European Journal of Obstetrics & Gynecology and Reproductive Biology 238 (2019) 90–94

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Reproductive complications in celiac disease patients in Slovenia

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ARTICLE INFO

Article history:
Received 15 March 2019
Received in revised form 6 May 2019
Accepted 14 May 2019

Keywords:
Abortion
Celiac disease
Gestational disorders
Infertility
Pregnancy

ABSTRACT

Objective: Celiac disease is associated with higher risk of infertility, recurrent abortions, and adverse outcomes in pregnancy and in puerperium. The aim of the study was to analyse the association between celiac disease and reproductive disorders in the group of celiac patients and compare these to healthy controls.

Methods: A retrospective case-control matched study. The association between celiac disease and menstrual cycle, gyneco-obstetrical complications was assessed with a questionnaire specifically developed for the study. 144 celiac women and 61 celiac men, members of Slovenian Celiac Society, together with 71 healthy women and 31 healthy men participated in the study.

Results: A higher percentage of celiac women (27.1%) had difficulties in conception of the first child when compared to healthy controls (12.7%) ($p = 0.042$). In addition, celiac women experienced more complications than healthy controls during the pregnancy, such as abortions or intrauterine growth retardation ($p < 0.005$). In our study, the prevalence of reproductive problems was not the same in celiac males and females. Altogether 2 celiac men (3.3%) reported having fertility problems, however, the difference between male cases and controls was not statistically significant ($p = 0.548$).

Conclusion: Physicians should examine women with unexplained infertility, recurrent abortions or intrauterine growth retardation for undiagnosed celiac disease. Compared with healthy women, women with celiac disease have increased risk of spontaneous abortions, preterm delivery and fewer successful pregnancies.

Introduction

Celiac disease (CD) is one of the most common chronic digestive disorders with an overall worldwide prevalence of 1% [1]. Among European countries, large variations exist. In Slovenia the prevalence is approximately 1% [2]. However, taking into account the detection of CD among healthy blood donors and through different screenings, the true prevalence in general population might be higher [3,4]. During the last few decades, clinical pattern of the disease has shifted from classical manifestations in children to atypical clinical manifestations, which made the diagnosis challenging [3,5]. The pathology behind CD starts with the modification of the barrier function of the intestinal mucosa, which allows dietary gluten peptides to reach the subepithelial lymphatic tissue and trigger the adaptive and innate immune response associated with the disease [5]. Histological changes of the intestinal villi with accompanying malabsorption of nutrients, makes CD involved in the development of many conditions such as, micro- and macro- deficiencies, anaemia, bone reabsorption, fertility problems etc. [6]. Deficiency of certain vitamins affects reproductive health in different ways. Zinc deficiency may impair the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) that leads to secondary amenorrhea, spontaneous abortion, and pre-eclampsia [7]. Deficiency of selenium might affect the synthesis and secretion of both LH and FSH [7]. Moreover, the deficiency of folic acid has a negative impact on proliferating tissues in the embryo, especially in neuronal cell development [8]. The severity of malnutrition directly correlates with the frequency of gynecologic and obstetric disorders [9]. According to Wong et al (2000) [10] both zinc and selenium could be responsible for male subfertility. The reduction of zinc concentration in seminal fluid is correlated with an increase of semen pH [11–13]. Therefore, assessing the zinc status in CD women and men, might be beneficial part of the preconception counselling [3]. Next, selenium status is important in the spermatogenesis process [14]. Besides nutritional deficiencies, immune-mediated impairment of the physiologic processes that occur during the implantation of an embryo and/or during the

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https://doi.org/10.1016/j.ejogrb.2019.05.015
0301-2115/

development of placenta in CD women is equally important [8]. It has been observed that patients with CD on gluten free diet frequently show increased levels of anti-tTG antibodies which could be directly involved in placental – related pregnancy complications [8]. The role of gliadin in inducing of an inflammatory reaction in celiac women with negative impact on fetus has been described as well as coagulation alterations and endometrium inflammation [9].

The first association between CD and reproductive disorders was made in 1970 when Morris et al. described three infertile patients with untreated CD. In his study, all three of the patients became pregnant after the introduction of gluten free diet (GFD) [15]. Since then, growing number of studies have shown that CD may impair reproductive health of an individual and due to the subtle symptoms the disease may present itself, it is not surprising that women in childbearing age are frequently diagnosed with CD [16–19]. Some studies speculate that the prevalence of CD in unexplained infertility might be as high as 4–8% [20,21]. The study of Ciacci et al., from 1996 showed increased incidence of miscarriages in pregnant CD women that was an almost 9-fold increased risk compared to healthy (non CD) women [22]. The only available therapy for CD is a strict, lifelong, gluten free diet (GFD). The adherence to GFD gradually results in the resolution of symptoms and mucosal healing and with that the improvement of nutritional imbalances [23].

To our knowledge, the association between celiac disease and reproductive health disorders in childbearing women in Slovenia has not been characterized yet. We therefore decided to analyze whether women with celiac disease had more frequently gyneco-obstetrical problems than non-celiac women.

Material and methods

This retrospective case-control matched study was conducted between August and December 2017. The inclusion criteria for the cases was confirmed CD by a specialist of gastroenterology relying on one or more specific serology tests and the small intestinal biopsy. Case group consisted of 61 men (29.8%) and 144 women (70.2%) with confirmed diagnosis of CD between 30 and 51 years of age. After obtaining a written informed consent, patients with CD were asked to complete an anonymous survey. The first part of the questionnaire was designed to analyze the history of CD in details, i.e. symptoms of the disease, age at diagnosis, the diagnostic procedure, their diet, accompanying diseases, etc. Next, participants described their fertility history, including whether they experienced complications in pregnancy, such as miscarriages, preterm births, birth weights, methods of delivery and if they had been successful in delivery of one or more child. Additionally, patients answered questions about their education, socioeconomic status, overall health, lifestyle, etc. Men received different questionnaire than women, lacking the questions regarding gestational problems.

A group of 102 of healthy women and men aged between 30 and 53 served as controls. Every fifth person was recruited during the visit of their general practice doctor and after excluding any gastrointestinal disorder. Healthy controls were also chosen to match the age, sex and level of education of the cases.

After obtaining a written consent, all controls were administered the same standardized questionnaire used for the cases but without questions regarding CD. As in cases, men received different questionnaire than women. The data were collected from the questionnaires in an electronic database and were further analyzed. The study was approved by the National Medical Ethics Committee on 29 November 2014 (No. 49/09/14).

Data were presented by frequencies and percentages for categorical variables, or by means ± standard deviations for continuous variables. The two groups were compared using the Chi-square test or the Fisher's exact-test for 2×2 tables. The independent samples *t*-test was used to compare the two groups by age. The statistical analyses were conducted using IBM SPSS ver.25 (IBM Corp., Armonk, NY). $P < 0.05$ was considered statistically significant.

Results

CD patients (a total of 205), who participated in the study were active members of Slovenian Celiac Society. Altogether, 102 of controls, 31 men (30.4%) and 71 women (69.6%) accepted to participate and were enrolled in the study (Table 1). All cases adhered to GFD. The mean age of women in the celiac group was 40.6 ± 6.2 and in the control group 41.1 ± 6.3 (p = 0.581).

181 (88.3%) of celiac patients had siblings which was similar to controls (87.3%; N = 89) (p = 0.853). The area of residence and the distribution overlapped between those of celiac patients and the healthy controls. 103 (50.2%) of the cases and 50 (49%) of the controls live in the urban area, mostly in Ljubljana, the capital of Slovenia, and Maribor (second largest town in Slovenia). The level of education was similar and did not significantly differ between the cases and controls with 118 (57.5%) of cases and 50 (49%) of controls having bachelor degree or higher (p = 0.593).

The diagnosis of CD was in all cases confirmed by biopsy. In addition, the serum levels of anti-transglutamminase antibodies (anti-tTG) have been analyzed in 57.1% of celiac patients (N = 117), anti-endomysial antibodies (EMA) had been assessed in 52.7% of celiac patients (N = 108), the serum levels of anti-gliadin antibodies (AGA) had been measured in 18% of the cases (N = 37) and 52% (N = 106) had HLA genomic typing for DQ2/DQ8 performed.

The diagnosis of CD in the majority of participants in the study was confirmed relatively late. Only 8% of the study participants had CD confirmed in the first two years of life; 4.8% between the age of 2 and 6; 16.5% between 6 and 18 years of age and the largest percentage of the cases (71.7%) after 18 years of age. The most common non-GI concomitant disorders observed in CD patients were anaemia (15.6%), thyroid disease (23.9%), rheumatic

Table 1
Descriptive characteristics of the study population.

	CD patients N (%)	Controls N (%)	Total N (%)	p-value
Sex				1.000**
Male	61 (29.8)	31 (30.4)	92 (30)	
Female	144 (70.2)	71 (69.6)	215 (70)	
Marital status				0.002*
Married	113 (55.1)	64 (60.7)	177 (57.7)	
Single	35 (17.1)	2 (2.0)	37 (12.1)	
Divorced	9 (4.4)	7 (6.9)	16 (5.2)	
Widowed	3 (1.4)	0 (0.0)	3 (1.0)	
Civil union	45 (22)	29 (28.4)	74 (24.1)	
Smoking status				0.069**
Smokers	27 (13.2)	22 (21.6)	49 (16.0)	
Non-smokers	178 (86.8)	80 (78.4)	258 (84.0)	
Alcohol consumption				1.000**
Yes	119 (58.0)	60 (58.8)	179 (58.3)	
No	86 (42.0)	42 (41.2)	128 (41.7)	
Substance use				0.123**
Yes	27 (13.2)	7 (6.9)	34 (11.1)	
No	178 (86.8)	95 (93.1)	273 (88.9)	
Regularly take medication				0.090**
Yes	70 (34.1)	25 (24.5)	95 (30.9)	
No	135 (65.9)	77 (75.5)	212 (69.1)	

* χ^2-test.
** Fisher's exact-test.

disorders (24.9%), diabetes mellitus (3.9%), selective IgA deficiency (4.4%), and autoimmune disease of the liver (3.4%).

The mean age at menarche was 12.7 ± 1.3 years for celiac patients, which was not statistically significant when compared to healthy controls (12.5 ± 1.2 years) (p = 0.237).

70 (34.1%) of the celiac disease patients takes some kind of medication regularly and as expected, CD patients reported visiting their physician more frequently than the controls (p < 0.001) (Table 2).

The difference in the number of children statistically differed between the CD patients and controls (p = 0.002). In particular, 33.2% (N = 68) of CD patients (women and men) and 14.7% (N = 15) of controls did not have any children. Furthermore, CD patients more frequently had only one child when compared to controls, i.e. 21.5% (N = 44) of cases versus 37.3% (N = 38) of controls. Healthy controls tended to have larger families than CD patients.

Significantly more CD women, 27.1% (N = 39), reported having difficulties with conceiving of the first child versus 12.7% (N = 9) of healthy controls (p = 0.042). Furthermore, 23 (11.2%) of women with CD reported being treated for infertility, which was statistically significant when compared to 7.8% (N = 8) of healthy controls (p = 0.425).

Our results showed that CD women had their first child later than the controls, i.e. 18.3% (N = 22) of CD women and 6.7% (N = 4) of controls had their first child after 31 years of age. In other age groups the difference was not as profound and the difference did not meet statistical significance (p = 0.213) (Fig. 1).

CD women (31.7%; N = 38) more often experienced spontaneous abortion than healthy controls (13.3%; N = 8) (p = 0.011) (Fig. 2). In addition, slightly more women with CD (39.2%; N = 47) experienced complications during the pregnancy than healthy controls (31.7%; N = 19), however the difference did not reach statistical significance (p = 0.412).

Intrauterine growth retardation occurred more often in women with CD (11.7%; N = 14) when compared to 1.7% (N = 1) of the healthy controls (p = 0.01). The percentage of cesarean section was similar in celiac women (11.7%) and in healthy controls (10.0%) (p = 0.807).

Of the 180 women who had delivered a child, significantly (p = 0.026) more women in the CD group (35.8%) reported at least one premature delivery (< 37 weeks gestational age) than women in the control group (16.7%). Furthermore, women with CD (N = 24; 20%) more often had difficult birth with complications than healthy controls (N = 10; 16.9%), however this difference did not reach statistical significance (p = 0.752). Two pregnancies ended with stillbirth in CD women which was statistically significant when compared to none in control group (p = 0.02).

In CD patients, a lower birth weight could be observed, which was statistically different from the birth weights of the controls (p = 0.011) (Table 3).

We also analyzed the breastfeeding in CD patients and controls and the difference between the two groups was found statistically significant (p = 0.034) (Table 4).

Men mostly denied having problems with infertility. Only 2 (3.3%) CD men declared having problems with fertility while none of the controls mentioned having the same problem.

Table 2
Physician visit frequency of celiac disease patients and healthy controls.

	CD patients N (%)	Control N (%)	Total N (%)	p-value
Every month	10 (4.9)	6 (5.9)	16 (5.2)	<0.001
More than once a year	117 (57.1)	33 (32.4)	150 (48.9)	
Less than once a year	63 (30.7)	42 (41.2)	105 (34.2)	
Rarely	15 (7.3)	21 (20.6)	36 (11.7)	

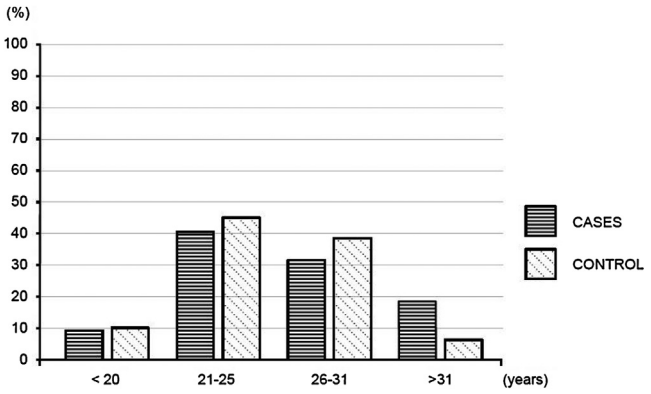

Fig. 1. The age of women at first pregnancy.

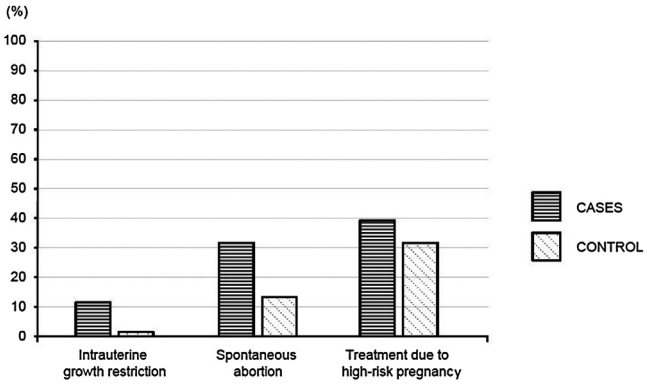

Fig. 2. Complications in pregnancy.

Table 3
Birth weight of the first newborn in celiac and healthy women.

	CD women N (%)	Controls N (%)	Total N (%)	p-value
< 2500 g	17 (14.2)	2 (3.3)	19 (10.6)	0.011
2501-3000 g	42 (35.0)	13 (21.7)	55 (30.6)	
3001-3500 g	36 (30.0)	29 (48.3)	65 (36.1)	
> 3500 g	25 (20.8)	16 (26.7)	41 (22.8)	

Table 4
Duration of breastfeeding.

	CD women N (%)	Controls N (%)	Total N (%)	p-value
< 1 month	33 (27.5)	9 (15.0)	42 (23.3)	0.034
1–6 months	51 (42.5)	22 (36.7)	73 (40.6)	
> 6 months	36 (30.0)	29 (48.3)	65 (36.1)	

Discussion

During the last two decades, a significant progress has taken place in understanding of CD. The mean age at diagnosis is increasing, and it is more often recognized in women without classic symptoms [24,25]. There is a significant evidence that untreated CD adversely affects both male and female reproduction. However, females are more commonly affected than males, and of CD patients presenting during their fertile years, a female to male ratio of almost 3 to 1 has been observed [26].

Our results showed that age at menarche in CD patients was comparable to healthy women. The study of Sferlazzas and colleagues (2008) is similar to our study suggesting that the age

at menarche in patients with CD is irrespective of the age at diagnosis of CD and/or dietary management [27]. This indicates the importance of genetic predisposition, which might be more relevant than the age at the diagnosis or nutrition.

When analyzing marital status, our results showed that 17.1% of CD patients and 2.0% of the controls were single which indicated that the burden of celiac disease decreased the chances of having a normal marriage among CD patients. In our study, significantly more CD patients had no children when compared to healthy controls. Also, CD patients had more often only one child. This could reflect a shorter fertile life span of the CD patients and also the complexity of the disease itself, where women have to manage their disease first and enter remission before pregnancy.

Many studies have shown that celiac disease could be often found in patients with unexplained infertility [3,8,10,28]. We confirmed this in the present study where 11.2% of CD women had been treated for infertility.

Infertility in male is seen as alteration in sperm concentration and/or mobility and/or morphology in at least one sample of two sperm analyses collected [26]. While there are numerous studies assessing infertility in women with CD, evidence regarding the fertility in male with CD is relatively scarce. Most of these studies investigate the rate of infertility in men with CD and probable pathogenesis behind it [29–31]. Our results show that men mostly denied having problems with infertility. Only 3.3% reported having fertility problems, however, despite suggested answers (oligospermia, asthenospermia, teratospermia and gonadal dysfunction), none of them specified the actual cause of infertility. The latter also reflects the traditional role of a male in Slovenian society and the silence surrounding male infertility.

Women with CD more frequently experienced difficulties with conceiving of the first child than healthy women. Our findings are consistent with other studies reporting a higher prevalence of CD in women seeking fertility treatments [21,24,32,33,35]. In our study, the number of pregnancies that ended in a spontaneous abortion in women with CD was observed to be significantly higher than in the healthy women (31.7% vs. 13.3%). Similarly, the study of Gasbarrini and colleagues showed that up to 50% of women with untreated CD experience an unfavourable outcome of the pregnancy [35]. Sher and Mayberry also noted a higher incidence of spontaneous abortions in CD women [34].

More complications during the full term pregnancy were observed in CD women than in healthy women. This could also be attributed to the fact that CD women had their first child later (>31 years of age) than healthy controls when such complications are more likely to occur even in healthy pregnancy. Also, intrauterine growth retardation was more often observed in CD women than in the healthy controls. A similar finding was reported in the study of Gasbarrini et al (2000) where the rate of intrauterine growth retardation was 15% in CD women [35]. A possible explanation for this lies in the abnormal placentas of CD mothers and in the stronger expression of tTG in both cytotrophoblasts and extra villous trophoblasts compared with the healthy women [36]. Authors speculated that tTG is required for proper formation of decidual cells and thus has an effect on embryo implantation and pregnancy, which was confirmed in the study of Shiener et al. [37]. When compared to healthy women, a shorter gestation and lower birthweight have been observed in women with CD [37–40]. The latter was confirmed in our study, as significantly more women with CD experienced a premature delivery that healthy controls (35.8% vs. 16.7%). A study of Khashan and colleagues found that women with undiagnosed CD had a higher risk of small or very small for gestational age and for pre-term birth in comparison with women with CD on GFD [39]. Also in our study CD women more frequently delivered babies weighting less than 2500 g. In our study, stillbirth occurred in two women with CD, as opposed to none in the healthy women. A similar finding was observed in the study of Sher and Mayberry (1996) where seven mothers with untreated CD experienced a stillbirth compared to two healthy women [34].

Our results show that the prevalence of cesarean section in women with CD was not higher than in the healthy women. In our study, CD women were breastfeeding a shorter period of time compared to healthy women and rarely breastfed their infants beyond recommended 6 months. A similar observation was made in two other studies [18,22].

Overall, higher prevalence of reproductive and pregnancy complications in CD women implies the possibility of considering CD as one of the potential causes of fertility problems in both women and men. It is necessary to increase the awareness of celiac screening among medical practitioners in all women with suspected fertility challenges.

Disclosure of interest

The authors report no conflict of interest.

Funding statement

The authors received no specific funding for this study.

Data statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Author contributions

M.Š.P., V.V., E.T., and D.M.T conceived the study. M.Š.P., V.V., E.T., and D.M.T prepared the manuscript structure, M.Š.P., V.V, E.T., and D.M.T wrote the manuscript and prepared the figures, M.Š.P., V.V., E.T., and D.M.T revised the manuscript, have approved the final written manuscript text.

Acknowledgments

We are grateful to all those who responded to the questionnaire and participated in this study, and the Slovenian Celiac Society for assistance in distributing the questionnaire and their crucial administrative help. The authors would also like to thank World Federation of Scientists. Researcher MŠP was their scholarship holder, which enabled her personal development during the course of the study.

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