

RISK OF INFERTILITY IN PATIENTS WITH CELIAC DISEASE: a meta-analysis of observational studies

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ABSTRACT – *Context* - Celiac disease is an autoimmune disorder of the small intestine associated with several extra-intestinal features, such as reproductive disorders. The relationship between celiac disease and infertility has been previously assessed, with conflicting results. *Objective* - We seek to determine the relationship between celiac disease and infertility. *Methods* - Data was extracted from case-control or cohort design studies from 1966 to December 2013 using the MEDLINE-Pubmed, EMBASE, LILACS and Cochrane Library databases. We analyzed two kinds of trials: those assessing the risk of infertility in subjects with already diagnosed celiac disease, and those evaluating the prevalence of undiagnosed celiac disease in subjects with a diagnosis of infertility. *Results* - The search yielded 413 potentially relevant studies for revision, 12 of which were finally included for analysis. A significant association was found between women with a diagnosis of infertility and undiagnosed celiac disease [OR 3.09 (95% CI 1.74-5.49)]. When considering those studies assessing the occurrence of infertility in subjects with already-diagnosed celiac disease, no difference was found between celiac disease patients and control subjects [OR 0.99 (0.86-1.13)]. *Conclusion* - Undiagnosed celiac disease is a risk factor for infertility. Women seeking medical advice for this particular condition should be screened for celiac disease. Adoption of a gluten-free diet could have a positive impact on fertility in this group of patients.

HEADINGS - Celiac disease. Infertility female. Diet gluten-free.

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder triggered by intestinal exposure to gluten, a protein commonly found in wheat, barley and rye. Typical manifestation of CD consists of early onset of malabsorption-related symptoms, while atypical forms of the disease are commonly diagnosed during adulthood and frequently related to extra-intestinal manifestations⁽⁸⁾.

Several extra-intestinal features have been associated with CD, such as metabolic osteopathy, anemia, and dermatitis herpetiformis⁽²³⁾. There has been evidence indicating a link between CD and reproductive disorders, such as recurrent abortions⁽³⁾.

The relationship between CD and infertility has been previously assessed by several studies, with contradictory results^(13, 20). Hence, we sought to perform a systematic review and meta-analysis of current evidence on this particular subject.

METHODS

Criteria for study inclusion

Meta-analysis was performed according to the

recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group⁽²⁸⁾. Controlled studies with case-control or cohort study designs were considered for review. Uncontrolled observational studies and case series were excluded. Two kinds of studies were analyzed in-depth: those assessing the risk of infertility in subjects with previously diagnosed CD, and those evaluating the prevalence of undiagnosed CD in subjects already diagnosed with infertility.

Search strategy

A computer-assisted search was performed from 1966 to December 2013 in the MEDLINE-Pubmed, EMBASE, LILACS and Cochrane Library databases. The search strategy consisted of the MESH terms “celiac disease” or “celiac sprue” and “infertility” or “genital diseases, female” or “sterility”. There was no language restriction. We reviewed the bibliography of identified relevant papers. Additionally, abstracts from Digestive Disease Week and United European Gastroenterology Week 2008-2013 were manually reviewed.

Two authors independently performed the bibliographic search for potentially relevant studies.

Declared conflict of interest of all authors: none
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Compatible abstracts were reviewed to check compliance with eligibility criteria. The findings of each author were then compared. If there was disagreement towards a particular study, its inclusion was decided by a third author. If there was evidence of duplicated data, original papers' authors were contacted in order to determine study inclusion or exclusion.

Quality assessment

Methodological quality of included studies was evaluated by two authors in an independent manner using the Newcastle-Ottawa assessment scale for case-control and cohort studies⁽²⁷⁾. If disagreement on a particular subject was encountered, a third author resolved the difference.

Statistical analysis

Meta-analysis was performed using REVMAN software (Review Manager Version 5.1. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2011). Heterogeneity was evaluated using the I² and chi square test. Because of anticipated variability in patient population and study design, a random-effect model was used. The first analysis included studies assessing the occurrence of non-diagnosed CD in patients suffering from infertility; the outcome was described as an Odds Ratio (OR) with a 95% confidence interval (95% CI). In a second analysis, we included studies evaluating the odds of infertility in patients previously diagnosed with CD. We also used an OR with a 95% CI in order to describe the latter. Sensitivity analysis was performed according to heterogeneity or if significant methodological quality differences were found. Funnel plots were performed in order to assess potential publication bias.

RESULTS

The search identified 413 bibliographic citations. Of these, 395 were excluded, and eighteen potentially relevant studies were evaluated. Six studies were excluded because they did not fulfilled eligibility criteria: three studies lacked a control group^(5, 13, 17), a large population-based study⁽⁹⁾ was not designed to compare infertility prevalence in celiac subjects and used U.S. general population as a control group; another study⁽²⁰⁾ used an inadequate control group (previously known prevalence of silent CD in the northern Sardinian population) and another one⁽⁷⁾ assessed the risk of infertility only in male subjects and used Crohn's disease patients as control group. Finally, as shown in Figure 1, twelve studies were included for analysis. Two of the analyzed studies were population-based cohort studies (Zugna 2010 and Tata 2005) which evaluated the risk of infertility in a CD population^(29, 31). Two other studies (Molteni 1990 and Sher 1994) were case-control studies evaluating the odds of infertility in a CD group compared to a non-celiac control group^(21, 25). Finally, eight studies (Collin 1996, Kohlo 1999, Shamaly 2004, de Silva Martins 2006, Tiboni 2006, Kumar 2010, Khoshbaten 2011, Hogen Esch 2011)

assessed the occurrence of non-diagnosed CD in subjects suffering from infertility compared to apparently healthy controls^(4, 6, 12, 14, 15, 16, 24, 30). Two studies included data on male partners also evaluated for non-diagnosed CD versus controls (Khoshbaten 2011, Hogen Esch 2011).

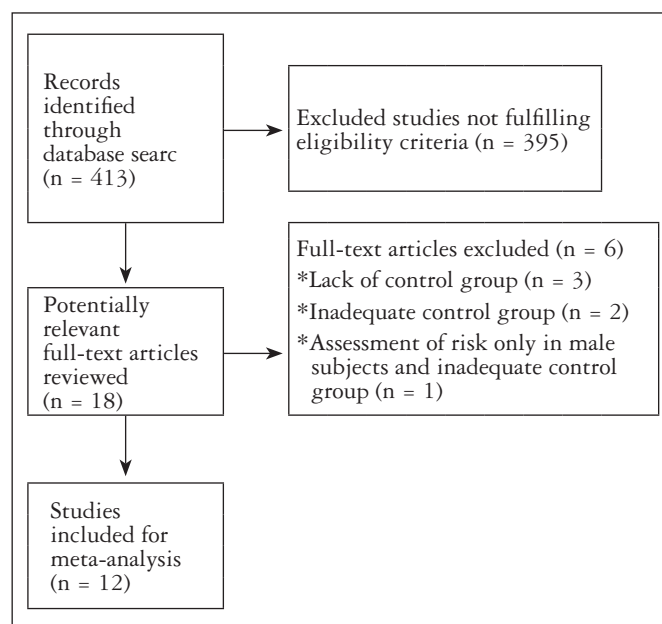


FIGURE 1. Flow chart outlining the study selection process

Characteristics of included studies are summarized in Table 1. Infertility was assessed in a similar fashion in most studies; however, this was not clearly stated in the studies by Moltoni et al., Sher et al., Zugna et al. and Tata et al. Three studies (Shamaly 2004, Kumar 2010 and Khoshbaten 2011) evaluated patients with unexplained infertility (UI) only.

Methodological assessment of included studies is described in Table 2. No study was excluded due to methodological limitations.

Non-diagnosed celiac disease in subjects with infertility

Meta-analytical findings of the first condition are described in Table 3. Overall, 4471 subjects were included in this analysis. No heterogeneity was observed (I² 0%; *P* 0.67), and a significant association was found between women with a diagnosis of infertility and CD [OR 3.09 (95% CI 1.74-5.49)]. Sensitivity analysis was also performed; studies assessing all kinds of infertility (not only UI) were also excluded. No relevant differences were found as a result [OR 3.41 (1.65-7.03)]. Further sensitivity analysis was carried out by excluding studies that did not use anti-transglutaminase and/or anti-endomysium antibodies for initial CD screening (Collin 1996); again, no significant difference was found in the result [OR 2.95 (1.64-5.31)].

Meta-analysis of studies which evaluated CD in male partners versus control subjects included 2054 patients and

TABLE 1. Characteristics of included studies

Author	Location	Subjects	Controls	Type of infertility assessed	Celiac disease definition	Outcomes
CASE-CONTROL AND CROSS SECTIONAL STUDIES						
Molteni et al. ⁽²¹⁾	Italy	38 newly diagnosed celiac disease women with normal sexual life without contraceptive method	38 women from hospital staff or IBS outpatients, matched for age, origin and sexual behavior	Not clearly stated	Jejunal biopsy and GFD response	Infertility in CD Group = 4/38 (10.52%); Infertility in control Group = 3/38 (7.89%)
Sher et al. ⁽²⁴⁾	United Kingdom	68 celiac disease women from previously performed epidemiologic study	68 sex and age- matched, healthy individuals from the same community (one described source= patients' relatives)	Not clearly stated	Not clearly stated	Infertility in CD Group = 11/68 (16.17%); Infertility in control Group = 1/68 (1.47%) (subject to recall bias)
Collin et al. ⁽⁴⁾	Finland	150 women evaluated for infertility; 50 women with ≥ 2 abortions [mean age 31 (22-42)]	150 women w/normal obstetric history undergoing sterilization	All kind; 98 (65.3%) unexplained (UI)	Screening w/IgA AG+antireticulin; confirmed by biopsy	CD in infertility Group = 4/150 (2.7%); 4/4 UI (4.1%); CD in control Group = 0/150
Kohlo et al. ⁽¹⁵⁾	Finland	129 women evaluated at the department of obstetrics and gynecology	51 apparently healthy women working at hospital	All kind; 47 (36.43%) UI	IgA AE (not confirmed by biopsy)	CD in infertility Group = 1/129 (0.77%); 1/1 UI (1/47=2.12%); CD in control Group = 1/51 (1.96%)
Shamaly et al. ⁽²³⁾	Israel	192 women attending infertility clinic (age range 18-44)	210 women attending pediatric clinic (age range 18-44)	UI	IgA AtTG; IgA AE; confirmation by biopsy	CD in infertility Group = 5/192 (2.6%); CD in control Group = 1/210 (0.48%)
Tiboni et al. ⁽²⁹⁾	Italy	200 women undergoing ART (mean age 35 \pm 5)	200 apparent healthy women with at least 1 child	All kind; 26.5% UI	Screening w/IgA AtTG+ IgA AE; confirmation by biopsy	CD in infertility Group = 5/200 (2.5%); 0/5 UI. CD in control Group = 2/200 (1%)
da Silva Martins et al. ⁽⁶⁾	Brazil	200 women attending hospital due to infertility	400 women attending hospital for other reason than infertility	All kind	Screening w/ IgA AE; confirmation by biopsy	CD in infertility Group = 3/200 (1.5%); CD in control Group = 0/400
Kumar et al. ⁽¹⁶⁾	India	230 women attending infertility clinic (mean age 29.7 \pm 4)	305 women w/ normal obstetric history	UI	IgA/IgG AG; IgA AtTG+ IgA AE	CD in infertility Group = 13/230 (5.6%); CD in control Group = 4/305 (1.3%)
Khoshbaten et al. ⁽¹⁴⁾	Azerbaijan	100 women attending infertility clinic (w/ male Partners) (mean age 29 \pm 6)	200 apparently healthy couples with at least 1 birth	UI	IgA AtTG (confirmed by biopsy)	CD in infertility Group = 8/100 (8%); CD in control Group = 7/200 (3.5%); CD in male Partners = 5/100 (5%); CD in male controls = 4/200 (2%)
Hogen Ersch et al. ⁽¹²⁾	Netherlands	1038 women attending to infertility clinic (mean age 32.3; range 20-45) (w/male Partners)	1432 healthy community adults (716 female)	All kind; 34% UI	IgA AtTG; IgA AE (endoscopy not offered)	CD in infertility Group = 6/1038 (0.58%); CD in UI = 2/351 (0.57%); CD in control. Group = 2/716 (0.28%); CD in male Partners = 4/1038 (0.39%); CD in male controls = 3/716 (0.42%)
COHORT STUDIES						
Tata et al. ⁽²⁸⁾	United Kingdom	1521 celiac women in fertile age (18-44 y) between 1987-2002	7732 women without CD matched by age, sex, general practice and follow-up time	Not applicable	Records from GPRD (criteria not specified)	Births in CD Group = 341 (median follow-up = 4.3y); births in control Group = 1903 (median follow-up = 4.9y); HR 1.01 (95% CI 0.91-1.14)
Zugna et al. ⁽³⁰⁾	Sweden	11495 celiac women born between 1920-1990	51109 women without CD matched by age, sex, calendar period and county of residence	Not applicable	Swedish regional biopsy data	Births in CD Group = 6870; HR 1.04 (95% CI 1.01-1.07)

IBS: Irritable bowel syndrome, AE: Anti-endomysium, GFD: Gluten-free diet, AtTG: Anti-transglutaminase, CD: Celiac disease, HLA: Human leukocyte antigen, AG: Anti-gliadin, GPRD: General practice research database, UI: Unexplained infertility, HR: Hazard ratio

TABLE 2. Methodological characteristics of included studies

CASE-CONTROL AND CROSS_SECTIONAL STUDIES								
Author	Case definition adequate?	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment	Non-response rate
Molteni et al. ⁽²¹⁾	Yes	Consecutive series	Hospital and community controls	No history of disease	Sex, age and origin adjustment	Questionnaire	Yes	Not stated
Sher et al. ⁽²⁴⁾	Not clear	Consecutive series	Community (cases' friends or relatives enrolled)	No history of disease	Sex and age adjustment	Questionnaire	Yes	67% response rate in cases; 66% in controls
Collin et al. ⁽⁴⁾	Yes	Consecutive series	Hospital controls	No history of disease	No adjustment	Laboratory + biopsy when +ve screening	Yes	Not stated
Kohlo et al. ⁽¹⁵⁾	Yes	Consecutive series	Hospital controls	No history of disease	No adjustment	Laboratory	Yes	Not stated
Shamaly et al. ⁽²³⁾	Yes	Consecutive series	Hospital controls	No history of disease	Age and sex adjustment	Laboratory + biopsy when +ve screening	Yes	Not stated
Tiboni et al. ⁽²⁹⁾	Yes	Consecutive series	Hospital controls	No history of disease	No adjustment	Laboratory + biopsy when +ve screening	Yes	Not stated
da Silva Martins et al. ⁽⁶⁾	Yes	Consecutive series	Hospital controls	No history of disease	Age and sex adjustment	Laboratory + biopsy when +ve screening	Yes	Not stated
Kumar et al. ⁽¹⁶⁾	Yes	Consecutive series	Hospital controls	No history of disease	No adjustment	Laboratory	Yes	Not stated
Khoshbaten et al. ⁽¹⁴⁾	Yes	Consecutive series	Hospital controls	No history of disease	No adjustment	Laboratory + biopsy when +ve screening	Yes	Not stated
Hogen Ersch et al. ⁽¹²⁾	Yes	Consecutive series	Community	Not stated	No adjustment	Laboratory	Yes	Not stated
COHORT STUDIES								
	Representativeness of exposed cohort	Unexposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at the start of study	Comparability of cohorts	Assessment of outcome	Was follow-up long enough?	Adequacy of follow-up
Tata et al. ⁽²⁸⁾	Representative	Same community	Not clear if biopsy was required	Yes	Adjusted for age, sex, general practice and follow-up time	Record linkage	Yes	Not applicable
Zugna et al. ⁽³⁰⁾	Representative	Same community	Adequate (biopsy database)	Yes	Adjusted for age, sex, calendar period and county of residence	Record linkage	Yes	Not applicable

TABLE 3. Meta-analysis of case-control studies assessing frequency of undiagnosed celiac disease in infertility patients

Study or Subgroup	Infertility		Control		Weight	Odds Ratio	M-H, Random, 95% CI	Year	Odds Ratio	M-H, Random, 95% CI
	Events	Total	Events	Total						
Collin et al. ⁽⁴⁾	4	150	0	150	3.9%	9.25 [0.49, 173.25]	1996			
Kohlo et al. ⁽¹⁵⁾	1	129	1	51	4.2%	0.39 [0.02, 6.37]	1999			
Shamaly et al. ⁽²³⁾	5	192	1	210	7.1%	5.59 [0.65, 48.27]	2004			
da Silva Martins et al. ⁽⁶⁾	3	200	0	400	3.8%	14.19 [0.73, 276.16]	2006			
Tiboni et al. ⁽²⁹⁾	5	200	2	200	12.1%	2.54 [0.49, 13.24]	2006			
Kumar et al. ⁽¹⁶⁾	13	230	4	305	25.7%	4.51 [1.45, 14.01]	2010			
Hogen Esch et al. ⁽¹²⁾	6	1038	2	716	12.9%	2.08 [0.42, 10.31]	2011			
Khoshbaten et al. ⁽¹⁴⁾	8	100	7	200	30.3%	2.40 [0.84, 6.81]	2011			
Total (95% CI)		2239		2232	100.0%	3.09 [1.74, 5.49]				
Total events	45		17							
Heterogeneity: Tau ² = 0.00; Chi ² = 4.95, df = 7 (P = 0.67); I ² = 0%										
Test for overall effect: Z = 3.84 (P = 0.0001)										

did not show a significant association [OR 1.63 (95% CI 0.6-4.46)], as described in Table 4. Figure 2A shows the funnel plot of included studies mentioned above, with no significant asymmetry (Egger test, $P = 0.3$).

Infertility in subjects with diagnosed celiac disease

When considering studies assessing the occurrence of infertility in subjects with CD, 33636 subjects were included for analysis. No difference was found between CD patients and control subjects [OR 0.99 (95% CI 0.86-1.13)], as described in Table 5. Significant heterogeneity was corrected by the exclusion of one of the studies (Sher 1994), which did not alter the result of the analysis [OR 0.97 (0.92-1.03)]. Figure 2B shows funnel plot of these studies, with an asymmetry that could be related to a publication bias (Egger test, $P < 0.001$).

DISCUSSION

Our meta-analysis evaluates the association between a frequent reproductive disorder such as infertility and CD.

According to our results, non-diagnosed untreated CD constitutes a risk factor significantly associated with infertility in women. When comparing studies that enrolled patients previously diagnosed with CD, this association is not as evident as in the former context. This could be related to the effect that adoption of a gluten-free diet (GFD) may have on this particular health issue.

The association between CD and female reproductive disorders has been previously described⁽³⁾. It is well known that CD increases the risk of recurrent miscarriages, low weight at birth, early menopause and other pregnancy disorders^(10, 11, 18, 19, 26). It is also known that these kinds of complications appear to diminish once a GFD is implemented.

Infertility is defined as the impossibility of conceiving after 12 months of unprotected intercourse⁽¹⁾. It can be related to both male and female factors, with the latter subdivided into ovarian, tubal, endometrial or unexplained causes. It is relatively frequent, with approximately 8%-12% of couples with women at child-bearing age carrying this condition⁽²⁾.

TABLE 4. Meta-analysis of case-control studies assessing frequency of undiagnosed celiac disease in the male partners of infertility patients

Study or Subgroup	Infertility		Control		Weight	Odds Ratio		Year	Odds Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI			
Hogen Esch et al. ⁽¹²⁾	4	1038	3	716	44.4%	0.92 [0.21, 4.12]		2011	-	
Khoshbaten et al. ⁽¹⁴⁾	5	100	4	200	55.6%	2.58 [0.68, 9.82]		2011	-	
Total (95% CI)		1138		915	100.0%	1.63 [0.60, 4.46]			-	
Total events	9		7							
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.01$, $df = 1$ ($P = 0.31$); $I^2 = 1\%$										
Test for overall effect: $Z = 0.96$ ($P = 0.34$)										

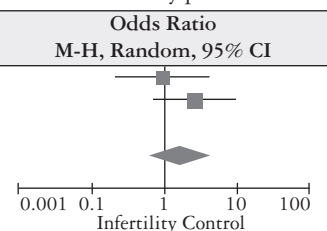


TABLE 5. Meta-analysis of case-control studies assessing frequency of undiagnosed celiac disease in infertility patients

Study or Subgroup	Celiac Disease		Control		Weight	Odds Ratio		Year	Odds Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI			
Molteni et al. ⁽²¹⁾	4	38	3	38	0.8%	1.37 [0.29, 6.59]		1990	-	
Sher et al. ⁽²⁴⁾	11	68	1	68	0.4%	12.93 [1.62, 103.22]		1994	-	
Tata et al. ⁽²⁸⁾	1001	1521	5124	7732	44.0%	0.98 [0.87, 1.10]		2005	-	
Zugna et al. ⁽³⁰⁾	1296	4466	5842	19705	54.8%	0.97 [0.90, 1.04]		2010	-	
Total (95% CI)		6093		27543	100.0%	0.99 [0.86, 1.13]			-	
Total events	45		17							
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.16$, $df = 3$ ($P = 0.10$); $I^2 = 51\%$										
Test for overall effect: $Z = 0.17$ ($P = 0.86$)										

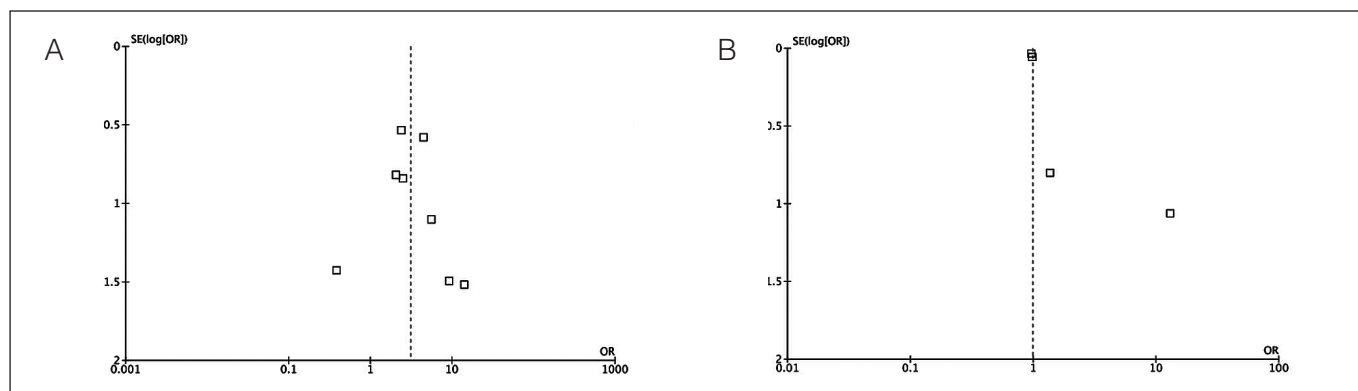
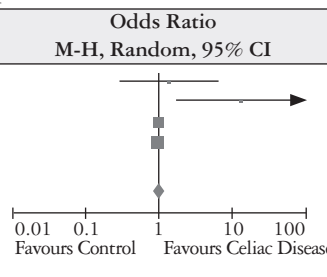


FIGURE 2. Funnel plot assessing for publication bias among (A) studies assessing undiagnosed celiac disease risk in patients with infertility. (B) studies assessing risk of infertility in already-diagnosed celiac disease

Reports on infertility risk in CD patients are far from scarce, but often show non-definite, sometimes conflicting results. Jackson et al.⁽¹³⁾ described a cohort of women suffering from infertility that were tested for CD by means of serology. This study found a relatively low frequency of CD among infertile women compared to the background rate in the general U.S. population. Choi et al.⁽⁵⁾ tested women assisting at an infertility clinic for CD; although an increased prevalence overall was not found, CD was more frequent in those women with UI; again, this study lacked a control group.

Case-control and cross-sectional studies assessing the risk of CD in infertile patients also show conflicting results. The largest study published by Hogen Esch et al.⁽¹²⁾ included 1038 patients attending to an infertility clinic and 1432 controls. They did not find a significant difference in CD prevalence between groups; it is worth mentioning though that they only performed serological tests to determine CD prevalence. Da Silva Martins et al.⁽⁶⁾ published the only experience so far in a South-American setting: they included 200 patients attending an infertility clinic and 400 control subjects. They also were not able to find a significant CD prevalence among infertile women.

Only the study by Kumar et al.⁽¹⁶⁾ proved a significant association between CD and infertility. The other studies included in this analysis did not reach a statistically relevant difference, probably due to insufficient sample size. However, as revealed in our meta-analysis, the pooled OR is significantly increased.

These results contrast with those derived from cohort and case-control studies including previously diagnosed CD subjects. Tata et al.⁽²⁹⁾ published a large cohort study that assessed 1521 CD women in fertile age and 7732 non-CD women matched by age, sex, general practice and follow-up time. They found that the birth rates in both groups with a similar median follow-up time (4.3 vs 4.9 years) were similar (HR 1.01 95%CI 0.91-1.14). What is more, Zugna et al.⁽³¹⁾ published an even larger cohort study including 11495 women with CD and 51109 controls: they also did not find an excessive risk of infertility in the CD cohort. These results contrast with those from studies that included non-diagnosed CD. A potential explanation for this difference may be that in the cohort studies, CD patients were already treated: this may underline that GFD may cause a reversal of infertility

problems in celiac women. Cohort studies including already-diagnosed CD women did not assess GFD compliance, so it is not possible to conclude that gluten ingestion may actually be a risk factor for developing infertility in CD subjects. However, Zugna et al.⁽³¹⁾ found that although women with CD had normal fertility overall, fertility levels decreased in the last two years preceding CD diagnosis. This emphasizes the fact that untreated CD is a risk factor for infertility and that GFD may be sufficient to correct this abnormality.

There is no clear explanation why these two entities are associated. CD is associated with many extra-intestinal diseases that have an immunological basis. Persistent inflammation can produce some serological markers that may have an impact in the development of infertility⁽²²⁾. As seen with other extra-intestinal diseases, early introduction of a GFD may decrease the risk of this complication. Further studies should focus on this particular subject.

Although evidence is relatively scarce, studies evaluating male partners failed to show a significant association between infertility and CD. However, these studies do not mention a relationship between CD and certain factors related to male infertility, such as hypogonadism or semen quality deficiencies. Farthing et al.⁽⁷⁾ described a high frequency of seminal alterations and sexual dysfunction in a cohort of CD male patients compared to Crohn's disease subjects.

Limitations must be taken into consideration. Among all of the studies analyzed, heterogeneity in CD definition and serological tests used for screening were found. Most of them, however, required histological confirmation. Secondly, the impact that GFD may exert cannot be estimated due to the design of included studies. Furthermore, the impact of poor adherence to GFD cannot be calculated from available evidence. Although funnel plot analysis doesn't suggest a significant publication bias when considering studies assessing CD risk in subjects with infertility, there is a significant asymmetry in the funnel plot of studies assessing risk of infertility in already-diagnosed CD patients.

In conclusion, this meta-analysis shows that undiagnosed CD is in fact a risk factor for infertility. This may have a significant impact on the management of infertility, since women seeking medical advice for this particular condition should be screened for CD. Ultimately, adoption of a GFD could have a positive impact on fertility in this group of patients.

Lasa JS, Zubiaurre I, Soifer LO. Risco de infertilidade em pacientes com doença celíaca: uma meta-análise de estudos observacionais. *Arq Gastroenterol.* 2014;51(2):144-50.

RESUMO - Contexto - A doença celíaca é uma doença auto imune do intestino delgado associada a manifestações extra-intestinais, tais como distúrbios reprodutivos. A relação entre a doença celíaca e a infertilidade foi previamente avaliada, com resultados conflitantes. **Objetivos** - Procuramos determinar a relação entre a doença celíaca e a infertilidade. **Método** - Utilizou-se dados extraídos de estudos de projeto de caso-controle ou coorte de 1966 à dezembro de 2013 utilizando o MEDLINE-Pubmed, EMBASE, LILACS e Cochrane Library. Foram analisados dois tipos de ensaios: os que avaliam o risco de infertilidade em pacientes com doença celíaca já diagnosticados e, os que avaliam a prevalência da doença celíaca não diagnosticada em indivíduos com diagnóstico de infertilidade. **Resultados** - A busca resultou em 413 estudos potencialmente relevantes para a revisão, 12 dos quais foram finalmente incluídos para análise. Foi encontrada uma associação significativa entre as mulheres com diagnóstico de infertilidade e doença celíaca não diagnosticada [TR 3,09 (IC 95% 1,74-5,49)]. Ao considerar esses estudos avaliando a ocorrência de infertilidade em pacientes com doença celíaca já diagnosticada, não foi encontrada diferença entre os pacientes com doença celíaca e controles [TR 0,99 (0,86-1,13)]. **Conclusão** - A falta de diagnóstico para a doença celíaca é um fator de risco para a infertilidade. As mulheres que procuram o conselho médico para esta condição particular, devem ser examinados para a doença celíaca. A adoção de uma dieta sem glúten pode ter um impacto positivo sobre a fertilidade neste grupo de pacientes.

DESCRITORES - Doença celíaca. Infertilidade feminina. Dieta livre de glúten.

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