

Celiac Disease and the Risk of Infertility

Pablo Olivera MD, Juan Lasa MD*

Gastroenterology Section, Internal Medicine Department, CEMIC, Buenos Aires, Argentina

*Corresponding author: drjuanslasa@gmail.com

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Abstract Celiac Disease is a chronic inflammatory disease, caused by an abnormal immune response triggered by intestinal exposure to dietary gluten, the protein fraction of wheat, rye and barley, in genetically susceptible individuals. Among atypical presentations of Celiac Disease, reproductive disorders and adverse pregnancy outcomes have been reported. Infertility is defined as the impossibility of conceiving after 12 months of unprotected intercourse. It can be related to both male and female factors, with the latter subdivided into ovarian, tubal, endometrial or unexplained causes. Celiac Disease has been related to infertility, but the evidence is inconclusive. In this review, we discuss the effect of Celiac Disease in both male and female fertility, as well as the possible mechanisms that may be involved.

Keywords: *celiac disease, gluten free diet, infertility*

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1. Introduction

Celiac disease (CD) is a chronic inflammatory disease, caused by an abnormal immune response triggered by intestinal exposure to dietary gluten, the protein fraction of wheat, rye and barley, in genetically susceptible individuals. This genetic susceptibility to develop CD has been attributed to the presence of HLA DQ2 and DQ8 haplotypes, which are necessary but not sufficient for the development of the disease, since HLA DQ2 is carried by approximately a third of the general population [1,2].

CD is a systemic disease, which can have different forms of presentation, with a wide clinical range. Typical symptoms are malabsorption-related and include chronic diarrhea, weight loss, abdominal bloating or iron-deficiency anemia, which in classic forms of CD usually lead to the diagnosis during childhood. However, CD can also present with several non-gastrointestinal symptoms and it may not be easily recognized until adulthood. As a systemic disease, CD may affect many organs; hence, it may present as dermatitis herpetiformis, aphthous stomatitis, osteopenia, hypertransaminasemia, dental enamel defects and various neurological complications such as depression or ataxia [3]. Malignant complications such as enteropathy-associated T-cell lymphoma and adenocarcinoma of the jejunum are infrequent.

An association with autoimmune disorders is often seen in CD, and include type 1 diabetes, autoimmune thyroiditis, Sjögren's syndrome, systemic lupus erythematosus, autoimmune hepatitis, primary biliary cirrhosis, IgA deficiency, Addison's disease, atopy, systemic and cutaneous vasculitis, psoriasis, and polymyositis [4].

Among atypical presentations of CD, both female and male infertility problems and adverse pregnancy outcomes have been described [1,2]. Infertility is defined as the impossibility of conceiving after 12 months of unprotected intercourse [5]. It can be related to both male and female factors, with the latter subdivided into ovarian, tubal, endometrial or unexplained causes. It is a relatively frequent condition, affecting approximately 8% to 12% of couples [6].

CD has been related to infertility, but the evidence is inconclusive. In this review, we discuss the effect of CD in both male and female fertility, as well as the possible mechanisms that may be involved.

2. Female Infertility in Celiac Disease

In the last four decades, there has been a growing number of reports describing a association between fertility problems and CD. In 1970, Morris et al. reported three celiac patients with infertility, who were able to give birth after dietary gluten restriction [1], establishing the possible relationship between these two entities, and the potential beneficial role of gluten free diet (GFD). On the contrary, Jackson et al described a cohort of women suffering from infertility that were tested for CD by means of serology [7]. The authors compared the prevalence of positive findings to the background rate in the general US population: they found that their cohort had a lower prevalence. Another inconclusive finding was reported by Choi et al, who studied women attending to an infertility clinic [8]. They failed to find a higher prevalence of CD than the one reported in the general US population. It is worth mentioning however that these two studies lacked an adequate design for this purpose.

Several case-control studies have been published, and they share common features [9,10,11]. Firstly, they include patients with a diagnosis of unexplained infertility, which means that potential ovarian, tubarian and endometrial causes were already ruled out. Most of them used antigliadin, antitransglutaminase or antiendomysium antibodies to screen the patients enrolled in their studies, and biopsy was reserved for those patients with positive serology. Interestingly, most of them fail to find a statistically significant increased prevalence of CD in women with unexplained infertility – a finding that becomes significant when pooled analysis is performed [12].

More recently, in a large Swedish population-based cohort study, Zugna et al. included 11495 women with CD and 51109 controls, and found a similar fertility rate of both groups, but the fertility of celiac women was decreased in the 2 years preceding CD diagnosis [13].

In a case-control study, Sher et al. observed that celiac patients had a significant smaller mean number of children compared with controls before diagnosis of CD, but after diagnosis and GFD, the number of children were similar in both groups [14].

These data strongly indicate that impaired fertility is more common in patients with active CD when a GFD is unlikely to have been initiated, and show the benefit of gluten restriction in these patients. On the other hand, based on the results of case-control studies, unexplained infertility may have a significantly higher risk for CD, so it may be reasonable to exclude CD in women with this condition, after excluding other potential diagnoses.

2.1. Possible Pathogenic Mechanisms

The exact mechanisms underlying infertility in CD are still not clear, but several hypotheses have been described. Probably, the malabsorption in these patients, and the subsequent nutrient deficiency has a role in the pathogenesis. However, infertility cannot be explained solely by malabsorption and other mechanisms such as autoimmunity may have a role.

The villous atrophy seen in CD, generally leads to malabsorption and may produce deficiencies in micronutrients such as zinc, selenium or folic acid [15-20]. Both zinc and selenium deficiencies cause impaired synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which subsequently cause abnormal ovarian axis function, spontaneous abortions, secondary amenorrhea, and pre-eclampsia [21,22]. Folic acid deficiency has also been implicated in the pathogenesis of infertility in CD. Folic acid has an important role in nucleic acid metabolism, and therefore has an impact in rapidly proliferating tissues like the embryo.

Nevertheless, in different series, celiac infertile women with total or subtotal villous atrophy failed to show signs of nutritional deficits [23,24,25]. For example, in the series published by Collin et al., celiac patients showed neither severe malnutrition nor signs of trace element deficiency; only two had iron deficiency [23].

Consequently, current evidence does not support nutritional deficiencies and malabsorption as the main pathological mechanism of infertility in CD. In recent years, other possible mechanisms to explain its pathogenesis have been investigated, such as autoimmune mechanisms.

Anti-tissue transglutaminase antibodies (anti-tTG), appear to be not only a diagnostic marker in celiac patients on gluten-containing diet, but also have been implicated in the pathogenesis of many CD manifestations [26,27,28], including fertility and pregnancy complications. The enzyme transglutaminase can be found in many organs, and may have a role in interactions of cells with the surrounding extracellular matrix [29], in processes of cell adhesion, migration and spreading. It has been demonstrated that this enzyme is present in endometrial cells and also in stromal and trophoblast placental cells [30]. Therefore, circulating anti-tTG may bind to placental and endometrial cell surfaces, preventing implantation. It has been demonstrated that anti-tTG class IgA can bind directly to the syncytial surface of the placenta, inhibiting tTG activity and compromising placental function [31]. Also Di Simone et al. showed that anti-tTG class IgG bind in vitro to human trophoblast, and cause decreased invasiveness, decreased activity of cellular matrix metalloprotease and cellular apoptosis [32]. The same group demonstrated an additional mechanism mediated by anti-tTG: they showed that these antibodies have a detrimental effect on human endometrial angiogenesis [33]. These observations provide an immune-mediated mechanism for infertility and adverse pregnancy outcomes seen in active CD.

3. Male Infertility in Celiac Disease

Compared with the number of studies evaluating female infertility in CD, evidence regarding celiac male partners fertility is relatively scarce. Although the existence of reports dating back to the 1950's stating a possible association between CD and male infertility [34], recent studies have failed to show an increased prevalence of CD in this population. In a relatively large Dutch case-control study, Hogen Esch et al. described no differences in terms of CD prevalence between infertile male and the general population [11]. In a Swedish population-based cohort study, Zugna et al. compared fertility in 7121 men with biopsy-proven CD with 31677 controls. They found that there were no differences in the cumulative number of children during fertile years between men with CD and controls, and there were no difference in fertility before and after the diagnosis of CD [35].

4. Conclusions

There is increasing evidence to support a possible association between CD and infertility. This complication may not be exclusively due to a deficiency in micronutrients absorption, and an autoimmune mechanism may contribute to its development. Women presenting with infertility without a clear cause should be screened for CD. Although more evidence is needed, there seems to be a beneficial role of GFD in terms of fertility, judging from the results of large cohort studies.

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