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Celiac disease: a hidden cause of infertility and pregnancy complications?

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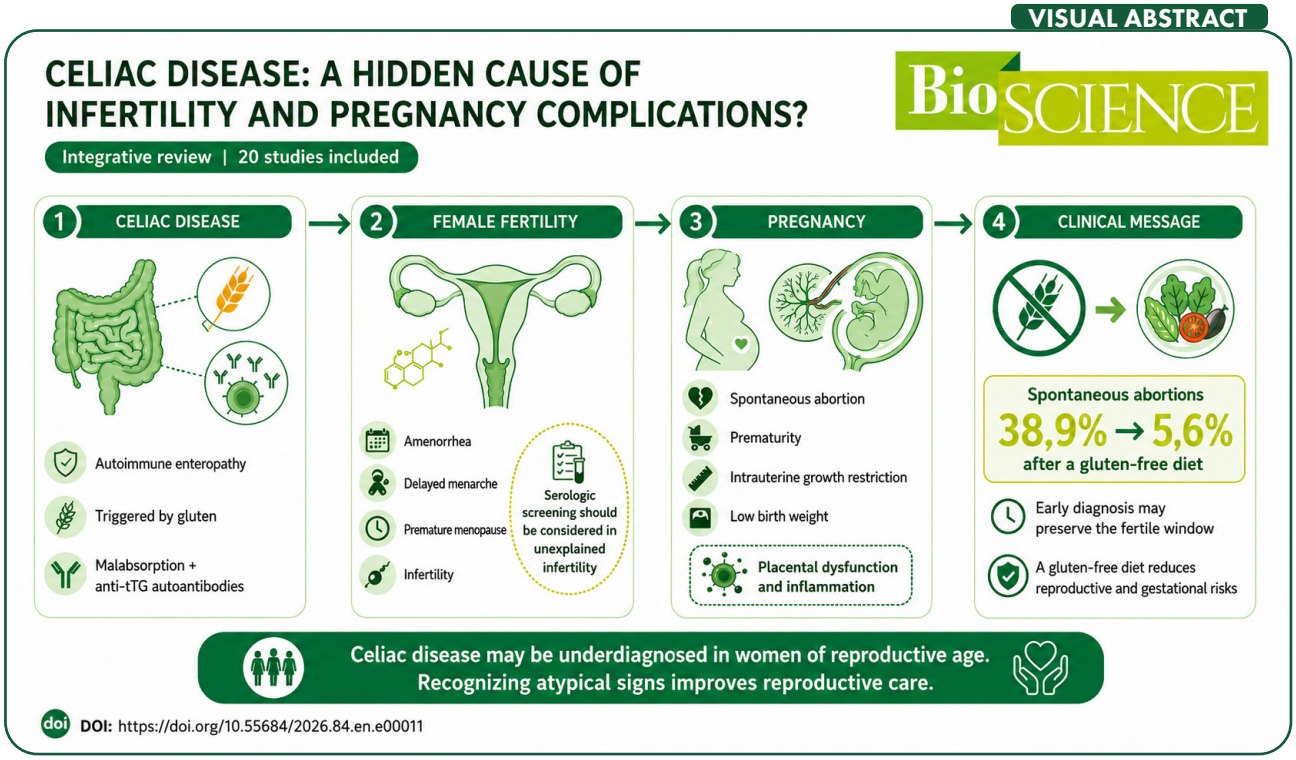
VISUAL ABSTRACT



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Central Message
Celiac disease is an autoimmune and genetic enteropathy triggered by gluten ingestion that has significant impacts on the female reproductive cycle and pregnancy. Symptoms such as amenorrhea, late menarche, early menopause, and others due to irregularities in pituitary hormones are found as signs of female fertility. In the gestational period, it can be manifested by impaired placental development, increased risk of prematurity, intrauterine growth restriction, low neonatal weight, and miscarriage. However, adopting a gluten-free diet can avoid the aforementioned manifestations.

Perspective
Celiac disease has an extensive list of symptoms and is commonly associated only with gastrointestinal symptoms. This premise, in the face of a discordant diagnostic technique, can generate several consequences, such as female infertility, with the risk of losing the fertile period, and compromising the health of the mother and fetus during pregnancy. Therefore, based on a greater amount of research and the recognition of these signs, the diagnosis and treatment of atypical cases would be facilitated, reducing or even eradicating the aforementioned adversities.

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ABSTRACT

Introduction: Celiac disease is a chronic and autoimmune enteropathy that manifests itself in individuals who are genetically susceptible to the action of environmental factors, in which the main one is gluten. In addition to symptoms such as chronic diarrhea and abdominal pain, the disease is also associated with extraintestinal symptoms, such as infertility and gestational impacts.

Objectives: To synthesize the main aspects of celiac disease and its implications for female fertility and the gestational period.

Method: Review made with material and analysis selected from searches on the virtual platforms SciELO, Google Scholar and PubMed, through the descriptors: "celiac disease", "gestational period" and "infertility" and their correspondents in English and Spanish, and in the book Treaty of Gastroenterology from Undergraduate to Graduate Studies (2nd edition).

Results: A total of 24 articles were included.

Conclusion: Celiac disease has a significant impact on fertility and pregnancy; however, the effects can be reduced or even eradicated with the implementation of a gluten-free diet. However, the greatest challenge persists in the identification and diagnosis of celiac women who are of childbearing age, due to the lack of clinical specificity, genetic variability, and the extent of environmental factors that impact the disease.

KEYWORDS: Celiac disease. Pregnancy. Infertility.

INTRODUCTION

Celiac disease (CD) is a chronic and autoimmune enteropathy triggered by the ingestion of gluten, a protein present in grains such as wheat, rye, and barley. The disease manifests itself in genetically susceptible individuals, carriers of the DQ2 and/or DQ8 haplotype of class II of the human leukocyte antigen (HLA) system, together with the action of environmental factors. The consumption of gluten implies an autoimmune response that inflames and degrades the villi of the mucosa of the small intestine, generating hyperplasia of its cells, and thus affecting the absorption of nutrients.[1-3]

As a result of nutritional malabsorption and changes in histological structure, it is common for gastrointestinal symptoms such as chronic diarrhea, abdominal pain and bloating, weight loss, among others, to manifest it.[1-3] However, CD has a wide spectrum of extraintestinal manifestations, which are often neglected in clinical diagnosis. Among them, female infertility and gestational complications stand out, which can present as amenorrhea, late menarche, early menopause, recurrent miscarriages and intrauterine growth restriction, even in asymptomatic women from a digestive point of view.[4,5]

The multifactorial etiology of these reproductive alterations ranges from nutritional deficiencies caused by malabsorption to autoantibody-mediated immunological alterations that directly affect endometrial and placental function.[4-6] In addition, frequent delay in diagnosis and early interventions can exceed a decade, favoring the loss of the fertile period.[5,6]

Thus, the objective of this review was to synthesize the main pathophysiological, nutritional, and immunological aspects of CD and its implications for female fertility and the gestational period, reinforcing the need for greater diagnostic attention for atypical cases of the disease.

METHOD

This is an integrative literature review, carried out from searches in the PubMed, SciELO and Google Scholar databases, in addition to consulting the book "Treatise on Gastroenterology: From Undergraduate to Postgraduate Studies" (2nd edition). Articles published between 2002 and 2024, in Portuguese, English, and Spanish, were included. The descriptors used were "celiac disease", "pregnancy" and "infertility", as well as their counterparts in English and Spanish, used alone or combined through Boolean operators (Table 1).

DISCUSSION

The physiopathology of CD results from the combination of the main genetic components (HLA-DQ2 or HLA-DQ8 haplotypes), environmental factors (such as gluten protein and related cereals), and the consequent production of circulating antibodies: tissue antitransglutaminase (TG2) and antiendomysial (EmA).[7-13]

Genetic factors

CD is a genetic disease of multifactorial and polygenic origin, in which different susceptibility genes act at different stages until the final development of the disease.[7,8,10] Studies based on molecular genetic methods have allowed the identification of variants associated with predisposition to CD, including loci CELIAC2 (5q33), CELIAC3 (2q33), CELIAC4 (19p13.1) and, mainly, CELIAC1, located in the 6p21 region of chromosome 6.[8,11-13]

In addition, as with other autoimmune diseases, a strong association was established between CD and the major histocompatibility complex class II (MHC), responsible for the presentation of antigens to the immune system. This genetic component plays a fundamental role in the variability of the disease, estimated at between 40% and 50%.[8] The main genetic factors of CHM related to CD correspond to HLA haplotypes, also located in the CELIAC1 region.

Approximately 90% of individuals with CD are carriers of a specific variant of HLA-DQ2 (DQA105:01, DQ2.[5],) while most of the others have HLA-DQ8 (DQA103, DQB103:02) or less frequent variants of

TABLE 1 — Synthesis of the studies incorporated in this review

Author(s) and year	Type of study	Objectives	Method	Conclusion
Lindfors et al.[1] (2019)	Narrative review	Synthesize the main aspects of celiac disease, including epidemiology, pathophysiology, clinical manifestations, diagnosis, treatment, and impact on quality of life.	Broad review of the scientific literature on celiac disease, with an integrated approach to immunological, genetic, environmental, diagnostic and therapeutic mechanisms.	Celiac disease is immune-mediated enteropathy triggered by gluten in genetically predisposed individuals, with intestinal and extraintestinal manifestations. The diagnosis depends on the association between clinical, serology and histology, with a gluten-free diet being the established treatment.
Lebwohl et al.[2] (2018)	Narrative review	Review epidemiology, pathogenesis, clinical presentation, diagnosis, complications, and management of celiac disease.	Critical review of the literature in the format of a clinical update article published in the Lancet.	Celiac disease affects about 1% of the population in many countries, with increasing incidence and varied clinical manifestations. Early recognition and adherence to the gluten-free diet are key to reducing complications.
Fasano and Catassi.[3] (2012)	Clinical review	To present a practical approach to the diagnosis, treatment and follow-up of patients with celiac disease.	Evidence-based clinical review, with discussion of clinical presentation, serology, intestinal biopsy, and dietary management.	Celiac disease has a broad clinical spectrum and may course with gastrointestinal or extraintestinal symptoms. The diagnosis requires adequate investigation even during gluten consumption, and the treatment consists of a gluten-free diet.
Kotze[4] (2004)	Descriptive observational study	OBJECTIVE: To evaluate gynecological and obstetric changes in Brazilian patients with celiac disease, relating them to nutritional status and adherence to the gluten-free diet.	Analysis of adult celiac patients according to nutritional status and evaluation of children/adolescents according to adherence to the gluten-free diet.	Patients with celiac disease had gynecological and obstetric alterations, such as late menarche, amenorrhea, and miscarriages. Severity was related to poorer nutritional status and non-adherence to the gluten-free diet.
Di Simone et al.[5] (2021)	Narrative review	Update pathogenic mechanisms that relate celiac disease to reproductive failure, infertility, and obstetric complications.	Review of evidence on immunological, inflammatory, nutritional, and placental mechanisms involved in the association between celiac disease and reproductive failure.	Celiac disease can compromise fertility and pregnancy by nutritional and immunological mechanisms, especially by the action of anti-tissue transglutaminase autoantibodies on the endometrium, trophoblast, and placenta.
Casella et al.[6] (2016)	Narrative review	To review the contribution of celiac disease to gynecological and obstetric changes.	Review of the literature on celiac disease in women of childbearing age, infertility, miscarriages, fetal growth and gestational outcomes.	Celiac disease is more prevalent in women during the fertile period and should be investigated in cases of infertility, recurrent miscarriages, and unfavorable obstetric outcomes without a defined cause.
Ludvigsson and Murray.[7] (2019)	Epidemiological review	Describe the epidemiology of celiac disease, including prevalence, incidence, population factors and geographic distribution, prevalence, incidence, population factors, and geographic distribution.	Review of epidemiological studies on celiac disease in different populations, with analysis of variations by age, sex, region, and diagnostic methods.	Celiac disease is a common chronic inflammatory condition of the small intestine, triggered by gluten in genetically susceptible individuals, with relevant global prevalence and variation according to population and diagnostic strategy.
Marinho et al.[8] (2016)	Textbook	Present clinical, pathophysiological, diagnostic and therapeutic foundations of gastroenterological diseases, including celiac disease.	Gastroenterology textbook chapter aimed at undergraduate and graduate studies, with didactic synthesis of consolidated knowledge.	The treatise provides a conceptual basis for understanding celiac disease, including pathophysiology, clinical manifestations, diagnosis by serology and biopsy, and treatment with a gluten-free diet.
Pereira.[9] (2020)	Narrative literature review	Analyze the pathophysiology of celiac disease, elucidate its diagnostic methods, and highlight the importance of proper food labeling.	Narrative review prepared between July and December 2020, with a search in MEDLINE, SciELO, PubMed, Virtual Health Library and books, using descriptors related to celiac disease, treatment, signs, symptoms and diagnosis.	Celiac disease results from an inflammatory response to gluten in genetically predisposed individuals, leading to villous atrophy and malabsorption. Diagnosis is based on clinical evaluation, serological markers and endoscopic biopsy, with a gluten-free diet being the only proven treatment.
Iversen and Sollid.[10] (2022/2023)	Narrative review	Describe the immunobiological and pathogenic mechanisms of celiac disease.	Review of evidence on HLA-DQ2/DQ8, gluten peptide presentation, T lymphocytes, transglutaminase 2, and autoantibodies.	Celiac disease has a well-characterized pathophysiology, involving immune response to gluten, HLA predisposition, and production of autoantibodies against transglutaminase 2.
Nieto et al.[11] (2020)	Narrative review	To review causes, pathology, and nutritional assessment of the gluten-free diet in celiac disease.	Literature review on pathophysiology, nutritional deficiencies, and gluten-free diet composition.	Celiac patients may have nutritional deficiencies before and during the gluten-free diet, requiring adequate nutritional monitoring.
Caio et al.[12] (2019)	Comprehensive narrative review	To update knowledge on the pathophysiology, diagnosis, clinical manifestations, treatment and therapeutic perspectives of celiac disease.	Comprehensive review of the scientific literature on different aspects of celiac disease.	Celiac disease remains a challenging condition, with diverse phenotypes and the need for a better understanding of potential, seronegative, and refractory forms.
Gujral et al.[13] (2012)	Narrative review	To review the prevalence, diagnosis, pathogenesis, and treatment of celiac disease.	Review of studies on genetic, environmental, immunological and therapeutic factors.	Celiac disease results from the interaction between gluten, genetic predisposition, and immune response; Its prevalence is estimated to be about 0.5% to 1%, and the treatment is a gluten-free diet.
Husby et al.[13] (2020)	Clinical guideline / guideline	Update the ESPGHAN recommendations for diagnosis of celiac disease in children and adolescents.	Evidence review and expert consensus for diagnostic criteria, including serology, biopsy, and biopsy-free approach in selected cases.	Pediatric diagnosis should use specific serology, especially anti-TG2 IgA and total IgA; In specific situations, it can be diagnosed without biopsy according to established criteria.
Rubin and Crowe.[14] (2020)	Clinical review	Present practical updates on the diagnosis, clinical manifestations, and management of celiac disease.	Clinical review in didactic format, focused on medical practice.	Recognition of intestinal and extraintestinal manifestations is essential for timely diagnosis and for the institution of a gluten-free diet.
Oberhuber et al.[15] (1999)	Histopathological review / classification proposal	To review histological findings of celiac disease and to propose standardization of the anatomopathological report.	Review of histological changes in celiac disease based on Marsh's classification.	Histopathological standardization allows the classification of lesions of the intestinal mucosa, including increased intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy.
Harris et al.[17] (2012)	Narrative review	To review the clinical, endoscopic and histopathological aspects of celiac disease.	Review of the literature on clinical manifestations, endoscopic diagnosis, and histological alterations of CD.	The diagnosis of CD requires integration between clinical, serological, endoscopic and histopathological findings for greater diagnostic accuracy.
Skoracka et al.[18] (2021)	Narrative review	To assess the influence of nutrition on female fertility.	Review of studies on female fertility and associated nutritional factors.	Nutritional deficiencies can compromise female fertility, and adequate micronutrient intake is essential for reproductive function.
Freeman.[19] (2010)	Narrative review	To analyze reproductive changes associated with celiac disease.	Review of the literature on fertility, pregnancy and obstetric complications in celiac women.	Untreated CD is associated with infertility, recurrent miscarriages, and adverse pregnancy outcomes, and can be reversed with a gluten-free diet.
Tonai et al.[20] (2020)	Experimental study in animals	To investigate the effects of iron deficiency on female fertility.	Experimental model in mice subjected to iron deficiency, with evaluation of follicular development.	Iron deficiency impairs follicular development and reduces female fertility.
Sóñora et al.[21] (2014)	In vitro experimental study	To evaluate the effect of anti-tissue transglutaminase antibodies on human trophoblastic cells.	Culture of human trophoblastic cells exposed to anti-tTG antibodies.	Anti-tTG antibodies reduce proliferation and trophoblastic migration and increase apoptosis, contributing to gestational complications in CD.
Butler et al.[22] (2011)	Narrative review	To review the relationship between celiac disease and pregnancy outcomes.	Review of observational studies on pregnancy in women with CD.	Women with undiagnosed CD are at increased risk of miscarriage, prematurity, and fetal growth restriction
Boers et al.[23] (2019)	Case report	OBJECTIVE: To describe the gestational course in a patient with celiac disease.	Clinical report and brief review of the literature.	Early diagnosis and adherence to the gluten-free diet contribute to better maternal and fetal outcomes.
Tack et al.[24] (2010)	Narrative review	To review the epidemiology, clinical manifestations, and treatment of celiac disease.	Comprehensive review of the literature.	CD has a broad clinical spectrum and treatment based on a gluten-free diet remains the main therapeutic strategy.

HLA-DQ2, such as DQ2.2 (DQA102:01).[8,12,13]

However, despite this consistent association, the isolated presence of these haplotypes is not sufficient for the development of the disease. Although they are relatively common in the general population (30% to 40%), only about 2% to 5% of individuals with CD develop CD.[8] In this context, additional genes related to epithelial function, intestinal mucosal integrity, and metabolism also participate in the triggering of the disease.[7,8]

Environmental factors

Gluten protein is the main environmental factor that triggers and maintains the changes observed in CD. Gluten is present in wheat, rye and barley, and is composed of two main protein groups: glutenins and prolamins. Prolamins correspond to about 50% of the total gluten content and receive different denominations depending on the cereal of origin, such as gliadin in wheat, hordein in barley and secalin in rye. Oats, although they do not contain gluten in their natural composition, may show traces of this protein, as a result of cross-contamination during cultivation and processing, which can trigger reactions in some celiac patients.[9,10]

Gliadin, a monomeric gluten protein, represents the main toxic agent involved in the pathogenesis of CD and is classified into four fractions: alpha (α), beta (β), gamma (γ) and omega (ω). Due to its resistance to proteolysis, its digestion is incomplete, resulting in the formation of smaller fragments, such as gliadin-derived oligopeptides. These peptides are rich in proline and glutamine, and are recognized by the immune system, especially in the alpha-gliadin portion, which culminates in the activation of T lymphocytes.[9-11]

In addition to gluten, other environmental factors have been implicated in the development of CD, including the potentially protective role of breastfeeding, the occurrence of gastrointestinal infections, the use of antibiotics, and changes in the gut microbiota. The dysbiosis observed in celiac patients is characterized by an increase in Bacteroides spp. and a reduction in Bifidobacterium spp., including B. longum, when compared to healthy individuals, and does not seem to completely normalize even after the adoption of a gluten-free diet.[8-10]

Immunology

In CD, there is production of IgA-type autoantibodies directed against the enzyme tissue transglutaminase (TG2), widely expressed in mucosal cells, smooth muscles, endothelium, fibroblasts, and intestinal epithelium. TG2 plays a central role in catalyzing transamination and deamination reactions, converting glutamine residues into glutamic acid.[13] When partially digested gluten peptides reach the intestinal lamina propria, genetically predisposed individuals develop adaptive immune response dependent on TG2-mediated deamination of gliadin fragments.[11] This process increases the immunogenicity of gliadin by facilitating its binding to HLA-DQ2.2, HLA-DQ2.5, and HLA-DQ8 molecules in antigen-presenting cells. The autoantibodies generated may also contribute to extraintestinal manifestations of CD.[10]

At the same time, an innate immune response is established in the intestinal epithelium, characterized by intraepithelial lymphocytosis. Intraepithelial lymphocytes express receptors typical of natural killer (NK) cells, such as NKG2D and CD94/NKG2A, which recognize stress-induced surface glycoproteins, including A and B chains of MHC class I and HLA-E molecules, expressed on intestinal epithelial cells. The concomitant activation of adaptive and innate immune pathways contributes to the clinical and pathogenetic picture of CD.[11,12]

Trypsin-amylase inhibitors, which account for about 2% to 4% of wheat proteins, also participate in the activation of the innate immune response. Certain fractions of these inhibitors are capable of activating Toll-type receptors, such as TLR-4, inducing the release of proinflammatory cytokines by monocytes, macrophages, and dendritic cells, both in celiac and non-celiac individuals.[10-13]

Activation of specific T cells in the lamina propria results in changes in the number, distribution, and activation status of intraepithelial lymphocytes (IHLs). These lymphocytes are distributed throughout the intestinal epithelium, with a predominance in the basolateral region of the epithelial cells. Most of them have $CD8^+$ $\alpha\beta TCR^+$ or $\gamma\delta TCR^+$ phenotype, with functional characteristics similar to NK cells, being involved in the death of enterocytes and in the tissue remodeling observed in CD.[1,7,10–13] There is also a redistribution of ISLs, with an increase in their density at the ends of the villi.[10-13]

Interleukin-15 (IL-15), overexpressed by intestinal epithelial cells of patients with CD, plays a central role in the activation and proliferation of these lymphocytes. In addition, cytokines produced by lamina propria T cells, such as IL-2 and IL-21, additionally contribute to the activation of ISLs.[10-13]

Epithelial changes may also be secondary to $CD4^+$ T cell activation. In addition to ISL, other subtypes of innate lymphocytes are particularly abundant in childhood, highlighting a population similar to inborn lymphocytes type 1 (ILC1), interferon-secreting γ (IFN-γ), and a population of ISL highly responsive to IL-15, considered a precursor of the monoclonal expansions observed in refractory CD type 2, a premalignant condition resistant to a gluten-free diet.[11-13]

Diagnosis

The diagnosis of CD is based on a combination of clinical findings, serological tests, intestinal mucosal biopsy for morphological evaluation, and response to the gluten-free diet. However, diagnostic confirmation can be challenging due to the possible disagreement between clinical, serological, and histological data.[12]

In 2020, the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition

(ESPGHAN) updated its diagnostic guidelines for CD, proposing that, in specific situations, the diagnosis can be made exclusively based on serological tests, dispensing with the need for intestinal biopsy.[12]

Several serological markers have been used over the last decades, and the anti-tissue transglutaminase antibody (anti-tTG) is currently the initial test of choice. The detection of anti-tTG of the IgA type by means of the ELISA method has a sensitivity of approximately 92.5% and a specificity of 98%, constituting the most efficient marker for the diagnosis of CD, in addition to being useful in monitoring adherence to the gluten-free diet.[13]

Prior to serological analysis, serum total IgA is essential, as up to 3% of celiac patients have selective IgA deficiency, which can result in false negatives. In these cases, alternative immunoglobulin G (IgG) tests should be employed, including anti-endomysium (anti-EMA), anti-tTG, and anti-gliadin deaminated peptide (anti-DGP) antibodies.[13]

Small bowel biopsy, currently performed by upper gastrointestinal endoscopy, allows the evaluation of the morphological characteristic changes of CD, particularly in the Kerckring folds of the distal duodenum and proximal jejunum. In these regions, thickening, increased granulosity, congestion and, in some cases, atrophy are observed. Additionally, the visibility of blood vessels is increased in approximately 70% of celiac patients.[14,15]

The histological classification of intestinal lesions follows the Marsh-Oberhuber system (Table 2), which categorizes the findings into four types: Type 1 (infiltrative), Type 2 (hyperplastic), Type 3 (destructive, with subtypes a, b, and c), and Type 4 (hypoplastic). Type 0 or 1 lesions require further investigation before diagnostic confirmation, whereas type 2 or 3 lesions are considered compatible with the definitive diagnosis of CD.[14-16]

TABLE 2 – Original Marsh-Oberhuber classification where the presence of subcategories in Type III can be observed.[16]

TYPE	FEATURES	
TYPE 0	Normal mucosa	
TYPE I	Increased number of ISL and infiltrative lesion	
TYPE II	Crypt hyperplasia and increase in the number of ILLs with hyperplastic lesions	
TYPE III	Villous atrophy and crypt hyperplasia with destructive injury	III a - Partial III b - Subtotal III c - Total

Adapted from Harris et al.[17]

After the introduction of a gluten-free diet, the regeneration of the intestinal mucosa can take from 6 to 24 months, and this time varies between patients.[14]

Infertility in CD

Infertility is defined as the absence of conception after a 12-month period of regular, unprotected sexual activity. It is estimated that approximately 15% of couples around the world face difficulties in getting pregnant. Of these, 15% have idiopathic causes, 20% have combined male and female factors, and 35% have exclusively female infertility. Currently, about 80 million women are affected by infertility globally, representing a health challenge that demands attention from professionals in the area.[18]

In this perspective, female infertility is classified into two clinical forms: primary, when the woman has never had a pregnancy, and secondary, when the woman has already gone through one or more pregnancies, regardless of the outcome - childbirth or abortion - but with current difficulty in conception. In women with untreated CD, both forms of infertility have been observed, despite the variability among studies on the subject.[18]

According to a survey conducted in North America, among infertile women (7.4% to 14%), about 15% had infertility without a defined anatomical or hormonal cause. In these cases, the prevalence of CD was estimated to be between 4% and 8%.[6]

In Brazil, a study of 76 adult women with CD showed significant gynecological changes compared to patients with irritable bowel syndrome (control): menarche occurred later (13.7 ± 1.5 years vs. 12.8 ± 1.6 years; $p < 0.0001$), secondary amenorrhea was observed in 28% of patients with CD, and the rate of miscarriages was 24.4% per pregnancy - twice as high as in the control group (11.6%).[4]

In addition, CD is more prevalent among women of reproductive age, and may manifest with gynecological and obstetric symptoms such as amenorrhea, late menarche, early menopause, recurrent miscarriages, and unexplained uterine bleeding.[5,6,19]

Impact of malabsorption on fertility

Malabsorption, characteristic of CD, contributes significantly to gynecological and obstetric complications, even in nutritionally asymptomatic patients. In this line of care, the most relevant nutrients are: zinc, folic acid and iron.[5,6,19]

The lack of zinc may be responsible for alterations in the hypothalamic-pituitary-ovarian (HPO) axis, affecting the release of gonadotropin-releasing hormone (GnRH), and, consequently, the secretion of luteinizing hormones (LH) and follicle stimulating hormone (FSH). It is associated with secondary amenorrhea, infertility, miscarriages, congenital malformations, intrauterine growth restriction, prematurity, post-term pregnancy, and perinatal death.[5,6]

Folic acid is essential for embryonic tissue proliferation, especially in neural development. Its deficiency can increase embryonic apoptosis and be associated with early pregnancy losses.[5,6,19,20]

Iron is critical for organogenesis and normal follicular development. The lack of this mineral can affect the progression of the follicle secondary to the antral follicle, in addition to compromising endometrial vascularization.[20]

In addition to specific nutritional deficiencies, the overall degree of malnutrition correlates with the severity of gynecological changes. In the study of Kotze (2004)[4], patients with severe malnutrition

had the highest rates of secondary amenorrhea (45.5%) and miscarriages (37.2%). Interestingly, even eutrophic patients had anemia (47.6%), suggesting that intestinal malabsorption can occur even in the absence of apparent weight loss.

Shortened fertile window and gynecological complications

Studies indicate that about 50% of women with untreated CD and secondary infertility have experienced miscarriage or other gestational complications. However, the etiology of these losses is identified in only 60% of cases, making the clinical management of the remaining 40% difficult.[5,6]

CD can compromise female reproductive potential by reducing the fertile window by several mechanisms: high prevalence during the reproductive period, late menarche, early menopause, possibility of infertility as an isolated clinical manifestation, in addition to the often late diagnosis - which can take more than 10 years and is usually established between 40 and 50 years of age.[6]

In view of these factors, it is essential to highlight that CD can lead to the loss of the fertile period due to a combination of elements: late onset of ovarian function, early termination of the reproductive cycle, isolated gynecological manifestations that hinder clinical suspicion, and diagnostic delay that compromises timely interventions.[5,6]

Considering the strong association between CD and pregnancy losses - especially in women without gastrointestinal symptoms - serological screening for CD is recommended in cases of recurrent miscarriages or unexplained secondary amenorrhea. This recommendation is supported by Brazilian and international evidence and can be decisive for the patient's reproductive rehabilitation.[5,6,19]

Treatment

Infertility and gynecological-obstetric disorders associated with CD can be, in many cases, reversed or attenuated with the adoption of a gluten-free diet. Although this intervention does not solve all conditions, the benefits are significant. A Brazilian study showed that, after the introduction of the diet, the rate of spontaneous abortions fell from 38.9% to 5.6% ($p = 0.045$), reinforcing the role of gluten as a factor directly involved in pregnancy losses - even in patients without apparent malnutrition.[4]

In addition, correction of nutritional status is often necessary, due to the malabsorption of essential micronutrients such as zinc, iron, folic acid, folate, and selenium, which also play a key role in reproductive health.[6,19]

Shared immunological mechanisms in infertility and pregnancy

Adequate placentation and gestational success depend on multiple biological events, including trophoblast functional development and endometrial neoangiogenesis. In vitro studies demonstrated that anti-tissue transglutaminase (anti-tTG) antibodies promote a series of changes that impair placental function.[5]

The process of angiogenesis, together with the action of steroid hormones, is essential to promote endometrial modifications that make the endometrium receptive to the blastocyst and initiate the process of embryonic implantation. In this context, evidence shows that anti-tissue transglutaminase (anti-tTG) antibodies play a detrimental role in human endometrial angiogenesis.[5]

These autoantibodies bind directly to endothelial cells of the endometrium, reducing the formation of new blood vessels, both in vitro and in vivo models. Angiogenesis impairment is attributed to the ability of anti-tTG to inhibit the activation of extracellular matrix metalloproteinase-2 (MMP-2), disrupt cytoskeletal fibers, modify the mechanical properties of cell membranes, and inhibit intracellular phosphorylation of the focal adhesion kinase (FLAG) and ERK (extracellular signal-regulated kinase) signaling pathways).[5]

In addition, anti-TTG antibodies are able to interact directly with human trophoblastic cells in a dose- and time-dependent manner, promoting an increase in the rate of apoptosis and a reduction in trophoblast invasiveness. These effects are attributed to inhibition of the activity of extracellular matrix metalloproteinases (MMPs), which are essential for tissue remodeling during implantation.[5]

In an experimental study, Sóñora et al.[21] evaluated the effects of anti-tTG antibodies on the Swan-71 cell line, derived from human cytotrophoblasts. This lineage mimics the syncytial microvillous surface of the placenta, a region where tTG is strongly expressed, and plays an important role in the regeneration and healing processes during early implantation. The results showed that anti-tTG antibodies significantly reduce trophoblastic proliferation and migration, increase apoptosis, and interfere with the removal of apoptotic bodies, through mechanisms involving the interaction between tTG and the milk fat globulin–EGF factor.[21]

This autoimmune model of placental aggression offers a plausible explanation for the occurrence of infertility, early pregnancy losses, intrauterine growth restriction, and small-for-gestational-age newborns in women with untreated CD. The proposed pathophysiology is comparable to that observed in antiphospholipid antibody syndrome, also characterized by dysfunction at the maternal-fetal interface.[5,21,22]

In summary, the current evidence supports the existence of a model of placental damage mediated by anti-tTG autoantibodies, which contributes significantly to the reproductive failures associated with active CD in patients who do not adhere to the gluten-free diet. 5:21-23

Gliadin, the main antigenic fraction of gluten, induces an intestinal inflammatory response in CD, with possible systemic repercussions, including in the

uterine environment. Studies have shown that this protein activates peripheral T lymphocytes, promoting the secretion of inflammatory cytokines such as interferon-γ (IFN-γ) and interleukin-2 (IL-2), which can negatively alter endometrial receptivity.[2,3,5,10]

Dysregulation of the expression of angiogenic, pro-inflammatory, and anti-inflammatory cytokines during the implantation window compromises endometrial development, negatively impacting fertility and increasing the risk of pregnancy losses. In addition, high levels of IL-6 and C-reactive protein (CRP) have been identified in amniotic fluid and cervicovaginal fluid, correlating with spontaneous preterm birth. These findings reinforce the role of systemic and local inflammation as a relevant factor in the pathophysiology of reproductive failures associated with CD.[5,19]

Gliadin also promotes increased intestinal permeability through activation of the CXCR3–MyD88 pathway, leading to zonulin release and impairment of intestinal epithelial barrier integrity. This condition, known as leaky gut, favors the translocation of bacterial components, such as lipopolysaccharides, into the systemic circulation.[13,19,22,24] These bacterial products, when they reach the endometrium, activate the NALP-3 inflammasome, a key mechanism of innate immunity. This activation leads to the processing of the cytokines IL-1β and IL-18, contributing to the inflammatory uterine environment. Studies have demonstrated endometrial overexpression of these cytokines in women with idiopathic recurrent miscarriage, as well as abnormal activation of caspase-1 and AUC, central components of the inflammasome.[5,10,17,22]

The hypothesis of an intestine-endometrial axis, mediated by intestinal barrier dysfunction and secondary endometrial inflammation, emerges as an explanation for infertility and pregnancy losses in patients with CD. This pathophysiological interrelationship opens new perspectives for the approach of adverse reproductive outcomes in celiac women, even in the absence of classic gastrointestinal symptoms.[5,19,22]

Gestational outcomes in CD

Numerous studies have revealed an increased risk of preterm births, intrauterine growth restriction, low birth weight, and miscarriage in women diagnosed with CD after delivery. However, those diagnosed and users of a gluten-free diet ,did not have a higher risk of pregnancy when compared to undiagnosed women.[6,19,22,23]

In the placenta, tissue transglutaminase is expressed on another surface of the syncytiotrophoblast microvillus membrane and is accessible to maternal antibodies. Thus, anti-tTG antibodies can affect trophoblast survival by reducing the proliferation rate and promoting apoptosis, impacting the impairment of the functional development of the placenta.[19]

Therefore, during pregnancy, the pregnant woman should undergo multidisciplinary prenatal care. A gluten-free diet should be advised, and anti-tTG levels should be monitored, in addition to regular ultrasound examinations due to the risk of intrauterine growth limitation.[19]

CONCLUSION

In summary, CD exerts relevant impacts on female fertility and the course of pregnancy, which can be significantly reduced, and, in many cases, prevented through the early adoption of a gluten-free diet. However, the main challenge remains in the identification and timely diagnosis of celiac women of childbearing age, due to the clinical heterogeneity, genetic variability, and multiplicity of environmental factors involved in the disease.

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