PhD protocol/ study 3

The association between Celiac disease in women and time to pregnancy

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Background
Celiac disease (CD) is an immune-mediated disease with a permanent gluten-sensitive enteropathy, triggered by the ingestion of gluten proteins from wheat, barley and rye. Classical CD presents as a malabsorption syndrome with weight loss and diarrhoea. However, since the advent of serologic testing, most cases of CD have been found with no, minimal or non-classical symptoms (1). The diagnosis of CD is often missed or delayed for years resulting in underestimated prevalence of CD in the general population.

A Danish study using register data from the Danish National Patient Register found that 785 of 836,241 women had a diagnose of CD, corresponding to a prevalence of 0.094% (2). Only 10-15% of people with the condition are believed to be diagnosed, leaving thousands of people with unrecognised CD (3)(4)(5). The only known effective treatment of CD is a strict, life-long gluten free diet (1).

CD is linked to a group of non-classical symptoms comprised of male and female fertility and pregnancy problems, including reduced fertility: The prevalence of CD seems high among especially unexplained infertile women when screening this group (reported prevalence between 0.8% to 8%) (6). A single report on prevalence of CD in infertile men reported a prevalence of 1% (7). Several conditions influencing fertility is associated with CD, especially delayed menarche, early menopause and endometriosis (8)(9)(10). Several studies, including data from Denmark, show that untreated female CD is associated with miscarriage, intrauterine growth restriction, preterm delivery and low-birth weight (11)(12)(2)(13), but untreated CD in males does not seem to be a risk factor for unfavourable foetal outcome (2)(14). We found no published studies where the effect of CD on fecundability (the probability of conception per menstrual cycle for a sexual active couple using no birth control) has been assessed.

Aim
- To investigate whether CD is associated with reduced fecundability measured by increased time to pregnancy among women included in two Danish birth cohorts

Hypothesis
- CD in women reduces fecundability and leads to increased time to pregnancy

Description of data sources
The Danish National Patient Register (NPR) was established in 1977 (15). It contains information on inpatients in somatic wards in Danish hospitals, and from 1995, information on outpatients has been included.
The Danish National Birth Cohort (DNBC) was established in the years 1996-2002 (16). It contains information from nearly 92,000 mothers-to-be who were followed by interviews and questionnaires during their pregnancy and after giving birth. The first telephone interview was when they were 12 weeks pregnant, and here they answered questions about various aspects of the pregnancy and lifestyle. Specifically they were asked whether the pregnancy was planned and how long it took to become pregnant (Time to pregnancy).

The Aarhus Birth Cohort (ABC) was established in 1990 and is ongoing, including pregnant women intending to give birth at Aarhus University Hospital (17). It contains information from nearly 90,000 mothers-to-be, who answered questions on various aspects of the pregnancy and lifestyle, when they were between 8-18 weeks pregnant. Specifically they answered questions about whether the pregnancy was planned and how long it took to become pregnant (Time to pregnancy).

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Design: Cohort study

Data sources: DNBC, ABC, NPR. DNBC and ABC will be merged into one large data set and linked to data from NPR, using the personal identification number (CPR-number).

Study population: Pregnant women included in DNBC or ABC. Eligibility to this study will be restricted to a woman’s first pregnancy registered in DNBC or ABC. Women with unplanned pregnancies and pregnancies caused by fertility treatment with semen from a donor will be excluded.

Exposure: Information on CD will be obtained from the NPR (1977-1993 ICD8 269.00 + 269.98 and 1994-2014 ICD10 K90.0). Since CD may be latent and not diagnosed for several years, women will be categorised in three groups according to the timing of a CD diagnosis. Women with a CD diagnosis registered at least 90 days before the index date (conception of pregnancy) are considered as “treated CD” (on gluten free diet,(18)(19)). Women with a CD diagnosis dated less than 90 days before the index date are considered as “untreated CD”.

Different “time-windows” between index pregnancy and diagnosis will be analysed. “Non-CD” includes women never registered with CD in the NPR. Data will be categorised in treated CD, untreated CD and non-CD.

Covariates: Information on maternal risk factors for infertility such as pre-pregnancy BMI, parity, age at conception, smoking status, alcohol use, fertility treatment, pre-pregnancy diabetes type I +II and thyroid disease will be obtained from DNBC, ABC and NPR.

Outcome: Time to pregnancy. Pregnancies from other types of fertility treatment will be classified as TTP > 12 months (donor semen treatment will be excluded).

Women will be classified as infertile, if Time to pregnancy for the couple was larger than 12 months.
Power calculation: To estimate numbers of women with CD, we performed a preliminary data extraction in DNBC and found a prevalence corresponding to 0.14%. Expected size of study population: 134,000 women, expected size of women having a Time to pregnancy of more than 12 month: 20,500 women (15%), expected size of exposed population (CD): 214 (0.14%), expected size of untreated CD: 160 (75% of all CD). Finding an OR of 1.6, the statistical power will be 84%.

Statistical analysis
The software STATA version 13 will be used. Logbooks will be kept over data files and do-files. Multivariate analysis such as logistic regression and time to-event analysis will be used, adjusting for potential confounders chosen a priori.

Ethics
An application to the The Danish Data Protection Agency (Region Midtjylland paraplyanmeldelse) has been submitted 05.12.2014 for permission to store all data. All information will be kept confidential, and data will be anonymised and new generated data will be handed over to DNBC at project end.

Responsibility and practical issues
The study is a part of a 3-year PhD project with start in November 2014. All applications, data management, analysis and article drafts and any practical issues in relation to the study are the responsibility of PhD student Louise Bang Grode.

Publication
The following publication is planned and will be sought published in an international peer reviewed journal: “Time to pregnancy among women with untreated celiac disease”. In addition, the intention is to communicate the results further by oral presentations and posters, both nationally and internationally.
References


