Coeliac Disease and Fertility

Introduction
Coeliac disease (CD) is an important reproductive risk factor for both genders, as it can exacerbate problems related to nutritional deficiencies that, through various mechanisms, can interfere with the endocrine and immune systems of both men and women\(^1\).

Clinical and epidemiological aspects
By examining the clinical and epidemiologic studies available in the literature, a coherent set of reproductive tract disorders related to CD can be outlined. The reproductive alterations most frequently found in women affected by CD include: infertility\(^2\)\(^3\)\(^4\), spontaneous abortions\(^4\), amenorrhea and shorter fertility period (delayed puberty, early menopause)\(^5\)\(^6\). Moreover, delays in the intrauterine foetal growth are not excluded\(^10\).

Infertility
In a case-control study on women with infertility for unexplained reasons\(^2\), 4.1% (4 out of 98 patients) of the cases were affected by CD in comparison to 0 out of 150 controls. Even more recent studies have confirmed a higher CD incidence in women with infertility problems\(^3\). Thus, it seems possible that, in some patients, unexplained infertility can be the consequence of a clinically silent disease, it being its first and, sometimes, only symptom. However, the correlation between infertility and coeliac disease remains controversial. The results of a recent study\(^9\) show that fertility of CD women is similar to that of general female population, but at an older age. Data of 521 coeliac women were compared with those of 7732 non-coeliac women. The percentage was 48.2 and 47.7 live births per 1000 people-year for coeliac and non-coeliac women respectively. The fertility percentage, specific by age, showed that coeliac women have a lower fertility if younger, but a greater fertility if older than non-coeliac women. This increment in relative fertility remained with age, regardless whether women had been subjected to CD treatment or not. Finally, the lower fertility of coeliac women may be correlated not as much to the difficulties in conceiving as to problems arising during pregnancy, such as recurrent abortions and intrauterine death.

Spontaneous abortion
A study on untreated coeliac patients\(^4\) reported a 17.8 % prevalence of abortion. This percentage can go down to 2.4 % if an adequate diet is introduced. This difference is even more evident if only patients with repeated abortions are considered, for whom a gluten-free diet (GFD) can reduce the risk nine-fold (49.3 % vs. 7.7 %). Therefore, women with a history of multiple abortions should be submitted to clinical tests for CD\(^10\).

Menarche and alteration of the menstrual cycle
Coeliac women, even if affected by subclinical CD, have their menarche at an older age. A case-control study carried out on 180 women in Italy in 1990\(^5\) reported that the menarche takes place at about 13.5 years of age among the coeliac population, whereas in normal subjects this event occurs at 12 years of age. In more recent times, another study\(^6\), on analysing the menstrual history of 200 Brazilian women, proved a significant delay in puberty in coeliac patients in comparison to the control group, including patients with irritable colon syndrome (IBS).
This difference, although more evident in subjects with a severe nutritional state, was also observed in subjects presenting with an adequate nutritional state, but who continued to assume gluten. In coeliac patients not complying with the gluten-free diet, a greater frequency of secondary amenorrhea has also been found. In one study, secondary amenorrhea was present in 38.8 % of women with untreated CD, in comparison to 9.2 % of non-coeliac women used as controls; in another study, this was observed in 28% of coeliac women, with a different prevalence depending on whether they complied with a gluten-free diet or not (respectively 12.5 % and 30.0 %) and irrespective of their nutritional state. These data are particularly important in relation to a study mentioning previous amenorrhea among the risk factors of postmenopausal osteoporosis in women.

**Age at menopause**

An example is given by a research study according to which the mean age of CD women with was younger (approx. 47.6 years) as against the non coeliac women used as controls (approx. 50.1 years). These data call for a reflection, in the sense that, as the age at menopause gets younger among CD women, the risk of developing osteoporosis at an earlier age increases; like in the case of amenorrhea, age at menopause is included among risk factors for osteoporosis.

**Unfavourable pregnancy outcomes**

Epidemiological studies have shown that children born from coeliac women have a greater risk of low weight birth and greater risk of delayed foetal growth. Furthermore, recent studies have found that these female reproductive disorders are more frequent among undiagnosed coeliac women (Table 1) and that the restoration of the intestinal mucosa leads to an improvement of the foetal nutritional support which also affects the overall perinatal outcome.

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<th>Table 1. Unfavourable pregnancy outcomes.</th>
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<td><strong>Low birth weight (b)</strong></td>
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<td>Undiagnosed CD</td>
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<td>Diagnosed CD</td>
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<td><strong>Extremely low birth weight (c)</strong></td>
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<td>No CD</td>
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<td>Diagnosed CD</td>
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<td><strong>Preterm birth (d)</strong></td>
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<td><strong>Extremely preterm birth (e)</strong></td>
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<td>Undiagnosed CD</td>
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**NOTES**

(a) IntraUterine Growth Retardation  
(b) Weight <2500 g.  
(c) Extremely lorth <1500 g  
(d) Pre-term breks of gestation.  
(e) Extremely preks of gestation
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Coeliac disease and male reproductive system

With regard to the effects of coeliac disease on the male reproductive system, men, too, run a risk of higher infertility and other reproductive disorders in addition to a greater incidence of hypoaandrogenism. Interestingly, the presence of CD in the father is also a risk factor of low birth weight for his offspring. A study by Ludvigsson 10,597 low birth weight babies, observed that the majority of babies had coeliac mothers, 27 babies had coeliac fathers, 70 babies had coeliac siblings and 442 had both parents affected by CD. Babies with coeliac fathers weighed less than babies with non-coeliac fathers and, also, less than babies with fathers affected by other autoimmune diseases. In particular, newborns with coeliac mothers weighed 222 g less than the average population and newborns with coeliac fathers weighed 266 g less; for coeliac fathers, the risk of having low birth weight babies was 5 times higher than that of the general population (11 vs 2.5%).

Pathogenesis

At present, the pathogenetic mechanism underlying the genito-reproductive system disorders is unknown; however, the following hypotheses have been suggested:

- Alteration of the nutritional state and micronutrient deficiency (iron, zinc, folic acid, vitamin B12, vitamin B6, vitamin K). With regard to the chronic malabsorption of vitamins, in CD folic efficiency is very well known. Follic acid is an essential vitamin for the metabolism of nucleic acids, a deficit which particularly affects the tissues characterised by rapid proliferation, such as the haemopoietic system, the embryo and the seminiferous epithelium. Furthermore, in male subjects, deficiencies of liposoluble vitamins, such as vitamin A and E are not to be underestimated. Vitamin A, regarded as a protection factor for the epithelia, plays a major role in the functionality of Sertoli cells as well as in the first stages of spermatogenesis. Vitamin E, an antioxidant factor, plays various important roles in male reproductive health, such as the correct differentiation and functionality of the epididymal epithelium, the maturation of spermatic cells and the secretion of proteins by the prostate. Moreover, the antioxidant effect can be protective for agents carrying out an endocrine activity, many of which have testicular stroma and seminiferous epithelium as specific targets.

- 5 alpha-reductase deficit. Tissue reencyistance of the hormones circulating in men with gluten enteropathy and intestinal villous atrophy has been suggested as a cause. In particular, gonadic dysfunction is thought to be due to the reduction of testosterone conversion into DHT caused by low levels of 5 alpha-reductase (an enzyme responsible for the reduction of testosterone into alpha-dihydrotestosterone in males). In CD, this leads to the disruption of the hypothalamic-pituitary axis.

- Immune mechanisms: it should be clarified that the HLA locus involved in the predisposition to CD is also important for other autoimmune diseases. DPG could onGFD estore the normal micronutrient absorption, but not other mechanisms that may have been triggered off. Furthermore, overt CD can reactivate or appear during the last stage of pregnancy or during breastfeeding. This may suggest that, also under these circumstances, immune and hormonal alterations that are typical of pregnancy or puerperium can play a role.

- Oxidative stress can be associated with chronic CD, with a subsequent increase in free radicals of lipid and protein origin. The activity of the xanthine oxidoreductase system in the bowel is one of the main sources of free radicals and is much more evident in CD of the clastic asr, even subclinical CD can be characterised by an oxidoreductive imbalance shown by plasma indicators, such as carbonilic groups of protein origin.

Conclusions

In the past years, reports on the existence of a possible association between coeliac disease and reproductive tract disorders have increased. As reproductive alterations are reversible, a timely diagnosis and the introduction of a gluten-free diet are of paramount importance. Thus, the use of early CD indicators, such as vitamin and/or iron deficiencies, andrologic or endocrinologic dysfunctions, should allow a prompt adoption of prevention and treatment strategies.
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Essential bibliography