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OBSERVATION

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Reproductive changes associated with celiac disease

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Abstract

Celiac disease is a mucosal disorder of the small intestine that may be triggered by dietary exposure to gluten in genetically-susceptible individuals. The disorder is often associated with diarrhea, malabsorption and weight loss along with other extra-intestinal complications. Reproductive changes have been described, including impaired fertility and adverse pregnancy outcomes possibly related to immune-mediated mechanisms or nutrient deficiency. Other possible pathogenetic factors that may alter placental function include maternal celiac disease autoantibodies binding to placental transglutaminase, and genetic mutations that may facilitate microthrombus formation. Reports noting activation during pregnancy or the puerperium may be important, and suggest that celiac disease may also be hypothetically precipitated by maternal exposure to one or more fetal antigens.

Key words: Celiac disease; Infertility; Pregnancy; Postpartum celiac disease; Fetal outcome

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INTRODUCTION

Celiac disease is an immune-mediated mucosal disorder primarily affecting the small intestine in genetically-susceptible individuals[1]. It may be triggered by dietary exposure to gluten, and frequently causes chronic diarrhea, malabsorption and weight loss[1]. In some patients, extra-intestinal or autoimmune changes may occur, e.g. hepatobiliary[2], neurological[3], or endocrine disorders, such as hypothyroidism and insulin-dependent diabetes in children[4]. Of particular interest has been the effect of celiac disease and its treatment on fertility and pregnancy[5]. In recent years, there has been an increased recognition of possible changes in male and female fertility in celiac disease as well as the potential for adverse outcomes in pregnancy and the post-partum period that may lead to miscarriages and premature low birth weight fetal deliveries (Table 1).

ALTERATIONS IN FEMALE FERTILITY

Celiac disease continues to be increasingly recognized as a clinically silent disorder with limited or few intestinal symptoms, such as mild diarrhea. Often, females with reproductive disorders or pregnancy complications have no overt symptoms, or at most, fatigue associated with iron-deficiency anemia. As a result, reduced fertility in females or changes that include delayed menarche, amenorrhea and early menopause may conceivably be the initial clinical feature that ultimately results in a diagnosis of celiac disease. As serological screening has resulted in an appreciation that celiac disease may occur in up to 1%-2% of the general population, it is not surprising that this disorder is more readily detected in young women of childbearing age. Indeed, young women are still the most common

Table 1 Reproductive changes in celiac disease

Altered female fertility	Delayed onset of menarche, amenorrhea, early menopause, recurrent abortions, reduced rates of pregnancy
Altered male fertility	Gonadal dysfunction, altered sperm morphology and motility, reduced sexual activity
Alterations in pregnancy	Repeated miscarriages, premature delivery an impaired fetal growth with low birth weight, abnormal placental function
Postpartum activation of celiac disease	Hormonal or immune changes

group diagnosed with celiac disease. If changes in fertility can be documented in celiac disease, these may reflect underlying autoimmune complications of celiac disease or the negative nutritional effects of untreated disease.

Although some early case reports noted a possible association between celiac disease and infertility[6,7], systematic investigations have been limited and the precise definition of infertility *per se* may vary between studies. An extensive serological evaluation of 150 women with infertility from Finland demonstrated an apparently increased rate of celiac disease (i.e. overall rate, 2.7%)[8]. Similar results were later reported in 99 couples from Northern Sardinia (i.e. 3.03% of females)[9], and later, using more modern serological screening methods [i.e. tissue transglutaminase (tTGA), endomysial (EMA) antibodies] in 192 Arab women with unexplained infertility from Israel (i.e. 2.65%)[10]. In all three of these studies, small bowel biopsies were positive if abnormal serological screening results were present. As in most screening studies, however, biopsies in the serologically-negative screened populations were not done. Moreover, other studies have suggested that the evidence may not be quite as strong for a definite association with celiac disease. In a report from another center in Finland[11], a higher frequency of celiac disease in women with infertility or recurrent miscarriage could not be defined. A Czech study showed increased seropositivity in women with infertility, but unfortunately, biopsies were not reported[12]. Finally, in a selected Italian cohort of infertile women undergoing assisted reproduction techniques, a statistically significant result was not achieved[13].

Delayed onset of menarche, amenorrhea, early menopause, recurrent abortions and reduced rates of pregnancy in celiac disease may reflect an impairment of fertility. In 74 celiac patients from the United Kingdom[5], the reproductive period was longer for those on a gluten-free diet compared to those not on a diet but maternal health was not seriously impaired. A lower incidence of spontaneous abortions in celiacs on a gluten-free diet was also recorded. Similar results were reported in an Italian study[14]. In consecutively diagnosed celiacs compared to age- and "sexual behavior"-matched healthy controls, there was a significant delay in the mean age of menarche in untreated celiac patients (13.5 years compared to 12.1 years). Amenorrhea and repeated abortions were more common in the celiac group, but onset of menopause did not significantly differ. Studies from Poland and Italy[15,16] also evaluated menarcheal age of celiac girls with reference to maternal menarcheal age. In one[15], menarcheal age of celiac girls appeared to be regulated by a gluten-free diet, while in the other[16], menarcheal age in celiac disease was not delayed, but was affected by maternal menarcheal age. A further evaluation from the United Kingdom[17] suggested that celiacs are subfertile with an increased incidence of stillbirths and perinatal deaths. However, after diagnosis of celiac disease and treatment with a gluten-free diet, some markers of infertility (e.g. miscarriage rates) may be corrected. Finally, in a study from Brazil[18], adherence to a gluten-free diet and resultant nutritional status was emphasized as an important and relevant factor in reproductive disorders developing in untreated celiac disease.

Nutritional studies in celiac disease during pregnancy are very limited. For example, zinc, selenium and folic acid deficiency have been noted in some studies[19-21], but most of these have been completed in children so that these studies do not appear to offer a definitive explanation for altered fertility in women during their reproductive years with untreated disease. Others have offered contradictory data in untreated celiac disease: reduced vitamins and trace elements were not evident, or significant malnutrition was not present[7-10]. In another report, evidence of poor vitamin status in celiacs despite a gluten free diet was reported[22], but this was contradicted by a detailed and more recent and important evaluation that documented histological recovery[23]. An alternative mechanism for reduced fertility may be immune-mediated, possibly by compromising placental function[24].

Clearly, further studies are needed to precisely define the role of altered absorption and resultant nutritional changes on female fertility in untreated celiac disease as well as the effects of a gluten-free diet, especially with restoration of normal nutritional status. In addition, immune-mediated changes in placental function need to be explored in celiac disease.

ALTERATIONS IN MALE FERTILITY

Studies estimating prevalence of male infertility in celiac disease have been rare. In an infertile couples study from Northern Sardinia[9], a single male out of 99 (or about 1%) tested positive for celiac antibodies, including EMA. Later the typical small bowel biopsy findings of untreated celiac disease were detected. Although the prevalence in a comparable control population was not provided, it is likely that an effective evaluation for infertility in a couple would best include assessment of both sexes for underlying celiac disease.

Early studies from the United Kingdom on male gonadal dysfunction described a reversible state of androgen resistance in celiac disease[25]. Later, in a further series of studies[26-29] on male gonadal function, consecutive males with celiac disease were evaluated and compared to males of similar age and nutritional status with Crohn's disease. Almost 20% of married celiacs had infertile marriages[26]. 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[26]. Others reported the presence

of oligospermia[27]. Specific nutrient deficiencies and detection of anti-sperm antibodies did not appear to be a factor in male infertility[26]. Plasma hormone levels were also determined[28]. Plasma testosterone and free testosterone index were increased while dihydrotestosterone was reduced. These hormone levels appeared to normalize, with an improved small bowel architecture on a gluten-free diet. Serum luteinizing hormone was also raised and interpreted to reflect androgen resistance. These endocrine changes, suggestive of androgen resistance and hypothalamic-pituitary dysfunction, were interpreted to be relatively specific to celiac disease, but an association with disordered spermatogenesis was not determined[28]. Further studies of gonadotropins were also performed[29]. Exaggerated gonadotrophin responses were apparently unrelated to plasma concentrations of testosterone, dihydrotestosterone, estradiol or the free testosterone index. Elevated prolactin levels were also noted but these were not related to impotence or infertility. These studies that suggested deranged pituitary regulation of gonadal function in celiac disease in males were hypothesized to be part of a wider disturbance of central regulatory mechanisms of endocrine function in celiac disease. Interestingly, less significant, but similar alterations in male sex hormone status occur in dermatitis herpetiformis[30], a skin disorder closely linked to celiac disease. These changes possibly also reflect, in part, the recognition of an autoimmune pituitary process associated with celiac disease and reported to be directly associated with an impairment in linear growth[31].

As many of these studies appeared almost three decades ago, it is striking that very little additional new, even descriptive, information on male infertility in celiac disease has appeared. However, two more recent Italian publications have explored sexual behavior[32,33]. In one study, sexual behaviors in treated and untreated celiac disease patients were examined using a questionnaire and compared to healthy controls[32]. Sexual satisfaction, including frequency of intercourse, was reduced in celiac patients, but improved after a year of treatment with a gluten-free diet. In the other[33], sexual habits appeared to be very different in celiacs who were never treated with a gluten-free diet.

ALTERATIONS IN PREGNANCY

Celiac disease, especially if untreated, appears to increase the risk of repeated miscarriages and premature deliveries, and impaired fetal growth with reduced birthweight[34]. In addition, adverse effects on the mother may also occur, as indicated by a recent German study which demonstrated that the rate of cesarean delivery was increased if the parents had celiac disease compared to other digestive disease controls as well as controls from eye or dental outpatient clinics[35].

In a case-control study from Italy that evaluated 94 untreated and 31 treated celiacs, the relative risks of either abortion or delivering a low birthweight baby were increased while the duration of breast feeding was significantly reduced[36]. All of these changes were apparently corrected with a gluten-free diet[36]. Higher incidences of either miscarriages or spontaneous abortions were also recorded from other centers located in different countries including Argentina, Italy and the United Kingdom[5,14,17,37].

Reduced birthweight and intrauterine growth retardation have also been recorded in several other studies from different European centers[38-41]. In one of these studies from Italy[39], the investigators also noted that celiac disease was a more common disorder than most of the diseases normally screened for in pregnant women in their healthcare facility. In another of these studies[40], undiagnosed maternal celiac disease appeared to be a far greater risk factor than diagnosed celiac disease, but in a subsequent report, undiagnosed celiac disease was not associated with an unfavorable outcome of pregnancy[42]. Other studies noted that paternal celiac disease did not appear to be a risk for an adverse pregnancy outcome[43,44].

Mechanisms involved in the impairment of pregnancy outcome in celiac disease have been explored to a limited degree. 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[45]. 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[24]. Furthermore, recent studies in celiac women on the role of genetic prothrombin variants in early pregnancy loss suggested that the 4G variant of the plasminogen activator inhibitor-1 gene may predispose to miscarriage[46]. 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.

FURTHER CONCLUDING ISSUES

Interestingly, delivery of a preterm infant has been conversely linked to later definition of underlying celiac disease in the parent, particularly underlying maternal celiac disease. In 905 preterm infants born in Lombardy, Italy, 1714 parents (868 women, 846 men) were screened for celiac disease using EMA and tTGA (followed by duodenal biopsy confirmation). In these, a higher prevalence of celiac disease in mothers of low birthweight infants was defined[47]. Thus, selective screening for celiac disease may be useful. However, the potential value and cost-effectiveness of screening for celiac disease in all women of reproductive age has not been fully determined.

Also intriguing is the repeated, but uncommon, definition of underlying maternal celiac disease following delivery in the puerperium[48-51]. Activation of celiac disease during the puerperium has been hypothesized to be related to immunologic or hormonal factors, or both[48]. Occasionally, anemia is evident during the prior pregnancy[49] or the presentation may be acute[50] leading to speculation

that activation of celiac disease may result from maternal exposure to fetal antigens[50]. In addition, presentation of underlying celiac disease may not be evident during an initial pregnancy, but may only appear after a second or later pregnancy[51]. Additional studies that explore the specific immunological changes occurring during the post-partum period may shed additional light on immune-mediated changes that occur in unrecognized celiac disease.

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