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Review Article

# Is There a Linkage between Celiac Disease and Adverse Pregnancy Outcomes?

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## Abstract

Celiac disease is an autoimmune disorder that occurs in genetically predisposed people in which the ingestion of gluten leads to damage in the small intestine that clinically presents with malabsorption related symptoms. However it is known that celiac disease can also be the underlying cause of several non-gastrointestinal symptoms. This review summarizes the studies and data acquired on the relationship between celiac disease and gynecological/obstetric disorders. In the last decades numerous studies highlighted the existence of a linkage between celiac disease and gynecological/obstetric disorders such as delayed menarche, early menopause, amenorrhea or infertility and adverse pregnancy outcomes. Although much has been reported on such a linkage, not as much has been explored and understood about the pathogenic mechanisms underlying such clinical presentations in patients with celiac disease. Studies conducted on the subject showed intestinal malabsorption, direct role of gliadin, coagulation alterations, immune-modulated mechanisms and endometrial inflammation as main triggers of gynecological/obstetric disorders in celiac patients. At the present the knowledge of such mechanisms and the way they act and interact is however insufficient and further studies are needed to get a better and exhaustive understanding of the matter.

**Keywords:** Celiac disease; Infertility; Pregnancy; Autoimmunity; Personalized medicine

## Introduction

Celiac Disease (CD) is an autoimmune enteropathy which affects as many as 1% of the population worldwide [1]. The disease is triggered by and abnormal immune response to dietary gluten, a protein component found in wheat, barley and rye, and it only occurs in genetically susceptible individuals. The genetic susceptibility to develop CD is known to be carried by HLA class II molecules DQ2 or DQ8, responsible for presenting disease-related peptides to T lymphocytes.

Of the 1% of the general population affected by the disease only a percentage of 20% to 50% shows subjective symptoms [2]. Although the classical form of CD presents with malabsorption related symptoms such as chronic diarrhea, steatorrhea, abdominal distension, nausea, vomiting, anemia and fatigue, CD can also be the underlying cause of several non-gastrointestinal symptoms which can lead to a delay in the diagnosis of the disease itself [3]. Among such non-gastrointestinal symptom of particular interest have been disorders of fertility, such as delayed menarche, early menopause, amenorrhea or infertility, and adverse pregnancy outcomes, such as recurrent abortions, Intrauterine Growth Restriction (IUGR), Small for Gestational Age (SGA) babies, Low Birth Weight (LBW) babies or preterm deliveries [3,4].

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The aim of this review is to highlight what has been understood in the last decade about the existing linkage between CD and gynecological/obstetrical disorders particularly focusing both on pregnancy complications and outcomes, and on the underlying molecular pathogenic mechanisms.

### Disorders of fertility

The first description of the existence of an association between CD and disorders of fertility was made by Morris et al. [5] in 1970 when they first described three infertile patients with CD who became pregnant after having been on a gluten free diet. Further investigations have been done throughout the years on such a linkage.

CD has been found in 4% to 8% of patients with unexplained infertility [5] and has been shown that CD has an increased prevalence particularly during the fertile period [6]. These patients often present with no gastrointestinal symptoms, fact that leads to a delay in the diagnosis of CD and in its treatment. Interestingly, it has been observed that fertility was reduced in the two years preceding the diagnosis and that this returned to normal ranges following diagnosis and treatment of CD [4]. However, such an improvement of the gynecological problems does not happen in all patients, since the positive effect on fertility of a gluten free diet is rationalized by the improvement of nutritional imbalance caused by the intestinal malabsorption typical of CD [6].

Moreover several studies have reported an increased incidence of menstrual cycle disorders in women with CD *vs.* healthy controls [4] among which can be seen delayed menarche, early menopause, amenorrhea, oligomenorrhoea, dysmenorrhoea and menorrhagia. In a case-control study conducted by Collins et al. [7] the age of menarche in celiac girls has been shown to be delayed for more than 2 years and in another study Sher and Mayberry [8] found that the mean age at menopause in CD patients was 47.6 compared to 50.1 in controls. As far as amenorrhea is concerned, in a Ferguson et al. [9] study amenorrhea has been shown to be more common in the celiac group.

### Adverse pregnancy outcome

Maternal CD is known to be associated with adverse pregnancy outcomes such as recurrent miscarriage, low birth weight, Small for Gestational Age (SGA), Intrauterine Growth Restriction (IUGR) and pre-term birth [4]. Several studies have been conducted on the subject from which interesting finding emerged.

A study by Gasbarrini et al. [10] showed that women with undiagnosed CD present with a higher risk of recurrent miscarriage that rises up to nine times compared with treated patients. In a study by Ciacci et al. [11] was shown how putting the patients on a gluten free diet lead to a reduction of the relative risk of miscarriage by approximately nine times, however it must be taken into consideration that such case-control study was limited by small numbers.

Among adverse pregnancy outcomes, IUGR is one of major concerning being responsible for a 5-20-fold increase in perinatal mortality and for implying a higher risk of perinatal morbidity and life-long consequences [4]. Different studies have been conducted on such association between maternal CD and IUGR that was shown to vary considerably with odds ratio of 1.6 and 6.0 reported [11-13]. Such studies also highlighted that variations exist as regards treated *vs.* untreated CD [4].

Numerous studies have also been conducted to analyze the relation between CD and adverse pregnancy outcomes such as pre-term delivery and low weight children at birth. These studies showed that CD women have a higher prevalence of pre-term delivery [14], and in case of an undiagnosed CD and higher risk of low birth weight (<2500 g) [13] and of SGA infants [15].

### Underlying pathogenic mechanisms

In female patients with CD, the disease may lead to disorders of fertility and pregnancy alterations through a variety of different, still not properly and completely understood, mechanisms.

### Intestinal malabsorption

Undiagnosed CD, as a permanent autoimmune enteropathy, leads to a small intestine mucosal inflammation and damage resulting in a condition of intestinal malabsorption that may cause folic acid, vitamin B12, fat-soluble vitamins, and iron and zinc deficiencies [4]. Among these zinc deficiency may alter the synthesis and secretion of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) leading to an alteration of the hypothalamic- hypophyseal-ovarian axis, secondary amenorrhea and spontaneous abortion [4,16]. Folic acid deficiency, owing to the action of such vitamin in nucleic acid metabolism, leads instead to a negative impact on rapidly proliferating tissue in the embryo [2,4]. However malnutrition has not been a constant feature among women with CD and alterations of fertility and pregnancy [4].

### Direct role of gliadin

In two studies has been investigated the role of gliadin, the alcohol soluble fraction of gluten which is the primary antigen leading to an inflammatory reaction in the small intestine in CD. These studies showed that gliadin is responsible for the induction of an inflammatory reaction characterized by the production of cytokines [13] that may have negative effects on the fetus [17]. Furthermore, gliadin itself can activate peripheral blood T cells, as measured by proliferation, expression of the activation markers and cytokine secretion (interferon-γ and interleukin-2), which affect the intrauterine environment [18].

### Coagulation alterations

Recent studies have shown as adverse pregnancy outcome, especially early pregnancy loss, could be related to alterations in coagulation. A 4G variant of plasminogen activator inhibitor-1 gene was shown to be likely capable of affecting placental and/or fetal microvascular function in a way that may lead to miscarriage [19].

### Immune-mediated mechanisms

Although all of these findings can help to shed light on the intricate pathogenic mechanisms of fertility and pregnancy alterations in CD, nowadays the most promising field of research on the matter appears to be that of autoimmunity. CD is an autoimmune disease in which the ingestion of gluten triggers the production of circulating anti-transglutaminase (anti-tTG) autoantibodies.

A study by Di Simone et al. [20] showed that circulating anti-tTG antibodies are responsible for impairing the placental function. It this study human primary trophoblastic cells, isolated from term placenta, was exposed to anti-tTG immunoglobulin G (IgG) antibodies *in vitro*. Trophoblast has a pivotal role in ensuring the synchronized interaction in the adhesion and invasive events that occurs at the embryo-maternal interface after implantation and its differentiation is characterized by the development of Extravillous Trophoblast (EVT) that migrates into the maternal myometrium. Anti-tTG IgG showed a specific dose- and time-dependent binding to human trophoblast, which after being exposed to such autoantibodies showed an impaired invasiveness, a decreased activity of cellular Matrix Metalloprotease (MMP) and greater percentage of cellular apoptosis assisted by the expression of indicators of trophoblast damage such as TdT-mediated dUTP digoxigenin nick end labeling (TUNEL) and annexin V.

Deeper understanding of the subject has been reached in a study by Di Simone et al. [21] that focused on the effect of circulating anti-transglutaminase type 2 (anti-TG2) autoantibodies on the process of endometrial angiogenesis and decidualization which are prerequisites for placental development. In particular the study showed how anti-TG2 antibodies bind to Human Endometrial Endothelial Cells (HEECs) and decrease newly formed vessels both *in vitro* and *in vivo*. Impaired angiogenesis is due to the ability of anti-TG2 antibodies to inhibit the activation of HEEC matrix metalloprotease-2 (MMP-2), to disarrange cytoskeleton fibers, to change the physical and mechanical properties of cell membranes and to inhibit the intracellular phosphorylation of FAK and ERK. Anti-TG2 was thus found to inhibit endometrial angiogenesis by altering TG2-dependent migration of HHECs and extracellular matrix degeneration.

Furthermore, a study by Sóñora et al. [22] investigated the effects of anti-tTG autoantibodies from sera of patients with CD on cytotrophoblast cell line (Swan-71 cells) that was taken as a model for tTG localizes to the syncytial microvillous surface of human placenta. As the early implantation period is characterized by important tissue remodeling and changes, and tTG contributes to injury healing in such delicate processes, the study aimed to investigate the effects of celiac sera containing anti-tTG antibodies on injury healing and cell migration of trophoblast cell. It came out that anti-tTG antibodies reduce proliferation rate and migration of trophoblast cells, promote apoptosis levels and are able to interfere with the clearance of trophoblast apoptotic bodies through a mechanism involving MFG-E8 (milk fat globulin-EGF factor 8)-tTG interaction.

### Endometrium inflammation

A study by D'Ippolito et al. [23] showed for the first time a

higher proportion of HLA DQ2/DQ8 positivity in women with RPL as compared to controls (fertile women). HLA DQ2/DQ8 haplotypes codify for the DQ2/DQ8 proteins that, in celiac patients, are responsible for presenting the immunogenic gluten peptides to DQ2/DQ8-restricted CD4+ T cells. Once activated, CD4+ T cells trigger a complex immune response that leads to increased production of interferon (INF) γ, Tumor Necrosis Factor (TNF) α, and autoantibodies like anti-tTG, anti-endomysium and anti-gliadin antibodies. This process will eventually lead to the disruption of tight junction in the intestinal epithelium generating a leaky gut condition.

Interestingly, a study by Tersigni et al. [24] showed and existing linkage of the endometrial Nalp-3 inflammasome over expression and activation, with a leaky gut condition in woman with idiopathic RPL. Thus, it has been hypothesized that leaky gut, occurring for reasons that have not been understood yet, allows the passage of antigens through the intestinal barrier that might lead to an inflammation status of the endometrium. Further studies are needed to find out whether there is a connection among HLA DQ2/DQ8, leaky gut and endometrial inflammation in women with adverse pregnancy outcomes and CD [25,26].

## Conclusion

This paper has reviewed the epidemiologic association between CD and gynecological/obstetric disorders and the potential pathogenic mechanisms underlying such linkage. Although it has been widely demonstrated by numerous studies the association between CD and gynecological/obstetric disorders such as infertility, menstrual cycle disorders and adverse pregnancy outcomes, the understanding of the pathogenic mechanisms of this conditions is still in its infancy. There are many and complex factors such as malnutrition due to intestinal malabsorption, coagulation alterations, endometrial inflammation and immune-mediated mechanisms that have been shown to lead to the complex and different alterations seen in patients with CD and adverse pregnancy outcomes. However, at the present the knowledge of such mechanisms and the way they act and interact is insufficient, thus further studies are needed to get a better and exhaustive understanding in order to open the way to new rational designed therapeutic approaches that might improve pregnancy outcomes through a personalized medicine.

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