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Journal of Immunology & Clinical Research

Review Article

Mode of Delivery and Inflammatory Disorders

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Submitted: 10 July 2013

Accepted: 02 August 2013

Published: 14 August 2013

Keywords
- Mucosal inflammation
- Inflammatory disorders
- Cesarean

Abstract

Mucosal inflammation is characterized by mucosal recruitment of activated cells from both the innate and adaptive immune systems. In addition to immune cells impairment, it has been recognized that some of the inflammatory diseases can be associated with an alteration in gut microbiota and gut physiology. Although the change in enteric gut microbiota or their products is considered to be important in regulating gut physiology, it is not clear whether changes early in life can affect the offspring's susceptibility to develop inflammatory diseases. Due to the potential role of the mode of delivery in the gut colonization, Cesarean section (c-section) may play an important role in bacterial colonization and immune activation, and later in life, in the promotion of inflammatory conditions. Associated with the increased rate of c-section, this review addresses the research on the interface between the mode of delivery, development of gut microbiota and susceptibility of the offspring to develop inflammatory diseases. The studies reviewed in this article demonstrate that c-section modifies the gut microbiota composition and modifies the immune cells to produce pro-inflammatory mediators leading to increased susceptibility to inflammation. By selecting c-section in the decision of delivery mode, this may affect, later in life, the children's susceptibility to develop chronic inflammatory disorders.

ABBREVIATIONS: CD: Crohn's Disease; IBDs: Inflammatory Bowel Diseases; IL: Interleukin; INF: Interferon; TNF: Tumor Necrosis Factor; UC: Ulcerative Colitis

INTRODUCTION

The Cesarean section rate has been steadily rising in United States from 4.5% in 1965 [1] to nearly 33% [2] in 2010. In developing countries, such as China and Brazil, this number accounts for 40% and 45% [3], respectively. The high prevalence of the condition compared to the number of women in need of c-section (5 to 10%) suggests that the difference of approximately 30% is only a socio-economical trend without any clear medical indication. Unnecessary c-section increases the probability of short- and long-term complications in both neonates and mothers. For the mother, the later is associated with direct complications, such as infections, hysterectomy, blood clots, future infertility, as well as indirect complications ranging from ectopic pregnancy to uterine rupture. For the neonates, c-section is associated with health problems as will be described in this review.

Several studies attempted to identify the reasons for increased c-section rate in both developed and developing countries. These studies revealed that although there are minor differences among population, the number of c-sections has gone up in all subcategories including, but not limited to: the age at first birth, the health state, the number of babies and the ethnicity [4]. Therefore, this increase in favor of c-section cannot just be attributed to the mothers' desire or to the practitioners. A national survey of U. S. women who gave birth in 2006 demonstrated that only 0.06% of the mothers have declared to have c-section on their request without any medical reason [5]. This survey further indicated that 25% of mothers experienced pressure from the health practitioner to undergo c-section [5]. It is possible that fear of error and malpractice liability may have driven this increase, however, this effect does not account for the possibility of a natural increase [6]. Other factors contributing to the high c-section rate can be divided into the following four categories: a) Common labor interventions (continuous fetal monitoring, labor induction when cervix is not ready); b) Uninformed choice of vaginal delivery; c) Economical reasons (hospital work organization, financial incentives); d) Limited awareness of adverse effects related to c-section. Taken together, these data suggest that the environment surrounding the expectant mother shapes the choice of the mode of delivery and may contribute to the current high c-section rate in some countries, despite evidence demonstrating that offspring are more susceptible to diseases.

The aim of this review is to demonstrate the overall impact of the mode of delivery on the long-term development of the gut microbiota, and subsequently, the susceptibility of the offspring to develop inflammatory disease during their childhood and adulthood.

C-section and Inflammatory diseases

Immediately after birth, the gastrointestinal associated lymphoid tissue and the mucosa transition from a sterile protected system to a bacterially colonized mucosa. When compared to regular vaginal delivery, c-section leads to a modified bacterial colonization of the newborn's intestine [7-11] (Figure 1). According to the "hygiene hypothesis", the increasing prevalence of allergic disease is mainly caused by a decreased exposure to certain microbial environments during early life. A defect in microbial priming may alter the development of the immune system; therefore, the immune system will be prone to promote the increased incidence of autoimmune disease and allergies [12,13]. Conversely, higher exposure to allergens decreases the risk of developing allergic disorders, which has been demonstrated by several epidemiological studies in the context of the use of daycare [14], pet ownership [15] and exposure to a farm environment [16] (Figure 1). Taken together, a limited exposure to bacteria as early as during the delivery may alter the bacterial first colonization, which may later affect the susceptibility of the offspring to develop inflammatory diseases. In this review some of the major inflammatory diseases will be discussed.

Gastroenteritis

Gastroenteritis is common infection of the stomach and the colon and most types are highly infectious. Bacteria, parasites or viruses may cause acute gastroenteritis, and patients may develop vomiting and diarrhea. A German study demonstrated that children (up to age 12 months), exclusively breast fed during the first four months of life and born *via* c-section from a parent with a predisposition to allergy had a 2-fold increase of reported diarrhea [17]. A Swedish study also reported c-section to be associated with a 30% increase in risk of developing gastroenteritis in young children [18]. Conversely, using large Danes cohorts, a recent study found that neonates under 5 years delivered by c-section had a 5% increased risk of developing intestinal bacterial infections when compared to vaginal delivery [19]. Form these three studies, it is not clear if the mode of delivery can affect the development of infections, therefore, more epidemiological studies from different countries need to be performed to exclude any societal effect, and data using experimental models could strengthen this hypothesis.

Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) are idiopathic chronic, recurrent intestinal disorders of complex pathogenesis, which include Crohn's disease (CD) and ulcerative colitis (UC). The estimated prevalence is **500/100,000** persons [20]. These diseases often present in adolescence or young adulthood and hence affected individuals have a long burden of disease with significant psychosocial, physical and economic impacts. In Canada, IBD represents a public health issue due to their impact on patient quality of life (estimated costs: $1.7 billion) [20,21].

The etiopathogenesis of IBD is multifactorial, involving an aberrant immune response to some environmental antigens in genetically predisposed individuals. The apparent therapeutic beneficial effect of biological therapy [tumor necrosis factor-(TNF-α) –neutralizing antibody] [22], corticosteroids and thiopurines, underscores the importance of the dysregulated immune response. However, some patients are resistant to these

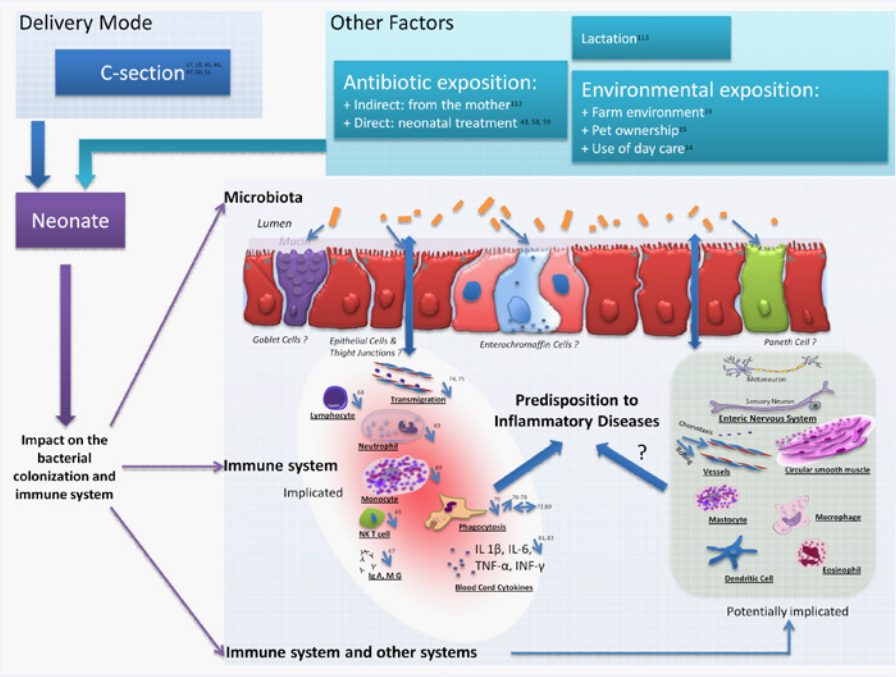

Figure 1 Immune system and other systems.

drugs, and all of these therapeutic agents have adverse side effects [23,24]. For the most ill patients, monoclonal antibodies to TNF-α are used. These agents are expensive; require indefinite use for maximal effectiveness, and concern for infectious and potentially even malignant complications [25] limit the enthusiasm for introducing these agents earlier in the treatment paradigm.

Over the last two decades, it has been shown that a complex network of events at molecular, cellular, and tissue levels underlie inflammation and remodeling that eventually lead to the development of IBD symptoms. Cell proliferation, migration and angiogenesis, are cardinal cellular events that are tightly regulated by various mediators and mechanisms in physiological conditions. However, environmental antigens exposure impairs regulatory mechanisms in IBD patients leading to pathological features including gut inflammation. Recently a lot of attention has been given to gut microbiota and its implication in the development of IBD. Several pieces of evidences demonstrate that a significant dysbiosis is associated with the inflammatory state of the gastrointestinal tract [26-28].

The gastrointestinal tract immunologically recognizes the external environment. The gut-associated lymphoid tissues generate either immunoinflammatory responses for rejection of potential pathogens, or an active immune response of tolerance for dietary and microbial antigens that does not induce clinically relevant inflammation [29]. Paradoxically, either diminished or exacerbated immune signaling might trigger the breakdown of intestinal homeostasis, leading to inflammation [30]. IBD is characterized by dysregulated immune responses towards the intestinal microbiome [30]. Either primary dysregulation of the mucosal immune system leads to excessive immunological responses to a normal microbiome, or changes in the composition and functional properties of the gut microbiome elicit pathological responses from a normal mucosal immune system [31]. The latter raised the hypothesis that an altered gut microbiome has a key role in the pathogenesis of IBD. Because the diversity of the gut microbiome has been shown to be reduced and markedly distinct in those with IBD [27,32], there is a large interest in the role of normal commensal flora in IBD etiology [33] (*e. g.* the *dysbiosis* hypothesis [26,28,34,35]). Moreover, antibiotic use has been shown to alter gut microbiome [36] and alterations have been shown to be long-lasting [36,37]. Murine IBD models demonstrate that colitis can be induced or ameliorated through alteration of microbiome *via* the use of different antibiotics [38,39]. Also, there is evidence suggesting an association between prior antibiotic usages and developing IBD in pediatric and adult-onset IBD [40-42]. In particular, researchers in Manitoba have shown that children with IBD were more likely than healthy controls to have received antibiotics in their first year of life [43]. Hence neonatal gut microbiome development may be critical for the ultimate development of IBD

Limited studies exist correlating the mode of delivery and the offspring's susceptibility to develop IBD later in life. To date (July 2013), only four papers refer to the mode of delivery and the increased risk of developing IBD. One of the first papers published on this topic described no correlation between the two factors [44]. In this context a case-control study was designed, birth data were recorded from patient diagnosed with CD (n=1096), UC (n=763) and healthy controls by a self-administrated questionnaire. However, a major part of the cohort was born before the increase of c-section rates and mostly adults over 40-years old were included; therefore, only a small number of participants delivered by c-section (UC=6%, CD=6.5%) were included. A second case-control study targeted a younger population (average age: 13 years) with (374 CD and 169 UC patient) [45]. In this study, patients with IBD were not more likely than healthy subjects to be borne by c-section.

Conversely, two studies suggested a significant association between c-section and IBD. The first publication demonstrated a correlation between the mode of delivery and the onset of CD [46]. The strength of this study relies on the large well-defined birth cohort used that allowed an examination of perinatal and child risk factor but also consideration of temporal changes over time. When examined according to perinatal characteristic, the CD incidence was associated with elective c-section. The authors demonstrated that the cumulative incidence of pediatric onset of CD was significantly higher in children born in 1992-1998 when compared to 1983-1991. It has to be noted that elective c-section, was documented as more prevalent in the 1992-1998 group; however, adjustment for this factor did not alter the difference in CD risk between the two periods, indicating that other factors are also increasing the overall incidence of CD. Finally, a Danish study revealed an association between the mode of delivery and CD and UC [47]. The authors used a cohort of more than 2 million persons born between 1973 and 2008 and demonstrated that persons born by c-section have a 14% increased risk of developing IBD before age of 36 compared to vaginal delivery, this risk reaches almost 30% in young children (<15 years). Indirectly, a recent study from our center demonstrated that the use of antibiotic during the first year of life is associated with increased risk of IBD in childhood [43], highlighting the importance of factors that can change the gut microflora early in life.

Taken together, the data indicate that depending on the country and the type of population studied, a significant relation may exist between the mode of delivery and the susceptibility to develop IBD later in life. More data from other countries need to be generated to confirm the role of c-section and the susceptibility to IBD. In parallel, although, animal microbiota does not represent the human microbiome, more data using experimental models need to be conducted to clarify the impact of c-section on the offsprings' susceptibility to develop intestinal inflammation.

Celiac disease

Celiac disease affects between 0.3 and 1% of the population [48]. It's a chronic form of enteropathy affecting the small intestine in genetically predisposed adult and children. Prerequisites for developing celiac disease are dietary exposure to gluten-containing foods or related prolamins and genetic susceptibility (HLA-DQ2 or DQ8 haplotype) [49]. In the context of celiac disease, a paracellular and/or transcellular translocation of gluten into the submucosa is associated with an alteration of the epithelial barrier, leading to an over activation lamina propria lymphocyte. Although this enhanced permeability occurs during the pathogenesis, it is possible that this event might occur earlier in life in those patients. Therefore, the potential delay of

colonization due to c-section might induce an early enhancement of epithelial permeability for antigens.

To date only two studies have described a potential correlation between the mode of delivery and celiac disease. The first, using a retrospective study based on 123 individuals, found a significant enhanced likelihood of being born by c-section in children with celiac disease compared to control subjects (odds ratio: 1.8 (95% confidence interval: 1.13-2.8) [45]. However, this study did not distinguish between elective and emergency delivery. During elective delivery-section, all the children avoid the maternal vaginal flora and the birth canal compared to emergency deliveries where c-section is performed after the protective amniotic membranes have ruptured. This allows for ascending colonization of the amniotic fluid with vaginal microflora; this colonization is biologically similar to that in vaginal deliveries. A more recent study found a positive association with elective c-section and celiac disease, confirming the potential importance of the first colonization and its role in the development of celiac disease. However, per se c-section does not influence the risk of celiac disease [50]. In this context, more studies need to be performed to determine the exact role of c-section in this context.

Allergic disorders and asthma

Most of the earlier studies trying to determine if there is a significant correlation between the mode of delivery and rhinoconjunctivitis and atopic dermatitis failed to do so and this can be attributed to the limitation of the population studied. In an early retrospective cohort study, Renz-Polster et al., studied 8953 children aged from 3 to 10 years and children diagnosed with allergic rhinoconjunctivitis, asthma, atopic dermatitis, or food allergies were identified [51]. The children's sex, birth weight, birth order, postnatal exposure to antibiotics as well as the mothers' age, ethnicity, education, marital status, smoking status during pregnancy, and use of asthma or hay fever medications were identified. Their results demonstrated that the risk of being diagnosed with rhinoconjunctivitis or asthma was significantly higher in children born by c-section than in those delivered vaginally. The latter condition was associated with a gender specificity related to girls. In this study, the authors demonstrated that 26% of children born by c-section were later diagnosed with allergic disease *vs* 22% of the children delivered vaginally. This small increase represents a substantial excess burden of morbidity. However, the authors were not able to find any association between mode of delivery and atopic dermatitis. The data were confirmed by a second study demonstrating a 30% increase in the risk for developing symptoms of asthma that led to hospital admission in c-section children older than 1year [18]. These results support the hypothesis that c-section might be associated with an increased risk for subsequent allergic manifestations in the child and that a dysbalance of intestinal colonization could be a common pathogenic factor. A number of different studies have demonstrated that the composition of the gut flora differs between allergic and normal children [52,53], as well as it has been described the importance of the normal intestinal microflora for the development of oral tolerance [54,55]. These results can be correlated with therapeutic clinical studies demonstrating the beneficial effect of oral supplementation of probiotic bacteria in allergic symptoms [56,57]. There is also evidence that early antibiotic treatment, disturbing the ecological balance of the gut microflora, could predispose to allergic disease [58,59]. Taken together these data suggest an association between allergic disease and a potential abnormal intestinal microbial colonization.

Mode of delivery and immune activation

For a decade now it has been suggested that c-section is the cause of a prolonged immunological immaturity [18,60-62] and susceptibility to various diseases [63-65]. However, there are a limited number of studies that have demonstrated the correlation between c-section and immune activation.

To date, the broader hypothesis relies on the assumption that the lack of challenge to the immune system may cause a dysbalance of T helper type 1/2 (Th1/Th2/Th17) cell responses, that ultimately modifies the development of antigen tolerance [66]. Several data suggest that the mode of delivery modifies the immunological balance of the newborn. Studies have identified differences in blood cord biomarkers following c-section when compared to vaginal birth [67]. During vaginal delivery labor leads to leukocytosis, which is selective for monocytes, natural killer (NK: $CD3^{-}/16^{+}/56^{+}$) cells [68,69] and also neutrophils [69-72]. In the absence of labor, neonates delivered by c-section have significantly less leukocytes [73], NK cells, neutrophils and monocytes in their blood cord [9,69]. Furthermore, cord blood leukocytes of babies born by c-section have lower *in vitro* transmigration ability and low expression of cell surface adhesion molecule CD11b/CD18 when compared to the leukocytes isolated from infants delivered vaginally [74,75].

To mount an effective immune reaction, phagocytosis plays a major role. In the context of c-section, the data are unclear. After c-section the phagocytic activity has been reported to be increased [76-78], decreased [79] or unchanged [72,80].

In addition, the leukocytes activity [74,75] through proinflammatory cytokine release can also be affected. Interleukin (IL) -4r, IL-1β, IL-6, and tumor necrosis factor (TNF) -α have been demonstrated to be lower after c-section [81,82] in blood cord. These data were almost confirmed in a study demonstrating a lower level of INF-g and C-reactive protein in the liver of piglets [83] delivered by c-section. However, these results are inconsistent with data demonstrating an opposite effect in TNF-α serum concentrations of piglets born by c-section. Nevertheless, a trend was found for lower levels of INF- g [84] and IL-6 [85].

Beside the cytokine profile the number of immune secreting IgA, IgM and IgG can be modified. During the first year of life, the total number of IgM, IgA and IgG secreting cells has been demonstrated to be higher in infants born by c-section compared to vaginal delivery, reflecting a decrease of antigen exposure [67]. These findings suggest that mode of delivery can alter gene expression with functional significance for the innate immune system.

C-section and Gut Microbiota

Beyond the first colonization and the postnatal period and into adulthood, the microbiome is necessary to induce regulatory mechanisms intended to keep both mucosal and systemic

immunity in balance. Many species of bacteria have been shown to have specific effects on the host. For example, segmented filamentous bacteria, which adhere closely to the intestinal epithelium [86], have been shown to induce Th17 responses [87] and increase the number of T_{reg} cells in both the small intestine and colon [88]. Polysaccharide A associated with *Bacterioides fragilis* is proposed to deactivate macrophages phagocytosis [89]. Mono-colonization with *Bacterioides fragilis* promotes T_{reg} cells and induces anti-inflammatory cytokine IL-10 production, which results in protection from chemically induced colitis [90]. Another key group of microbes are *Clostridium coccoides* and *Clostridium. leptum* (clusters IV and V respectively), which protect against IBD [91]. Additionally, mono-colonization with Clostridia (46 species from clusters IV and V) in Germ Free mice strongly promotes IL-10 producing T_{reg} cells [92].

Because intestinal bacteria have been implicated in IBD [93-95], increasing c-section practices might have an impact on the incidence and clinical expression of these diseases through altered intestinal colonization patterns early in life. It was commonly believed that during intrauterine development the fetal intestine is sterile. However, few studies have revealed that different species of bacteria, such as *Escherichia coli*, *Enterococcus faecium*, *Staphylococcus epidermidis*, and *Streptococcus* spp. can be present in the meconium and umbilical cord, suggesting the maternal gut bacteria can be translocated via the blood stream, and thus, initial colonization of the gut might have been started up even before birth [96-100]. However, there is still debate about this phenomenon [101] and it is not clear if the presence of bacteria in the intrauterine environment is systematic or exceptional, and if systematic, would these bacteria be able to colonize the infant's gut? and if yes, can these early colonizers have an impact on later stages of the development of the infant's gut microbiota? or their influence is overcome by rapid and vast colonization of the gut during the first few days of life after birth?

Following parturition, the two critical stages of intestinal bacterial colonization are in the first few days after birth and during weaning [11,102,103]. As the infant becomes exposed to the maternal bacterial flora of the birth canal during vaginal delivery, the rate of colonization increases [11] and within days the intestinal tract becomes colonized by large numbers of bacteria. Because of the differences in the structure and diversity of the vaginal and gut microbiota, the intestinal microbiota of the newborns would be very different from those of adults. The phylogenetic diversity of the gut microbiota are initially very low but during the first few months, changes in the anatomical structure and function of the intestinal wall, combined with the increase in the size of the digestive tract result in proliferation of new ecological niches that promote microbial diversity [104,105]. During this adaptation process most of the initial colonizers will be replaced by adult-like microbiota [101]. In the course of this process the core microbiota of the intestine become more stable and less sensitive to disturbances. The core microbiota of adults, which is mainly composed of Firmicutes (mainly represented by *Clostridium* spp., *Faecalibacterium* spp. , *Ruminococcus* spp. and *Lactobacillus* spp.) and Bacteroidetes (mainly represented by *Bacteroides* spp. and *Prevotella* spp), remains relatively stable for most of a healthy adult's life [106,107]. Other phyla, such as Actinobacteria (includes *Bifidobacterium* spp.), Proteobacteria (includes Enterobacteriaceae family), or Verrumicrobia (includes *Akkermansia* spp.), although present in low abundance, are equally important and play key roles in the functional stability of the gut microbiome [106,107]. Of course, variations in the composition, proportion and functional properties of the intestinal microbiome would exist among individuals. Some of these variations are probably originated from the initial development of the microbiota at birth, and are influenced later by dietary and environmental factors [108], which ultimately shape adults susceptibility to inflammatory disorders and infectious diseases throughout the life.

Mode of delivery has been demonstrated to have a strong influence on early gut colonization. Newborns delivered by c-section are not exposed to maternal vaginal and fecal bacteria at birth, but mainly to skin bacteria [11], therefore, the normal colonization pattern is disturbed [7-11,109]. As such, it is observed that the gut microbiota of vaginally delivered newborns is dominated by *Lactobacillus*, *Prevotella*, and *Sneathia,* which are reflective of vaginal microbiome, while the microbiota of newborns delivered by c-section are dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium*, which are predominant on the surface of skin [110,111]. Although the life-long implications of the composition of the intestinal flora in the newborn are unknown, it has been suggested that disturbed colonization patterns might favor outgrowth and persistence of pathogenic bacteria, compromising mucosal barrier function leading to excessive bacterial translocation, or a microbiome dysbalance between protective and "harmful" bacteria. Thus, colonization with *Bacteroides* species is delayed at least 1 year among children delivered by c-section compared with children delivered vaginally [7,8,109], which might affect the child's subsequent risk of IBD. Accordingly, children and adults with active IBD have been reported to have a deficit in mucosa-associated *Bacteroides* species compared with control patients [94,95].

CONCLUSION

Birth is a critical time that will impact the functional stability of the gut microbiota and immune system for the rest of our life. Through this review we highlighted the conflicting literature regarding the relation between the mode of delivery and the offspring's susceptibility to develop inflammatory diseases later in life. Beside the mode of delivery other factors can also influence the development of the immune system and the first gut colonization. For example, prenatal maternal antibiotics used to treat infections in the mother/neonate or postpartum antibiotics used to prevent suspected sepsis in the infants have catastrophic impact on the gut and vaginal microbiomes and thus can impact the proper colonization of the gut after birth and influence the interactions between the host and the microbes. Data have demonstrated that maternal antibiotics are associated with an increased risk of necrotizing enterocolitis [112] and as already presented, antibiotics during the first year is associated with increased risk of IBD in childhood [43].

Besides the use of antibiotics, breastfeeding can also influence the gut colonization patterns. Gut microbiota in breast-fed infants display a dominance of *bifidobacteria*, whereas formula-fed infants show a broader microbiome [113]. This can be attributed

to the richness of oligosaccharide components present within the milk [114]. Breast milk can also be the source of colonizing bacteria for the infants [115], and bacteria content can differ depending on the mode of delivery. Mothers giving birth by elective c-section have an increased level of *Carnobacteriaceae* and a decreased levels of *Leuconostocaceae* when compared to those who gave birth through vaginal deliver [116].

As discussed, intestinal colonization by the microbiota between the first few days after birth through the next four years of life represent a critical control point during which immune tolerance and disease susceptibility develop as a result of responses to enteric bacteria. Mode of delivery has a strong influence in the first gut colonization, which will impact the lifelong stability of the microbiome and thus susceptibility of individuals to inflammatory diseases. Overall, c-section should be limited to medical reasons, for the benefit of the mother and the babies.

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Cite this article

Khafipour E, Ghia JE (2013) Mode of Delivery and Inflammatory Disorders. J Immunol Clin Res 1: 1004.