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ORIGINAL ARTICLE ***Reproductive epidemiology***

Reproductive life in women with celiac disease; a nationwide, population-based matched cohort study

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STUDY QUESTION: How does celiac disease (CD) influence women's reproductive life, both prior to and after the diagnosis?

SUMMARY ANSWER: Prior to the diagnosis of CD, an increased risk of adverse pregnancy outcomes was seen, whereas after the diagnosis, no influence on reproductive outcomes was found.

WHAT IS KNOWN ALREADY: CD has been associated with several conditions influencing female reproduction and pregnancy outcomes including spontaneous abortion and stillbirth.

STUDY DESIGN, SIZE, DURATION: A nationwide matched cohort study following 6319 women diagnosed with CD and 63166 comparison women and identifying reproductive events between the ages of 15 and 50 years.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Through linkage of several Danish national health registers, we identified all women diagnosed with CD between 1977 and 2016. We identified an age- and sex-matched comparison cohort and obtained data on reproductive outcomes for both cohorts. Adjusted stratified Cox and logistic regression models were used to estimate differences in reproductive outcomes between women with and without CD.

MAIN RESULTS AND THE ROLE OF CHANCE: Comparing women with diagnosed CD with the non-CD women, the chance of pregnancy, live birth and risk of stillbirth, molar and ectopic pregnancy, spontaneous abortion and abortion due to foetal disease was the same. However, prior to being diagnosed, CD women had an excess risk of spontaneous abortion equal to 11 extra spontaneous abortions per 1000 pregnancies (adjusted odds ratio (OR) = 1.12, 95% CI: 1.03, 1.22) and 1.62 extra stillbirths per 1000 pregnancies (adjusted OR = 1.57, 95% CI: 1.05, 2.33) compared with the non-CD women. In the period 0–2 years prior to diagnosis fewer pregnancies occurred in the undiagnosed CD group, equal to 25 (95% CI: 20–31) fewer pregnancies per 1000 pregnancies compared to the non-CD group and in addition, fewer undiagnosed CD women initiated ART-treatment in this period, corresponding to 4.8 (95% CI: 0.9, 8.7) fewer per 1000 women compared to non-CD women.

LIMITATIONS, REASONS FOR CAUTION: Validity of the diagnoses in the registers was not confirmed, but reporting to the registers is mandatory for all hospitals in Denmark. Not all spontaneous abortions will come to attention and be registered, whereas live- and stillbirths, ectopic and molar pregnancies and abortion due to foetal disease are unlikely not to be registered. We adjusted for several confounding factors but residual confounding cannot be ruled out.

WIDER IMPLICATIONS OF THE FINDINGS: These findings suggest that undiagnosed CD can affect female reproduction and the focus should be on early detection of CD in risk groups.

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Key words: gluten intolerance / pregnancy outcomes / fertility / births / celiac disease / pregnancy / stillbirth / spontaneous abortion

Introduction

Celiac disease (CD) is an immune-mediated disease with a permanent gluten-sensitive enteropathy caused by the ingestion of gluten proteins from wheat, barley and rye. Gluten proteins induce T-cell mediated inflammation in the small-bowel and an autoimmune response to self-proteins, mainly tissue-transglutaminase (Sollid, 2002). The classical symptoms are diarrhoea, vitamin and mineral deficiencies and failure to thrive (Wierdsma *et al.*, 2013). However, most patients suffer from mild symptoms or non-classical symptoms, and therefore, the disease often remains undetected for many years (Tiboni *et al.*, 2006). The disease is diagnosed by serology and confirmed by biopsies of the small-bowel classifying the degree of inflammation and villous atrophy. CD affects up to 1% of the population in Europe and the USA with some regional differences (Catassi *et al.*, 2015). In Denmark, 180/100 000 persons had a diagnosis of CD in 2016, with a female/male ratio of 2:1 (Grode *et al.*, 2018), but a screening study found a prevalence of 479/100 000 Danes (Horwitz *et al.*, 2015), indicating that undiagnosed CD is frequent and that CD autoimmunity and inflammation of the small-bowel may be present before the clinical symptoms leading to a diagnosis.

CD has been associated with several conditions influencing female reproduction and pregnancy outcomes. A meta-analysis by Singh *et al.* (2016) showed that women with infertility had 3.5 times higher odds of having CD, and women with unexplained infertility had six times higher odds of having CD compared to controls (Singh *et al.*, 2016). To date, several studies found higher risk of delayed menarche, early menopause, endometriosis, recurrent pregnancy loss, intrauterine growth restriction (IUGR), preterm delivery, postpartum haemorrhage, low birth weight (LBW) and stillbirth in women with CD compared to non-CD women (Bona *et al.*, 2002; Ludvigsson *et al.*, 2005b; Freeman, 2010; Khashan *et al.*, 2010; Kumar *et al.*, 2011; Santonicola *et al.*, 2011; Stephansson *et al.*, 2011; Abdul Sultan *et al.*, 2014; Tersigni *et al.*, 2014). However, other studies found no association between CD in women and reproductive outcomes (Tata *et al.*, 2005b; Sharshiner *et al.*, 2013; Dhalwarni *et al.*, 2014). Besides effects of vitamin and mineral deficiencies, there is very little research on the possible mechanisms of CD affecting reproduction. Ludvigsson *et al.* (2005) studied offspring of celiac mothers and reported a lower placental weight in mothers who were later diagnosed with CD compared to non-CD mothers, which could explain the LBW and IUGR. In addition, it has been demonstrated that transglutaminase antibodies affect the angiogenesis in the endometrium (Di Simone *et al.*, 2013), is involved in apoptosis and delayed injury healing affecting the embryo–maternal interface after implantation (Di Simone *et al.*, 2010; Sóñora *et al.*, 2014) and seem to inhibit placental tissue transglutaminase activity (Anjum *et al.*, 2009). The disease is frequently diagnosed during childhood or the childbearing years and women with CD may have concerns regarding whether the disease influences their capability to reproduce. The aim of this population-based nationwide study was to examine how CD in women and several reproductive outcomes are associated, both prior to and after diagnosis of CD, using data from the Danish national registries.

Materials and Methods

Data sources

A unique civil personal registration number is assigned to all Danish residents at birth or at first immigration, allowing the linkage of national data from different registries. The Danish National Patient Register contains information on all hospital contacts in Denmark—both in somatic wards (from 1977) and from outpatient and emergency visits (from 1995). The diagnostic codes used in the register are classified according to the Danish versions of the International Classification of Diseases, eighth revision (ICD-8) from 1977 to 1993 and 10th revision (ICD-10) since 1994 (Schmidt *et al.*, 2015).

Data from the Danish National Patient Register were linked to data from the Danish Civil Registration System (established in 1968 and containing demographic, emigration and vital status information on all persons residing in Denmark), the Danish Medical Birth Register (established in 1973 and containing information on all births at home or in a hospital in Denmark), and the Danish ART Register (established in 1994 and containing information on all women treated with ART in both private and public fertility clinics in Denmark) (Sørensen *et al.*, 2009; Schmidt *et al.*, 2014; Bliddal *et al.*, 2018).

Cohort with CD

The source population consisted of the entire Danish female population in the period between 1977 and 2016. Women with CD were identified in the Danish National Patient Register using the ICD-8 code 269.00 and ICD-10 code K90.0, either as a primary or secondary diagnosis. All women registered with one of these codes were included in the cohort. Date of first occurrence of a CD diagnosis in the register was used as the date of diagnosis (index-date). We included only women who contributed with follow-up time in the registries during their reproductive age, which we defined as at least 15 years of age at the end of 2016 and <50 years at the beginning of 1977.

Comparison cohort without CD

A comparison cohort was randomly selected through the Danish Civil Registration System. For every woman with CD, 10 women without a CD diagnosis and living in Denmark on the index-date were matched on date of birth. The comparison cohort consisted only of women who were known not to be diagnosed with CD until the end of the study period in 2016.

Outcome measures

Data on induced and spontaneous abortions, molar and ectopic pregnancies were obtained from the Danish National Patient Register (Table I).

Table I Hierarchy of pregnancy outcomes deciding which to keep if two different outcomes were coded in the same pregnancy (1. First choice–6. Last choice) and the corresponding ICD-8 and ICD-10 codes.

Ranking	Outcome	ICD-8 codes	ICD-10 codes
1	Birth (both live and still)	65*, 660, 661, 662	O80–O84*
2	Molar pregnancy	63 429, 63 460, 63 469, 6450	O01*
3	Ectopic pregnancy	631	O00*
4	Spontaneous abortion	643, 644, 6451, 6454, 6457, 6459	O02–O03*
5	Induced abortion due to foetal disease	6413, 6414	O053–O054
6	Induced abortion, all others	640, 6410, 6411, 6412, 6415–17, 6442, 4455, 4456, 4458	O04*, O050–52, O055–O059, O06*

*Including subgroups.

Data on all live and stillbirths were obtained from the Danish Medical Birth Register. As not all pregnancies with an early spontaneous termination will be registered in the patient registries, the true rate of pregnancies was not assessed. However, we assume that the likelihood that an early pregnancy loss ends up in the registers is the same for the CD and the non-CD group. In Denmark, the cut-off between abortion and stillbirths was defined as birth of a dead foetus after 28 full gestational weeks before 1 April 2004 and after 22 full gestational weeks afterwards. If, by error, the same pregnancy was coded with different end-dates, we chose the first date of registration, and if the same pregnancy was coded with different types of outcome, we selected the outcome according to a hierarchy depicted in Table I. Date of conception was calculated by using gestational age (GA) at pregnancy-end obtained from the Danish National Patient Register. If GA was missing (n = 11 155), we imputed the median GA for that particular pregnancy outcome. Additionally, we obtained information on ART-treatments from the Danish ART Register.

Covariates

Information on parity at index-date was obtained from the Danish Medical Birth Register. Parity (1, 2 or 3+) was defined as the number of times a woman had given birth (both live and stillbirths). Information on morbidity of interest was retrieved from the Danish National Patient Register. Information on date of birth and death or immigration was obtained from the Danish Civil Registration System.

Statistical analysis

We first examined characteristics of the women at the index-date according to CD or non-CD group.

Reproductive outcomes after diagnosed CD

To estimate the rate of experiencing a pregnancy, we used a stratified Cox proportional hazards model to estimate crude and adjusted hazard ratios (HRs) with 95% CIs comparing women diagnosed with CD and women without a CD diagnosis. Time since diagnosis was used as the time scale. Follow-up started at the index-date or the age of 15 years, which ever came last. Follow-up ended at conception date of first pregnancy, date of emigration, date of death, age of 50 years or 26 June 2017, which ever came first. A stratified Cox model was also used to estimate the rate of initiation of a first ART-treatment. In this model, follow-up started at the index-date, the age of 15 years or the start of the ART-register in 1994, which ever came last. Follow-up ended at date of initiation of first ART-treatment, date of emigration or death, the age of 50 years or 26 June 2017, which ever came first. The stratified Cox models implied that each CD diagnosed woman was only compared with her matched reference women and then a summary estimate was calculated.

To model the probability of the different pregnancy outcomes, we used a logistic regression model to estimate odds ratios (OR) with 95% CIs. These analyses were conducted separately for each outcome of interest and included all pregnancies after index-date. To explore different time-windows of exposure, we divided time since diagnosis of CD into the following categories: 0–2 years, 3–5 years and >5 years after index-date.

Adjusted models included variables chosen a priori based on prior knowledge (Sjöberg *et al.*, 2013; Wiebe *et al.*, 2014) and using directed acyclic graphs (Greenland *et al.*, 1999). We adjusted for parity, diabetes type 1, autoimmune thyroid disease (Graves and Hashimoto's disease), and the maternal chromosomal abnormalities Downs and Turner syndrome. In the analysis of pregnancy outcomes, only women experiencing a pregnancy were included. To keep as many cases as possible in the analysis, matching was not maintained; instead, we adjusted for age at conception and year of index-date. In addition, we used robust standard errors to account for the fact that several women contributed with more than one pregnancy to the analyses.

Reproductive outcomes prior to a CD diagnosis

Since CD can be 'undiagnosed' for a long period of time (Rubio-Tapia *et al.*, 2009), and is probably untreated during this period, we explored how different pregnancy outcomes prior to the index-date were associated with a later diagnosis of CD. To examine these associations, we estimated the ORs for CD between women with and without adverse pregnancy outcomes prior to the index-date. We included the period from index-date and backwards to the age of 15 years of the woman or the beginning of the registries. To explore different time-windows until the CD diagnosis, we divided time before diagnosis of CD into the following categories: 0–2 years, 3–5 years and >5 years prior to index-date. We used conditional logistic regression accounting for the matching and adjusting for comorbidities.

Sensitivity analyses

More than one CD diagnosis registered in the Danish National Patient Register could increase the validity of the diagnosis (Sander *et al.*, 2016). To assess the reproductive outcomes in women possibly exposed to a more valid CD diagnosis or more severe disease, we performed a sensitivity analysis including only women with at least two contacts with a diagnosis of CD in the Danish National Patient Register. In this analysis, the index-date was the date of the second registration in the register to avoid conditioning on the future. In addition, to avoid bias due to selective fertility (Wilcox, 2010), we used only the first pregnancy after index-date in the

Cox model. In the logistic model, we first included all pregnancies and subsequently ran a sensitivity analysis only including the first pregnancy As the Danish National Patient Register may not have national coverage until years after it was established, a sub-analysis restricting the CD cohort to women diagnosed from 1987 was performed.

All analyses were performed using Stata 14 (Stata Corp, College Station, TX, USA).

Ethical approval

The study was approved by the Danish Data Protection Agency (J No. 1-16-02-186-15). In Denmark, studies based on register data do not require ethical approval.

Results

Study population

Initially, 7625 women with a diagnosis of CD were identified in the Danish National Patient Register. Only women who contributed with follow-up time in the registries during their reproductive age were included, corresponding to 6319 with at least one diagnosis of CD and 63166 matched women without CD.

The descriptive characteristics at index-date of the CD diagnosed women and the comparison women are presented in Table II. The majority of the CD women (60.3%) were diagnosed during their reproductive age and 15% during childhood (age <15 years). Women diagnosed with CD more often had a diagnosis of diabetes type 1, thyroid disease and Downs or Turner syndrome. At index-date, the average number of pregnancies in the two cohorts was similar (1.1 pregnancies per woman) and mean age at first pregnancy was also approximately the same.

Reproductive outcomes after diagnosed CD

The overall adjusted HR for achieving a first pregnancy with any outcome during the follow-up was 1.00 (95% CI: 0.93, 1.06) and no significant differences occurred in the time-intervals after diagnosis, comparing diagnosed CD with non-CD women. In addition, no

Table II Characteristics of women with a first time diagnosis of celiac disease (CD) during the period 1977–2016 and the non-celiac disease comparison women.

	CD cohort (*N* = 6319)	%	Comparison cohort (*N* = 63 166)	%
Age at CD diagnosis, years				
<15	974	15.4	9709	15.4
15-49	3812	60.3	38 156	60.4
≥50	1533	24.2	15 301	24.3
Year of CD diagnosis				
1977–1986	327	5.2	–	
1987–1996	654	10.3	–	
1997–2006	1603	25.4	–	
2007–2017	3735	59.1	–	
Diabetes Type 1	268	4.2	403	0.6
Thyroid disease	115	1.8	457	0.7
Downs or Turner syndrome	42	0.7	58	0.1
IVF treatment (at least one)	111	1.8	1379	2.2
Parity, *n*				
0	3761	59.5	37 568	59.5
1	838	13.3	9194	14.6
2	1232	19.5	11 671	18.5
≥3	488	7.7	4733	7.5
Mean age at first pregnancy, years (SD)	25.9 (5.2)		25.8 (5.4)	
Age group at first pregnancy, years				
<25	1293	45.6	13 538	46.7
25–34	1387	49.0	13 740	47.4
35–50	153	5.4	1697	5.9
Pregnancies				
No	3486	55.2	34 189	54.1
One	781	12.4	8738	13.8
Two	951	15.0	9738	15.4
≥Three	1101	17.4	10 501	16.6
Pregnancies total	7286	1.15 per woman	72 166	1.14 per woman

statistically significant differences in HRs for initiating ART-treatment were found (Table III). As can be seen from Fig. 1 and Table IV, no statistically significant differences in adjusted ORs for the different adverse pregnancy outcomes were found, comparing diagnosed CD with non-CD women.

Reproductive outcomes prior to a CD diagnosis

Overall, there was no difference in the number of pregnancies occurring prior to the index-date in the undiagnosed CD group compared to the non-CD group. However, in the period 0–2 years prior to the diagnosis, fewer pregnancies occurred in the undiagnosed CD group, corresponding to 25 (95% CI: 20, 31) fewer pregnancies per 1000 pregnancies compared to the non-CD group. Subsequently, significantly fewer live births occurred in that same period among the undiagnosed CD group, equal to 27 (95% CI: 21, 33) fewer live births per 1000 live births (adjusted OR 0.63 (95% CI: 0.55, 0.73)), whereas more than 5 years prior to diagnosis, slightly more live births occurred among the undiagnosed CD-group (adjusted OR 1.06 (95% CI: 1.00, 1.12)). The excess risk of an adverse pregnancy outcome was 15 per 1000 pregnancies (95% CI: 7, 23) to women with undiagnosed CD compared to the non-CD women (adjusted OR 1.15 (95% CI: 1.06, 1.24)), with the highest risk in the period more than 5 years prior to diagnosis (Fig. 1). The overall adjusted OR of stillbirth was 1.62 (95% CI: 1.05, 2.33) corresponding to 1.62 (95% CI: 0.03, 3.21) more stillbirths per 1000 pregnancies to the undiagnosed CD women compared to the non-CD and with a statistical significant higher risk in the period more than 5 years prior to diagnosis. The overall adjusted OR for spontaneous abortion was 1.12 (95% CI: 1.03, 1.22) corresponding to 11 (95% CI: 4–19) more spontaneous abortions per 1000 pregnancies to the undiagnosed CD group, again with a statistically significant higher risk in the period more than 5 years prior to diagnosis (adjusted OR 1.12 (95% CI: 1.02, 1.24)). The CD women had significantly fewer abortions on mothers request (16 (95% CI: 8, 24) fewer per 1000

Table III Hazard Ratios for first pregnancy and first ART-treatment after index-date in celiac disease compared to non-celiac disease women, total and according to time-intervals.

	N, 0–2 years	HR (95% CI) Crude and adjusted[a] 0–2 years	*N*, 3–5 years	HR (95% CI) Crude and adjusted[a] 3–5 years	*N* >5 years	HR (95% CI) Crude and adjusted[a] >5 years	N Total	HR (95% CI) Crude and adjusted[a] Total
First pregnancy	369	0.92 (0.83, 1.02)	210	0.93 (0.81, 1.07)	455	1.03 (0.93, 1.13)	1036	0.96 (0.90, 1.02)
	3937	0.97 (0.87, 1.08)	2250	0.96 (0.83, 1.10)	4648	1.03 (0.93, 1.14)	10 843	1.00 (0.93, 1.06)
First ART-treatment	22	0.81 (0.52, 1.25)	22	1.11 (0.71, 1.72)	72	1.03 (0.81, 1.32)	116	0.99 (0.82, 1.20)
	267	0.73 (0.46, 1.15)	194	1.03 (0.66, 1.67)	710	1.02 (0.79, 1.31)	1171	0.96 (0.79, 1.17)

[a]Adjusted for diabetes type 1, thyroid disease, Downs and Turner syndrome. *N*, number; HR, hazard ratio.

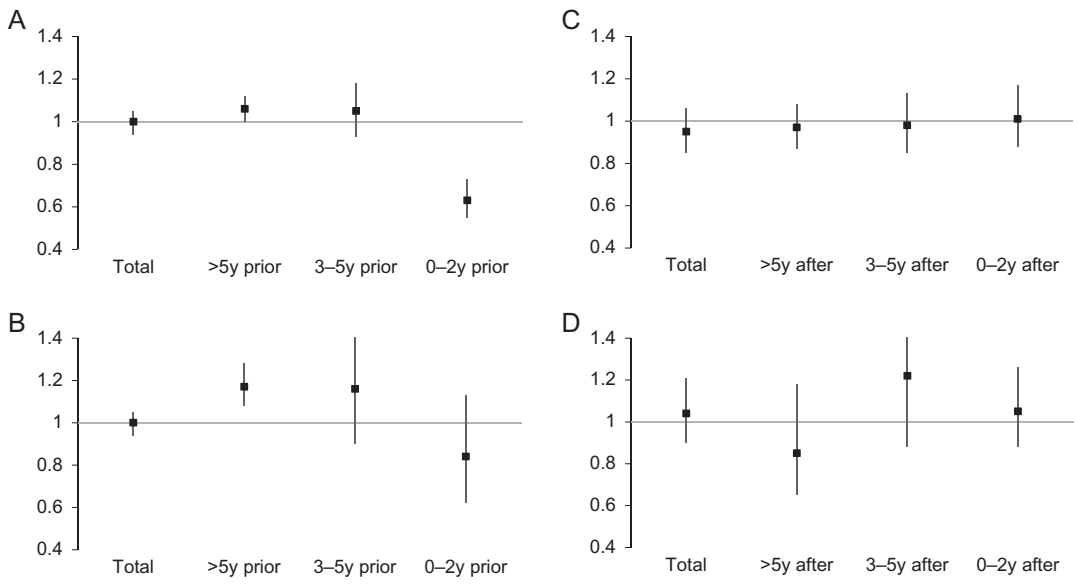

Figure 1 Adjusted OR for live births and adverse pregnancy outcomes prior to and after index-date in celiac disease compared to non-celiac disease women; total and according to time-intervals. Adjusted OR (95%CI) for live births (A) and adverse outcomes (B) prior to index-date. Adjusted OR (95%CI) for live births (C) and adverse outcomes (D) after index-date.

Table IV **Odds ratio for different pregnancy outcomes of all pregnancies occurring *after index-date* in celiac disease compared to non-celiac disease women, total and according to time-intervals**

		Events 0–2 years	Pregnancies/ 1000 women 0–2 years	Events 3–5 years	Pregnancies/ 1000 women 3–5 years	Events >5 years	Pregnancies/ 1000 women >5 years	Events (%) Total	Pregnancies/ 1000 women Total
Number of pregnancies (%)	CD	440 (20.4)	69/1000 women	364 (16.9)	59/1000 women	1355 (62.8)	221/1000 women	2159	352/1000 women
	Non-CD	4786 (22.1)	76/1000 women	3843 (17.8)	62/1000 women	13005 (60.1)	211/1000 women	21 634	351/1000 women
Outcome of pregnancies		**0–2 years**	**OR (95% CI) Crude adjusted[a] 0–2 years**	**3–5 years**	**OR (95% CI) Crude adjusted[a] 3–5 years**	**> 5 years**	**OR (95% CI) Crude adjusted[a] > 5 years**	**Total**	**OR (95% CI) Crude adjusted[a] Total**
Pregnancies with live birth	CD	331	0.93 (0.81, 1.07)	274	0.96 (0.83, 1.11)	968	1.06 (0.95, 1.17)	1573 (72.9)	1.00 (0.89, 1.12)
	Non-CD	3524	1.01 (0.88, 1.17)	2837	0.98 (0.85, 1.13)	9406	0.97 (0.87, 1.08)	15 767 (72.9)	0.95 (0.85, 1.06)
Pregnancies with adverse outcome[b]	CD	48	0.78 (0.57, 1.06)	51	1.16 (0.84, 1.60)	177	1.07 (0.89, 1.27)	276 (12.8)	1.02 (0.88, 1.17)
	Non-CD	614	0.85 (0.65, 1.18)	441	1.22 (0.88, 1.69)	1672	1.05 (0.88, 1.26)	2727 (12.6)	1.04 (0.90, 1.21)
Stillbirth	CD	1	1.00 (0.12, 7.82)	1	0.67 (0.09, 5.03)	5	1.32 (0.52, 3.35)	7 (0.3)	1.11 (0.51, 2.43)
	Non-CD	10	1.07 (0.14, 7.93)	15	0.70 (0.09, 5.39)	38	1.36 (0.54, 3.45)	63 (0.3)	1.15 (0.53, 2.51)
Spontaneous abortion	CD	42	0.80 (0.58, 1.13)	44	1.18 (0.84, 1.65)	151	1.10 (0.91, 1.33)	237 (11.0)	1.05 (0.90, 1.22)
	Non-CD	520	0.89 (0.63, 1.26)	375	1.26 (0.89, 1.77)	1384	1.10 (0.91, 1.33)	2279 (10.5)	1.08 (0.92, 1.26)
Molar pregnancies	CD	0	NA	0	NA	2	0.95 (0.20, 4.49)	2 (0.1)	0.65 (0.15, 2.80)
	Non-CD	6		4		21	0.87 (0.23, 3.39)	31 (0.1)	0.65 (0.19, 2.37)
Ectopic pregnancies	CD	4	0.63 (0.23, 1.74)	4	1.21 (0.43, 3.42)	11	0.61 (0.33, 1.12)	19 (0.9)	0.69 (0.42, 1.12)
	Non-CD	63	0.68 (0.25, 1.85)	33	1.25 (0.23, 16.98)	180	0.58 (0.30, 1.07)	276 (1.3)	0.67 (0.41, 1.10)
Induced abortion, foetal disease	CD	1	0.67 (0.09, 5.06)	2	1.43 (0.33, 6.28)	8	1.64 (0.78, 3.46)	11 (0.5)	1.42 (0.75, 2.66)
	Non-CD	15	0.71 (0.09, 5.66)	14	1.07 (0.28, 4.09)	49	1.31 (0.59, 2.91)	78 (0.4)	1.19 (0.63, 2.25)
Induced abortions on mothers request	CD	61	0.94 (0.72, 1.23)	39	0.67 (0.48, 0.97)	210	1.10 (0.92, 1.32)	310 (14.4)	0.99 (0.85, 1.15)
	Non-CD	648	1.07 (0.81, 1.41)	568	0.77 (0.55, 1.10)	1927	1.11 (0.92, 1.32)	3140 (14.5)	1.04 (0.90, 1.22)

[a]Adjusted for cluster effect of woman, age at conception, index-year, parity, diabetes type 1, thyroid disease, Downs and Turner syndrome.
[b]Excluding induced abortions on mothers request.
NA: Not applicable.

pregnancies) and less undiagnosed CD women initiated ART-treatment with 5 fewer (95% CI: 1, 9) per 1000 women compared to the non-CD group, with the strongest association in the period 0–2 years prior to diagnosis. The overall adjusted OR for molar pregnancy was 1.07 (95% CI: 0.48, 2.28) and ectopic pregnancy 1.19 (95% CI: 0.97, 1.45), with a small statistically significant increased risk of ectopic pregnancy in the period more than 5 years prior to diagnosis among the undiagnosed CD group (adjusted OR 1.27 (95% CI: 1.03, 1.57)). No increased risk of abortion due to foetal disease was seen in any of the time-intervals (Fig. 1 and Table V).

Sensitivity analyses

For the sensitivity analysis, we were able to confirm at least two hospital contacts with a CD diagnosis in the Danish National Patient Register in 4028 cases (63.7%), corresponding to 39 760 matched comparison women. Redefining the cohort to include only women with at least two contacts did not change the overall estimates notably regarding the chance of a first pregnancy (adjusted HR = 1.03, 95% CI: 0.93, 1.12) or the probability of any adverse outcomes in pregnancies after the index-date (Supplementary Information Table S1). Prior to the diagnosis of CD, comparing women with at least two contacts with non-CD women, the overall adjusted OR for any adverse pregnancy outcome became somewhat stronger (1.24 (95% CI: 1.13, 1.37)). The association with spontaneous abortion became slightly stronger (adjusted OR = 1.23, 95% CI: 1.10, 1.36) and the association for stillbirth became somewhat weaker (adjusted OR = 1.37, 95% CI: 0.83, 2.28), however, with overlapping CIs (Supplementary Information Table S1). No significant changes were seen in the overall risk of different pregnancy outcomes restricting to only the first pregnancy after index-date or when restricting the cohort to women diagnosed after 1987 (results not shown).

Discussion

In this nationwide register-based study, women diagnosed with CD had the same chance of experiencing a pregnancy and for a pregnancy ending in a live birth and same risk of different adverse pregnancy outcomes, as women without a diagnosed CD. On the other hand, women with a CD diagnosis had a higher probability of having experienced an adverse pregnancy outcome prior to the diagnosis of CD, especially spontaneous abortions and stillbirths. Also, they had fewer induced abortions on mothers request and less had ART-treatment compared to non-CD women. However, the number of previous live births was similar in women with and without CD. Since the disease can be latent for a long period, these findings indicate that undiagnosed CD, and therefore probably untreated, might increase the risk of adverse pregnancy outcomes. However, after the diagnosis of the disease, and then probably following a gluten-free treatment, the increased risk seems to disappear. These results match the hypotheses of the possible negative effect of both vitamin and mineral deficiencies and transglutaminase antibodies on different processes related to implantation and survival of a pregnancy. Our findings are also consistent with those of Ludvigsson et al (Ludvigsson *et al.*, 2005b) who reported that maternal undiagnosed CD was a risk factor for unfavourable foetal outcomes and lower placental weight. Studies show that treatment with a gluten-free diet can lead to elimination of circulating transglutaminase antibodies within months and to full recovery of the small-bowel in 66% of adult patients within 5 years after diagnosis and if diagnosed as a child 95% may have full bowel recovery (Rubio-Tapia *et al.*, 2010). Thus, the negative processes are more likely to be present in untreated periods, i.e. the time prior to the diagnosis.

Our results expand on previous studies by specifically looking at several reproductive outcomes in both diagnosed and undiagnosed CD in a large population of CD women. In a large Swedish study by Zugna *et al.* (2010) they found normal fertility in CD women measured on number of children, but decreased fertility up to 2 years before diagnosis of CD. In the undiagnosed CD group, we also found a decreased number of pregnancies and live births in the period 0–2 years prior to the diagnosis, which supports the findings of Zugna *et al.* Using data recorded from general practitioners in the UK, Tata *et al.* compared CD women with non-CD women and found increased risk of spontaneous abortion (rate ratio (RR): 1.28, 95% CI: 1.06, 1.61) when looking at their overall fertile period. The risk of ectopic pregnancy and stillbirth was increased, but not statistically significantly. The risk of termination (abortion on mother's request) was the same in the two groups. When comparing the CD women's overall fertility, but separated in prior to and after diagnosis, they found no differences between the periods (Tata *et al.*, 2005a). Sultan et al from the UK found a non-statistically significant increased risk of stillbirth, both prior to and after diagnosis, compared to non-CD women (Abdul Sultan *et al.*, 2014). In a meta-analysis, Tersigni *et al.* (2014) found increased risk of spontaneous abortion (RR: 1.39 95% CI: 1.15, 1.67) but no increased risk of unexplained stillbirths in CD women. We did not separate explained and unexplained stillbirths since we had no information on this from the registers and the results of stillbirth are based on small numbers and should be interpreted with caution. We found no differences in use of ART-treatment after diagnosis of CD, which is in line with results from a recent study from the UK by Dhalwarni *et al.* (2014), finding the risk of clinical recorded fertility problems (e.g. referral to ART-treatment) to be the same when comparing women with diagnosed CD to non-CD women. However, prior to the diagnosis, we found that fewer women in the undiagnosed CD group initiated ART-treatment, especially in the period 0–2 years prior to the diagnosis, suggesting that they experienced less infertility than the non-CD group during this period. This finding is inconsistent with a hypothesis of decreased fertility, with fewer pregnancies and consequently fewer live births in the same period and also inconsistent with the findings by Zugna *et al.* of a decreased fertility up to 2 years prior to diagnosis. We cannot explain this finding, but it could be that the undiagnosed CD women experience fatigue or other symptoms leading to hesitation to reproduce and initiate ART-treatment.

We adjusted for diabetes type 1, autoimmune thyroid disease and the two genetic syndromes Turner and Downs, because these conditions are known to be associated with CD and reproductive outcomes in women. Adjusting for these potential confounding factors did not change the estimates substantially in any of the analyses.

For women with diagnosed CD, it is reassuring that no impact on reproduction was found, which is in line with results from an increasing number of studies. The results of the reproductive outcomes prior to the CD diagnosis, with higher risk of adverse pregnancy outcomes, support the idea that it is the untreated disease, which potentially may have a negative impact on the female reproduction. These findings suggest that the focus should be on early detection of CD, especially among women experiencing spontaneous abortions and stillbirths.

Table V Odds ratio for different pregnancy outcomes of all pregnancies occurring before index-date in celiac disease compared to non-celiac disease women, total and according to time-intervals.

		Events >5 years	Pregnancies/1000 women >5 years	Events 3–5 years	Pregnancies/1000 women 3–5 years	Events 0–2 years	Pregnancies/1000 women 0–2 years	Events (%) Total	Pregnancies/1000 women Total
Number of pregnancies (%)	CD	6362 (87.3)	1007	557 (7.6)	88	367 (5.0)	58	7286	1153
	Non-CD	61141 (84.7)	968	5563 (7.7)	88	5461 (7.5)	87	72166	1143
Outcome of pregnancies		**>5 years**	**OR (95% CI) Crude adjusted[a] >5 years**	**3–5 years**	**OR (95% CI) Crude adjusted[a] 3–5 years**	**0–2 years**	**OR (95% CI) Crude adjusted[a] 0–2 years**	**Total**	**OR (95% CI) Crude adjusted[a] Total**
Pregnancies with live birth	CD	4730	1.06 (1.00, 1.12)	404	1.05 (0.93, 1.17)	254	0.63 (0.54, 0.73)	5388 (73.9)	0.99 (0.94, 1.05)
	Non-CD	45 286	1.06 (1.00, 1.12)	4074	1.05 (0.93, 1.18)	3950	0.63 (0.55, 0.73)	53 310 (73.8)	1.00 (0.94, 1.05)
Pregnancies with adverse outcome[b]	CD	733	1.18 (1.09, 1.29)	76	1.16 (0.90, 1.49)	54	0.83 (0.62, 1.12)	863 (16.0)	1.16 (1.07, 1.25)
	Non-CD	6112	1.17 (1.08, 1.28)	670	1.16 (0.90, 1.49)	670	0.84 (0.62, 1.13)	7452 (14.0)	1.15 (1.06, 1.24)
Stillbirth	CD	31	1.82 (1.22, 2.71)	0	NA	2	2.64 (0.46, 15.19)	33 (0.5)	1.68 (1.14, 2.47)
	Non-CD	180	1.75 (1.17, 2.61)	20		9	2.71 (0.47, 15.6)	210 (0.3)	1.62 (1.05, 2.33)
Spontaneous abortion	CD	579	1.14 (1.03, 1.25)	67	1.27 (0.97, 1.66)	47	0.87 (0.63, 1.19)	693 (9.5)	1.13 (1.04, 1.23)
	Non-CD	4955	1.12 (1.02, 1.24)	552	1.27 (0.97, 1.66)	565	0.87 (0.63, 1.22)	6072 (8.4)	1.12 (1.03, 1.22)
Molar pregnancies	CD	8	1.20 (0.56, 2.59)	0	NA	0	NA	8 (0.1)	1.03 (0.47, 2.20)
	Non-CD	60	1.25 (0.58, 2.68)	7		6		73 (0.1)	1.07 (0.48, 2.28)
Ectopic pregnancies	CD	106	1.26 (1.01, 1.55)	8	1.00 (0.44, 2.27)	3	0.40 (0.12, 1.29)	117 (1.6)	1.17 (0.95, 1.42)
	Non-CD	841	1.27 (1.03, 1.57)	69	0.99 (0.44, 2.23)	77	0.39 (0.12, 1.28)	987 (1.4)	1.19 (0.97, 1.45)
Induced abortion, foetal disease	CD	9	1.30 (0.64, 2.66)	1	0.42 (0.06, 3.14)	2	1.33 (0.25, 7.14)	12 (0.2)	1.11 (0.60, 2.06)
	Non-CD	75	1.26 (0.62, 2.59)	22	0.47 (0.06, 3.64)	13	1.57 (0.28, 8.84)	110 (0.2)	1.12 (0.60, 2.09)
Induced abortions on mothers request	CD	899	0.89 (0.83, 0.96)	77	1.19 (0.91, 1.54)	59	0.82 (0.60, 1.10)	1035 (14.2)	0.90 (0.84, 0.97)
	Non-CD	9744	0.89 (0.82, 0.96)	819	1.20 (0.92, 1.56)	841	0.81 (0.60, 1.10)	11 404 (15.8)	0.90 (0.84, 0.97)
At least one ART-treatment[c]	CD	84	0.92 (0.73, 1.16)	15	0.70 (0.41, 1.18)	12	0.46 (0.26, 0.83)	111 (2.0)	0.79 (0.65, 0.97)
	Non-CD	908	0.91 (0.72, 1.15)	214	0.68 (0.40, 1.17)	257	0.41 (0.23, 0.73)	1379 (2.5)	0.76 (0.62, 0.93)

[a]Adjusted diabetes type 1, thyroid disease, Downs and Turner syndrome.
[b]Excluding induced abortions on mothers request.
[c]Including women diagnosed from 1994 (women *N* = CD: 5619/non-CD: 56 166).
NA: Not applicable.

Strengths and limitations

The strengths are the nationwide population coverage of the registers with mandatory reporting, leading to a large sample size and practically complete follow-up of 40 years and minimizing the risk of selection bias. Data in the national registries are prospectively recorded with a high degree of objectivity and low risk of recall bias. However, our study can be subject to misclassifications of the exposure to CD since we were not able to validate the CD diagnosis with histology results. Moreover, it can be difficult to define the exact time of disease onset, since the disease can be unrecognized for many years before contact with the healthcare system. According to a Danish validation study, the diagnosis of CD in the registries has a positive predictive value of 72% in children, if the diagnosis occurs in at least two contacts (Sander *et al.*, 2016). When we restricted the analysis to women with at least two contacts, it did not change the results of the risk of different pregnancy outcomes after the diagnosis of CD substantially. Using only the first pregnancy after index-date, the association for any adverse pregnancy outcome became stronger with an adjusted HR of 1.15 (95% CI: 0.96, 1.39) compared to an adjusted HR of 1.04 (95% CI: 0.90, 1.21) taking all pregnancies into account, but no statistically significant changes were found. Associations with adverse pregnancy outcomes can be overestimated if only the most recent pregnancy is taken into account. Selective fertility may produce this bias, because experiencing an adverse pregnancy outcome often leads to a new pregnancy, whereas a live birth typically leads to paucity or total stop of new pregnancies. We avoid this potential bias in the analysis where we use the first pregnancy only, although then the sample size decreases, and uncertainty increases.

Not all infertile couples seek medical assistance and early spontaneous abortion may not come to the woman's attention or be presented in the medical information, therefore we cannot rule out a higher rate of these two outcomes. However, this misclassification will probably be non-differential and draw estimates toward no differences. It is more unlikely that a live birth, stillbirth, a molar or an ectopic pregnancy should be unrecognized or not registered. We obtained information on several relevant covariates and controlled for potential confounders, however, we cannot rule out residual confounding. We did not have information on maternal cigarette smoking, BMI and ethnicity. An inverse association between cigarette smoking and CD has been reported in some studies, whereas other studies did not confirm this (Austin *et al.*, 2002). A large study by Ludvigsson *et al.* (2005a) did not find any association between smoking status in pregnant women and a subsequent diagnosis of CD. Studies show that CD women on a gluten free diet have a lower BMI compared to healthy control subjects (Bardella *et al.*, 2000). The confounding effect of both smoking and BMI on CD and pregnancy outcomes is probably negative, and not adjusting for this will draw the association towards the null hypothesis. Ethnicity may be considered as a confounder, however, only small variations in CD prevalence in different ethnic groups has been found (Krigel *et al.*, 2016) and the Danish population is very homogeneous (~88% is of Danish ethnicity) (Statistics Denmark, 2016). When excluding control individuals diagnosed with CD during the follow-up time, the control group becomes less diseased. In this study, it will probably not have any notable impact on the estimates since CD overall is a rare disease and the chance of matching a control who will be diagnosed with CD during follow-up is minimal.

Conclusion

Diagnosed CD was not associated with fewer pregnancies, live births or increased risk of adverse pregnancy outcomes, however, undiagnosed CD seemed to be associated with a higher proportion of stillbirths and spontaneous abortions and fewer pregnancies and subsequently fewer live births occurred in the period 0–2 years prior to diagnosis. These results suggest that early diagnosis of CD is of importance.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

All authors contributed to the study design, acquisition, analysis and interpretation of the data and revision of the article. All authors read and approved the final article.

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Conflict of interest

The authors report no conflicts of interest in this work.

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