Celiac disease and infertility: a mini review

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Summary

Celiac disease (CD) is a chronic enteropathy whose clinical manifestations vary greatly. The atypical symptoms of CD, usually seen in older children and adults, include reproductive changes, such as infertility, recurrent miscarriage, intrauterine growth restriction and preterm delivery. Those changes can involve both women and men. The etiology of infertility in women can be related to a deficiency in essential nutrients, a shortened reproductive period or deregulation of the immune system. In men, instead, infertility is linked to gonadal dysfunction. Abnormalities of sperm morphology and motility are found in both untreated and treated patients.
In conclusion, the reproductive changes in the celiac patient are multifactorial in nature. These pathological manifestations are correlated to different concurrent genetic, nutritional and environmental factors, besides exposure to gluten. However, a strict gluten free diet is important to prevent fertility disorders in adulthood.

Key words: Celiac disease, infertility/subfertility, diet.

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Riassunto

La malattia celiaca (MC) è un'enteropatia cronica le cui manifestazioni cliniche variano notevolmente. I sintomi atipici della MC, che si riscontrano più frequentemente negli adolescenti e negli adulti, comprendono anche disordini della sfera riproduttiva (infertilità, aborto spontaneo ricorrente, ritardo di crescita intrauterina e prematurità). Tali disordini possono interessare sia le donne che gli uomini. L'eziologia dell'infertilità nelle donne può essere correlata a: carenza di nutrienti essenziali, riduzione del periodo riproduttivo ed alterazioni del sistema immunitario. Negli uomini invece l'infertilità sembra legata ad una disfunzione gonadica, consistente in anomalie della morfologia e della motilità degli spermatozoi. Tali alterazioni sono riscontrabili sia nei pazienti non trattati che in quelli trattati.
In conclusione, le alterazioni della sfera riproduttiva nel paziente celiaco hanno un'eziopatogenesi multifattoriale. Esse sono correlate, oltre che all'esposizione al glutine, a fattori genetici, nutrizionali e ambientali concomitanti. Una dieta priva di glutine è quindi fondamentale per prevenire l'insorgenza di infertilità in età adulta.

Parole chiave: malattia celiaca, infertilità, dieta.

Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten-containing grains in susceptible individuals. The disease was first described in 1888 by *Samuel Gee*, who reported patients with malabsorption related to a reversible atrophy of intestinal mucosa of the small bowel. The term celiac disease was used in the second half of the 1940's for the first time and at that time gluten sensitivity was observed exclusively in children (1). The prevalence of CD in the general population is about 0,5-1% with a female predominance (female/male: 3/1); however, it may vary in different geographical areas. The genetic

predisposition is related to human leucocyte antigen (HLA) class II genes: most CD patients are HLA-DQ2 positive, while those remaining are usually HLA-DQ8 positive (2). The clinical manifestations of CD show wide variation, and the clinical spectrum is extensive, including cases with either typical intestinal or atypical extraintestinal features, silent forms and potential forms (3). The atypical clinical picture is usually seen in older children and adults and may include persistent anemia due to iron, folic acid or vitamin B12 deficiency, hypertransaminasemia, osteoporosis, neurological symptoms (epilepsy, ataxia), hypoproteinemia, hypocalcaemia, dermatitis herpetiformis, recurrent cankers, hematologic signs and reproductive changes (4, 5). This form corresponds to 50-90% of undiagnosed cases. In cases of potential CD the immuno-serologic tests and family history are positive, but the histopathologic examination yields a negative result (6, 7). Untreated celiac disease has been associated with higher rates of infertility, recurrent miscarriage, intrauterine growth restriction (IUGR), preterm delivery, preeclampsia, placental abruption, stillbirth and fetal malformations (i.e. cardiac malformations, neural tube defects) (8).

Several studies have demonstrated the implications of celiac disease on the reproductive health of women and some of them suggest a higher prevalence of undiagnosed celiac disease in patients with infertility. In this regard, in 2003 *Fasano et al.* published a very large study examining the prevalence of undiagnosed CD in American patients of both genders. That study reported a 6.25% prevalence of celiac disease in patients presenting with "*idiopathic*" infertility though the genders of those patients were not specified (9). In 2011, *Choi et al.* enrolled 191 patients, ages 25–39, who presented to their center for care of either primary or secondary infertility of at least 12 months duration. In the screened population of infertile women 2,1% had CD. The observed frequency of 2,1% was not significantly different from that in an age-matched North American population, but in patients with unexplained infertility, the CD prevalence of 5,9% was significantly higher (10).

The etiology of infertility seems to be related to many mechanisms of action. First of all, a deficiency in essential nutrients such as iron, folic acid, vitamin B12, zinc and selenium in the mother may be found; but nutritional factors are probably not of major importance in the unfavorable outcomes (11). In addition, coeliac women have a shortened reproductive period with delayed menarche and early menopause. Moreover, dysregulation of the immune system has been evoked to account for the adverse outcome of pregnancy in apparently healthy women with only relatively minor nutritional disturbances. According to this theory, it has been demonstrated that the placentas in mothers affected with celiac disease appear to be abnormal. In particular, TTG expression and apoptosis were reported to be increased in trophoblast cells using immunohistochemical analysis and in situ hybridization methods, suggesting a possible mechanism of injury in both the fetal and maternal parts of the placenta (12). Others have noted that maternal celiac disease autoantibodies bind directly to the syncytiotrophoblast and inhibit placental tissue transglutaminase activity suggesting a possible mechanism for compromised placental function (13). Early pregnancy loss could conceivably relate to some alteration in coagulation affecting placental or fetal microvascular function. Additional studies are needed to further explore and elucidate these mechanisms.

Identifying celiac disease in infertile woman would be beneficial if institution of a gluten free diet could improve fertility and pregnancy outcomes.

This hypothesis is plausible and has been suggested by case reports and small prospective studies (14-16). A gluten-free diet would be an attractive infertility treatment option. Identification of celiac disease in infertile woman would also be helpful given the higher rate of serious illnesses and mortality in patients with untreated celiac disease.

As opposed to the findings in women, gonadal dysfunction is demonstrated in coeliac men.

Semen analysis revealed marked abnormalities in sperm morphology and motility, similar to Crohn's disease, with sperm morphology apparently improving following removal of dietary gluten (17). Moreover, in men CD exerts a known effect on gonadal function, as teratozoospermia and asthenozoospermia (in 46% and 75% respectively), which has proven to be reversible upon a gluten-free diet (18). In addition, the father's disease may also influence the course of pregnancy and the expected outcome of delivery significantly. Namely, the genomes of both parents have a decisive role in relation to normal embryogenesis and satisfactory placental function, and from this aspect paternal genes may conceivably be even more important than maternal ones (19). Furthermore, in celiac men plasma hormone levels are altered. Plasma testosterone and free testosterone index are increased while dihydrotestosterone is reduced, indicating androgen resistance. These hormone levels appear to normalize with improved small bowel architecture on a gluten-free diet (17). However sexual behavior is compromised: sexual satisfaction, including frequency of intercourse, is reduced in celiac patients, but improves after a year of treatment with a gluten-free diet (17). However, there has not been much research to show the link between celiac disease and male infertility. In fact most of the studies on fertility in celiac men were performed in the 1970s and 80s (20-23), indicating a huge unmet need for updated information.

In conclusion, it has been reported that the pathology of CD on reproduction is multifactorial in nature. These pathological manifestations are correlated to different concurrent genetic, nutritional and environmental factors, besides exposure to gluten.
However, it is imperative to follow a strict gluten free diet to reduce the influence of risk factors upon the pregnancy. Gluten sensitivity should be considered in pathological states of pregnancy even in symptom free patients. Assessment and therapy of anti-TTG positive patients and follow-up of pregnancies in female patients with CD always require multidisciplinary cooperation. In addition, we wish to emphasize that, regarding pregnancy outcomes, male members of the couples should also be taken into account.

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