Adherence to medical treatment in relation to pregnancy, birth outcome & breastfeeding behavior among women with Crohn's disease

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PREFACE

The present thesis is based on the following manuscripts:

1. **Nielsen MJ**, Nørgaard M, Holland-Fisher P, Christensen LA. Self-reported antenatal adherence to medical treatment among pregnant women with Crohn's disease. Alimentary Pharmacology & Therapeutics 2010;32:49–58.

2. **Julsgaard M**, Nørgaard M, Hvas CL, Grosen A, Hasseriis S, Christensen LA. Influence of medical treatment, smoking and disease activity on pregnancy outcomes in Crohn's disease. Scandinavian Journal of Gastroenterology 2014; 49: 302–308

3. **Julsgaard M**, Nørgaard M, Hvas CL, Grosen A, Hasseriis S, Christensen LA. Self-reported adherence to medical treatment, breastfeeding behaviour and disease activity during the postpartum period in women with Crohn's disease. Scandinavian Journal of Gastroenterology 2014; 49: 958-966.

1. INTRODUCTION

Crohn's disease (CD) is an idiopathic, chronic inflammatory disease of the intestine, characterized by periods of remission and active intestinal inflammation that may require hospitalization.[1] The aetiology of CD remains unknown, but it is thought to be caused by a complex interaction of genetic[2] and environmental factors[3] – including tobacco, dietary components and stress – resulting in an inappropriate activation of the mucosal immune system driven by a loss of tolerance towards gut commensal bacteria.[4] The incidence rate of CD in women in Northern Denmark is 10.7/10[5] (95%, CI: 8.8-12.5), with a peak among women of reproductive age.[5] The prevalence of CD is 151 per 100.000 inhabitants in Northern Denmark. The incidence has increased during the past decades in industrialized countries including Denmark.[5-10]

CD patients experience recurrent episodes of abdominal pain, diarrhoea, bleeding, malabsorption, and weight loss when suffering of relapse in CD, and some patients develop fistulae and other extra-intestinal complications.[11,12] Within the intestine, CD is characterized by a transmural, patchy granulomatous inflammation that preferentially affects ileocecal transition but may affect any part of the gastrointestinal tract.[13] To induce and maintain remission, medical treatment with anti-inflammatory and immunosuppressive drugs is often needed during both asymptomatic and symptomatic stages of the disease, and this is also the case in pregnancy.[14-17] In general non-adherence to medical treatment among non-pregnant IBD patients has been found to be between 30-45%.[18]

Whilst pregnancy is not thought to affect the activity of CD,[19,20] studies suggest that disease activity during pregnancy worsen pregnancy outcomes, particularly increasing the incidence of preterm birth.[21-23] Furthermore, it has been established that smoking during pregnancy reduces fetal growth.[24]

Breastfeeding has been shown to have many beneficial effects on child health.[25] In CD, information on breastfeeding rates, predictors for non-breastfeeding and the influence of breastfeeding on disease activity is sparse and somewhat conflicting.[26-28]

The scope of this thesis was (1) to investigate predictors and prevalence rates of non-adherence to maintenance medical treatment in CD prior to, during and after pregnancy, (2) to assess pregnancy outcome stratified by medical treatment and smoking while accounting for disease activity, and (3) to assess breastfeeding rates and the impact of breastfeeding on the risk of relapse in CD.

2. BACKGROUND

2.1. MEDICAL TREATMENT OF WOMEN WITH CD DURING PREGNANCY & LACTATION

For decades it was believed that the placenta protected the embryo and the fetus from all noxious agents. However in the early 1960s, the thalidomide catastrophe, with a significant increase limb malformations of newborns exposed in utero to thalidomide, changed this perception.[29] Since this discovery other teratogens, such as diethylstilbestrol and 13-cis-retinoic acid have been identified.[30,31]

Pharmacokinetic studies have shown that most drugs can cross the placenta, including drugs used to treat CD.[32-34] The fetus is especially vulnerable during organogenesis during the first trimester and the rapid fetal growth stage in the third trimester.[35,36]

Most drugs used to treat CD are used during pregnancy and lactation.[37] Of particular note is that methotrexate is contraindicated due to increased risk of congenital malformations (CM).[38] It is also contraindicated when breastfeeding because it may accumulated in the child's tissues, and thereby interfere with cellular metabolism in the infant.[39] The treatments listed below are the ones most frequently used in the Central Denmark Region and North Denmark Region in the treatment of fertile women with CD, and therefore most relevant for this thesis.

2.1.1. 5-aminosalicylic acid

5-ASA has previously been widely used in the treatment of non-pregnant and pregnant patients with CD. The clinical effect in CD has been questioned in recent years. However, in prospective studies among a pregnant European IBD population approximately half of the pregnant CD patients received maintenance treatment with 5-ASA.[16,40]

A 2008 meta-analysis of seven studies, with a total of 2200 IBD pregnancies, where 642 patients received 5-ASA treatment and 1158 received no medical treatment for IBD, reported no significant increased risk of CM (OR: 1.16; 95% CI: 0.76-1.77), stillbirths (OR: 2.38; 95% CI: 0.65-8.72), spontaneous abortions (OR: 1.14; 95% CI: 0.65-2.01), preterm delivery (OR: 1.35; 95% CI: 0.85-2.13), and low birth weight (LBW) (OR: 0.93; 95% CI: 0.0.46-1.85). Excretion of 5-ASA is low in breast milk, and in conventional dosing maternal treatment is generally without risk for the suckling infant.[32] Of note, there has been a case of induction of severe reversible watery diarrhoea in an infant after exposure to 5-ASA in breastmilk.[41]

2.1.2. Corticosteroids

A prospective controlled study from 2004 of 311 pregnancies and a nationwide cohort study from 2011 of all live births over a 12-year period among 51,973 pregnancies exposed to glucocorticoid during the first trimester did not find an increased risk of major malformations or oral clefts.[42,43] In fact the nationwide study by Hviid et al. did not find any adverse pregnancy outcomes after in utero exposure to corticosteroids.[42] These data are very reassuring, because a meta-analysis from 2000 of four case-control studies found a significant increase in the risk of oral clefts among infants exposed in utero to corticosteroids (OR: 3.35; 95% CI: 1.97-5.69).[44]

Maternal treatment with corticosteroid is compatible with breastfeeding.[45,46] Öst and colleagues demonstrated that the milk/serum concentration ratio increased with increasing serum concentration.[46] However at a daily dose of 80 mg prednisolone, the infant would ingest <0.1% of that dose; this corresponds to <10% of the infants endogenous cortisol production.[46] To minimize infant exposure, it has been suggested to postpone breastfeeding 4 hours post dose.[46]

No population-based studies have investigated the risk of adverse pregnancy outcome after in utero exposure to budesonide. A case series of eight pregnant CD women treated with 6-9 mg budesonide, which has an extensive first-pass hepatic metabolism, found no increased risk of adverse pregnancy outcomes.[47]

2.1.3. Thiopurines

Thiopurines (azathioprine and 6-mecaptopurine (6-MP)) are mainly used in patients with moderate to severe disease to maintain remission. 6-MP crosses the placenta and 6-MP and 6-thioguanine (6-TGN) have been found in fetal blood.[34,48] Studies among infants born to women with IBD have not found any increased risk of CM in infants exposed in utero to thiopurines.[48-53] Studies on other adverse pregnancy outcomes have been somewhat conflicting. Some studies have found an increased risk of spontaneous abortion, preterm birth, and LBW,[54-56] whereas others have not found any increased risk.[49,50,52,53,57] Adverse pregnancy outcomes could have been caused by confounding by disease activity rather than by the use of thiopurines in pregnancy. However, a recent prospective study among 30 infants exposed in utero to thiopurine found that 60% had neonatal anaemia.[48] As a result of this finding the authors recommend that all children exposed in utero to thiopurines should be tested for anaemia after birth.[48]

The major part of 6-MP is excreted in breast milk within the first 4 hours after drug intake.[58] The estimated maximum exposure of drug to the infant is <0.008 mg 6-MP/kg bodyweight/day, equivalent to less than 1% of the maternal dose.[58] These data underpin the recommendations in the consensus report by ECCO that thiopurine treatment is compatible with breastfeeding.[59] However, if the nursing mother is concerned, the exposure can be reduced further if the mother uses a breast pump to discard the first portion of milk produced after medication intake.[58]

The long-term effects of in utero exposure to thiopurines on infant health status were evaluated in a prospective multicenter follow-up study among 30 children exposed to thiopurine and 340 non-exposed children.[60] No differences with regard to psychosocial health and global medical status were found in children up to 6 years of age.[60]

2.1.4. Anti-Tumour Necrosis Factor Alpha

The two anti-TNF-α drugs infliximab (IFX) and adalimumab (ADA) both contain IgG1 antibodies and cross the placenta in increasing amounts from around the second trimester until the end of pregnancy.[61] While this protects the infants from exposure during the crucial period of organogenesis, IFX and ADA can be present in the infant for several months from birth, raising concerns about increased risk of infections and response to vaccines.[61-63] Studies on intentional use of IFX and ADA during pregnancy for maintaining remission of CD suggest that anti-TNF-α is safe in pregnancy and that there is no increase in adverse pregnancy outcomes including CM.[33,33,63,64] However long-term effects still need to be elucidated. The effect of discontinuing anti-TNF-α prior to gestational week (GW) 30 resulted in relapse in two of 13 ADA treated and no relapses occurred among the 12 IFX-treated women.[65] However in all but one of the infants, there were

detectable levels of anti-TNF-α, but significantly lower levels than when treatment continued after GW 30.[65] If remission in CD occurs, cessation of anti-TNF-α prior to GW 30 is a good option in order to reduce the amount of drug transfer to the infant.

Although the data available are limited, it has been found that anti-TNF-α treatment seems safe while breastfeeding, but the drugs used are excreted in breast milk, albeit in amounts that are much less than those in maternal serum.[66-68]

2.1.5. Metronidazole and Ciprofloxacin

The antibiotics metronidazole and ciprofloxacin can be used for short courses of treatment during pregnancy.[59] Two meta-analysis have not found an association between adverse pregnancy outcome and administration of metronidazole or ciprofloxacin during pregnancy.[69,70] A national prospective cohort study of 228 women exposed to metronidazole confirmed previous findings of no increased risk of adverse pregnancy outcomes including CM.[71] Data regarding metronidazole and ciprofloxacin treatment whilst breastfeeding are limited. Ciprofloxacin treatment is generally thought to be safe.[51] However both the American Gastroenterological Association and European reviews conclude that long-term use of metronidazole is not compatible with breastfeeding due to potential toxicity.[37,51,72] Therefore treatment with metronidazole should thoroughly be discussed with the breastfeeding women, because it is excreted in breast milk in higher quantities than other drugs, but the exposition is less than 10% of the recommended daily dose as treatment of an infection in an infant.[62]

2.2. ADHERENCE

2.2.1. Terminology

A number of terms have been used to describe the concept of non-adherence to medical treatment. Compliance, adherence, and concordance have all been used to define instances in which a patient does not follow the prescribed regimen, but each term has specific meanings. The differences between these terms are summarized in Table 1, as defined by Horne et al. in the report for the National Coordinating Centre for NHS Service Delivery and Organization R & D (NCCSDO) in the United Kingdom (UK).[73]

A key area of this thesis is to describe adherence to medical treatment during the 6-month pre-conception period, during pregnancy, and during the 6-month postpartum period. The word “adherence” was chosen to describe a patient’s drug taking behaviour, because it is the term preferred by the World Health Organization (WHO).[74]

2.2.2 Adherence to medical treatment

A systematic review of 17 papers including 4,322 IBD patients found that non-adherence to medical treatment ranged from 7 to 72%, with most studies reporting that 30-45% of patients were non-adherent.[18] This review demonstrated that the methods of measuring non-adherence and the definition of good adherence vary considerably.[18] Currently, there is no definitive benchmark for good adherence, but it is often defined as a reported consumption of more than 80% of prescribed medications in studies among IBD patients.[75,76] Generally, good adherence is associated with improved treatment outcomes across conditions.[77] Few, if any, studies have investigated CD patient’s risk of relapse in case of non-adherence. However UC patients who were non-adherent with medication had more than a fivefold greater risk of recurrence than adherent patients ($P<0.001$).[75] It is well documented that relapse during pregnancy increases the risk of adverse pregnancy outcome. However one could speculate to what degree non-adherence is associated with adverse pregnancy outcome if a pregnant woman remains in remission after having decided to decrease her daily dose of prescribed medication, and this might reflect that a lower concentration is sufficient for therapeutic effect in this individual, and thereby she is reducing the fetal exposure to medicine. More data are needed to elucidate the complex interplay between the pharmacokinetics and – dynamics of the different drugs in pregnant women and the factors of importance for the patient’s decision to alter the dose.

Because non-adherence seems to be a predictor of relapse in IBD, non-adherence may therefore also partly be responsible for increased medical health care costs. For example, a single centre retrospective study from the United Kingdom among 172 cases of CD found that relapse was associated with a 2.1 increase in 6-month costs for CD patients successfully managed as outpatients, but a 20-fold increase in costs in the event of hospitalization.[78]

Table 1. Terminology – compliance, adherence, and concordance[73]

Compliance is defined as: ‘The extent to which the patient’s behaviour matches the prescriber’s recommendations.’ However, its use is declining as it implies lack of patient involvement.
Adherence is defined as: ‘The extent to which the patient’s behaviour matches agreed recommendations from the prescriber.’ It has been adopted by many as an alternative to compliance, in an attempt to emphasize that the patient is free to decide whether to adhere to the doctor’s recommendations and that failure to do so should not be a reason to blame the patient. Adherence develops the definition of compliance by emphasizing the need for agreement.
Concordance is a relatively new concept, predominantly used in the UK. Its definition has changed over time from one which focused on the consultation process, in which doctor and patient agree on therapeutic decisions that incorporate their respective views, to a wider concept which stretches from prescribing communication to patient support in medicine taking.

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2.2.3. Reasons for non-adherence

Experts in the field of non-adherence to medical treatment recommend addressing the specific reasons for non-adherence on an individual patient level, rather than only focusing on risk factors contributing to non-adherence across large populations.[79,80] Reasons for non-adherence can be divided into unintentional and intentional.[79] Unintentional non-adherence happens when the patient intends to take the medical treatment, but is prevented from doing so.[79,80] The reasons for this might be due to forgetfulness, cost of medical treatment, or inability to understand the daily dosing regimen. An intentionally non-adherent patient may choose not to take or decrease the daily dose of medication for a variety of reasons, such as lack of belief in the necessity of the medication, perception that medical treatment is fundamentally harmful, and concerns about side-effects, but also practical aspects such as costs and administration form.[79,80] For both unintentional and intentional non-adherent patients, there might be a combination of practical and perceptual barriers that influence their choices.

Perceptual factors for non-adherence are multiple and complex. Horne et al. concluded that based on non-pregnant IBD patients' beliefs and concerns about medical treatment, patients can be classified into four distinct attitudinal groups with different risks of non-adherence.[79] In respect to the level of concern and thoughts on necessity for medical treatment, patients can be categorized into four "attitudinal group" – accepting, ambivalent, sceptical and indifferent (Figure 1); for instance, if a patient believes the medical treatment is necessary and has few concerns, she/he will be categorized as "accepting", and the likelihood of adherence will be high. Whereas a patient who does not really believe the medical treatment is necessary and has a lot of concerns will be classified as "sceptical", and therefore the likelihood of being adherent will be low.[79] These issues indicate that in order to improve adherence to medical treatment, factors of concern should be addressed when counselling IBD patients regarding medical treatment prior to, during, and after pregnancy.

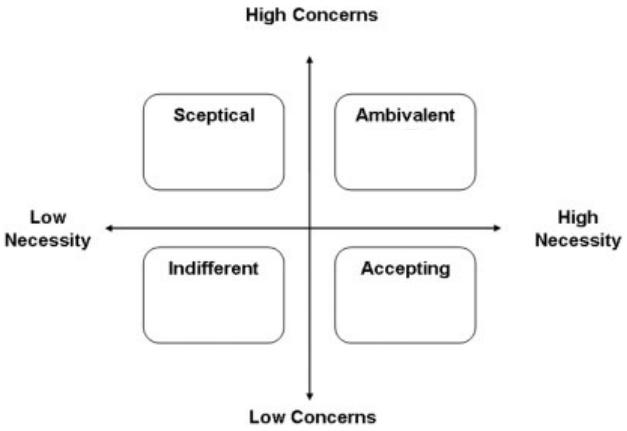

Figure 1. Attitudinal analysis of beliefs about maintenance medical treatment.[79]
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2.2.4. Measurement of adherence

There is no gold standard for how adherence should be measured, but different methods have been developed.

2.2.4.1. Drug measurements

The presence of a drug or its metabolite in serum or urine in CD patients confirms that the patient has taken the medication within a period before the analysis.[81-83] However, it reflects poorly on a patient's adherence status. From the drug level, it is not possible to quantify the manner in which the patient has taken the medication or detect fluctuations in adherence between hospital visits.[84] Moreover, the measurements can be very expensive, and if they are, their use may be impractical for studies including large number of patients and daily clinical practice.

2.2.4.2. Pill counts

A pill count is a simple measurement of adherence in which adherence is calculated by subtracting the number of tablets returned from the number of tablets issued. However pill counts have been found to overestimate adherence behaviour.[84] Some patients may deliberately remove some tablets from the container before returning it for the purpose of hiding their non-adherent behaviour.[84]

2.2.4.3. Electronic medication monitoring

Electronic medication monitoring devices use microchip technology to record and download data to a computer for review and analysis to describe the actual date and time that a dose is removed from a container. Although precise data on the manner in which patients use the medication are provided, the method has drawbacks similar to the pill count method. Electronic medication monitoring devices cannot assure that a dose that was removed was actually consumed or administered correctly. Moreover the devices are very expensive, and therefore impractical for studies including large number of patients.[84] Furthermore, it has been found that some patients experience higher levels of anxiety, depression, and somatic complaints as a result of knowing that their behaviour was under surveillance.[85] According to WHO, women are twice as likely to experience depression and anxiety in pregnancy compared with non-pregnant women, and the risk is further increased in the year following delivery.[86]

2.2.4.4. Prescription refill using pharmacy claims data

Centralized records of medication redemption provide researchers with an additional source of information which can be used in the measurement of adherence. In these settings, the proportion of medication obtained by the patient defines an upper limit for the proportion consumed. However, pharmacy claims data only report that the refill was obtained, they do not report medication use.[84] Moreover for study purposes, there will always be a specific period of investigation. Some patients may have stock-piled medication prior to the period of investigation, resulting in an underestimation of adherence.[87]

2.2.4.5. Self-reporting

Self-report measures are a simple and inexpensive method of adherence measurement, and it is most likely that those reporting non-adherence are being truthful.[84] In general there are three methods of self-reporting: adherence-specific questionnaires, patient-kept diaries, and patient interviews with specific questions regarding the accuracy of medication regimen adherence. The interviewer's skills and the construction of the questions can affect the accuracy and the validity of the self-reported method.[84] Therefore it is of utmost importance that the wording of the question should be in a non-judgmental tone. Of note, previous studies have shown that self-reported non-adherence correlates well with pill counts,[88] electronic monitoring, and pharmacy refill records.[89] Therefore self-reporting is a useful tool when investigating adherence to medical treatment among pregnant women with CD.

2.2.5. Adherence in CD

Multiple studies conducted around the world by different investigators have revealed different risk factors for non-adherence.[75,76,90-94] However, study design, patient population, and data collection instruments all play a role in explaining the different outcomes. A number of demographic, clinical, and treatment factors in the literature are often associated with non-adherence in IBD, such as single status,[76] male gender,[76] three times daily dosing,[94] more than four concomitant medications,[76] fulltime employment,[94] symptomatic remission in IBD,[75,94] and disease duration.[91,93] However a recent systematic review of 17 papers that included 4,322 participants reported that no demographic, clinical, or treatment variables were consistently associated with non-adherence.[18] Of notice was that a patient's

belief about medication was associated with non-adherence in three out of four studies.[18] This indicates that it is important to focus on patients' attitudes towards the drug when investigating adherence to medical treatment.

In the previously mentioned cross-sectional study in the UK by Horne and colleagues in which 1871 patients with IBD completed questionnaires on patients' beliefs about medical treatment and adherence to medical treatment,[79] unintentional non-adherence was reported by 28% of the population. Intentional non-adherence as a result of altering the prescribed dose of medical treatment was reported by 32%, and 17% reported they intentionally missed doses of medical treatment. A total of 9% had stopped taking their medication altogether, varying from occasionally to always.[79] The attitudinal analysis showed that nearly half (48%) of the patients were "accepting" their medical treatment, and a large proportion of the population (42%) were "ambivalent" about medical treatment. A few participants were sceptical (6%) or indifferent (4%) regarding their medical treatment. Compared to those who were "accepting" medical treatment, participants in all three other attitudinal groups were significantly more likely to be non-adherent.[79]

2.3. DISEASE ACTIVITY AND PREGNANCY

If conception occurs during a period of remission, about one-third of CD patients will experience relapse during pregnancy, and this relapse rate is similar to that in non-pregnant women with CD during a 9-month period.[16,20,40,95,96] On the other hand, two-thirds of CD patients with active disease at the time of conception will experience continuing disease activity during pregnancy.[20,97,98] These findings have been verified by Riis et al. in a European cohort study among a population of 93 CD women and 173 UC women with a 10-year follow-up period.[99] Moreover most studies have found that women with remission in CD during pregnancy have risks similar to those of the general population regarding spontaneous abortion, pregnancy-related complications, and adverse pregnancy outcomes.[100,101] Relapse around conception and/or during pregnancy has been associated with miscarriage, preterm births, and LBW.[20,22,95,100-102] As concluded in the European Crohn's and Colitis Organization (ECCO) consensus report, conception should preferable occur during remission, and if relapse occurs, aggressive medical treatment is needed to obtain remission in CD to ensure the best possible outcome of pregnancy.[59]

2.4. PREGNANCY OUTCOMES IN WOMEN WITH CD

During the past 50 years, multiple studies have focused on pregnancy outcomes in women with IBD. The largest study to date addressing the influence of IBD on pregnancy outcome is a meta-analysis by Cornish et al. from 2007.[103] In total 1,952 women with CD were compared with a control group of women with no IBD.[103] Women with CD were more likely to experience premature birth (OR: 1.97; 95% CI: 1.36-2.87), LBW (OR: 2.82; 95% CI: 1.42-5.60) and caesarean section (CS) (OR: 1.65; 95% CI: 1.19-2.29), but the impact of disease activity was not evaluated.[103] A recent prospective ECCO-Epicom multicentre case-control study of 145 women with CD, where the majority were in remission (85.8%), and matched non-IBD controls found no statistically significant difference in the frequency of abortions, preterm deliveries, LBW, CS, or CM.[40] A large epidemiological population-based study in Denmark and Sweden among 2,377 cases of maternal CD compared with 869,202 women with no diagnosis of CD found increased risk of very preterm birth (GW <32) (POR 1.76; 95% CI: 1.51-2.05), moderate preterm birth (GW 32-36) (POR 1.86; 95% CI: 1.38-2.52), small for gestational age (SGA) (POR 1.22; 95% CI: 1.00-1.49), and CS (POR 1.93, 95% CI: 1.76-2.12).[23] Adverse birth outcome appeared to be correlated with severity of CD, as measured by history of previous surgery and hospital admissions, instead of the specific clinical activity of the disease during pregnancy.[23] A population-based cohort study of 163 births in 111 CD women in which medical records were reviewed to assess disease activity found that if moderate to high CD activity occurred, the risk of preterm birth was increased more than 3-fold.[22] Therefore, as previously stated, maintenance of remission in CD during pregnancy is essential even though aggressive medical treatment is needed.[59]

It is well documented that smoking during pregnancy reduces fetal growth.[24] However, no studies have investigated whether medical treatment for CD in general is a predictor of lower birth weight in women with CD compared with an untreated CD control group after stratifying for smoking and disease activity.

2.5. BREASTFEEDING BEHAVIOUR IN WOMEN WITH CD

The leading paediatric societies in Europe and North America recommend that breastfeeding should be the primary form of nutrition for at least the first 24 weeks of life.[25] Currently 95-99% of mothers in Denmark start breastfeeding after birth,[104] which may be a reflection of the Danish health care system's effort to provide public information on the nutritional, anti-infective, and immunologic benefits of breastfeeding.[105]

A recent review concluded that breastfeeding among non-IBD women exerted a protective effect against developing early-onset of IBD (OR: 0.69; 95% CI: 0.51-0.94), which confirms previous findings.[106] Few studies have been published on breastfeeding behaviour in women with CD, and a great variation in rates of breastfeeding has been found ranging from 29.3% to 81.9%.[26-28,107] A Spanish study found that a significantly lower rate of breastfeeding among those who gave birth after the diagnosis of IBD as compared to those giving birth before diagnosis of the disease.[27] Breastfeeding behaviour in women with CD in Denmark has not previously been investigated.

4.6. BREASTFEEDING AND DISEASE ACTIVITY IN WOMEN WITH CD

In general, the postpartum period does not appear to constitute a time of risk for increased disease activity compared with the general CD population unless the patient has had active disease around conception/during pregnancy or resumes smoking.[59,99,108] After adjustment for smoking status, alcohol use, maternal age, Caucasian ethnicity, and number of prenatal visits, a large community-based cohort study from America among 461 pregnant women with IBD, of which a third had CD, found no increased risk of relapse during the postpartum period if the patient had been in remission during pregnancy.[109]

The influence of breastfeeding on the risk of relapse in CD remains controversial. An American retrospective study by Kane et al. among 82 CD patients found a correlation between breastfeeding and relapse during the postpartum period, and even after adjustment for medication cessation, the correlations remained significant (OR: 2.1; 95% CI: 1.1-8.5).[26] On the other hand, a population-based Canadian registry study among 90 CD patients found comparable postpartum relapse rates in breastfeeders versus non-breastfeeders (OR: 0.8; 95% CI: 0.2-9.9),[28] and these data were confirmed by a Spanish retrospective study among 117 IBD patients.[27]

2.7. CONCLUSION

Based on the existing literature, it is clear that active disease at the time of conception seems to be the main factor predisposing to adverse pregnancy outcomes such as premature delivery and low birth weight among women with CD.[21] Medical treatment is often needed to ensure remission, which is also the case around conception, during pregnancy and lactation.[16,37] Non-adherence rates to maintenance medical treatment of 30-45% have been reported.[18] No consistent predictors for non-adherence were associated with non-adherence.[18] However prevalence rates of non-adherence and specific predictors for non-adherence during conception, pregnancy, and lactation have never been investigated.

Smoking reduces fetal growth,[24] but no studies have investigated whether medical treatment is associated with lower birth weight after stratifying for smoking and disease activity among medical treated CD women compared with untreated CD women.

Data regarding breastfeeding rates and breastfeeding's influence on disease activity are limited and somewhat conflicting.[24,26-28] Therefore studies in this area are warranted.

3. AIMS

The aims of the thesis were:

1. Determine adherence and investigate predictors and prevalence rates of non-adherence to maintenance medical treatment among women with CD prior to and during pregnancy (paper I).

2. To assess pregnancy outcomes among women with CD stratified by medical treatment and smoking status while accounting for disease activity (paper II).
3. Determine adherence and examine predictors and prevalence rates of non-adherence to maintenance medical treatment among women with CD in the postpartum period (paper III).
4. Assess breastfeeding rates and the impact of breastfeeding on the risk of relapse (paper III).

4. MATERIALS AND METHODS

This thesis consists of three prevalence studies. These studies were based on data from a questionnaire and medical registers of the Central Denmark Region and North Denmark Region, equivalent to one-third of the entire Danish population. (Figure 2) In Denmark, the National Health Service provides tax-supported health care for all inhabitants. Apart from guaranteeing free access to general practitioners, hospitals, and public clinics, the insurance programme refunds part of the costs associated with the purchase of most prescribed drugs.

4.1 DATA SOURCES

4.1.1. Registers

4.1.1.1. The Danish Civil Registration System (CRS)

The CRS was established in 1968.[110] The CRS registers all citizens in Denmark with a unique 10-digit civil personal registration number (CPR number). The CPR number is assigned to all Danish residents shortly after birth or immigration. The CPR number allows unambiguous linkage between all Danish public registers at an individual level. The CRS also holds information on date of birth, sex, residence, and vital status of all Danish citizens.

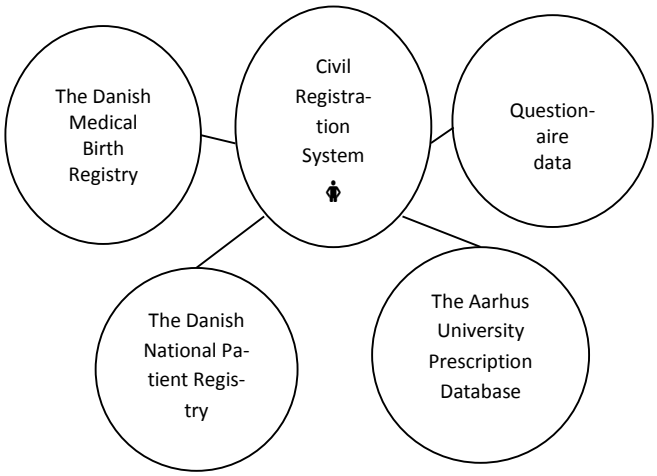

Figure 2. Data sources

4.1.1.2. The Danish National Patient Registry (DNPR)

The DNPR contains information on all patients admitted to any Danish somatic hospital since 1977.[111] It covers 99.4% of all discharges from Danish hospitals. Outpatient visits at hospitals have been included since 1995. It includes the dates of admission and discharge, surgical procedures performed, and up to 20 discharge diagnoses. All coding is conducted by medical doctors according to the International Classification of Diseases (ICD), 8th edition (ICD-8) from 1977-1993 and the 10th edition (ICD-10) since 1994. The code K 50 served to identify patients with CD.[112]

4.1.1.3. The Danish Medical Birth Registry (DMBR)

The DMBR contains information on all births in Denmark since 1 January 1973, recorded by the attending midwives or medical doctor.[113] Each record includes data on characteristics of the mother (including age at delivery, citizenship, residence, marital status, parity, mode of delivery, and self-reported smoking status recorded at the first antenatal care consultation) and the newborn (including vital status at birth, sex, birth weight, body length, and gestational age). Gestational age is estimated based on ultrasound in the first trimester followed by adjustment in the second trimester (GW 17-22).[114] The conception date was calculated as birth date minus gestational age in days plus 14 days. From the registry we identified all singletons born to women with CD, and all singletons born to mothers without a recorded diagnosis of CD during the study period in the same regions of Denmark.

4.1.1.4. The Aarhus University Prescription Database (AUPD)

The AUPD holds data collected by community pharmacies on all prescriptions redeemed by out-patients in the Central and North Regions of Denmark. [115] The pharmacies use electronic accounting systems to secure reimbursement from the National Health Service. Denmark's tax-supported system refunds part of the costs associated with the purchase of most prescribed drugs. The database provides information on the patients CPR-number and all reimbursed prescribed drugs according the Anatomical Therapeutic Chemical Classification System (ATC) and dispensing

date. The AUPD does not track in-hospital medical treatment.

To assess the validity of self-reported use of medication for CD, we retrieved data from AUPD. We identified all prescriptions for medicine used to treat CD from August 1, 1999 to July 31, 2006 for each pregnant woman with CD. We used the following ATC codes to identify CD-specific medicines: A07EC01–04, L04AX01, L01BB02, A07EA01–02, A07EA06, H02AB06–07, P01AB01, and J01MA02.

4.1.2. Questionnaire

A questionnaire was developed specifically for the three studies in this thesis. Please see Appendix IV

4.1.2.1. Development of questionnaire

The questionnaire was divided into five sections. A section on general information including diagnosis, whether the pregnancy had been planned, if the woman previously had given birth to a child while knowing she had CD, and mode of delivery. Details concerning date of birth, child weight, length and sex of the child were obtained from the DMBR and printed in the individual questionnaire to confirm the relevant pregnancy and the correctness of the data. Moreover three sections with identical questions for the following periods: 6 months prior to conception, during pregnancy and 6 months postpartum. The themes in these sections included number and types of drugs prescribed, the administration form of medical treatment, counselling regarding medical treatment, adherence to medical treatment, reasons for non-adherence, relapse in CD, lifestyle factors such as smoking and alcohol intake. In respect to adherence to medical treatment, the women were asked to evaluate their average daily intake of prescribed medication (0-49%, 50-80%, or >80% of the recommended daily dose). We defined good adherence as a reported consumption of more than 80% of prescribed medications.[116] Reasons for taking less than 80% of daily prescribed medication were stated. The question about smoking had four categories: on a daily basis, occasionally, former smoker, and non-smoker. The participant was classified as a smoker if she had chosen daily basis or occasionally. Alcohol intake was stated as average number of standard drinks per week. The final section focused on aspects of breastfeeding including counselling regarding medical treatment and breastfeeding, change of medical treatment due to breastfeeding, and reasons for not breastfeeding.

4.1.2.2. Pilot testing

The questionnaire was pilot-tested for comprehension and ability to discriminate answers in 20 randomly selected women with CD from the study population. Answers and comments were evaluated by the authors, which led to only minor changes in the final design, for instance, wording of questions, changing medical terms such as gastroenterologist to “specialist in bowel diseases”, and women were allowed to state more than one reason for non-adherence.

4.1.2.3. Data entry

All data from the questionnaires were entered into a database specifically designed for the project and verified by double entry. Discrepancy let to control of the original questionnaire. Data were transferred to the statistical program STATA (Statacorp LP, College Station, Texas, USA).

4.1.3. Medical records

4.1.3.1. Disease activity

In the questionnaire, the women were specifically asked if they experienced CD relapse during the 6 months prior to conception, during pregnancy or during the 6 months postpartum. Women who answered no to this question were classified as being in remission. The medical records of each woman answering yes to the question were reviewed to verify relapse in CD (papers II and III). The Harvey-Bradshaw Index (HBI) was used to assess CD activity during the postpartum period.[117] CD was considered to be inactive if HBI was ≤ 4 points. An increase in disease activity (HBI ≥ 5) with a duration of at least 1 week occurring during the postpartum period was considered a relapse. Mild, moderate, and severe activity in CD was equivalent to HBI scores of 5-7, 8-16, and >16, respectively.

4.2 STUDY DESIGN

A population-based prevalence design was applied in all three studies.

4.3 STUDY POPULATION & OUTCOME

We invited all women who had given birth to a singleton between 1 January 2000 and 31 December 2005 and who had been diagnosed with CD at least 1 year prior to their date of conception to participate. Multiple births were not included because these pregnancies may be more complicated than singleton pregnancies.[118] If a woman gave birth more than once during the study period, we only included the first pregnancy. The CD diagnosis was confirmed by reviewing each woman’s medical record prior to dispatch of the questionnaires. All eligible women were asked to complete a postage-prepaid 14-page questionnaire. Information on name, address, and vital status was obtained from the CRS, which also provided the unique CPR number used to link data between the questionnaire and the registers.

4.3.1. Paper I (Adherence prior to and during pregnancy)

The primary outcomes of interest were adherence rates, predictors for and prevalence rates of non-adherence to medical treatment prior to and during pregnancy. We defined good adherence as a reported consumption of more than 80% of prescribed medications.[116]

4.3.2. Paper II (Pregnancy outcome)

The primary outcomes were gestational age, stillbirth (delivery of a dead fetus after 28 weeks of gestation), birth weight, body length, sex of the child, mode of delivery, and maternal age at delivery. We examined the association between CD and these pregnancy outcomes stratified by medical treatment and smoking status while accounting for disease activity. SGA was defined as a birth weight more than 2 standard deviations below the mean for children of similar gestational age, according to the reference curve of estimated fetal growth.[119] We defined preterm birth as a live birth before 36 weeks of gestation.[23] For live born children, DNPR was used to identify CM diagnosed during the first year of life. The codes for CM were Q0.00 to Q89 in ICD-10.[112] The diagnoses of congenital dislocation of the hip (Q65.0-6) and undescended testis (Q53) were not included because of expected poor validity.[120] Chromosomal abnormalities (Q90-99) were also excluded.

4.3.3. Paper III (Postpartum adherence and breastfeeding behaviour)

The primary outcomes of interest were adherence rates, predictors for and prevalence rates of non-adherence to medical treatment during the postpartum period as well as breastfeeding's impact on the risk of relapse. We defined good adherence as a reported consumption of more than 80% of prescribed medications.[116]

4.4 DATA COLLECTION

The postage-prepaid 14-page questionnaire was mailed to all potential participants. Non-responders received a reminder after 3 weeks and again after 8 weeks if there was no response. To calculate the body mass index (BMI) of the participants, their bodyweight and height prior to pregnancy was needed. Unfortunately a question regarding height was not included in the questionnaire. Therefore a postage prepaid postcard regarding the height was sent to all the women who initially had returned a filled-in questionnaire.

Drug prescription data were obtained from the AUPD, maternal surgical procedures and CM from the DNPR, maternal and pregnancy outcome data from the DMBR.

4.5 SAMPLE SIZE CALCULATION

In Denmark the prevalence of CD was 150 per 100.000.[121] In the population of 1.6 million inhabitants in the Central Denmark Region and North Denmark Region thus expected approximately 2400 persons with CD, of whom 1500 would be women.[5] Half of these women were expected to fall pregnant after debut of CD equivalent to 750 women. A study period of six years represent 30% of the reproductions period, we therefore assumed that approximately 250 women with CD would have given birth during the study period. The prevalence of medical treated pregnant CD women was not known, but we assumed that it would be 50% yielding approximately 125 women with CD in medical treatment to be evaluated regarding predictors and prevalence rates of non-adherence. The response rate to the questionnaire was estimated to be 70%, resulting in an expected study population of 98 women. Since we wanted to identify a difference in adherence of 60% compared with non-pregnant women,[76,122] a study population of at least 78 women with an expected adherence rate of 40% among pregnant women would give a power of 95%.

4.6 STATISTICS

Redemption of a prescription for CD-specific medication registered in the prescription database was used as a reference standard when validating the accuracy of self-reported medical treatment (**papers I – III**). We computed the positive predictive value (PPV) as the proportion of women reporting to receive medical treatment who were also registered with a prescription in the prescription database, i.e., the numerator was the number of women who reported use of medication and who fulfilled a prescription, and the denominator was the number of women who reported to receive medication.

Paper I: For the two pregnancy periods, we constructed frequency tables of major study variables. We cross-tabulated planned pregnancy, previous pregnancy with the CD diagnosis, counselling, and smoking status by non-adherence status and estimated prevalence odds ratios (POR) using logistic regression models, and calculated exact 95% confidence intervals (CI) for a binomial distribution.

Paper II: We constructed frequency tables of major study variables. A logistic regression analysis was used to compute the crude and adjusted POR as estimates of relative risk, with associated 95% CIs for preterm birth, SGA, CS, CM, and stillbirth. We adjusted for parity (1 or more than 1) and maternal smoking (yes/no). We constructed a two-sample t-test for the birth weight of children born to mothers who had treated or untreated CD. We calculated 95% CIs, assuming a binomial distribution.

Paper III: We constructed frequency tables of major study variables. We cross-tabulated planned pregnancy, previous pregnancy with the CD diagnosis, counselling, and smoking status by non-adherence status and estimated POR using logistic regression models and calculated exact 95% CIs for a binomial distribution.

4.7 APPROVAL AND ETHICS

The study was approved by the National Board of Health, by the University of Aarhus Institutional Review Board, and by the Danish Data Protection Agency before any patients were recruited. No approval from the Danish Ethical Committee was needed according to the Danish law. All women gave informed written consent to the authors to obtain information from their hospital records.

5. RESULTS IN SUMMARY

After linking data from the DNPR and DMBR, 154 potential candidates with CD were identified among a population of 1.6 million inhabitants. We further identified 87,338 singleton pregnancies in women without a registered diagnosis of CD within the study period in the two regions in Denmark.

After review of medical records, 21 (14%) women were excluded because the CD diagnosis could not be confirmed. One woman had passed away, leaving a study population of 132 women with CD. Of these women, 105 (80%) returned a filled-in questionnaire and were included in the analyses in papers I-III.

Medical treatment was provided to 54 (51.4%) during the 6-month pre-pregnancy period (paper I), 55 (52.4%) during pregnancy (papers I & II), and 59 (56.2%) during the 6 months after delivery (paper III). Within the medically treated population, 46, 48, and 48 had filled a prescription for relevant medication, yielding PPVs of 85.2% (95% CI: 72.9-93.4) prior to, 87.3% (95% CI: 75.5-94.7) during, and 81.4% (95% CI: 69.1-90.3) after pregnancy, respectively. We observed no substantial difference between the PPVs within the three periods of investigation. According to the AUPD, approximately half of the non-responders had redeemed a prescription for a drug used to treat CD, indicating that the group of non-responders did not vary substantially from the group of responders regarding the proportion who received medical treatment (papers I-III).

5.1. PAPER I

The characteristics of the women in medical treatment prior to and during pregnancy are outlined in Table 2. Three-quarters and two-thirds stated adherence to medical treatment prior to and during pregnancy, respectively. A fifth of the women stated non-adherence in both periods of investigation. The main reason for

non-adherence was quiescence in CD. Fear of a negative effect on fertility/fetus also played role for non-adherence especially during pregnancy. Forgetfulness was only stated as reason for non-adherence by a single woman.

Although our estimates in general were imprecise smoking before pregnancy seemed to be a predictor of non-adherence (POR 3.41, 95% CI 0.8-14.7). Counselling regarding medical treatment (POR 0.69, 95% CI 0.2-2.9), previous CD pregnancy (POR 0.52, 95% CI 0.1-2.3), and planned pregnancy (POR 0.58, 95% CI 0.1-2.8) all seemed to decrease the likelihood of non-adherence.

During pregnancy, the prevalence of smokers was markedly reduced and smoking, did not seem to change the likelihood of being non-adherent (POR 0.89, 95% CI 0.2-4.0). Further this also seemed to be the case for counselling (POR 0.97, 95% CI 0.1-10.4). However previous CD pregnancy (POR 0.75, 95% CI 0.2-3.0) and planned pregnancy (POR 0.55, 95% CI 0.1-2.7) seemed to decrease the likelihood of non-adherence.

Table 2: Characteristics of women with Crohn's disease in medical treatment who gave birth to a singleton.

	Prior to pregnancy N = 54[A]		During pregnancy N=55[A]	
Characteristics	N	(%)	N	(%)
Remission according to the patients	39	(72.2)	35	(63.6)
Flare	7	(13.0)	5	(9.1)
Medical treatment counselling	32	(59.3)	44	(80.0)
The counsellors profession:				
Gastroenterologist	31	(96.9)	41	(93.2)
General practitioner	0	(0.0)	1	(2.3)
Gynaecologist	1	(3.1)	2	(4.6)
The advice from the counsellor:				
Increase medical treatment	0	(0.0)	1	(2.3)
No changes in medical treatment	23	(71.9)	33	(75.0)
Decrease in medical treatment	1	(3.1)	1	(2.3)
Stop medical treatment	6	(18.8)	4	(9.1)
Another kind of advice	2	(6.3)	5	(11.4)
Adherence to medical treatment[B]	41	(75.9)	37	(67.3)
Non-adherent to medical treatment	11	(20.4)	11	(20.0)
Reasons for non-adherence:				
Quiescent Crohn's disease	8	(72.7)	8	(72.7)
Fear of negative effect on fertility/the fetus	2	(18.8)	5	(45.5)
Forgetfulness	1	(9.1)	1	(9.1)
Another reason	2	(18.8)	1	(9.1)
Did administration form influence on adherence:				
Yes	1	(1.9)	3	(5.5)
No	48	(88.9)	42	(81.8)

[A] 51 women received medical treatment 6 months prior to and during pregnancy.
[B] Intake of >80% of daily prescribed dose

5.2. PAPER II

The overall number of women given birth was 105 of whom 55 received medical treatment during pregnancy. Infants born to mothers with CD who had received medical treatment during pregnancy seemed not at increased risk of preterm birth, SGA, CM, or stillbirth when compared to infants born to untreated mothers with CD (Table 3). None of the 16 CD women who received thiopurines gave birth to a child with a CM. No adverse pregnancy outcomes were identified among the four children born to mothers who had been exposed to infliximab prior to conception. Nine women with CD (8.6%) gave birth preterm. All but two of the women gave birth by CS. None of the babies were SGA. Among the medical treated women 52.8% received treatment with 5-ASA, which was more than expected but this finding was confirmed by data from the prescription database.

Stratification of maternal disease activity in respect to birth weight was not possible because 95.2% were in remission during pregnancy. Irrespectively of medical treatment, there was a substantial difference in birth weight between children of CD non-smokers (3475 grams; 95% CI, 3368-3581) and CD smokers (3257 grams; 95% CI, 3137-3378), corresponding to a significant difference in mean birth weight of 218 grams.

Birth weight among infants born to women with CD stratified by medical treatment and smoking status are shown in Table 4. Among women with CD who received medical treatment, lower birth weight was significantly more common among children of mothers with CD who smoked. The difference in mean birth weight was 274 grams. Maternal medical treatment during pregnancy did not seem to have a negative influence on the child's birth weight.

Table 3. Prevalence and crude prevalence odds ratios (POR) for adverse pregnancy outcomes among women with Crohn's disease receiving medical treatment or no medical treatment during pregnancy

	medical treatment		no medical treatment		Crude POR (95% CI)*	
	n	(%)	n	(%)		
Total	55	(52.4)	50	(47.6)		
Preterm	4	(7.3)	5	(10.0)	0.71	(0.18-2.79)
Small for Gestational age	0	(0.0)	1	(2.0)	-	-
Caesarean Section	23	(41.8)	17	(34.0)	1.40	(0.63-3.08)
Congenital Malformation	2	(3.6)	3	(6.0)	0.60	(0.10-3.76)
Stillbirth	0	(0.0)	0	(0.0)	-	-

*When stratified for parity (1/>1) and maternal smoking (yes/no), these estimates remained unchanged (data not shown).

Table 4. Birth weight among infants born to women with Crohn's disease

	Medical treatment during pregnancy			No medical treatment during pregnancy		
Characteristic	n = 50*	Mean (g)	95% CI	n = 49**	Mean (g)	95% CI
Non-smoker	24	3504[a,b]	3372-3636	29	3450[c,b]	3281-3619
Smoker	26	3230[a,d]	3072-3341	20	3324[c,d]	3097-3550

*data are missing for five women and **data are missing for one woman.
[a]p = 0.002 and [b,c,d]p > 0.05

5.3. PAPER III

The characteristics of the medically treated women during the postpartum period are outlined in Table 5. Two-thirds of women stated adherence and 17% stated non-adherence to medical treatment during the 6-month post-partum period. The main reasons for non-adherence were fear of medication transmission to breast milk and quiescence in CD. Forgetfulness was only stated as reason for non-adherence by a single woman. Counselling regarding medical treatment (POR 0.5, 95% CI 0.1-2.2), previous CD pregnancy (POR 0.55, 95% CI 0.1-2.5), and planned pregnancy (POR 0.63, 95% CI 0.1-3.8) all seemed to decrease the likelihood of non-adherence although we had low

statistical precision. Of note, non-adherence was twice as frequent among non-smokers as among smokers (POR 0.55, 95% CI 0.1-2.5).

The majority (87.6%) of the 105 women breastfed their infant. The breastfeeding rates did not seem to vary substantial among medically and non-medically treated women (POR 0.53, 95% CI 0.15-1.84) or among those with a vaginal birth and those who were delivered by CS (POR 1.0, 95% CI 0.3-3.2). Among 59 medical treated women, 84.4% breastfed their infants, with a median duration of breastfeeding of 5 months (range 1-36 months). Among 46 women who did not receive medical treatment, 91.3% breastfed their infants, with a median duration of 7 months (range 1 to 19 months).

Crude and adjusted odds ratios for risk of relapse among the entire population and only medical treated women with CD are presented in Table 6. Although our estimates were imprecise relapse might potentially be explained by non-adherence or smoking, while breastfeeding seemed protective.

Table 5. Characteristics of women with Crohn's disease who gave birth to a singleton and received medical treatment in the postpartum period.

Characteristics	N	(%)
Patients in medical treatment	59	(56.2)
Remission	44	(74.6)
Relapse	15	(25.4)
Received medical treatment counselling	34	(57.6)
The counsellor's profession:		
Gastroenterologist	34	(100.0)
General practitioner	0	(0.0)
Gynaecologist	0	(0.0)
Another person	0	(0.0)
The advice from the counsellor:		
Increase medical treatment/drug intake	10	(27.0)
No changes in medical treatment	23	(62.2)
Decrease medical treatment	1	(2.7)
Stop medical treatment	3	(8.1)
Another kind of advise	0	(0.0)
Adherent to medical treatment[A]	39	(66.1)
Non-adherent to medical treatment	10	(17.0)
Stated reasons for non-adherence:		
Fear of medication transmission to breast milk	6	(60.0)
Quiescent CD	6	(60.0)
Forgetfulness	1	(10.0)
Another reason	1	(10.0)
Did administration form influence adherence:		
Yes	1	(2.0)
No	42	(82.4)

[A] Intake of >80% of daily prescribed dose

Table 6. Crude and adjusted POR's for risk factors for relapse among the general CD population and only medical treated CD women during the postpartum period, respectively.

General CD population			
	N (%)	**Crude POR (95% CI)**	**Adjusted POR (95% CI)[A]**
Smoking	34 (32.4)	1.85 (0.62-5.54)	-
Breastfeeding	92 (87.6)	0.33 (0.10-1.26)	0.37 (0.09-1.50)
Previous pregnancy	40 (38.1)	0.47 (0.14-1.60)	0.45 (0.13-1.55)
>30 years of age at delivery	53 (50.5)	1.06 (0.31-3.61)	1.16 (0.32-4.21)
Medical treated CD women			
Smoking	24 (40.7)	1.44 (0.44-4.83)	-
Non-adherence[B]	10 (17.0)	1.25 (0.26-6.00)	1.36 (0.28-6.74)
Breastfeeding	50 (84.8)	0.33 (0.07-1.56)	0.35 (0.07-1.70)
Previous pregnancy	23 (39.0)	0.38 (0.10-1.42)	0.40 (0.11-1.49)
>30 years of age at delivery	27 (45.8)	1.13 (0.33-3.91)	1.27 (0.34-4.78)

[A] Prevalence odds ratios adjusted for smoking
[B] Intake of <80% of daily prescribed dose

6. DISCUSSION

6.1. DISCUSSION OF MAIN FINDINGS IN RELATION TO THE EXISTING LITERATURE

In the following subsection the main findings in relation to the aims of papers I-III will be discussed in relation to the exiting literature.

6.1.1. Adherence rates, predictors, and prevalence rates of non-adherence to maintenance treatment (aims 1 & 3, papers I & III).

The overall adherence to medical treatment was high prior to, during, and after pregnancy, and higher than previously reported among non-pregnant IBD patients.[92,122] Non-adherence to medical treatment was reported by approximately a fifth of the women. A major part of women cited quiescence in CD as a primary reason for non-adherence. Fear also played an increasing role during the three periods of investigation. To our knowledge no studies have investigated reasons for non-adherence in pregnancy and the postpartum period among women with CD. However, in accordance with our data, a recent systematic review among non-pregnant IBD patients found that patients' beliefs about medication were associated with non-adherence in three of four studies.[18] Horne et al. also concluded that the way in which patients judge their personal need for medical treatment relative to their concerns about medical treatment can be a significant barrier to adherence.[79] Our findings indicate that fear and thereby ignorance plays a role for non-adherence in pregnancy and the postpartum period.

We further found that forgetfulness did not seem to play a role for non-adherence in the three periods of investigation. Published data regarding forgetfulness as a reason for non-adherence have been conflicting. In accordance with our data, Ediger et al. found that forgetfulness only explained a minor part of the observed non-adherence.[92] In contrast, forgetfulness was a major reason for non-adherence among the general IBD population according to Kane et al. and D'Inca et al.[75,91] This might indicate that reasons for non-adherence may be altered in the conception period and during pregnancy and lactation, highlighting special needs for counselling.

Prior to and after pregnancy, more than 50% of the CD women received counselling on medical treatment, which was mostly provided by a gastroenterologist. Although we had low statistical precision, our studies are the first to indicate that counselling may substantially decrease the risk of non-adherence prior to pregnancy and in the postpartum period. During pregnancy, a marked increase in counselling was seen, although it did not affect adherence. However, we may speculate that it had a positive effect on persistence with treatment, although we have no data to support this speculation. Our questionnaire did not specifically include questions regarding the patient-physician relationship, but Nguyen et al. found that the patient-physician relationship in general, and patients' trust in physicians in particular, was a significant positive predictor of adherence to medical treatment in patients with IBD.[123] How accurate women remember medical counselling may differ according to adherence. We anticipated that women with poor adherence to a higher degree would report that their gastroenterologist had

advised them to discontinue their treatment. Yet, our results in the two papers did not support any conclusions regarding this area.

Smoking was associated with non-adherence prior to pregnancy. In accordance with two other studies, the prevalence of smokers among patients with CD was markedly reduced during pregnancy,[96,108] and an association between smoking status and non-adherence could not be detected during pregnancy. The prevalence of smoking increased again in the postpartum period, but did not reach the same high level as prior to pregnancy. The pattern of smoking prior to, during, and after pregnancy was similar to the findings of Agret and colleagues.[108] Of notice was that non-adherence was twice as common among non-smokers compared to smokers in the postpartum period, while smokers demonstrated a nearly two-fold increased risk of relapse compared with non-smokers. These results could potentially be interpreted in two ways: smokers may overestimate their own adherence to medical treatment and smoking has a negative effect on disease activity.

We were the first to demonstrate that non-adherence to medical treatment seemed less likely in all three periods of investigation if the woman had been pregnant before while knowing that she had CD compared with primiparous CD women, and if the pregnancy had been planned. These results also underline the importance of counselling women in the fertile age regarding medical treatment and pregnancy, especially primiparous women and in case of unplanned pregnancy.

6.1.2. Pregnancy outcomes among women with CD (aim 2, paper II)

While previous studies have primarily compared CD women with a non-IBD background population when investigating the birth weight of newborns,[21,96,124,125] we extended these findings by stratifying data according to medical treatment and smoking. The overall number of 105 women is low, and stratification according to medical treatment resulted in low statistical precision. However, maternal medical treatment during pregnancy did not seem to influence child birth weight among women with CD. In contrast to this, maternal smoking was negatively associated with child birth weight among women with CD, especially among women who received medical treatment. This difference could not be explained by differences in disease activity because the vast majority of women (95.2%) were in remission. Previous studies have similarly found a causal relationship between cigarette smoking and fetal growth restriction.[24] Further, it has been shown that smoking is associated with more complicated CD,[126] including an increased need for steroids and immunosuppressants in CD smokers compared with CD non-smokers.[127] However, our results indicate that when counselling medically treated women with CD, it is important to stress that smoking cessation is of utmost importance because the risk of lower birth weight is even more pronounced among the medically treated women who smoke.

In the majority of the studies examining the impact of CD medication on pregnancy outcomes, such as preterm birth, SGA, CM, and stillbirth, women with CD were compared with populations of non-IBD women.[103] Few studies have, as in our study, addressed the safety of medical treatment, comparing pregnant women with CD with untreated women with CD.[50,52,128] It is challenging to make a definitive conclusion on medical treatment for CD and the risk of adverse pregnancy outcome due to the small sample size, however our finding that the risk of adverse birth outcomes seemed unrelated to maternal medical treatment is in accordance with most previous studies.[50,52,128] On the other hand, two epidemiological studies reported increased risks of preterm birth and stillbirth in CD women who had received medical treatment compared with untreated women.[56,129] In these studies, as is also stated by the authors, disease activity was not assessed. Therefore, if medical treatment was associated with active disease, it may have been disease activity rather than medical treatment that caused these increased risks. A population-based cohort study including 163 births by 111 CD women found that in cases of moderate to high CD activity, the risk of preterm birth was increased more than 3-fold.[22] Because most women in our study were in remission, our risk estimates, despite low statistical precision, most likely reflect the effect of medical treatment and not disease activity. Our study therefore underscores the international recommendations emphasizing the importance of remission in CD during pregnancy to minimize the potential risk of adverse pregnancy outcomes.[51,59]

In line with previous studies showing that bowel resection may be associated with preterm birth,[96,109] more than half of the women giving birth moderately preterm in our study had undergone bowel resection prior to conception. Still, none of these babies were born SGA.

Our sample size does not allow for a definitive conclusion on medical treatment for CD and the risk of CM. Still, our findings did not give any indication of an increased risk of CM following medical treatment during pregnancy. None of the 16 women exposed to thiopurines during pregnancy gave birth to children with CM. However, these results are in accordance with those of previous studies and ECCO guidelines.[51,59,128]

The finding of a high 5-ASA use in pregnancy was surprising because both European and Danish National guidelines do not generally recommend medical treatment with 5-ASA for CD.[130,131] However a prospective study conducted in the same timeframe as the present, in 12 European countries in 2003-2006 found a similar high use of 5-ASA in pregnancy among CD patients.[16] The finding of a high 5-ASA use thus might reflect medical treatment in the past. The medical treatment of CD has been through an extensive evolution during the past decade. Anti-TNF-α treatment is now a more common treatment for moderate-severe CD as monotherapy or in combination with thiopurines, also in pregnancy.

6.1.3. Breastfeeding rates and the impact of breastfeeding on the risk of relapse (aim 4, paper III).

Our finding that the majority of women were breastfeeding for approximately 6 months irrespective of medical treatment correlates well with the recommendation from the leading paediatric societies in Europe and North America that breastfeeding should be the primary form of nutrition for at least the first 24 weeks of life.[25] In line with our data, two recent studies from North America found high breastfeeding rates among women with CD (81.9% and 72%).[28,132] CD women in the present study were breastfeeding at a rate similar to the national rate in Denmark.[104]

Although breastfeeding rates did not vary by medical treatment and type of drug, we found that a minor subset

(14.0%) of the women who breastfed discontinued or altered their prescribed medical treatment due to fear of medication interactions, which is in accordance with the findings of Moffatt et al.[28] In contrast, Kane et al. found a much higher proportion (74%) of IBD women discontinued medical treatment if breastfeeding, most often after discussion with an obstetrician or paediatrician rather than a gastroenterologist.[26] The high proportion of women in the present study who received counselling from a gastroenterologist possibly played an important role in their choice to continue medical treatment while breastfeeding.

It is challenging to make a definitive conclusion on CD activity and breastfeeding due to relatively small sample sizes in the literature.[26-28] In accordance with our findings, Moffatt et al. and Manosa et al. found no increased risk of relapse in breastfeeders compared to non-breastfeeders.[27,28] Even after adjusting for medication cessation, Kane et al. did find a correlation between disease activity and breastfeeding among women with CD, with an OR of 2.1 (95% CI 1.1-8.5). However, as the authors stated, the sample size of breastfeeding CD women was small. Because most of the women (87.6%) in our study were breastfeeding, any comparison between breastfeeding and non-breastfeeding women should be made with caution due to low statistical precision. However, in accordance with Moffatt et al., our findings suggested a protective effect of breastfeeding on the risk of relapse during the postpartum period.[28] Physiologically plausible explanations for why breastfeeding may decrease disease activity in women with CD have been suggested. In a meta-analysis, Cornish et al. found a significant increase in the relative risk of developing CD in current oral contraceptive users, likely due to the elevated serum levels of oestrogen and progesterone.[133] Lactation in women is also associated with a unique endocrine repertoire. Lactation delays the resumption of normal ovarian cycles by disrupting the pattern of pulsatile release of gonadotropin releasing hormone (GnRH) from the hypothalamus and hence luteinising hormone (LH) from the pituitary gland. The inadequate pulsatile of LH will result in substantially lower oestrogen and progesterone.[134] Therefore, the unique drop in oestrogen and progesterone seen in lactating women with established CD may explain why the women in the present study had a decreased risk of high disease activity.

6.2. DISCUSSION OF METHODS

In assessing the validity of the findings in papers I-III, one needs to address bias in selection or measurement, confounding, and chance (Figure 3)

6.2.1. Selection bias

Selection bias is the systematic difference between the group selected and the full group from which the selected study group stems.[136] Selection bias due to differential recruitment was avoided because of the population-based design. Conducting an investigation among IBD patients using a questionnaire has previously been shown to be difficult because response rates tend to be low, thereby increasing the risk of selection bias.[79,137,138] However in the prevalence studies in this thesis (papers I-III), the response rate was high (80%). Information from the AUPD showed that the proportion of women in medical treatment was similar in the group included in our three studies and in the group of non-responders to the questionnaires. However, we do not know whether non-participants were more

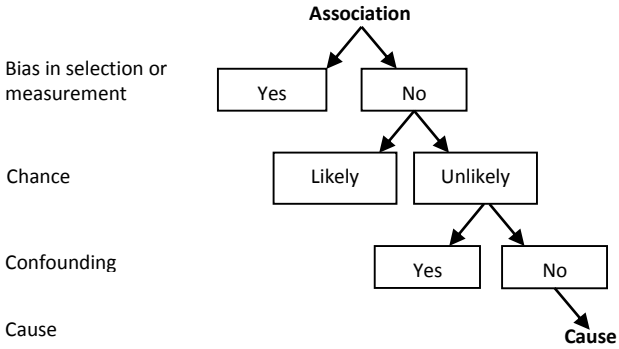

Figure 3. Association and cause. Adapted and reprinted with permission from the authors Robert & Suzanne Fletcher and the publisher Lippincott, Williams & Wilkins.[135]

or less likely to report non-adherence to medical treatment compared to participants.

In paper II we did not capture data on women with early pregnancy loss (miscarriage and induced abortions) because these data are not listed in the DMBR. Thus, we did not capture CM that might have been present in lost embryos. If the prevalence of early pregnancy loss differed between the non-medically treated and medically treated, selection bias could be present.[139]

Short disease duration has been found to increase the likelihood of non-adherence.[93] Therefore to diminish short disease duration's potential effect on adherence in papers I and III, the diagnoses of patients included in the studies had to be established at least 1 year prior to the 6-month pre-pregnancy period.

6.2.2. Measurement (Information bias)

Information bias may arise when the information collected is erroneous. Misclassification of the exposure, the outcome, or any confounding factors can cause such errors.[140] Misclassification can be differential or non-differential. Differential misclassification can either exaggerate or underestimate the true association, whereas a non-differential misclassification tends to produce a bias towards the null.[140]

The discharge diagnosis of CD was coded prospectively by the physician in charge of the discharge. However, the use of discharge diagnosis from the DNPR for the identification of cases can also cause problems, since at least five sources of error have been described: a) variation in coding procedures, b) coding errors, c) incomplete coding, d) lack of specificity in available codes, and e) error in the clinical diagnosis.[141] The CD diagnosis in the DNPR was found to have a very high validity (97%) two decades ago.[142] The very high validity of the CD diagnosis in the DNPR could not fully be confirmed in our studies. After review of all medical records, 21 (14%) had to be excluded due to misclassification of the CD discharge diagnosis in the DNPR, yielding a high validity of 85.7% of the CD diagnosis in the DNPR. The majority of the misclassified CD patients had not had any contact with a department of gastroenterology, whereas a few had been seen due to bowel-related issues; therefore these cases may represent errors in coding. In the studies, the specificity was further increased because we asked the participants to confirm

their diagnosis. Of the 80% who returned filled-in questionnaires, all cases of CD was found to be correct.

The data quality in the DMBR is reported to be high.[143,144] However, in study II the PPV of medical birth outcome were even higher than in the DMBR, because all pregnancy outcome data retrieved from the DMBR was printed in the individual questionnaires for the women to confirm the correctness of the data. In all cases, the data was found to be correct among the 80% who returned filled-in questionnaires.

Smoking status from the first antenatal care around GW 12-16 is prospectively recorded in the DMBR. A third of those who reported to be smokers during pregnancy in paper I were not listed as smokers in the DMBR, indicating that the completeness of smoking status in the DMBR is low. We can only speculate about reasons for this, but it might be that women early in pregnancy wish to stop smoking because they are aware of the negative consequences of smoking on the fetus, and therefore declare themselves as non-smokers. Retrospectively, they might have an increased tendency to declare the correct smoking status because they now have a healthy infant. In all three papers, we used the self-reported smoking status. Still, we cannot rule out that we may have classified some smokers as non-smokers. Yet such bias would lead to an underestimation of the association between smoking and non-adherence in papers I and III and smoking's influence on the risk of relapse in paper III. Furthermore, it would lead to an underestimation of the negative influence on birth weight found in paper II.

All measurements of non-adherence have strengths and weaknesses. Estimation of non-adherent behaviour is prone to differ, independent of the method applied. We used a measure of self-reported non-adherence to medical treatment[145] because previous studies have shown that this method correlates well with pill counts,[88] electronic monitoring, and pharmacy refill records.[89] The use of multiple measures within a study has been recommended.[84] Although we did not choose two measurements of non-adherence, we did compare self-reported medical treatment with data from the AUPD to calculate the PPV. Among the responders to the questionnaire, two (3.7%), seven (12.7%) and ten (17.0%) women skipped the question regarding adherence to medical treatment prior to, during and after pregnancy, respectively. This is a limitation to the study, because if their adherence status had been known it might have influenced our relative risk estimates in a negative or positive manor in paper I and III.

To our knowledge no gold standard for medication adherence in IBD patients or pregnant IBD patients exists. Kane et al. recently concluded, after using the self-reported Morisky 8-Item Medication Adherence Questionnaire, that adherence to medical treatment in IBD is complex and cannot be predicted reliably by a self-reported survey tool validated for other chronic conditions.[146] Moreover, reasons for non-adherence might change in the conception period, during pregnancy, and in the postpartum period compared with the general CD population. Our questionnaire was therefore developed based on our clinical experience in gastroenterology in collaboration with clinical epidemiologist with experience in designing questionnaires. The questionnaire was pilot-tested for comprehension (content validity) and for respondents' ability to discriminate answers (construct validity) by reviewing the patients' questionnaire. It is, however, a weakness of our studies that it was not possible to use a standardized validated questionnaire.

In order to decrease the risk of typing errors when entering the data from the questionnaire into a database, double entry of each questionnaire was performed. Discrepancy let to control of the original questionnaire.

We found a high validity of self-reported use of medication prior to pregnancy (PPV 85.2%), during pregnancy (87.3%), and in the post-partum period (81.4%). Although we found a high concordance between self-reported medical treatment and the AUPD, we only evaluated the redemption of prescriptions specifically during the 6 months before pregnancy, during pregnancy, and 6 months after delivery. Therefore, we did not take into account that some women may have stockpiled medication prior to the period of investigation and used this medication during the period of investigation. If present, such a bias would have led us to underestimate the concordance between self-reported medical treatment and the AUPD.

Misclassification of non-adherent patients as adherent patients could bias our results regarding predictors for non-adherence. Yet, such a bias would lead us to underestimate the associations found in papers I and III.

The retrospective nature of the questionnaire-based studies (papers I-III) makes them prone to recall bias. Recall bias can affect both the accuracy of the data (e.g. medical treatment or relapse in CD) and the interpretation of the experiences, depending on the outcome of the pregnancy.

In respect to medical treatment, we found a 14.8% (paper I), 12.7% (papers I and II) and 18.6% (paper III) discrepancy between self-reported medical treatment and data from the AUPD prior to, during, and after pregnancy, respectively. Still, despite the high concordance, we cannot entirely rule out recall bias regarding medical treatment. We were unable to determine whether patient recall affected our relative estimates. Self-reported relapse in CD could potentially be another source of recall bias. After review of medical records, we found all cases of self-reported relapse to be valid (papers II and III). However it is a limitation to the study that only journals of women stating relapse were checked regarding disease activity. During pregnancy, the vast majority of CD women stated that they were in remission. We therefore concluded that disease activity could not be an important confounder when assessing the effect of medical treatment on birth outcome. If some of the women who reported remission in disease actually had activity our estimates thus could be confounded by disease activity.

Our studies included women who gave birth over a 6-year period. It is likely that women who gave birth in the first part of this period had a higher risk of recall bias than women giving birth in the latter part of the study period. However, we did not observe any patterns of difference between these two groups of women; thus we had no indication that recall bias should differ by time in the present studies.

6.2.3. Confounding

A confounder is a factor related to both exposure and outcome. However, it cannot be a factor in the pathway between exposure and outcome, and its presence must be imbalanced between groups.[140] Confounding therefore results in a mix of different influential factors and it can be reduced either in study design or in analysis.

There are several methods to account for confounders in observational studies. We used stratification in multivariate analyses. It would have been relevant to use statistical methods to adjust for the influence of known confounders on the estimates in the multivariate analysis regarding predictors for non-adherence in papers I and III.[140] However, a model with such variables included was not possible because of the low number of observations.[136]

Comparing pregnancy outcome among medically treated with medically un-treated women in study II, we found the two groups were compatible regarding years since diagnosis, age, BMI, IBD surgery prior to pregnancy, and planned pregnancy. Factors which all independently could have been potential confounders. When the multivariate analysis regarding adverse pregnancy outcome were stratified for parity (1/>1) and smoking (yes/no) the odds ratios remained unchanged (paper II).

Confounders that we have not measured cannot entirely be ruled out. We did not ask the women questions regarding socio-economic factors, and this hindered our ability to control for confounding in relation to income, education, or occupation, which may be related to drug use in pregnancy.[147,148] Because of the null result in paper II regarding risk of adverse pregnancy outcome, any confounding would need to be by factors associated with maternal medical treatment and also with a reduced risk of adverse pregnancy outcomes overall. No such factors have been identified, to the best of our knowledge.

When investigating adverse pregnancy outcome and birth weight in study II, it was important to take disease activity into account in an attempt to avoid confounding by indication. We found that the vast majority of women were in remission during pregnancy, and therefore it is unlikely that disease activity affected our estimates.

6.2.4. Chance

Chance, or random error, is closely related to precision, because the mean of a large number of unbiased observations tends to approximate the true value in the population, even though the individual samples may vary considerably.[140] Large studies are therefore more precise and contain less random estimation error than smaller studies. However, random variation can never be totally eliminated, so precision and chance should always be considered in assessments of clinical observations. In paper I-III, the precision was reflected by the width of the 95% CIs.

The statistical precision of the estimates for predictors for non-adherence prior to, during and after pregnancy (paper I and III) and for risk factors of relapse in the post-partum period (paper III) was low due to the number of included observations. Therefore some caution is warranted when interpreting the findings of these analyses as they were more sensitive to chance.

The precision of our risk estimates for adverse pregnancy outcomes in paper II remains low due to the low prevalence of adverse pregnancy outcomes. This was amplified by the relatively low number of CD women who had given birth within the six-year period.

6.3. FURTHER LIMITATIONS

A power calculation was performed prior to initiation of the study. Unfortunately we overestimated the number of CD deliveries, whereas the remaining estimates were less imprecise. However the overestimation resulting in low statistical precision reflected by the width of the confidence intervals in the three papers as previously discussed. Inclusion of women with UC and CD in the study could have been a way to increase our study population and thereby maybe increasing the statistical power to the analysis in the dissertation. However, since women with UC and CD differ in several aspects these women could result in a much more heterogeneous study population thereby increasing the potential for confounding. As an example, we anticipated that more CD than UC patients would receive systemic medical treatment, whereas more UC patients would receive local medical treatment. Moreover markedly more CD patients tend to be smokers than UC patients. These aspects could affect the results of the main aims of the study i.e. adherence, birth outcome and breastfeeding behaviour.

The final version of our questionnaire was 14 pages, and we assumed this was the limit for what the participants would accept to return a filled-in questionnaires. In order to insure a high response rate we therefore had to limit the number of included topics. The questionnaire therefore lacked specific questions for instance regarding disease extent, co-morbidities, socio-economic factors, supplementary intake of folic acid during pregnancy, how many years the participant had been a smoker, smoking of the partner and previous pregnancy outcomes. As a consequence we could not include such variables in our statistical analyses and confounding may be present.

6.4. GENERALIZABILITY

The internal validity discussed above is essential to the external validity of the study, and the generalizability of the study rests, among other things, on its internal validity. However, other aspects of the generalization must also be considered. Because we performed a retrospective questionnaire-based study, all aspects of the study are transferable to daily clinical practice. The Central Denmark Region and North Denmark Region, with a combined population of approximately 1.6 million, consist of rural areas, villages, towns and major cities. The two regions can therefore be considered representative of settings found in the other Danish regions.

7. MAIN CONCLUSION

The population-based data presented in this dissertation, despite low statistical precision, provide new insight about adherence in pregnancy and factors influencing birth weight. Based on the results obtained and our considerations regarding potential bias and confounding, our main findings were:

Paper I: Adherence to medical treatment prior to and during pregnancy was high in patients with CD despite fear of a negative effect on fertility/fetus. Adherence did not vary substantially between the periods investigated. Smoking seems to predict non-adherent behaviour, whereas counselling may decrease the likelihood of non-adherence prior to pregnancy. Experience from a previous pregnancy and planned pregnancy seem to have a positive influence on CD women's choice regarding medical treatment prior to and during pregnancy.

Paper II: In CD, smoking was negatively associated with child birth weight. This association was most pronounced among women who received medical treatment. Maternal medical treatment for CD did not seem to be a risk factor for adverse pregnancy

outcomes in a population in which the vast majority of patients were in remission.

Paper III: Adherence to medical treatment in the postpartum period was high in CD, despite fear of medication transmission to the breast milk. Counselling, experience from a previous pregnancy, and planned pregnancy seem to increase the likelihood of adherence. Relapse may be explained by non-adherence or smoking, while breastfeeding seems protective. Irrespective of medical treatment, breastfeeding rates were high among women with CD.

8. PERSPECTIVES AND FUTURE RESEARCH

This thesis provides new knowledge regarding adherence to medical treatment with thiopurines, corticosteroids, and 5-ASA around the time of conception and during pregnancy and lactation. We find the results of no adverse pregnancy outcome after exposure to medical treatment in pregnancy and no increased risk of relapse while breastfeeding reassuring although the low statistical precision does not allow any firm conclusions. Moreover, our data underpin the importance of non-smoking behaviour to ensure sustained disease remission[126] and to decrease the risk of giving birth to a child with lower birth weight.[24] All of these aspects are of great importance when counselling CD women of fertile age. However, this thesis also raises an important methodological issue regarding sample size. Although this study was conducted within a 6-year period in two Danish regions equivalent to a third of the Danish population, the precision of our risk estimates remains low due to the relative low number of CD deliveries, the low prevalence of adverse pregnancy outcomes, and disease relapse. Therefore, nationwide studies or preferably even larger studies based on an international collaboration could be the solution to enable sample sizes large enough to provide a larger precision of the estimates.[149]

In recent years, anti-TNF-α therapy has been introduced as induction and maintenance treatment of severe CD that fails to settle down with conventional medical therapy.[37,59] However, concerns regarding the use of these drugs during pregnancy and lactation are often raised by CD patients. Knowledge regarding the impact of exposure in utero to anti-TNF-α therapy for the infant's risk of complications to natural occurring infections and vaccinations during the first year of life is limited.[33,64,65,150,151] Elimination of anti-TNF-α after being exposed to these drugs in utero needs to more thorough investigated. Ongoing multicentre research projects such as ERA[152] and PIANO[132] will hopefully elucidate some of these issues.

If CD symptoms remit, current European reviews and guidelines suggest cessation of anti-TNF-α therapy in the last trimester of pregnancy to reduce fetal exposure.[51,59,153] However, no general attitude toward anti-TNF-α therapy in pregnancy exist among gastroenterologists and guidelines for recommendations to pregnant women regarding this treatment thus need to be established. From a patient perspective, it remains to be investigated what kind of counselling anti-TNF-α-treated CD women receive regarding pregnancy and lactation. What CD women perceive as risk regarding anti-TNF-α monotherapy or in combination with other drugs during pregnancy and lactation needs attention, and whether anti-TNF-α-treated women have any unmet needs in respect to medical counselling needs to be investigated. An insight into gastroenterologist prescribing practice and patients perceived risks, counselling, and unmet needs regarding medical treatment with anti-TNF-α therapy during pregnancy and lactation will lead to better counselling of anti-TNF-α-treated CD women in the fertile age.

9. SUMMARY

Background: Crohn's disease (CD) is common among women of fertile age, and it often requires maintenance medical treatment. Adherence to medical treatment among women with CD prior to, during, and after pregnancy has, however, never been examined. Although CD women have increased risk of adverse pregnancy outcomes, little is known about predictors for these outcomes in women with CD. In addition, the impact of breastfeeding on disease activity remains controversial.

Aims: The aims of this PhD thesis were to determine adherence to treatment and to investigate predictors for and prevalence rates of non-adherence to maintenance medical treatment among women with CD prior to, during, and after pregnancy; to assess pregnancy outcomes among women with CD, taking medical treatment, smoking status, and disease activity into account; to assess breastfeeding rates and the impact of breastfeeding on the risk of relapse.

Methods: We conducted a population-based prevalence study including 154 women with CD who had given birth within a 6-year period. We combined questionnaire data, data from medical records, and medical register data.

Results: Among 105 (80%) respondents, more than half reported taking medication with an overall high adherence rate of 69.8%. Counselling, previous pregnancy, and planned pregnancy seemed to decrease the likelihood of non-adherence, whereas smoking seemed to predict non-adherence prior to pregnancy, although our sample size prevented any firm conclusions. During pregnancy, the vast majority (95%) of CD women were in remission. The children's birth weight did not differ in relation to maternal medical treatment, but mean birth weight in children of smokers in medical treatment was 274 g lower than that of children of non-smokers in medical treatment. In our relatively small study CD women in medical treatment were not at increased risk of adverse pregnancy outcomes compared with un-treated women with CD. In total, 87.6% of CD women were breastfeeding, and rates did not vary by medical treatment. Smoking and non-adherence seemed to predict relapse in CD during the postpartum period, whereas breastfeeding seemed protective against relapse.

Conclusions: Although we generally had low statistical precision this thesis suggests that counselling regarding medical treatment may be an important factor for medical adherence among CD women of fertile age. In addition CD women in medical treatment did not seem at increased risk of adverse pregnancy outcome, but smoking predicted lower birth weight. Breastfeeding did not seem to increase the risk of relapse in CD.

ABBREVIATIONS

ADA	Adalimumab
Anti-TNF-α	Anti-Tumour Necrosis Factor Alpha
ATC	Anatomical Therapeutic Chemical Classification System
AUPD	Aarhus University Prescription Database
BMI	Body Mass Index
CD	Crohn's disease
CI	Confidence interval
CM	Congenital Malformations

CPR	Civil Personal Registration
CRS	Civil Registration System
CS	Caesarean Section
DMBR	Danish Medical Birth Registry
DNPR	Danish National Patient Registry
ECCO	European Crohn's and Colitis Organization
GnRH	Gonadotropin Releasing Hormone
GW	Gestational Week
HBI	Harvey-Bradshaw Index
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
IgG1	Immunoglobulin G1
IFX	Infliximab
LBW	Low Birth Weight
LH	Luteinising Hormone
OR	Odds Ratio
POR	Prevalence Odds Ratio
PPV	Positive Predictive Value
SGA	Small for Gestational Age
WHO	World Health Organization
5-ASA	5-aminosalicylic acid
6-MP	6-Mecaptopurine
6-TGN	6-Thioguanine

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