ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Maternal Prenatal, Perinatal and Postnatal Well-Being May Predict Risk of Celiac Disease

Disha Sharma[1], Moni Kumari[1,2], Ranjit Singh[2], Shifali Gupta[3], Parveen Bansal[4] and Malika Arora[1]*

[1]*Multidisciplinary Research Unit, Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, India*

[2]*Adarsh Vijendra Institute of Pharmaceutical Sciences, Saharanpur, UP, India*

[3]*Department of Pediatrics, Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, India*

[4]*University Centre of Excellence in Research, Baba Farid University of Health Sciences, Faridkot, Punjab, India*

***Corresponding Author:** Malika Arora, Multidisciplinary Research Unit, Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, India.

Received: February 16, 2021; **Published:** March 18, 2021

Abstract

Maternal wellbeing and history of abuse is associated with various risk factors. Children at high risk of various diseases may be benefitted from early identification and intervention. Maternal prenatal, perinatal and postnatal, factors are responsible for number of diseases and celiac disease is one of them. Celiac disease being genetic in nature is highly associated with health of the mother before birth, during delivery and after birth. Maternal eating habits, medicines used during pregnancy, microbiota, during pregnancy, age of gluten introduction in diet, mode of delivery, breast feeding, etc. are the major factors that affect the infant wellbeing in its neonatal stage and early childhood as well. These factors and their positive/negative association may be taken into consideration to design early intervention strategies for better well-being of child and mother, social benefit as well as to decrease the disease burden and economic gain. Hence keeping the above said points in mind, this manuscript has been compiled to critically discuss various prenatal, perinatal and postnatal factors and their association with risk of celiac disease development.

Keywords: *Breast Feed; Celiac Disease; Prenatal Factors*

Introduction

A direct relationship has been observed between the well-being of mothers and the development of their children at the time of their birth. The cognitive and physical development of infants may be influenced by the health, nutrition, activities, behaviour of their mothers during pregnancy and their pre-natal as well as post-natal health conditions. Various determinants such as genetic makeup, biological constraints generated by prenatal, perinatal and postnatal events as well as prior states of maternal health affects infant's health during the pregnancy period and even after delivery in early growth period. During pregnancy, maternal dietary behaviour, nutritional state and habits are likely to regulate and counter-regulate offspring's health. Early interventions and identifications of various diseases before birth or in early childhood not only enhance the health of children and the resources of families but also benefit the society by preventing and minimizing problems and their costly consequences. The immune system develops through interaction with the environmental factors and assumed that an early life event including foetal life plays a major role in it. Several studies have reported that early life events related to maternity, pregnancy, delivery and neonatal life influence the risk of developing Celiac disease (CD) later in the life of offspring's

[1-4].

Generally, Celiac disease (CD) is one of the most prevalent immune-mediated disease triggered by interplay of environmental and genetic factors [5]. As CD has a genetic component, so there is a greater chance that a child of a parent with CD may also develops the condition later in their life. If a mother has genes associated with CD, her child has a 50 percent chance of inheriting the genes. It has been observed that celiac disease develops approximately in 4 - 16% of children of those mothers who have been diagnosed with CD in their earlier life. CD commonly appears in early childhood; with typical symptoms of CD that is gastrointestinal-related symptoms such as diarrhoea, retarded growth and weight loss due to malabsorption. Since CD is a genetic disorder so maternal health affects CD to a higher extent. Maternal prenatal, perinatal and postnatal health conditions as well as activities needs to be examined properly in order to evaluate the risk of developing CD in offspring in their later life. Figure 1 represents overall maternal factors responsible for CD in offspring.

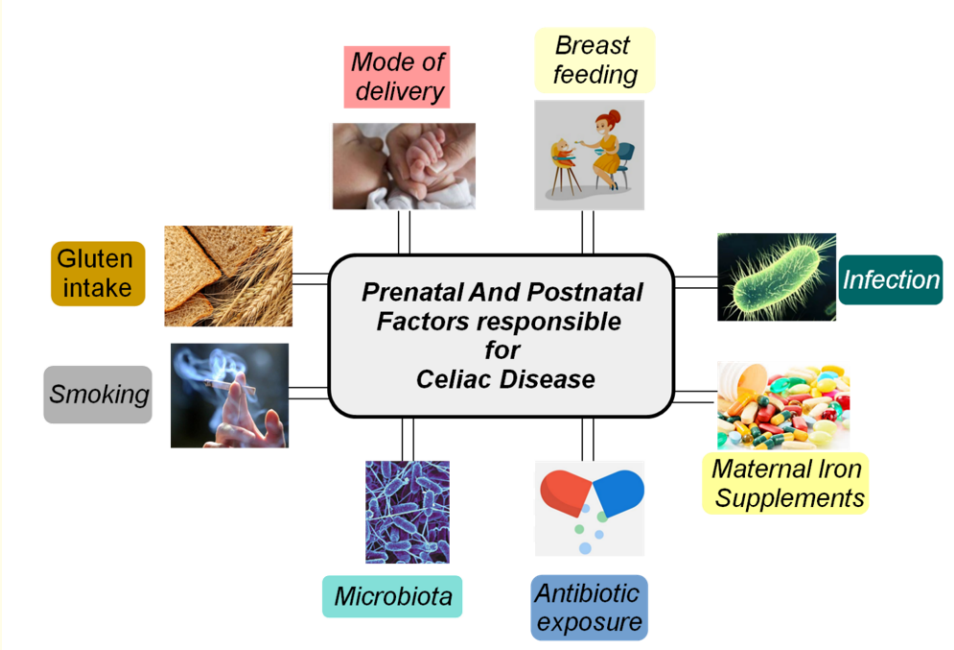

Figure 1: *Maternal factors responsible for CD in offspring.*

Till date there are number of studies that examined the effect of various prenatal, perinatal and postnatal factors responsible for CD but there is no compiled data available for the same at a single place. Hence authors intend to discuss all the current knowledge on prenatal, perinatal and postnatal factors in mothers and their children involved in CD pathogenesis at a single platform via this manuscript.

Prenatal factors

Prenatal events involve the development of the embryo and the foetus in mother's womb during the pregnancy and the factors which affect the growth of foetus and the health of mother are called prenatal factors of pregnancy. These factors include ingestion of gluten by CD affected mother, use of antibiotics and smoking during the time period of pregnancy which affects the development of infants.

Antibiotic exposure and its association with celiac disease

Antibiotics are one of the major environmental stressors which lead to the substitution of symbiotic bacteria by other under-represented potentially opportunistic bacteria responsible for onset of various diseases. Infant's gut colonization begins perinatally and is highly affected by maternal microbiota [6] and so antibiotic exposure to mother during pregnancy also causes disturbances in gut microbiota of their offspring [7]. These disturbances persist in the infant for several years. The use of antibiotics causes intestinal dysbiosis, reduced faecal diversity of microbiota and triggers early onset of disease [8]. There are number of studies that represent antibiotic-associated dysbiosis. In one of the studies antibiotics enhanced the elimination rate of *Bifidobacterium longum* and promoted the growth of *Bacteroides fragilis* [9]. In another study by Mårild K., *et al*. in 2014, no statistically significant association was found between antibiotic exposure during pregnancy and celiac disease in offspring [10]. The type of antibiotic given to mother during pregnancy is associated with the infection she develops at that time. So rather than antibiotics, the developed infection may also play a major role in immune programming of foetal as well as their risk of developing autoimmune disease. It is well known that probiotic/healthy microbiota helps in development as well as maturation of individual's immune system. So, if dysbiosis of healthy microbiota takes place due to use of antibiotics in mother during pregnancy, it will surely disturb the microbiota of offspring that may in future lead to improper immune system of offspring and development of various disorders such as CD. Study by Sander SD., *et al*. 2019 showed that, hospital acquired infection and use of antibiotics as a result independently increases the risk of CD through its effect on the gut microbiota [11]. Studies by Marild K., *et al*. 2013 and Canova C., *et al*. 2014 showed direct association of CD with dose-dependent effect of antibiotics [12,13]. Maternal infections treated with long term course of antibiotics showed increased risk of CD in their offspring's. In their study, penicillin V was found to be responsible for higher risk of CD. Cephalosporins being broad spectrum antibiotic can cause more damage to microbiota in comparison to other antibiotics. It has been observed that the dysbiosis of maternal microbiota occurs in the presence of antibiotics and their microbiota starts depleting. Probiotics such as *Lactobacillus* and bifidobacterial gets outnumbered by pathogenic bacteria which leads to indigestion of gluten peptides. The intestinal tight junction also gets loosened which allows passing of undigested gluten peptides through intestinal tight junction towards lamina propria. Inside lamina propria, the undigested gluten is identified as pathogen and so gluten specific immune responses get activated leading to intestinal inflammation and tissue destruction which finally causes gluten intolerance. The effect of antibiotics on intestinal microbiota of mother is shown in figure 2.

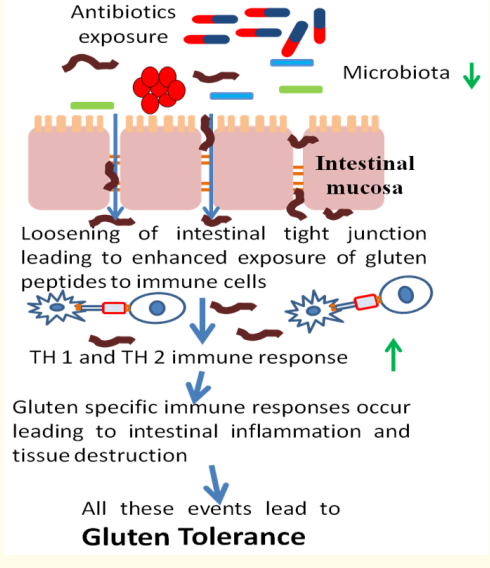

Figure 2: *Maternal microbiota during antibiotic exposure.*

Maternal gluten intake and its association with CD in offspring

Gluten is the significant environmental culprit for onset of CD. A person suffering with CD, especially the women who is pregnant should follow the strict gluten-free diet. During pregnancy, if she consumes gluten in her diet, the disease will get activated leading to assimilation of nutrients in both mother and child. Pregnant women with active celiac disease commonly lead to miscarriage or infertility. Till date there is no study that can conclude the exact role of gluten intake during pregnancy and its association with development of CD in offspring in their later life [14]. However, the mechanism is still unknown for the association of diet with CD during pregnancy, instead studies suggest that mother's diet during pregnancy is a major contributing factor for immune related disorders in their offspring. Maternal diet highly influences the immune system development of their offspring and thus can be a reason for onset of immune related disorders such as CD. Uusitalo., *et al*. in 2015 observed that the frequency of gluten-containing food consumption during late pregnancy is not directly associated with risk of celiac disease in the offspring, however the diet might have immune-modulating effect [14]. In another study by, Nicolai., *et al*. in 2020, it was observed that gluten intake by pregnant women increases the risk of CD in their offspring [15]. So, gluten diet should be avoided by pregnant women during pregnancy and further may be extrapolated to highlight the role of gluten diet in developing the CD in the offspring of already diseased mothers.

Maternal iron supplementation during pregnancy and risk of celiac disease in children

Globally iron deficiency during pregnancy is a major health threat in fertile women with increased morbidity, low birthweight, risk of miscarriage/stillbirth and impaired development in the infant [16]. To overcome the same, iron supplementation is recommended in such women. However, iron supplementation is not recommended routinely during pregnancy in countries like United Kingdom and Norway because of low prevalence of iron deficiency yet iron supplementation during pregnancy without its need has shown ill effects in their offspring. Iron supplementation through artificial iron sources have various adverse effects on the infant's health due to the availability of multiple additives in them [17]. It has been observed that if a mother sticks to natural sources of iron supplementation during her pregnancy, leads to decreased risk of CD in her child whereas it has been observed that routine supplementation of iron (synthetic sources such as drugs) to pregnant women increases the risk of celiac disease in their child. Størdal K., *et al*. (2014) performed a study and found that, celiac disease was more prevalent in children whose mothers were taking synthetic iron supplements during pregnancy in comparison to mother's who were not taking iron supplements [18]. They hypothesised that the reason for this association could be direct involvement of iron on adaptive and innate immune system. Iron supplementation can generate immune responses against food antigens. Iron accumulation in macrophages activates these immune responses into a pro-inflammatory M1 phenotype which enhances autoimmune conditions and chronic inflammation [19].

Smoking: Smoking is a well-known factor that affects maternal health as well as the health of their offspring. Smoking during pregnancy causes baby being born with various birth defects. To understand the effect of maternal smoking on offspring, Sandberg., *et al*. in 2002 performed a study and found weak positive association between CD and maternal smoking [20]. Abadie V., *et al*. in 2011 and Wingren CJ., *et al*. in 2012 also performed a study and found smoking was responsible for CD but was not independently responsible [5,21]. In addition, one study conducted by Jonas., *et al*. 2005 has highlighted the protective effect of smoking against CD in adults [22]. As far as maternal smoking is concerned, although the positive association has been evidenced yet the underlying mechanism has not been highlighted whereas no other study clearly indicates any such association. Smoking itself is injurious for health, so it is advisable that smoking must be prohibited during pregnancy and hence future research must be conducted on large groups that may verify exact association between CD and maternal smoking.

Perinatal factors: Perinatal period is the period just before and after birth which starts from 20th to 28th week of gestation and ends 1 to 4 weeks after birth. The factors that affect the mothers and offspring health during this period are called perinatal factors.

Season of birth/maternal infection and its association with CD

There are various maternal factors responsible for celiac disease in children, season of birth is one among them. Studies in the past revels that CD follows a seasonal pattern, and birth of Children during different seasons have different impact on the health of mother and her child. Different seasons may affect the prevalence of seasonal infections in pregnant women. It has been observed that healthy maternal intestine contains commensals and opportunistic bacteria in equal ratio. Commensals are known to help in digestion of gluten and related proteins. Thus, when intestine is healthy, gluten gests digested easily and no immune responses gets generated, while during infection probiotics gets eliminated by pathogens. The microbiota gets disturbed leading to improper digestion of gluten peptides. The undigested gluten disturbs intestinal tight junction barrier and travels to lamina propria. Within intestine, these are identified as pathogens by antigen presenting cells leading to generation of autoimmune responses such as intestinal inflammation and tissue destruction which finally causes gluten tolerance. This altered maternal microbiota affects the formation of healthy microbiota in their offspring and thus offspring's microbiota also gets disturbed. The alterations of microbiota in infected mother in contrast to healthy mothers and its role in gluten tolerance are shown in figure 3.

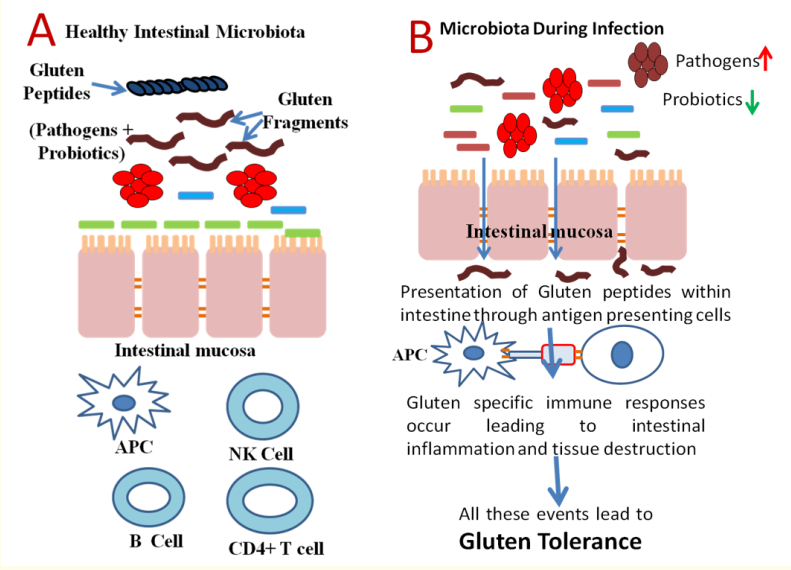

Figure 3: *Contrasting maternal microbiota during healthy condition and infection.*

Association between infection during various seasons and risk of development of CD in offspring has gained much attention recently but underlying mechanisms of seasonal variations are yet to be unfolded. However, Ivarsson., *et al*. in their study, reported that Swedish children below 2 years of age born in summer months of March to august has higher risk of CD than born in winter months because children born in summer season have been in uterus during winter time when chances of maternal infections are more [23]. But similar seasonal pattern was not found in children with CD diagnosed between 2 and 15 years of age. Other studies have also reported weak associations between paediatric CD and summer birth [4,24]. A study conducted in US found an association between spring birth and CD in boys diagnosed before 15 years of age [25]. Study by Marild K., *et al*. (2016) summarised the association between prenatal infection and CD risk in childhood but did not provide an overall risk estimate due to the limited amount of data [26]. Table 1 compiles various studies representing season of birth and its association with celiac disease.

S. No.	Year	Findings	Reference
1.	2003	An increased celiac disease risk in children born in the summer compared with the winter reflects causal environmental exposure(s) with a seasonal pattern.	[27]
2.	2006	A significant association between birth season and CD was not found.	[28]
3.	2009	Weak associations between paediatric CD and summer birth.	[29]
4.	2012	Weak associations between paediatric CD and summer birth.	[24]
5.	2013	Season of birth is an environmental risk factor for CD, particularly in boys diagnosed before age of 15 years. The results are consistent with a new theoretical model that integrates potential environmental factors (e.g. gluten introduction, ultraviolet-B exposure, vitamin D status) and acute viral gastrointestinal infections in early childhood. Significant association between birth season and CD was not found.	[25]
6.	2015	Summer birth was associated with a small increased risk of later CD.	[30]
7.	2016	Season of birth and region of birth are independently and jointly associated with increased risk of developing CD during the first 15 years of life. Seasonal variation in infectious load is the likely explanation.	[31]

Table 1: *Chronological studies on season of birth/maternal infection and its association with CD [33-40].*

Mode of delivery and its impact on CD in offspring

The mode of delivery highly affects the offspring's microbiota. There are various studies which represents direct association between offspring's microbiota and mode of delivery. The number of caesarean deliveries has been increased in the last few decades and the prevalence of CD becomes doubled. Caesarean delivery is associated with altered gut microflora in the child. Individual with CD have different microflora as compared to healthy individual and may contribute to impaired oral tolerance and abnormal mucosal immunity in CD individuals. In 2010, Decker., *et al*. reported increased risk of celiac disease after caesarean delivery in their retrospectively collected study [1]. Karl Marlid., *et al*. in a population-based nationwide study concluded that there is a positive association with later CD and caesarean delivery in elective, but negative association in emergency case of caesarean delivery [3]. The bacterial flora of the new-born also plays an important role in the development of celiac disease. The observation from different studies showed that babies born through caesarean section have an increased risk of developing CD in comparison to those born by vaginal delivery. Babies born vaginally predominantly acquire bacteria from maternal vaginal and perianal flora. The gut microbiota of vaginally delivered infants is similar to their mother vaginal microbiota compared to elective Caesarean born infants who have reduced microbial diversity and fewer Bifidobacterium species [32]. Table 2 represents mode of delivery and its association with CD.

S. No.	Year	Findings	References
1.	2009	A study from southern England reported non-significantly decreased risk of celiac disease for those born by caesarean section.	[2]
2.	2010	The mode of delivery and associated alterations in the development of the enteric homeostasis during the neonatal period might influence the incidence of celiac disease.	[1]
3.	2012	The positive association with elective, but not emergency, caesarean delivery is consistent with the hypothesis that the bacterial flora of the newborn plays a role in the development of celiac disease.	[3]

4.	2015	The risk of developing CD was significantly higher among children with type 1 diabetes than in the general Swedish population. The increased risk of having a double diagnosis of type-1 diabetes and CD was associated with being female, having a native Swedish mother, being born by Caesarean sections and being born in summer.	[4]
5.	2014	Showed that there was no association between elective caesarean section and celiac disease.	[13]
6.	2014	Children delivered by caesarean delivery had significantly increased risk of asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel disease, immune deficiencies, and leukaemia. No associations were found between caesarean delivery and type 1 -diabetes, psoriasis, or celiac disease. Caesarean delivery exemplifies a shared environmental risk factor in early life associating with several chronic immune diseases. Understanding commonalities in the underlying mechanisms behind chronic diseases may give novel insight into their origin and allow prevention.	[33]
7.	2015	There was no association between elective caesarean section and celiac disease.	[34]
8.	2016	Elective caesarean delivery and repeated maternal urinary tract infections during pregnancy are associated with increased risk of CD onset during childhood, suggesting the role of dysbiosis during early life. High maternal age and high income reduced the risk of CD, which might be due to infant-feeding practices and lifestyle.	[32]
9.	2017	In this cohort of children genetically predisposed to CD, the mode of delivery did not influence the risk of developing CD.	[35]
10.	2018	In this large registry-based study, mode of delivery was not associated with an increased risk of diagnosed celiac disease.	[36]
11.	2019	No association between peripartum antibiotics exposure or the mode of delivery and developing CD.	[37]

Table 2: *Chronological studies on mode of delivery and CD.*

Postnatal factors

Postnatal factors are those which affect the infant's health after the birth. These factors include gluten intake by child, breast feeding and microbiota composition.

Breast feeding: Breast milk is the natural nutrition for infants and provides immunity to infants against the diseases. Recent epidemiological studies suggest that early infant feeding practices may be important environmental risk factors for the development of CD. Ivarsson., *et al*. concluded that breastfeeding has protective effect against celiac disease, if infants were on breast-fed at the time of gluten introduction in their food. The child who remained on breast feed even after introduction of gluten in their diet were more protected from CD and the symptoms of CD were delayed in them [23]. Peters., *et al*. and Auricchio., *et al*. also showed that breast feeding was associated with a reduced risk of developing childhood CD [38,39]. Later, in a meta-analysis, the pooled risk for developing CD in breastfed children compared with those who were not breastfed at the time of gluten introduction was reduced by almost 50% [40]. Breast milk also promotes gut colonization by *Bifidobacterium* spp., leading to the association of this bacterial genus with the beneficial properties of infant's health attributed to breast-feeding. Retrospective studies have also shown that longer breast-feeding, and particularly, maintenance of breast-feeding when gluten is introduced, reduces the risk of developing CD or delays its onset [41].

In human milk, various bioactive substances are present which are involved in passive immune protection and in immunological development. A complex network of chemo-attractants and cytokines in human milk are thought to play a role in compensating for the

developmental delay of the neonate immune system and in preventing the development of immune-mediated diseases. Human milk contains cytokines and secretory immunoglobulins A (sIgA) content that differ depending on various factors, including the mother's immune status and dietary content of fatty acids, with potential consequences on infant health. The intake of probiotic bacteria has also been related to changes in breast-milk composition, including differences in cytokine content [42]. Olivares M., *et al*. concluded in their studies that when mothers with CD were compared with healthy mothers, they had low content of IL-12, TGF-β1 (cytokines), sIgA levels and no difference in content for IL-10, IL-13, TNF-α and HMO (human milk oligosaccharides) content. Breast milk microbiota composition compared in healthy mother with mothers with CD concluded that there is reduction in the gene copy of *Bifidobacterium spp*. and *B. fragilis* group. Therefore, these differences in breast milk composition could be one of the additional factors influencing the protective effects of breast-feeding on infant health [43]. Furthermore, wheat gliadins and other gluten peptides have been identified in breast milk using specific IgA-antibodies against gliadin, and the presence of gluten in breast milk may play a role in the induction of oral tolerance in breastfed infants [43].

S. No.	Year	Findings	References
1.	1983	Compared children breast fed for more than 30 days with those, breast fed for less than 30 days. Increased duration of breast feeding was associated with decreased risk of developing CD. Infants breast fed for less than 30 days were about four times more likely to develop CD compared with infant's breast fed for more than 30 days.	[39]
2.	1988	Children who were breast fed for less than 90 days were about five times more likely to develop CD compared with children breast fed for more than 90 days.	[45]
3.	2001	A significant protective effect on the incidence of celiac disease was suggested by the duration of breast-feeding (partial breast-feeding as well as exclusive breast-feeding).	[38]
4.	2002	The gradual introduction of gluten-containing foods into the diet of infants while they are still being breast-fed reduces the risk of celiac disease in early childhood and probably also during the subsequent childhood period.	[23]
5.	2003	No trend in antibodies to tissue transglutaminase was observed for the duration of breast feed. Children who first received gluten foods after age 6 months did not have increased risks for islet or celiac disease auto antibodies.	[46]
6.	2005	Breast feeding may offer protection against the development of CD. Breast feeding during the introduction of dietary gluten, and increasing duration of breast feeding were associated with reduced risk of developing CD. It is, however, not clear from the primary studies whether breast feeding delays the onset of symptoms or provides a permanent protection against the disease.	[41]
7.	2009	No significant association between breast feed and CD.	[2]
8.	2010	No association between breast feed duration and age at gluten introduction.	[47]
9.	2012	Potential risk factors for CD include prenatal events and infant feeding practice. With the exception that children who are breastfed at and beyond gluten introduction into the diet probably may be at a lower risk of developing CD, and that heavy gluten load early in life may increase the risk of future CD. Data on the impact of infant feeding are inconsistent.	[48]
10.	2014	There was no statistically significant association between maternal CD and breast-feeding at the time of gluten introduction.	[49]
11.	2015	Early feeding practices seem to have no impact on the risk of developing CD during childhood. In children without the genetic predisposition, the age and mode of gluten introduction do not influence the risk anyway.	[50]
12.	2019	Longer breastfeeding, and breastfeeding at the time of gluten introduction, postponed the onset of classic CD in patients up to two years. The association between the occurrence of CD and the time of introduction of gluten in this age group of patients has not been established.	[51]

Table 3: *Chronological studies on duration of breast feeding and its association with CD.*

In HLA-DQ2/8 haplotype infants, the gut microbiota was found to be further affected by feeding type, with breastfeeding having a protective effect against CD [23,44]. Breastfed babies had higher *Bifidobacterium longum, Clostridium leptum* and *Bifidobacterium breve* in comparison to formula fed babies, whose gut had higher counts of *Clostridium coccoides- Eubacterium rectale, Bacteroides fragilis* and *E. coli*. Breastfeeding thought to have a protective effect on the development of CD but could not be confirmed in some studies. The bacteria acquired during birth and first few months of life have a significant effect on commensal organisms in gut [44]. The adult gut microbiome is typically established by two years of age. Table 3 represents studies on impact of duration of breast feeding and its association with CD.

Age of gluten introduction: Gluten as we know is the trigger factor for developing CD and the age at which gluten was first introduced in the diet of child play a major role in this. There are number of studies in this regard. Ivarsson., *et al*. in their study concluded that gluten intake after 5 - 6 months of birth did not increase the risk of CD in children. Some studies suggest the lack of association between CD and gluten introduction timing [38,39,45]. Norris., *et al*. in their study observed that infants who first consumed gluten at the age of 1 - 3 months were at a 23-fold increased risk of CD and those who consumed gluten after the age of 6 months were at a 4-fold increased risk of CD [52]. Table 4 shows various guidelines of different countries for the introduction of gluten during childhood and table 5 shows various studies based on gluten intake and its impact on childhood CD.

Society/country	Year	Recommendation
Netherland	1999	Gluten should be included in diet after 6 months of age.
Poland	2007	Gluten introduction in diet should be after a full 4 months and before the end of 6 months while the child is still being breastfed.
European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)	2008	Gluten should be included in diet after 4 months and before 7 months of birth while the child is on breast fed as this can reduce the risk of CD and wheat allergy.
Isreal	2009	The national guidelines were in accordance with ESPGHAN guidelines.
Croatia	2010	Gluten should be introduced only after 4 months of birth preferably while still being breastfed.
Germany	2011	Gluten should be introduced in small amount not before start of 4 months and not after the end of 7 months while the child is still being breast fed.
Sweden	2011	Gluten should be introduced in small amount not before start of 4 months and not after the end of 6 months while the child is still being breast fed.
US (American Academy of Paediatrics)	2012	Any Complementary foods should be introduced between 4 and 6 months of age. Gluten-containing foods should be introduced while the infant is receiving only breast milk and not infant formula or other bovine milk products.

Table 4: *Gluten introduction - current recommendations [40].*

S. No.	Year	Findings	References
1.	2001	The age at which first gluten diet was exposed, appeared to affect the age of onset of symptoms.	[38]
2.	2002	The gradual introduction of gluten-containing foods into the diet of infants while they are still being breast-fed reduces the risk of celiac disease in early childhood and probably also during the subsequent childhood period.	[23]
3.	2005	Timing of introduction of gluten into the infant diet was associated with the appearance of CD in children at increased risk for the disease.	[52]
4.	2014	There was no statistically significant association between maternal CD and breast-feeding at the time of gluten introduction	[49]
5.	2015	The early feeding practices seem to have no impact on the risk of developing CD during childhood. In children without the genetic predisposition, the age and mode of gluten introduction do not influence the risk anyway.	[50]
6.	2019	Increased gluten intake at 18 months was associated with a modestly increased risk of CD later in childhood.	[53]

Table 5: *Chronological studies based on gluten intake and its association with CD.*

Microbiota of neonates and its role in developing CD

Microbiota acts as a major contributing factor in the pathogenesis of autoimmune diseases, including celiac disease. The intestinal microbiota is also involved in the pathogenesis of celiac disease, in addition to genetic variants and dietary gluten. There is a strong association between HLA-DQ2/8 haplotypes and CD, and microbiota is again a culprit for developing CD in child having these haplotypes. Several investigators have examined this association with the gut microbiota. Infants with HLA-DQ2 and HLA-DQ8 and first-degree relatives with CD have increased *Firmicutes* and *Proteobacteria* and less *Actinobacteria* and *Bifidobacterium*, suggesting that HLA genotype is associated with gut colonization by specific bacteria more prevalent in CD patients and their relatives [54].

Studies have reported differences in gut microbiota when compared patients having active celiac disease with healthy controls [55]. In a nationwide study by Sander DS., *et al*. (2019) among children in Denmark and Norway, found systemic antibiotics exposure during the first year of life to be associated with a later diagnosis of celiac disease. These findings indicate that childhood exposure to systemic antibiotics could also be a risk factor for celiac disease. Antibiotic exposure has a strong and sustained impact on the developing an unstable intestinal ecosystem [11]. Table 6 represents role of offspring microbiota on onset of CD.

S. No.	Year	Findings	References
1.	2007	• The proportions of total bacteria and Gram-negative bacteria were significantly higher in CD patients with active disease than in symptom-free CD patients and controls. • *Bacteroides* and *Escherichia coli* groups were significantly more abundant in CD patients with active disease than in controls, whilst these bacterial deviations were normalized in symptom-free CD patients. • The ratio of *Lactobacillus–Bifidobacterium* to *Bacteroides–E. coli* was significantly reduced in coeliac patients with either active or inactive disease compared with controls. • Overall, the higher incidence of Gram-negative and potentially pro-inflammatory bacteria in the duodenal microbiota of celiac children was linked to the symptomatic presentation of the disease and could favour the pathological process of the disorder.	[55]

2.	2010	• Delivery mode and feeding method influenced the faecal microbiota of European infants at 6 weeks., as expected, • The effect of country of birth was more pronounced, with dominant *bifidobacteria* in northern countries and greater early diversification in southern European countries.	[56]
3.	2015	The infant intestinal microbiome at approximately 6 weeks of age is significantly associated with both delivery mode and feeding method, and the supplementation of breast milk feeding with formula is associated with a microbiome composition that resembles that of infants who are exclusively formula fed.	[57]
4.	2015	CD mothers' breast milk is characterized by a reduced abundance of immune-protective compounds (TGF-β1 and sIgA) and *Bifidobacteria*. The reduction in these components could theoretically diminish the protective effects of breast-feeding on the child's future risk of developing CD.	[43]
5.	2016	Elective caesarean delivery and repeated maternal urinary tract infections during pregnancy are associated with increased risk of CD onset during childhood, suggesting the role of dysbiosis during early life. High maternal age and high income reduced the risk of CD, which might be due to infant-feeding practices and lifestyle.	[32]

Table 6: *Chronological studies based on role of microbiota in CD.*

Conclusion and Future Implications

Maternal wellbeing has a crucial impact on infant's health in its neonatal stage as well as in early childhood. Prenatal, perinatal and postnatal factors have a wide range of effects on development of celiac disease in children later in their life. Prenatal factors have lifetime consequences since it influences the health and immune system development of offspring. It has been observed that maternal health has consistent influence on infant and child development and such studies provide an opportunity to highlight various factors that may deteriorate the child health that can be overrule/optimized during pregnancy. The knowledge about the various factors affecting before or after birth deserves more attention so that prior counselling of pregnant women may be done for the betterment of their health. Moreover, history of negatively affecting parameters may help the healthcare policy makers to determine various approaches that may be helpful to support the health of pregnant woman and her to infant's health. In addition, it will also help to enhance the life course trajectory for children and families.

Bibliography

1. Decker Evalotte., *et al.* "Cesarean delivery is associated with celiac disease but not inflammatory bowel disease in children". *Gut Microbes* 2.2 (2011): 91-98.

2. Roberts SE., *et al.* "Perinatal risk factors and coeliac disease in children and young adults: a record linkage study". *Alimentary Pharmacology and Therapeutics* 29.2 (2009): 222-231.

3. Mårild Karl., *et al.* "Pregnancy outcome and risk of celiac disease in offspring: a nationwide case-control study". *Gastroenterology* 142.1 (2012): 39-45.

4. Adlercreutz Emma H., *et al.* "Perinatal risk factors increase the risk of being affected by both type 1 diabetes and coeliac disease". *Acta Paediatrica* 104.2 (2015): 178-184.

5. Abadie Valérie., *et al.* "Integration of genetic and immunological insights into a model of celiac disease pathogenesis". *Annual Review of Immunology* 29 (2011): 493-525.

6. Johnson Coreen L and James Versalovic. "The human microbiome and its potential importance to pediatrics". *Pediatrics* 129.5 (2012): 950-960.

7. Fallani Matteo., *et al.* "Intestinal microbiota of 6-week-old infants across Europe: geographic influence beyond delivery mode, breast-feeding, and antibiotics". *Journal of Pediatric Gastroenterology and Nutrition* 51.1 (2010): 77-84.

8. Mårild Karl., *et al.* "Infections and risk of celiac disease in childhood: a prospective nationwide cohort study". *American Journal of Gastroenterology* 110.10 (2015): 1475-1484.

9. Pozo-Rubio Tamara., *et al.* "Influence of early environmental factors on lymphocyte subsets and gut microbiota in infants at risk of celiac disease; the PROFICEL study". *Nutricion Hospitalaria* 28.2 (2013): 464-474.

10. Mårild Karl., *et al.* "Antibiotic exposure in pregnancy and risk of coeliac disease in offspring: a cohort study". *BMC Gastroenterology* 14.1 (2014): 1-7.

11. Sander Stine Dydensborg., *et al.* "Association between antibiotics in the first year of life and celiac disease". *Gastroenterology* 156.8 (2019): 2217-2229.

12. Mårild Karl., *et al.* "Antibiotic exposure and the development of coeliac disease: a nationwide case–control study". *BMC Gastroenterology* 13.1 (2013): 1-9.

13. Canova Cristina., *et al.* "Association of maternal education, early infections, and antibiotic use with celiac disease: a population-based birth cohort study in northeastern Italy". *American Journal of Epidemiology* 180.1 (2014): 76-85.

14. Uusitalo Ulla., *et al.* "Gluten consumption during late pregnancy and risk of celiac disease in the offspring: the TEDDY birth cohort". *The American Journal of Clinical Nutrition* 102.5 (2015): 1216-1221.

15. Lund-Blix., *et al.* "Maternal and child gluten intake and association with type 1 diabetes: The Norwegian Mother and Child Cohort Study". *Plos Medicine* 17.3 (2020): e1003032.

16. Peña-Rosas., *et al.* "Daily oral iron supplementation during pregnancy". *Cochrane Database of Systematic Reviews* 7 (2015).

17. Pavord Sue., *et al.* "UK guidelines on the management of iron deficiency in pregnancy". *British Journal of Haematology* 156.5 (2012): 588-600.

18. Størdal Ketil., *et al.* "Association between maternal iron supplementation during pregnancy and risk of celiac disease in children". *Clinical Gastroenterology and Hepatology* 12.4 (2014): 624-631.

19. Recalcati Stefania., *et al.* "Iron levels in polarized macrophages: regulation of immunity and autoimmunity". *Autoimmunity Reviews* 11.12 (2012): 883-889.

20. Sandberg-Bennich S., *et al.* "Coeliac disease is associated with intrauterine growth and neonatal infections". *Acta Paediatrica* 91.1 (2002): 30-33.

21. Wingren Carl Johan., *et al.* "Sex differences in coeliac disease risk: a Swedish sibling design study". *Digestive and Liver Disease* 44.11 (2012): 909-913.

22. Ludvigsson Jonas F., *et al.* "Smoking and celiac disease: a population-based cohort study". Clinical *Gastroenterology and Hepatology* 3.9 (2005): 869-874.

23. Ivarsson Anneli., *et al.* "Breast-feeding protects against celiac disease". *The American Journal of Clinical Nutrition* 75.5 (2002): 914-921.

24. Wingren Carl Johan., *et al.* "Coeliac disease in children: a social epidemiological study in Sweden". *Acta Paediatrica* 101.2 (2012): 185-191.

25. Tanpowpong Pornthep., *et al.* "Multicenter study on season of birth and celiac disease: evidence for a new theoretical model of pathogenesis". *The Journal of Pediatrics* 162.3 (2013): 501-504.

26. Mårild Karl., *et al.* "Current evidence on whether perinatal risk factors influence coeliac disease is circumstantial". *Acta Paediatrica* 105.4 (2016): 366-375.

27. Ivarsson Anneli., *et al.* "Children born in the summer have increased risk for coeliac disease". *Journal of Epidemiology and Community Health* 57.1 (2003): 36-39.

28. Stene Lars C., *et al.* "Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study". *American Journal of Gastroenterology* 101.10 (2006): 2333-2340.

29. Lewy Hadas., *et al.* "Seasonality of birth month of children with celiac disease differs from that in the general population and between sexes and is linked to family history and environmental factors". *Journal of Pediatric Gastroenterology and Nutrition* 48.2 (2009): 181-185.

30. Lebwohl Benjamin., *et al.* "Celiac disease and non-celiac gluten sensitivity". *BMJ* (2015):351.

31. Namatovu Fredinah., *et al.* "Season and region of birth as risk factors for coeliac disease a key to the aetiology?". *Archives of Disease In Childhood* 101.12 (2016): 1114-1118.

32. Namatovu Fredinah., *et al.* "Maternal and perinatal conditions and the risk of developing celiac disease during childhood". *BMC Pedi-*

Volume 8 Issue 4 April 2021
©All rights reserved by Malika Arora*., et al.*