and probiotics potentially affects the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract, improving the health of the host.[14] It has been recommended that during pregnancy, a probiotic treatment may represent an effective strategy to promote a healthy microbial composition in C-section born infants, while also to give prebiotic supplementation in infants exposed to early-life microbial perturbation, such as a C-section born infant. Furthermore, the combination of pre- and probiotics or synbiotics is thought to have synergistic beneficial effects on the immune and metabolic systems.[15] Thus, synbiotic should have a greater effect than the prebiotic or probiotic alone as shown in **Figure 3** on the mechanism of action and their effects.[16]

Regarding to the mechanism of action, then while providing the synbiotic intervention to the C-section born infants and children, we should consider to give nutritional modulation of maternal microbiota that might influence the development of the infant gastrointestinal tract. Using a hypothetical model, we can learn how maternal microbiota and microbial products could be transferred from mother to the fetal and neonatal gastrointestinal tract. It shows that dendritic cells can cross the paracellular space of the intestinal epithelium to take up bacteria directly from the intestine lumen. Following to that action then circulation of lymphocytes within the mucosal associated lymphoid tissue allows the maternal gastrointestinal tract microbiota to reach distant mucosal surfaces, including those found in the genitourinary and respiratory tracts, lactating mammary gland, salivary and lachrymal glands, as shown in **Figure 4**.[17]

This explanation inspires us to manipulate the maternal gastrointestinal microbiota composition through the use of pro-, pre or synbiotic and its subsequent impacts for the health of the newborn. To confirm the hypothesis, an Indonesian study can show the effect of probiotic provided to pregnant women since the 3rd trimester can be found in the colostrum and the 3-month breast milk.[18]

Finally, regarding to the composition of symbiotic, although we have already been informed on the properties of several microorganism considered as probiotics (such as Lactobacillus and Bifidobacterium), and prebiotics (such as oligosaccharides, i.e. FOS and GOS), however we still need further information on its combination as a synbiotic. So far, the most used and already marketed synbiotics are mixtures of oligosaccharides FOS and GOS with probiotics bacterial strain *L. plantarum*, *L. paracasei, L. rhamnosus, B. bifidum* or *B. lactis* that have been selected for the functional activities in the context of a specific combination formulation with prebiotics.[19] Several studies that showed a synbiotic combination of *L. casei* and dextran prevented the

cedar-pollen induced onset of nasal and ocular symptoms, and a combination of potato starch and *L. rhamnosus* reduced a disease score of atopic dermatitis, showing that there are specific synergistic effects of a combination of certain synbiotics. Therefore, future research should provide clinical evidence of certain combination formulation of synbiotics, especially to overcome dysbiosis resulted by the C-section.

Conclusion

Beside breast-feeding, translocation from the mother's intestinal microbiota and synbiotic supplementation are amongst nutritional intervention to support growth and development of C-section born infants and children. Regarding to the fact that synbiotic is thought to have synergistic beneficial effects on the immune and metabolic systems by compensated the delayed *Bifidobacterium* colonization in C-section born infants and modulates the production of acetate and the acidification of the gut, therefore, symbiotic for children in general and specifically for C-section infants and children may have an impact on healthy young children gut microbiota, although further research is certainly needed.

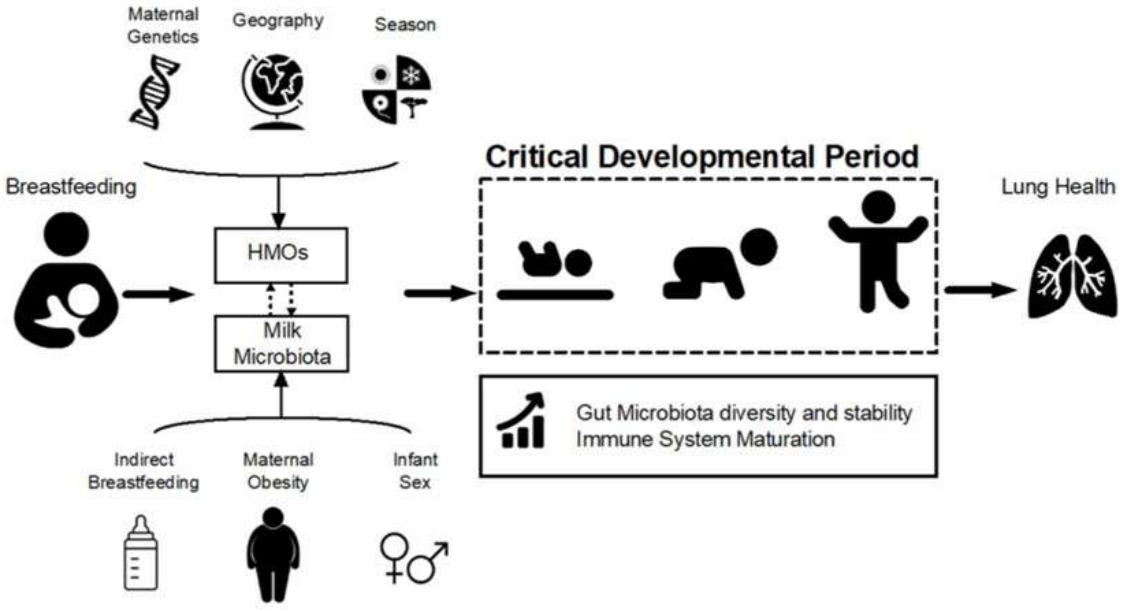

Figure 1. Hypothetical pathways of association between breastfeeding and lung health[7]

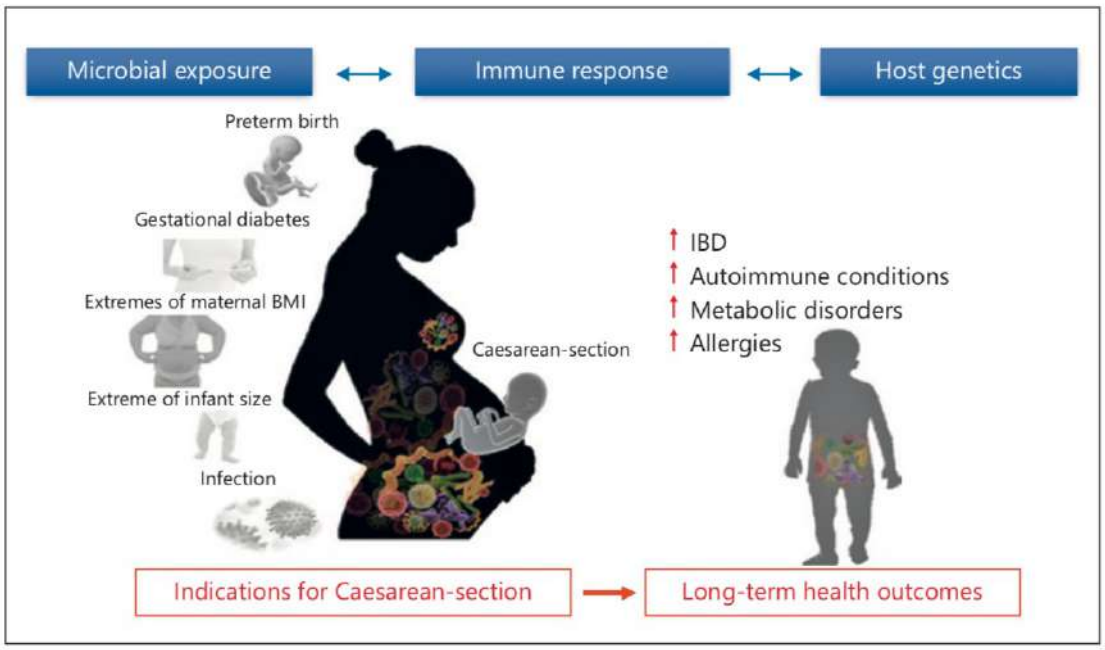

Figure 2. Contributing factors and conditions linked to C-section delivery[13]

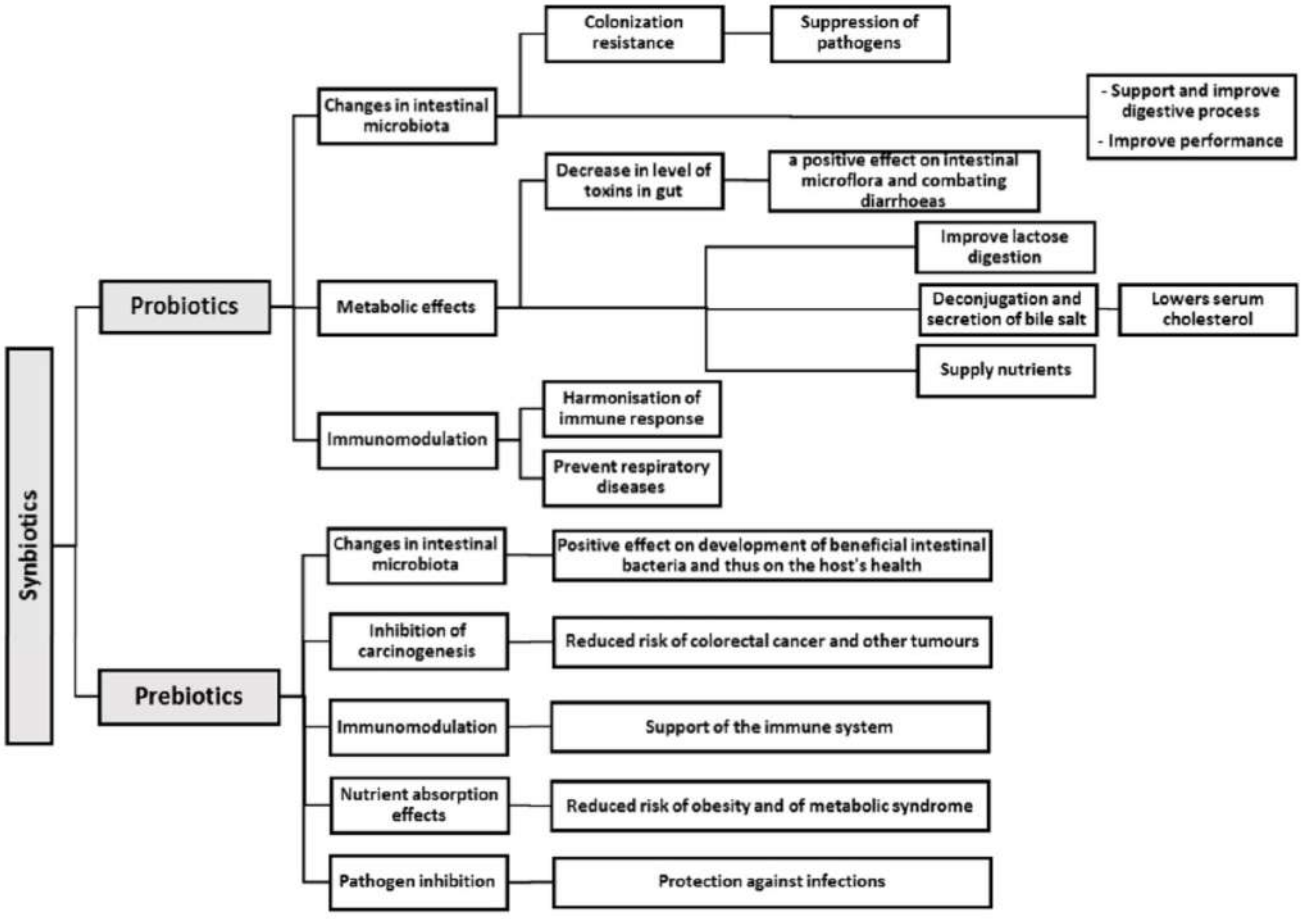

Figure 3. Mechanism of actions of synbiotics and their effects

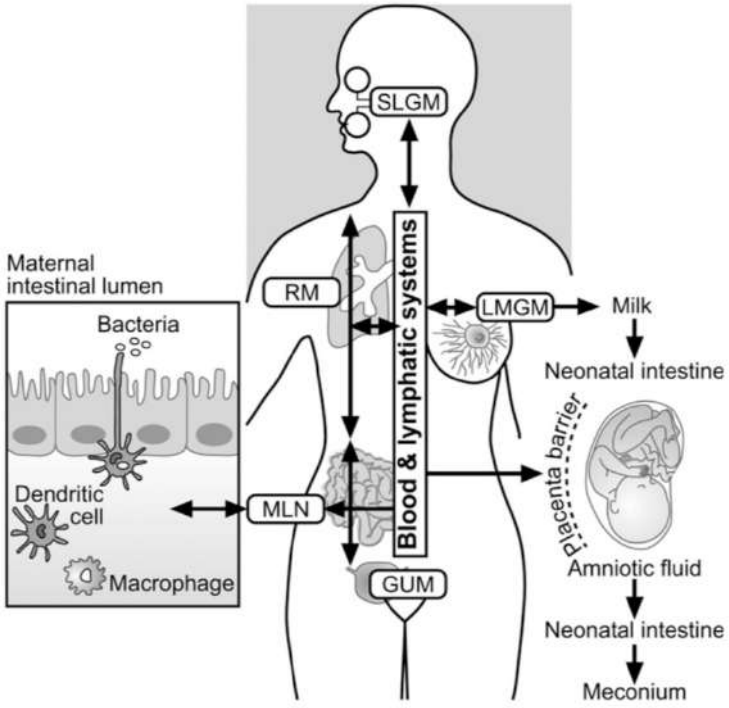

Figure 4. A hypothetical model of how maternal microbiota and microbial products may be transferred from mother to fetal's and neonatal's gastrointestinal tract

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

The role of obstetrician in reducing the risks of childhood allergy related to Caesarean birth: A literature review

Rima Irwinda[1], Febriansyah Darus[2], Peby Maulina[3]

1. *Department of Obstetric and Gynecology, Medical Faculty, Universitas Indonesia-Cipto Mangunkusumo National Hospital, Jakarta, Indonesia*
2. *Department of Obstetric and Gynecology, Gatot Soebroto Central Army Hospital, Jakarta, Indonesia*
3. *Department of Obstetric and Gynecology, Medical Faculty, Sriwijaya University, Palembang, South Sumatra, Indonesia*

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Abstract

Women's decision on birth mode should consider its risks and benefits, including long-term risks of Caesarean section among children. This study aims to present the current available evidences on the risks of Caesarean towards childhood allergy and how an obstetrician could prevent this outcome through nutrition and education. We searched articles from several online databases about the link between Caesarean, childhood allergy, and prenatal intervention. There were significant risks of childhood asthma and food allergy, but it was still unclear for allergic rhinitis and atopic dermatitis. Nutritional intervention could be done for pregnant women with consumption of probiotics and vitamin D supplementation. In addition, prenatal education is necessary to prepare better childhood outcomes.

Keywords: Caesarean section, prenatal education, children, obstetrician

Introduction

There is an increasing number of Caesarean deliveries throughout the world, including in Indonesia. In 2018, the rate of Caesarean delivery in Indonesia was 17.6%,[1] slightly higher than World Health Organization (WHO) recommendation rate which was around 10–15%.[2] Initially, Caesarean section (C-section) is performed due to life-threatening conditions towards mother and/or fetus. However, in present times, women have options to request for C-section, not necessarily related to medical indications. It is assumed that Caesarean delivery on maternal request (CDMR) is rising and contributes to the high rate of C-section. In US, the CDMR is estimated at 2.5% of all births.[3] In Indonesia, there had not been any studies which estimated the nation-based CDMR rate. Nevertheless, a study conducted in tertiary hospitals in Indonesia found that approximately 3.7% were performed on maternal request.[4]

The potential health risks of C-section in the short- and long-term, for mother, child, and subsequent pregnancies, have been widely discussed. Women who birth by C-section have higher risk for post-partum infection, thromboembolism, and even death, as short-term risk.[5] While in the long run, there are increasing risks of subfertility, ectopic pregnancy, placenta previa, placenta accreta, placental abruption, uterine rupture, and stillbirth, in subsequent pregnancy.[6]

Corresponding author:
Dr. dr. Rima Irwinda, SpOG(K)
Department of Obstetric and Gynecology
Medical Faculty, Universitas Indonesia
Email: rima.irwinda@yahoo.com

Additionally, children born by C-section have higher risk for asthma, overweight, obesity, and type 1 diabetes.[6] Nevertheless, C-section is not the only factor that contributes to child's allergy. Maternal factors, such as maternal obesity, gestational weight gain, maternal allergy, antibiotic use, and type of food consumption by the child, also modulate the risk of allergy in offspring.[7]

These health risks must be effectively delivered to mothers before deciding on the birth delivery mode. Prenatal care holds important role in preparing childbearing women for birth and to teach them about risks and benefits of C-section. Obstetricians play a key role in prenatal care, in giving advice and intervention to prevent unnecessary childhood outcomes in women choosing C-section method.

This article is part of Series on Caesarean Section. We aimed to describe the potential health risks of C-section on childhood allergy and the role of obstetrician in preventing this poor outcome by doing nutrition and education interventions.

Methods

We identified articles through various channels, e.g. international surveys and reports, national database, along with articles from electronic search engine. We searched for the frequency and trends of childhood allergy among those delivered via C-section, and also prenatal intervention to prevent it. Given the possibility of limited data, we include all type of articles and did not limit the publication year in our searching.

Results and Discussion

This review is classified into three main topics: 1) Risks of C-section towards childhood allergy; 2) Nutritional intervention; and 3) Prenatal education to prevent childhood allergy in infants born through C-section.

Risks of C-section on childhood allergy

Allergic disorders affect more than 30% of the children, and the prevalence of these diseases has been on the rise in recent years.[8] Major allergic diseases include asthma, rhinitis, atopic eczema, food allergy, and acute urticaria. These allergic diseases are complex multifactorial disorders, resulting from the combination of genetic and environmental factors.[9] Positive family history is one of the major risk factors for childhood allergic disorders. A child with maternal asthma has an odd risk of 2.26 (95% CI: 1.24–3.73) to develop childhood asthma, and higher risk (OR: 2.30; 95% CI: 1.17–4.52) if both parents had asthma.[10] Similar with other allergic diseases, if only father or mother had atopic dermatitis, the prevalence rate ratio was 1.9 (95% CI:0.3–11.8) and 1.5 (95% CI:0.4–5.5). The risk would increase to 2.3 (95% CI:0.4–13.7) if both parents affected.[11]

There is a hypothesis that the composition of gut flora in babies delivered through Caesarean are different than those through vaginal deliveries.[12,13] This could affect the initial colonizing events in infant's intestine, which could prolong immunological immaturity and potentially increase the risk of childhood allergic disorders. Caesarean babies undergo different procedure from babies born through vaginal deliveries. They are not directly exposed to maternal flora, therefore there is reduction of colonization in some bacteria, such as *Bacteroides fragilis* and *Bifidobacteria*, and increase in *Clostridia* and *Firmicutes*.[13]

Colonization rate of *Bifidobacterium*-like bacteria and *Lactobacillus*-like bacteria reached the rates of vaginally delivered infants at 1 month and 10 days, respectively. Infants born by Caesarean deliveries were significantly less often colonized with bacteria of the *Bacteroides fragilis* group compared with infants born through vaginal deliveries.[14] At 6 months the rates were 36% and 76%, respectively (p=0.009). The balance between *Bifidobacterium* and *Clostridium* species may affect immuno-physiological development, with a heightened risk for disease associated with fewer *Bifidobacterium* and more *Clostridium*.[15]

Our search found seven articles that discussed the association between delivery mode and childhood allergies. Table 1 presented the risk of developing asthma, allergic rhinitis, atopic dermatitis, and food allergies among children born by C-section. The highest risk with significant association was found in childhood asthma, followed with food allergy. While the risk for

allergic rhinitis and atopic dermatitis were still unclear. The articles searched are listed in **Table 1**.

Nutritional intervention

Nutrients from mothers are transported to the fetus across the placenta, including food allergens.[23,24] There is assumption that maternal diet during pregnancy could affect fetal immune development. Intake of relevant dietary supplements, avoidance specific food allergens, and overall dietary pattern of pregnant mothers should be carefully considered. The World Allergy Organization guideline recommends the use of probiotics in pregnant women at high risk for allergy in their children.[25] However, guidelines from US National Institute of Allergy and Infectious Disease[26] and the European Society for Pediatric, Gastroenterology, Hepatology, and Nutrition (ESPHGAN) do not support this.[27] The Australasian Society of Clinical Immunology and Allergy (ASCIA) recommends the consumption of oily fish up to 3 serves per week during pregnancy to prevent eczema.[28]

We searched for articles that include any maternal diet to prevent further eczema or asthma or allergic diseases in the offspring. Various type of diet was analyzed to determine the association with risk of allergy, i.e. prebiotics, probiotics, omega-3-fatty-acid, vitamin D supplementation, and avoidance of food allergens. In Table 2, we presented the effect of food supplement or nutrition intervention during maternal pregnancy towards the risk of childhood allergy. Overall, positive association was found between the use of probiotics and reduction risk of eczema or atopic dermatitis, with RR/OR below 1 (protective effect) for all included studies. Other positive correlation was seen in the consumption of prebiotic, omega-3-polyunsaturated-fatty-acid with food sensitization, fish oil, Mediterranean diet, zinc, vitamin D and E supplementation with the reduction risk of allergy in children. No evidence shows vitamin B and C supplementation, and avoidance of antigenic foods can reduce risk of allergy in children. Nevertheless, our review did not provide a thorough assessment on the specific type and amount of these nutrients. There are still more rooms to be explored in this field.

An association between low serum Vitamin D levels and the development of allergic diseases had been reported but this may not be causal. Besides that, in terms of allergic prevention, vitamin D supplementation may have no role in the primary prevention of allergic diseases. Moreover, increased Vitamin D supplementation in pregnant women did not confer protection against allergic diseases in their children had been reported by two recent randomized trials.[45] The articles searched can be seen in **Table 2**.

Educational intervention

Understanding the risk of Caesarean delivery and its possible effects upon mother and child is one of the basic knowledges that pregnant women should know. There are various non-clinical interventions, with health education as the core intervention to reduce birth with C-section.[56] Risks and benefits of Caesarean delivery should be informed before decision on birth mode is taken. Chen et al noted that health education provided by Obstetrician could reduce the risk of elective C-section from 66.8% to 53.7%.[57] Numerous studies also found that effective prenatal education would lead to better preparation for childbirth, including to reduce unnecessary C-section.[57] Other factors that also need to be taken into consideration for future review and researcher are related to the population of working mothers.[58] Economic burden of C-section born babies were also other health related indicator that need to be consider as points to be further discuss and analyzed in the future researches and reviews.[59,60]

We acknowledge that there are limitations to this review. The knowledge and competency development among birth attendants, including midwives and obstetric gynecologist are points that need to be thoroughly reviewed in order to get the full perspective on how medical practitioners could also plays role in mother's decision making on delivery mode. The viewpoints, knowledge update as well as education retention were mandatory to be discussed in future research.[61,62] The articles were not identified through a systematic searching strategy. Useful information and unpublished studies might have been missed. Nevertheless, we aim for studies which have best methodology, i.e. systematic review and meta-analysis. Additionally,

we did not perform critical appraisal for the included articles, and thus, we did not know the quality of these studies.

Conclusion

This review presents the potential risks of C-section on childhood allergies. Obstetrician holds a key role in providing information on nutrition and health education for pregnant mothers. Childhood asthma and food allergy were found to have positive association with C-section delivery mode. Consumption of probiotics, prebiotic, omega-3-polyunsaturated-fatty-acid, fish oil, Mediterranean diet, zinc, vitamin D and E supplementation are considered to be effective in reducing childhood allergies. However, further research still need to be done to understand the complex mechanism of how C-section could induce childhood allergies, and more interventions could be explored to prevent them.

Table 1. Risk of Caesarean delivery on childhood allergy

Author	Publication Year	Study Design	Respondents	Outcome OR/RR (95% CI)
Asthma				
Chu S et al[16]	2017	Cross-sectional	17,571 children	1.63 (1.18–2.24)
Renz-Polster H et al[17]	2005	Retrospective cohort	8,953 children	1.24 (1.01–1.53)
Huang L et al[18]	2014	Meta-analysis	26 studies	Overall risk: 1.16 (1.14 –1.29) Elective CS: 1.21 (1.17–1.25) Emergency CS: 1.23 (1.19–1.26)
Darabi et al[19]	2019	Meta-analysis	37 studies	Overall risk: 1.20 (1.15–1.25) Elective CS: 1.23 (1.20–1.26) Emergency CS: 1.18 (1.07–1.29)
Bager P et al[20]	2008	Meta-analysis	26 studies	1.18 (1.05–1.32)
Allergic rhinitis				
Chu S et al[16]	2017	Cross-sectional	17,571 children	1.18 (1.00–1.40)
Loo EXL et al[21]	2017	Prospective cohort	1,237 pregnant mothers	Infant aged 18 months: Adjusted OR: 0.8 (0.4–1.4) Infant aged 36 months: Adjusted OR: 0.8 (0.5–1.2) Infant aged 60 months: Adjusted OR: 0.9 (0.6–1.5)
Bager P et al[20]	2008	Meta-analysis	26 studies	1.23 (1.12–1.35)
Atopic dermatitis				
Renz-Polster H et al[17]	2005	Retrospective cohort	8,953 children	0.94 (0.75–1.19)
Bager P et al[20]	2008	Meta-analysis	26 studies	1.03 (0.98–1.09)
Food allergy				
Renz-Polster H et al[17]	2005	Retrospective cohort	8,953 children	1.34 (0.54–3.29)
Bager P et al[20]	2008	Meta-analysis	26 studies	1.32 (1.12–1.55)
Koplin J[22]	2008	Systematic review	4 studies	Increased risk of IgE mediated sensitization to food allergy in children born by CS

Table 2. Effect of maternal diet during pregnancy to reduce allergy risk in children

Author	Publication Year	Study design	Respondents	Risk of eczema/ atopic dermatitis	Risk of asthma/wheeze	Risk of food allergy / sensitization	Risk of allergic rhinitis
Probiotics							
Garcia-Larsen V et al[29]	2018	Meta-analysis	89 trials and 92 observational studies	0.78 (0.68-0.90)			
Zuccotti G et al[30]	2015	Meta-analysis	17 studies, 4755 children	0.78 (0.69-0.89)			
Cuello-Garcia CA et al[31]	2015	Meta-analysis	29 studies	0.71 (0.60-0.84)	0.94 (0.72-1.23)	1.08(0.73-1.59)	0.86 (0.44-1.70)
Li L et al[32]	2019	Meta-analysis	28 studies	0.67 (0.54-0.82)			
Zhang G et al[33]	2016	Meta-analysis	17 trials, 2947 infants			1.01 (0.66-1.55)	
Azad MB et al[34]	2013	Meta-analysis	20 trials		Asthma: 0.99 (0.81-1.21) Wheeze: 0.97 (0.87-1.09)		
Dang D et al[35]	2013	Meta-analysis	14 studies	0.69 (0.62-0.78)			
Pelucchi C et al[36]	2012	Meta-analysis	14 studies	0.79 (0.71-0.88)			
Prebiotics							
Cuello-Garcia C et al[31]	2017	Meta-analysis	6 studies	0.68 (0.40-1.15)	0.37 (0.17-0.80)	0.28 (0.08-1.00)	
Dang D et al[35]	2013	Meta-analysis	3 studies	0.80 (0.54-1.18)			
Omega-3-polyunsaturated fatty acid (fish oil)							
Garcia-Larsen V et al[29]	2018	Meta-analysis	89 trials and 92 observational studies			Sensitization to egg: 0.55 (0.40-0.76) Sensitization to peanut: 0.62 (0.40-0.96)	
Best KP[37]	2016	Meta-analysis	10 cohorts and 5 RCTs	0.53 (0.35-0.81)		Sensitization to egg: 0.55 (0.39-0.76) Sensitization to any food: 0.59 (0.46-0.76)	
Gunaratne AW[38]	2015	Systematic review	8 trials	Risk of any allergy below 36 months: 0.66 (0.41-0.98)			

Author	Publication Year	Study design	Respondents	Risk of eczema/ atopic dermatitis	Risk of asthma/wheeze	Risk of food allergy / sensitization	Risk of allergic rhinitis
				Risk > 36 months: 0.96 (0.84-1.09)			
Vahdaninia M et al[39]	2019	Meta-analysis	10 RCTs			Sensitization to egg: 0.54 (0.32-0.90) Sensitization to peanut: 0.62 (0.40-0.96)	
Klemens CM et al[40]	2011	Meta-analysis	5 RCTs		0.35 (0.15-0.79)	Sensitization to egg: 0.33 (0.16-0.70)	
Mediterranean Diet							
Biagi C et al[41]	2019	Systematic review	5 cohort studies, 2 cross-sectional		Persistent wheeze: aOR: 0.22 (0.08-0.58) Atopic wheeze: aOR: 0.30 (0.10-0.90) Current wheeze: OR: 0.71 (0.53-0.97)		
Zhang Y et al[42]	2019	Meta-analysis	18 observational studies		Wheeze ≤ 12 months: 0.92 (0.88-0.95) Asthma: 1.01 (0.94-1.09) Current wheeze: 0.76 (0.45-1.29)		
Nurmatov U et al[43]	2011	Meta-analysis	62 studies		0.22 (0.08-0.58)		
Vitamin D							
Shen SY et al[44]	2018	Meta-analysis	4 studies		Asthma at ≤ 5 years: 0.89 (0.77-1.04) Wheeze: 0.66 (0.53-0.82)		
Yepes-Nuñez JJ et al[45]	2017	Systematic review	1 RCT	0.96 (0.57-1.61)	1.12 (0.50-2.54)	1.92 (0.57-6.50)	0.76 (0.31-1.85)
Beckhaus AA et al[46]	2015	Meta-analysis	5 cohort studies		0.58 (0.38-0.88)		
Li W et al[47]	2019	Meta-analysis	6,068 participants		0.68 (0.55-0.83)		
Venter C et al[48]	2020	Meta-analysis	17 RCTs, 78 observational studies		0.72 (0.56-0.92)		
Vahdaninia M et al[49]	2017	Meta-analysis	5 RCTs		0.81 (0.67-0.98)		

Author	Publication Year	Study design	Respondents	Risk of eczema/ atopic dermatitis	Risk of asthma/wheeze	Risk of food allergy / sensitization	Risk of allergic rhinitis
Nurmatov U et al[43]	2011	Meta-analysis	62 studies		0.56 (0.42-0.73)		
Fish consumption							
Zhang G et al[50]	2017	Meta-analysis	1 RCT, 13 cohort studies	0.88 (0.75-1.04)	Wheeze: 0.94 (0.83-1.07) Asthma: 0.94 (0.75-1.18)		0.95 (0.62-1.45)
Song H et al[51]	2017	Meta-analysis	15 prospective studies		0.87 (0.75-1.02)		
Avoidance of antigenic foods							
Kramer MS et al[52]	2012	Systematic review	2 trials	1.01 (0.57-1.79)	2.22 (0.39-12.67)		
Vitamin E							
Wu H et al[53]	2018	Meta-analysis	10 studies		Asthma: 0.97 (0.95-1.00) Wheeze: 0.65 (0.56-0.75)		
Beckhaus AA et al[46]	2015	Meta-analysis	7 cohort studies		0.54 (0.41-0.71)		
Nurmatov U et al[43]	2011	Meta-analysis	62 studies		0.68 (0.52-0.88)		
Vitamin A							
Beckhaus AA et al[46]	2015	Meta-analysis	7 studies	0.76 (0.46-1.26)	0.97 (0.68-1.37)		
Vitamin B							
Beckhaus AA et al[46]	2015	Meta-analysis	4 cohort studies	Folic acid (B9): 0.91 (0.76-1.09) Vitamin B2 0.86 (0.74-1.01)	Folic acid (B9) 0.91 (0.49-1.68)		
Crider KS et al[54]	2013	Meta-analysis	5 studies		Folic acid: 1.01 (0.78-1.30)		
Vitamin C							
Beckhaus AA et al[46]	2015	Meta-analysis	6 cohort studies	0.95 (0.69-1.31)	0.99 (0.48-2.04)		
Zinc							
Beckhaus AA et al[46]	2015	Meta-analysis	6 cohort studies		0.57 (0.40-0.81)		
Fruit intake							
Seyedrezazadeh E et al[55]	2014	Meta-analysis	2 cohort, 13 cross-sectional		Wheeze: 0.81 (0.74-0.88) Asthma: 0.84 (0.79-0.89)		
Vegetable intake							
Seyedrezazadeh E et al[55]	2014	Meta-analysis	1 cohort, 10 cross-sectional		Wheeze: 0.89 (0.81-0.98) Asthma: 0.88 (0.82-0.95)		

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ORIGINAL ARTICLE

Perspective of Caesarean section delivery and its health risks on children among Indonesian pediatricians

Ray Wagiu Basrowi[1*], Tonny Sundjaya[1], Nova Lidia Sitorus[1], Bertri Maulidya Masita[1]

1. *Danone SN Indonesia*

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Abstract

An increasing trend of C-section delivery In Indonesia was found from 2% in 1986 to 16% in 2012. This delivery method was introduced to save women and their newborn baby's life. On the other side, it can increase short and long-term health risks for children. This study aims to assess and give an overview of the perspective on pediatrician as medical specialist in managing children of the C-section delivery history. A survey was conducted on 89 Indonesian Pediatricians using an online questionnaire. It was found that most pediatrician chose combination partial hydrolyze milk combined with synbiotic (a combination of prebiotic and probiotic) combination as nutrition intervention to decrease the allergy risk on children with C-section delivery mode, and there is a need to emphasize information about short and long-term health effects of C-section, especially in causing gut dysbiosis and its mechanism, information on non-medical causes of gut dysbiosis to increase awareness of recommending right symbiotic to decrease allergy risk in children with C-section history.

Keywords: C-section, allergy, synbiotic, infants, pediatrician

Introduction

Caesarian Section, or often called as C-section delivery mode was introduced to save women and their newborn baby's life and become a major obstetric intervention in the late nineteenth century, from life-threatening pregnancy and child-birth related complications.[1] In C-section delivery mode, infant is not in contact with maternal vaginal and enteric contents.[2] According to the World Health Organization (WHO), a global incremental percentage of C-section about 10-15% in both developed and developing countries since 1985.[3] In Indonesia, an increasing trend from 2% in 1986 to 16% in 2012 was found.[4] From Indonesia's Basic Health Research (*Riset Kesehatan Dasar/Riskesdas*), C-section was found to be increasing from 9.8% in 2013 to 17.6% in 2018 from all childbirths.[5,6]

Despite the fact that the aim of C-section delivery mode is to save lives and reducing the maternal and neonatal mortality rate from life-threatening pregnancy and child-birth, it has health risks that can be seen directly (short term health risks) and long term health consequences on children health.[7] Short term health risks include altered immune development,[7-9] reduced intestinal gut microbiome,[7,9,10] and increased likelihood of allergy and asthma.[7,11] For the long term, it was founded that C-Section to be associated with a greater possibility of late childhood obesity[7,11] and possibly influence child cognitive development.[7,12]

Corresponding author:
Dr. dr. Ray Wagiu Basrowi, MKK
Science and Medical Affairs Department
Danone SN Indonesia
Email: ray.basrowi1@danone.com

Ideally, C-section should be performed when medically necessary.

The colonization of gut microbiota has an important role in the development of immune system in infants' early life,[8,9,13] some of the microbiota colonization associated with allergy that linked to infection so both may share protective environment interaction.[13,14] However, the initial gut microbiota of infants born by C-section differed from a vaginal delivery.[10,13] C-section delivery may cause a dysbiosis of the gut microbiota which challenges the normal development of an immune system and can be associated with an increased risk of developing an allergy.[9,14]

The consequences of C-section delivery mode might have an impact on the First 1,000 Days of life.[15] Good nutrition during pregnancy and early childhood plays a foundational role in enabling a child to grow, develop and reduce disease risk.[16,17]

This survey aimed to explore the perspective of pediatricians as a medical specialist in managing children born via C-section that related to the C-Section delivery mode and its health risks on children.

Methods

An online survey was conducted to 89 pediatricians from March to April 2020, using Google-form survey platform and distributed through email and followed up with direct interview. Respondents were recruited from Danone HCPs (Health Care Practitioners) database and obtain informed consent regarding the purpose and ethical consideration of the study.

The questionnaire consists of 12 multiple choice questions, divided to 4 demographic questions and 8 questions related to C-section delivery history and its health risks on children. Knowledge and attitude were also explored.[18,19] This questionnaire was adapted and referred to previous study, and addressing 5 topics such as C-section impact on children, gut dysbiosis cause, gut dysbiosis effect, the importance of 1000 days of life, synbiotic effect.[7,10,14] The data presented in descriptive report.

Results

All of the 89 respondents participated in this survey were pediatricians, 43% of them had less than 5 years of service and majority (63%) worked in government affiliated hospital. Most of the respondents (93%) reported that they have consulted on children with C-Section delivery history in the last 3 months, and mostly (65%) received C-section patient consultation for more than 10 patients. The demographic characteristics of the respondents can be seen in **Table 1**.

The understanding of respondent on the impact of C-section toward future health of babies varies from altered immune system (56%) and potential risk of gut dysbiosis (43%) (**Figure 1**). In **Figure 2**, most of respondents (77%) understand that babies born with C-section will potentially have bigger risk of allergy in later life. However, as shown in **Figure 3**, on the further question related to the other cause of gut dysbiosis apart of C-section, respondents aware that antibiotic usage (55%), pollution exposure (35%) and obesity (10%) were also potential causative factors.

Table 2 shows that majority of respondents (91%) were aware on an increased risk of allergy due to gut dysbiosis, as they were also aware that both allergy risk and gut dysbiosis could potentially caused by C-Section delivery method (82%). Specifically on the nutrition intervention, 71% of respondents agree to recommend the partial hydrolyzed formula with synbiotic could potentially decrease risk of allergy among infants born with C-section and not exclusively breastfed.

Discussion

Studies showed that the increased rate of Caesarean section delivery in the last decades potentially contributed to the rising allergy epidemic.[7,11] Finding of our survey showed that the pediatricians in Indonesia also understand this potential risk and even aware the underlying mechanism which was include the potential gut dysbiosis in digestive system and its link to the immune system development. Recent studies showed that C-section is associated with delayed colonization gut microbial which is aberrant short-term immune responses to the newborn infant, which was also a

greater risk of developing an immune disease such as asthma, allergies, laryngitis and gastroenteritis.[7,9,10] Children born by Caesarean delivery had a higher possibility in developing food allergy compared with children who were born vaginally.[9]

Study revealed that a baby born vaginally have produced more cytokines implicated in neonatal immunity also their intestinal microbiota plays a role in the development of immune system in early life.[10] However, it is still unknown whether C-section causes a long-term effect on the immune system of the offspring that contributes to compromised future immune health.[8] Therefore, it is prudent to understand the consequences of C-section for children among pediatricians to reduce the burden of pediatricians in its diagnosis and treatment.

Theoretically, the first initial gut microbiota was transferred from mother to infant through the birth channel, ideally via vaginal.[10,13] The early establishment of gut microbiota is required to develop the immune system of newborn infant.[13,14] However, the initial gut microbiota of infants delivered by C-section differed from vaginally delivered infants and resemble the skin microbiota (such as *Staphylococcus, Acinetobacter*) rather than the mothers' vaginal microbiota (*Lactobacillus*).[9,10] Differences in the delivery mode in terms of gut microbiota colonization may explain the higher risks of allergy in infants born by C-section as compare to born vaginally because they had a different composition of protective bacteria.[13,14] Moreover, infants born by C-section also lacked of the early initiation of breast milk or colostrum which supposed to be the best source of gut micro biota development factors.[8,9,10,13]

Our study found that the respondents recognized antibiotic use, pollution exposure and obesity can cause gut dysbiosis. Previous research has suggested that antibiotic usage in early life was associated with the development childhood allergy and asthma, moreover, from cohort study reported that 65% children had received at least one antibiotic prescription during the first year of life[20]. Antibiotic can disturb the gut microbiota, possibly perturbing the developing immune system. It impacts on early immune developing that will increase the risk of immunologic problem like an allergy.[8,9,21] There are number studies examined the antibiotic exposure increased the risk of pediatric atopic or asthma.[9,21] Current medical care promotes the use of antibiotics have to change the pattern of infectious disease and bacterial exposure in infancy that the use of antibiotics should be reduced.

Currently, there is growing evidence that air pollution (i.e. smoke) is a risk of the factor of development allergy or asthma symptoms in children.[9,22] A study reported that maternal who exposure to air pollutant during pregnancy, is associated with an increased risk of allergic disease. The results stated that childhood allergic diseases are triggered by air pollution in third trimesters pregnancy, it might the transmission of maternal microbiota has impeded.[22] The link of obesity and gut dysbiosis have shown that breast milk from obese mothers contains differed various microbial than normal-weight mothers.[9]

Understanding the effects of gut dysbiosis among infants born by C-section is key for potential nutrition intervention, including supplementation prebiotic, probiotic or synbiotic formula.[8,13] Most respondents recognized that the use of synbiotic can reduce the allergy risks in children with C-section history, they also acknowledged the importance of proper nutrition intervention on the first thousand days of life among children with C-section history to prevent fatal allergy. A previous study proved that the formula supplemented with synbiotic (scGos/lcFos and *Bifidobacterium breve M16-V*) has opportunities to modulate the gut health and reduce severity of atopic dermatitis in infants born via C-section[14]. Also another study confirmed the synbiotic can reduce atopic dermatitis severity and reduce the symptom of asthma in 1 year follow-up the infants[23].

Given the uncertainty of predicting risk for allergy in the early life of children, prevention is of utmost importance. Pediatrician in this study agreed to recommend the partial hydrolyzed milk that combined with synbiotic to decrease allergy risk for infants born via C-section who were not breastfed. The combination of prebiotic and probiotic is able to compensate for the infants to restore the delayed *Bifidobacterium* colonization. Previous studies indicate that some allergies can be obviated by using synbiotic.[13,23,24] The aspect of cost-effectiveness and health economics review should also need to be taken into account when it comes to nutrition

intervention.[25,26] Therefore the perspective of respondents of this study toward synbiotic with the partial hydrolyzed milk to infants born via C-section is evidence-based and rational with existing studies.

Nevertheless, we identify that the limited numbers of respondents, which was less than 100 participants, was the major limitation of this study. The subjectivity of respondents may as well interfere the objectivity of the study through online survey-based. The knowledge competency as well as updated education program should also need to be considered in future research, as study showed that retaining medical staff's knowledge and quality of care through training on specific skills is strongly needed and potentially influence the skill and competency.[27,28] It is important to conduct better structured survey with bigger sample size to identify the in-depth perspective, understanding and knowledge of Indonesian pediatricians toward C-section and its impact to long-term health.

Conclusion

Overall, the knowledge and understanding of pediatricians toward C-section methods and its impact on long-term health of children were mainly recognizing the aspect of increased risk of allergy and potential gut dysbiosis. Although other factors such as antibiotic use and pollution should also be considered. Given the recent increase in C-section cases and the threat posed by gut dysbiosis and allergy-induced in infants, it is essential that better intervention made in the provision of care for infants born via C-section. Opportunities for improvement available as acknowledge by the pediatrician in using combination partial hydrolyzed milk combined with synbiotic as a nutrition intervention to decrease the allergy risk on children with C-Section delivery mode who were not breastfed.

Table 1. Demographic characteristic of respondents

Variables	Pediatricians	
	n	%
Length of services		
<5 years	38	43
5-10 years	22	25
10-15 years	12	13
>15 years	17	19
Affiliation		
Private hospital	56	63
Government hospital	33	37
Ever consulted children with C-Section history in the last 3 months		
Yes	86	97
No	3	3
Number of children with C-section history consulted per months		
<10 patients/ month	31	35
>10 patients/month	58	65

Table 2. Knowledge and attitude of children's health risk and C-section delivery history

Variables	Pediatricians	
	n	%
Knowledge on increase of allergy risk in children due to Gut dysbiosis		
Yes	81	91
No	6	7
Don't know	2	2
Knowledge of allergy risk and gut dysbiosis caused by children with C-section delivery history		
Yes	73	82
No	15	17
Don't know	1	1

Table 2. Knowledge and attitude of children's health risk and C-section delivery history (continued)

Variables	Pediatricians	
	n	%
Importance of nutrition on first 1000 days and allergy risk in children		
Yes	87	98
No	1	1
Don't know	1	1
C-Section baby without breastfeed and usage of partial hydrolyzed milk combined with synbiotic to decrease allergy risk in children		
Yes	63	71
No	14	16
Doubt/ uncertain	10	11
Don't know	2	2

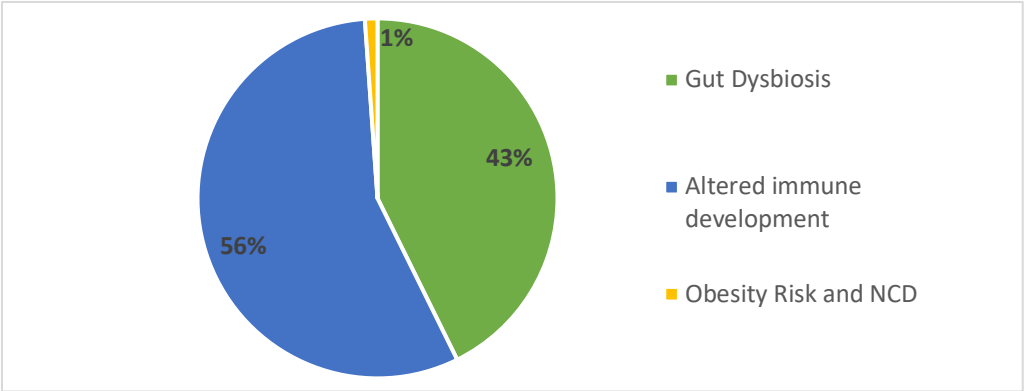

Figure 1. Knowledge of health risk of children with C-section history

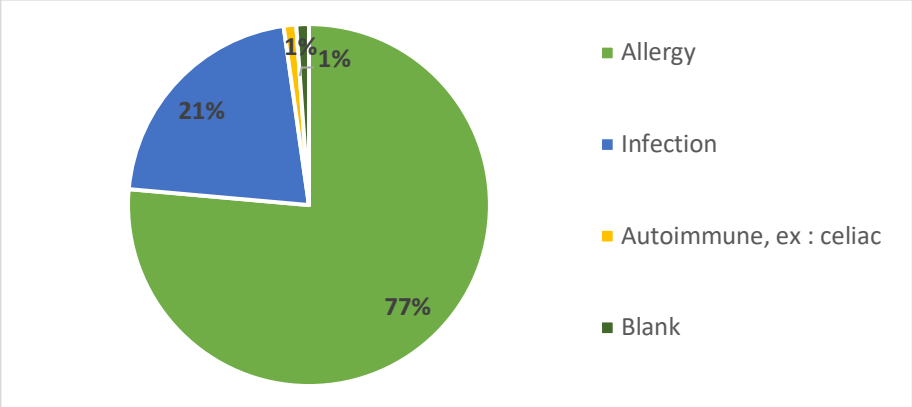

Figure 2. Knowledge on impact of children with C-section history to digestive and immune systems

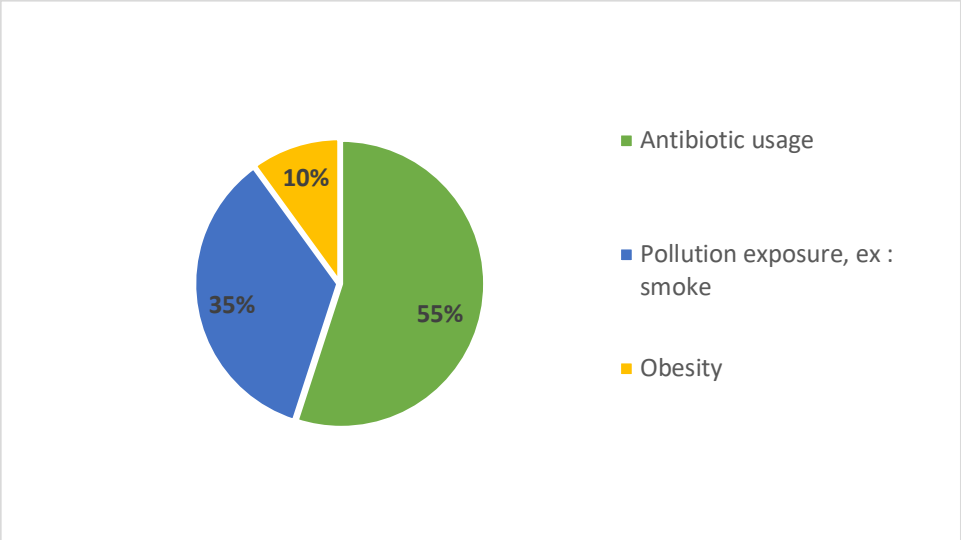

Figure 3. Knowledge on other causes of gut dysbiosis other than C-Section

Conflict of Interest

This study was funded by Danone SN Indonesia.

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