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CELIAC DISEASE- INFLUENCE ON FERTILITY, PREGNANCY COURSE, POSTNATAL OUTCOMES - LITERATURE REVIEW

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ABSTRACT

Celiac disease is a systemic autoimmune disease caused by the ingestion of gluten in genetically predisposed individuals and is considered a significant but not well-recognized cause of female reproductive health problems. In this paper, a literature review of the medical literature from PubMed/MedLine, Google Scholar, and Cochrane databases was conducted to identify literature on the relationship between celiac disease and fertility, pregnancy outcomes, and birth outcomes. The medical literature appears to indicate that untreated or undiagnosed celiac disease may contribute to problems of delayed conception, unexplained infertility, recurrent miscarriage, and other problems of disturbed reproductive health. Where the problem lies, is that there is a lack of early recognition of celiac disease in adults because of nonspecific presenting symptoms. In addition, active disease during pregnancy has been associated with adverse pregnancy and birth outcomes, including intrauterine growth retardation, low birth weight, small for gestational age babies, preterm birth, and even death of the baby. Often problems of conception are the first symptom of celiac disease. Evidence also suggests that adherence to a glutenfree diet may greatly mitigate these risks and improve reproductive and perinatal outcomes. Increased awareness of celiac disease among women presenting with unexplained infertility or poor pregnancy history may lead to early diagnosis and effective management of the disease. A good course of action for the future, would be to compile a list of people in each country, with celiac disease who could support one another.

KEYWORDS

Celiac Disease, Autoimmune, Pregnancy, Fertility, Newborn

CITATION

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1.1 Introduction

It is defined as a "chronic immune mediated enteropathy due to gluten sensitivity in genetically predisposed individuals." Celiac disease is present in 1% of the population. This disease develops in patients who most commonly carry the HLA-DQ2 or HLA-DQ8 haplotypes, which determine the presentation of gluten peptides to immune system cells and the initiation of an abnormal immune response [9, 14]. Although the classic clinical presentation includes gastrointestinal symptoms and malabsorption syndrome, it is now known that celiac disease is systemic in nature and may also manifest extraintestinally, including through reproductive disorders and obstetric complications [4, 9].

1.2. Methodology

This article is a medical literature review based on publications on PubMed/MedLine, Google Scholar and Cochrane Library. Publications written between 2015-2025 were included.

The selection process included both original research articles and review papers. The analysis focused on impact of celiac disease on fertility and pregnancy course, additionally discussing the potential side effects of maternal disease on newborn. Small case reports and studies with no clinical outcomes were not considered. The procedure of selecting studies was carefully pondered by the all authors. Eech of the authors independently pondered reviews of titles and abstracts, then followed full texts. Any doubts were discepted together until satisfying agreement was accomplished.

2.1. Patomechanism of Celiac Disease

The pathogenesis of celiac disease is complex and involves the interaction of various environmental, genetic, and immunological factors. Gluten and gliadin play a crucial role in the pathogenesis of celiac disease. The gliadin peptides, once they have passed the intestinal barrier, are deamidated under the influence of tissue transglutaminase 2. The deamidated peptides have a high affinity for HLA-DQ2/DQ8 molecules. This activates the CD4+T- lymphocytes in the small intestinal mucosa. This results in an enhanced proinflammatory reaction. This results in the production of inflammatory cytokines, intraepithelial lymphocyte activation, damage to enterocytes, crypt hyperplasia, and villous atrophy of the small intestine. This represents a histopathological sign of active celiac disease [9, 14]. At the same time, autoantibodies are also produced against tissue transglutaminase, endomysium, and deamidated gliadin peptides. This indicates the autoimmune nature of the disease [9, 12].

2.2. Methods of Diagnose

The diagnosis of celiac disease is based on a detailed investigation of the patient's presentation, serological tests, histopathological examination, and sometimes genetic tests. In clinical practice, the first step in the diagnosis of celiac disease is considered to be the measurement of IgA class antibodies against tissue transglutaminase (anti-tTG IgA) along with the measurement of total IgA to exclude the possibility of Selective IgA Deficiency (SIgAD). This is considered the first line test for celiac disease, while anti-endomysial antibodies are considered a highly specific test for the diagnosis of celiac disease. In contrast, antibodies against deamidated gliadin peptides (DGP) are not currently recommended as a baseline test, and their utility increases mainly in specific situations, particularly in cases of low IgA levels or IgA deficiency [18, 24]. Classic confirmation of the disease continues to rely on histological analysis of small intestine biopsies, while genetic testing for HLA-DQ2 and/or HLA-DQ8 serves a supplementary role, as a positive result alone does not determine the diagnosis [18].

It has also to be noted that serological tests for celiac disease have to be done when the patient is on a diet containing gluten; otherwise, it may lead to false negative results [18].

In the context of reproductive health, it has been noted that women with unexplained infertility, recurrent miscarriages, menstrual disorders, or iron-deficiency anemia are to be considered for tests for celiac disease [9, 18].

2.3. Differential Diagnosis

The differential diagnosis of celiac disease is a very important aspect in clinical practice, because of the extremely variable clinical picture of the disease (especially in adult patients) and the frequent oligosymptomatic and extraintestinal forms. Besides the classical gastrointestinal symptoms, such as diarrhea, weight loss, or signs of impaired absorption, the disease can also manifest through anemia, menstrual disturbances, infertility, multiple abortions, or chronic fatigue, all leading to an increased risk of being misdiagnosed.

Celiac disease is diagnosed much more often in women than in men. It is actually the extragastrointestinal symptoms that are the hallmark of newly diagnosed celiac disease in adulthood [9, 12, 14]. Therefore, celiac disease needs to be differentiated not only from other intestinal diseases but also from other conditions presenting predominantly with extraintestinal manifestations [9, 18]. In practice, it is of major interest to differentiate celiac disease from nonceliac gluten sensitivity, wheat allergy, irritable bowel syndrome, and other causes of malabsorption syndromes [23, 24, 30]. Nonceliac gluten sensitivity may present with symptoms similar to those of celiac disease, but it is not accompanied by typical autoimmune markers or characteristic changes in the small intestinal mucosa [23, 30]. Wheat allergy, on the other hand, is characterized by a different immune mechanism, most commonly IgE-dependent, and its diagnosis requires a different diagnostic algorithm [23]. In the case of irritable bowel syndrome, the similarity of clinical symptoms may lead to a delay in the diagnosis of celiac disease, particularly in patients without overt deficiency symptoms [12, 24]. The proper interpretation of serological and histopathological tests, as well as clinical data, plays a key role in the differential diagnosis, as mentioned in the previous paragraph of this paper. The differential diagnosis of celiac disease requires a comprehensive approach that combines the clinical picture with the results of additional tests and the exclusion of other diseases with similar manifestations [11, 12, 24].

2.4. Treatment

The cornerstone of the management of celiac disease is a strict and lifelong gluten-free diet.

It means the complete elimination of wheat, rye, and barley, and their derivatives from the general diet. It is the only approach that has been proved to be effective in the management of the disease and leads to the resolution of symptoms, normalization of immunological tests, and gradual healing of the mucosa of the small intestine [31, 32, 33, 34]. Gluten free dietary management should be supervised by an experienced clinical dietitian, since it is a difficult task and there is a high rate of unintentional gluten exposure, even when patients claim to be on a gluten free diet [31, 32]. Another aspect of the management of celiac disease is the correction of nutritional deficits, particularly of iron, folic acid, B12, D, and calcium [31, 33]. After the disease has been identified, monitoring of the patient at regular intervals is essential. It includes clinical evaluation, testing for specific antibodies related to the disease, evaluation of dietary compliance, nutritional assessment, and possible complications.

It is essential for long-term management of the disease not only to control the symptoms but also to avoid long-term complications of intestinal villous atrophy [32, 34, 35]. In some patients, where there is no improvement of symptoms or where there are persisting symptoms even after a strict gluten-free diet, treatment-resistant celiac disease might be considered.

It is usually associated with the ingestion of gluten by mistake but also requires differential diagnosis of the cause of the symptoms [32, 35]. A rare but severe form is refractory celiac disease, in which, after ruling out other causes, dietary management and glucocorticoids (most commonly budesonide or prednisone) are used [35]. Despite intensive research into non-pharmacological and pharmacological therapies, there are currently no drugs approved as an alternative to a gluten-free diet; potential new strategies are currently only supportive in nature and remain in the clinical trial phase [36].

3. Celiac Disease in Adults- Underrated Number of Diagnoses

When people do think about celiac disease, most of them believe that it affects children. However, surprisingly, there is an increasing number of new cases of cealiac disease being diagnosed in adulthood. In childhood, symptoms are easier to notice, whereas in adults they can be nonspecific and may not involve the digestive system at all. In many patients, the clinical picture of the disease differs from the classic manifestations of malabsorption syndrome and includes nonspecific symptoms such as chronic fatigue, anemia, menstrual irregularities, reduced fertility, or recurrent pregnancy loss [9, 12, 14]. The most common intestinal and extraintestinal symptoms are listed in Table 1, below. This type of clinical presentation contributes to delayed diagnosis, as patients are often diagnosed with other conditions, and celiac disease is not considered at an early stage of diagnosis [9, 18].

Studies on reproductive health also partly point to the problem of underdiagnosis.

Meta-analyses and review studies suggest that celiac disease is more common in certain groups of women with infertility or reproductive failure than would be expected based on the number of cases already diagnosed [10, 15, 23]. It should be emphasized that gynecological and obstetric symptoms may constitute the sole or predominant manifestation of celiac disease, which increases the risk of its being overlooked [9]. Characteristic extraintestinal symptoms of celiac disease, such as chronic inflammation, immune disorders, and nutritional deficiencies, may remain an undiagnosed underlying cause of reproductive disorders for a long time [12].

The concept of 'hidden celiac autoimmunity' (sometimes also called seronegative or latent celiac disease) has been reported, suggesting that some women, who otherwise would have been unrecognized, show signs of immune activation with immunological evidence of the disease [11]. Celiac disease that is not diagnosed or treated may later develop autoimmune conditions such as Hashimoto's disease. An additional factor complicating the accurate estimation of the number of patients is the self-initiation of a glutenfree diet before the completion of a full diagnostic workup, which may reduce the sensitivity of serological tests and complicate the interpretation of histopathological findings [18, 24]. Furthermore, the coexistence of non-celiac gluten sensitivity and other conditions with a similar clinical presentation can blur diagnostic boundaries and delay the establishment of a correct diagnosis [23, 30]. Consequently, it must be assumed that the actual number of adult patients with celiac disease remains higher than the number of formally diagnosed cases, and increased clinical vigilance regarding atypical and extraintestinal manifestations of the disease is crucial for improving detection rates [11, 12, 24].

Table 1. Intestinal and extraintestinal manifestations of celiac disease in adults

Intestinal manifestation	Extraintestinal manifestation
Chronic diarrhea	Iron- deficiency anemia
Abdominal pain	Chronic fatigue
Bloatedness	Foliate and witamin B12 deficiency
Weight loss	Menstraul disorders
Malabsorption	Declined fertility
Dyspeptic symptoms	Idiopathic infertility
Abdominal misease	Delayed conception
	Recurrent miscarriages
	Obstetric failures
	Premature delivery
	Fetal growth restriction

Elaborated by the author based on source data *[9,10,12,13,14,15,18,24,23,24,25,28,30]*

3.1 Celiac Disease- Influence on Fertility

Celiac disease is a long-term autommuned disorder that is increasingly reported as an influential factor associated with reproductive failure in addition to its manifestations affecting the gastrointestinal system. In a systematic review, it was indicated that celiac disease was an important factor associated with reduced female fertility, especially when not diagnosed or not actively treated, but not consentaneously established yet [9, 12, 14, 23, 30]. It is thought to be of particular concern in women with unexplained infertility, delays in conceiving, menstrual irregularities and a history of repeated pregnancy loss [9, 12, 18]. Celiac disease is one of the causes of so-called “idiopathic” infertility due to its nonspecific symptoms, as mentioned above. Therefore, in conjunction with the clinical presentation, consideration should be given to diagnosing celiac disease in patients who are struggling with infertility and also have any other clinical symptoms that may indicate celiac disease. [10]. Unfortunately, in clinical practice, celiac disease often remains undiagnosed for a long time, and reproductive disorders may be its first manifestation [11, 12]. The possible factors that lead to a reduction in fertility in celiac disease are believed to be multiple. The most common literature references chronic inflammation, autoimmune phenomena, the presence of autoantibodies and micronutrient deficiencies caused by malabsorption, such as iron, folic acid, vitamin B12, other vitamins and minerals [12, 18, 20, 24]. Several authors have also found a decrease in anti-Müllerian hormone concentration in women with celiac disease which could imply a possible negative impact of the disease on ovarian reserve [8]. On the other hand, some opinions in the existing literature believe that the negative effect of celiac disease on fertility is greater before pregnancy is diagnosed rather than after [16]. In the sequel, it should be recognized that celiac disease may constitute a potentially reversible cause of fertility disorders, and its early diagnosis and implementation of a gluten-free diet may be important for improving reproductive outcomes [12, 16, 18, 23]. For this reason, it seems reasonable to consider testing for celiac disease in women with unexplained infertility and other reproductive failures [9, 14, 25]. However, the validity of routine screening of all asymptomatic patients has not been confirmed [19].

3.2 Celiac Disease- Influence on Pregnancy Course

Can celiac disease cause complications during pregnancy? The clinical effects of celiac disease are not confined to the intestine but also have implications for pregnancy and the fetus. Literature evidence shows that poor obstetric outcomes are more common in women with celiac disease, especially those who are undiagnosed or untreated, than in the general population [5, 14, 28]. Chronic inflammatory processes (particularly in women with celiac disease who follow a diet containing gluten), autoantibodies, and micro- and macro-nutrient deficiencies (iron, folic acid, vitamin B 12) have a negative impact on embryo implantation, placental development, and fetal growth [12, 20]. These mechanisms are not yet fully understood, but they are multifactorial in nature and include both the consequences of chronic inflammation and immune disorders, as well as nutritional deficiencies secondary to damage to the intestinal mucosa [12, 20, 23, 24]. In the course of celiac disease, there may be inflammation within the endometrium as well as abnormalities in hemostasis, which together may create unfavorable conditions for proper embryo implantation [12]. Special emphasis is given to anti-tissue transglutaminase antibodies, which can influence not only the gastrointestinal tissues but possibly the uterine milieu and the trophoblast. Autoantibodies may exert a differential effect on the invasion

of trophoblast and disturb the angiogenesis of the endometrium, resulting in failure of implantation of embryo and early placentation [24]. Sustained immunoactivation and hyperexpression of pro-inflammatory cytokines (TNF-α, IFN-γ and IL-6) are supposed to interfere in the establishment of endometrial receptivity and immune tolerance at maternal-fetal interface [23]. Deficiencies of micronutrients may also impact on placental development. Folate and vitamin B12 both play important roles in a normal pregnancy development implying that developing any deficiencies within women who suffered from celiac disease can then contribute to adverse obstetric outcomes.

Hence, supplementation and correction of deficiencies is therefore very important for pregnant women with celiac disease [20]. The reviewed literature also highlighted an increased risk of miscarriage, preterm birth, fetal growth restriction, low birth weight, and other adverse perinatal outcomes [5, 13, 25, 28]. More recent studies also appear to support this hypothesis. [3, 27]. In women with celiac disease, the risk of preterm birth was approximately 35% higher, the risk of intrauterine growth restriction was more than double, and the risk of low birth weight was increased by approximately 63% [28]. A significantly higher risk of spontaneous miscarriage, fetal growth restriction, preterm birth, and lower mean birth weight (by an average of 176 g) was also confirmed in women with celiac disease [3, 5, 13]. It is important to note, however, that this risk is not the same for all patients. Adverse obstetric outcomes were primarily associated with undiagnosed celiac disease, whereas early diagnosis and treatment with a gluten-free diet were no longer significantly associated with the complications analyzed [5, 16]. Interestingly, among women following a strict gluten free diet during pregnancy, the median birth weight was higher, and the diet itself was not associated with worse obstetric outcomes [26]. When the diagnosis was made before the first pregnancy, perinatal complications were less common [25]. The authors agree that with early diagnosis and the implementation and strict adherence to a gluten free diet, perinatal outcomes may improve, and the risk of certain complications may decrease [7, 14, 26].

3.3. Celiac Disease- Fetal and Newborn Outcomes

Maternal celiac disease was an independent risk factor for low birth weight in newborns [1]. Some studies have also suggested a possible association between celiac disease and certain congenital anomalies and long-term health consequences in offspring, although these findings require further clarification [1, 2, 6, 13]. Celiac disease may be associated with an increased risk of heart defects and urinary tract defects in the child. According to the authors' calculations, the risk of heart defects was approximately 1.58 times higher, and the risk of urinary tract defects was approximately 1.56 times higher compared to pregnancies in women without celiac disease; the association was stronger when celiac disease was diagnosed only after delivery, suggesting greater significance of undiagnosed or untreated disease during pregnancy.

No significant association was found with other analyzed groups of defects, such as: central nervous system defects, genital defects, musculoskeletal defects, craniofacial clefts, defects of the respiratory system, gastrointestinal tract, abdominal wall, or chromosomal aberrations [6]. However it should be remembered that the child is at increased risk of neural tube defects which has links to compromised vitamin absorption and deficiency of folate and vitamin B12 which are also associations seen in women with celiac disease. [6, 20]. It also must be borne in mind that this is a potential risk and more clearly associated with the pathophysiology of the mother's disease, although, not all studies echo this. At the same time, it should be noted that not all studies confirm these associations. When a group of women with biopsy confirmed celiac disease was studied, no significant increase in the risk of low birth weight or fetal anomalies was observed [27]. This suggests that the impact of the disease may depend on the time of diagnosis, the degree of disease control, and adherence to a gluten-free diet [1, 3, 13, 27]. Nevertheless, the impact of maternal celiac disease on the child is not limited only to the period of pregnancy and the perinatal period. The offspring of women with celiac disease were found to have a higher long-term incidence of gastroenterological disease when followed up until the age of 18 [1]. An increased risk of long term infectious morbidity was observed in these children, with more frequent bacteremia and central nervous system infections; after adjusting for confounding factors, this risk remained significantly higher [2]. This means that maternal celiac disease may be associated not only with worse neonatal outcomes but also with the child's later susceptibility to certain health problems [1, 2]. With regard to the likelihood of a child developing celiac disease, it is suggested that both genetic predisposition and prenatal exposure contribute to the development of the disease.

Celiac disease is a familial disease; however, the onset of the disease is largely influenced by genetic predisposition linked to the presence of the HLA-DQ2 and HLA-DQ8 haplotypes. It is essential to understand that the lack of HLA-DQ2 and HLA-DQ8 is likely to rule out the disease from a clinical perspective; a positive test for an individual allele is not sufficient to diagnose the disease. It is difficult to provide precise data on the

inheritance of celiac disease based on the cited literature [17, 21, 22]. However, it is estimated that if the mother suffers from celiac disease, the child, as a first-degree relative, has a 10% risk of developing the disease. Note that the prevalence of celiac disease in the general population is 1%. It is assumed that the higher the intake of gluten by the mother during pregnancy, the higher the risk of celiac disease in the offspring, and the higher the intake of fiber, the lower the risk of developing the disease [21]. Overall dietary quality during pregnancy may modify the risk of celiac disease in the child [17]. For this reason, children of mothers with celiac disease should be considered a high-risk group requiring increased diagnostic vigilance and appropriately planned monitoring of their health.

4. Association With Other Autoimmune Diseases

A shared genetic background, particularly associated with the HLA-DQ2 and HLA-DQ8 haplotypes, as well as ongoing exposure to gluten in predisposed individuals, promotes the development of autoimmunity not only within the small intestine but also in other organs [12, 24, 30]. The literature highlights the fact that patients with celiac disease more frequently present with coexisting autoimmune diseases, which may have both diagnostic and prognostic significance [12, 14, 23]. Of particular clinical importance are autoimmune thyroid diseases, type 1 diabetes, and other autoimmune disorders, which can alter the clinical presentation of celiac disease and delay its diagnosis [14, 23, 30]. Chronic activation of the immune system, the presence of autoantibodies, and persistent inflammation may affect not only the course of celiac disease itself but also the development or exacerbation of coexisting autoimmune disorders [12, 24]. From a clinical practice perspective, the correlation between other autoimmune diseases and celiac disease is significant, as it should increase diagnostic vigilance for celiac disease, especially in cases of nonspecific or extraintestinal symptoms [9, 14, 23].

At the same time, a diagnosis of celiac disease may serve as a basis for a more thorough evaluation of the patient for the coexistence of other autoimmune disorders [12, 30].

When providing medical care to a patient with celiac disease, the possibility of another autoimmune disease should always be considered. Heightened vigilance benefits the patient and positively impacts long-term patient care [12, 14, 24, 30].

5. Future Directions. Discussion

Celiac disease in adults is a clinical picture with varied manifestations, which often makes it difficult to diagnose this pathology, especially if extraintestinal symptoms predominate [9, 11, 12, 14]. The data presented suggest that if celiac disease is not diagnosed or treated, it can negatively impact female fertility, lead to reproductive failure, and worsen pregnancy outcomes, including miscarriages, preterm birth, growth restriction, and low birth weight [5, 10, 12, 16, 25, 28]. However, the clinical significance of celiac disease does not only relate to the health status of the mother but also to the newborn's status, particularly the child's health, including the risk of certain complications during birth or later on [1, 2, 3, 6]. Nevertheless, the research data indicate the possibility of eliminating some negative effects of celiac disease on the course of pregnancy, including the improvement of pregnancy outcomes, if this pathology is diagnosed early and the patient starts the strict diet [5, 16, 18, 26]. It should therefore be stressed that the increased diagnostic vigilance of celiac disease in women of childbearing age, especially in cases of unexplained infertility, recurrent miscarriages, and complications of pregnancy, is of considerable importance not only for the health of the patient but also for the course of pregnancy and the development of the offspring [12,14,23].

In conclusion, although celiac disease is an autoimmune condition that is increasingly being diagnosed in adults, public awareness of the disease remains low. As a result, people with celiac disease may feel isolated after receiving their diagnosis and excluded, particularly in social meeetings. Hopefully, gluten free products are becoming more popular and what is more important, they are more available for everyone. Public and medical staff awareness must be increased to enable early diagnosis. There are no screening programs for celiac disease in Poland, and there is no registry of people diagnosed with celiac disease. Such the registry could bring patients together, allowing them to support one another and offer advice to each other.

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