Birth outcome in women with ulcerative colitis and Crohn's disease, and pharmacoepidemiological aspects of anti-inflammatory drug therapy

Bente Mertz Nørgård, MD, PhD

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Official opponents: Ebbe Langholz & Tine Brink Henriksen.

Correspondence: Bente Mertz Nørgård, Centre for National Clinical Databases, South, The Danish Clinical Quality Improvement Programme, OUH, Odense University Hospital, Entrance 101, Sdr. Boulevard 29, 5000 Odense C. Denmark.

E-mail: bente.noergaard@ouh.regionsyddanmark.dk

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This dissertation is based on the following eight original publications, referred to in the thesis by their Roman numerals:

I. Nørgård B, Fonager K, Sørensen HT, Olsen J. Birth outcomes of women with ulcerative colitis: a nationwide Danish cohort study. American Journal of Gastroenterology 2000; 95:3165-70

II. Nørgård B, Puho E, Pedersen L, Czeizel AE, Sørensen HT. The risk of congenital abnormalities in children born by women with ulcerative colitis: a population-based case control study. American Journal of Gastroenterology 2003; 98:2006-10

III. Nørgård B, Czeizel AE, Rockenbauer M, Olsen J, Sørensen HT. Population-based case control study of the safety of sulfasalazine use during pregnancy. Alimentary Pharmacology & Therapeutics 2001; 15:483-86

IV. Nørgård B, Fonager K, Pedersen L, Jacobsen BA, Sørensen HT. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy. A Danish cohort study. Gut 2003; 52:243-47

V. Nørgård B, Fonager K, Pedersen L, Rasmussen SN, Sørensen HT. Azathioprine, 6-marcaptopurine and birth outcome: a population-based cohort study. Alimentary Pharmacology & Therapeutics 2003; 17:827-34

VI. Nørgård B, Pedersen L, Jacobsen J, Rasmussen SN, Sørensen HT. The risk of congenital abnormalities in children fathered by men treated with azathioprine or 6-mercaptopurine before conception. Alimentary Pharmacology & Therapeutics 2004; 19:679-85

VII. Nørgård B, Pedersen L, Christensen LA, Sørensen HT. Therapeutic Drug Use in Women with Crohn's Disease and Birth Outcomes: A Danish nationwide cohort study. American Journal of Gastroenterology 2007; 102:1406-1413.

VIII. Nørgård B, Hundborg HH, Jacobsen BA, Nielsen GL, Fonager K. Disease Activity in Pregnant Women with Crohn's Disease and Birth Outcomes. A Regional Danish Cohort Study. American Journal of Gastroenterology 2007; 102:1947-1954.

Publication numbers I, III, IV have previously been part of a PhD thesis (Colitis ulcerosa, coeliaki og graviditet; en oversigt med speciel reference til forløb og sikkerhed af medicinsk behandling, 2002, by Bente Nørgård). Publications number II, V, VI, VII and VIII have not previously been presented with reference to achievement of an academic degree.

PREFACE AND ACKNOWLEDGEMENTS

This doctoral dissertation is based on research work carried out in 1999-2009, during my employment at the Institute of Epidemiology and Social Medicine, University of Aarhus, Department of Clinical Epidemiology, Aarhus University Hospital, Center for National Clinical Databases, Odense University Hospital and the University of Southern Denmark.

Numerous people have contributed significantly to the eight studies that this thesis is based on, and I wish to thank all persons who helped me through the work. First of all I want to thank all *my co-authors* for the supportive attitude, and for their important contributions to the publications. In particular I am indebted to my former colleagues at the Department of Clinical Epidemiology, Aarhus University Hospital, for conscientious collaboration and support. Especially, professor *Henrik Toft Sørensen*, and *Lars Pedersen* for their outstanding expertise in the fields of epidemiology and statistical analyses. My gratitude also goes to *my colleagues* at the Center for

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ATC	Anatomical therapeutic chemical
AZA	azathioprine
CAs	congenital abnormalities
CI	confidence interval
CD	Crohn's disease
CPR	civil registration number
HCAR	the Hungarian Congenital Abnormality Registry
HCCSCA	Hungarian Case Control Surveillance of Congenital Abnormalities
HDR	Danish National Hospital Discharge Registry
ICD	International Classification of Diseases
IBD	inflammatory bowel disease
IUGR	Intrauterine growth retardation
LBW	low birth weight
MBR	Danish Medical Birth Registry
OR	odds ratio
PI	Ponderal Index
SGA	small for gestational age
UC	ulcerative colitis

1. INTRODUCTION

The work gives (i) an introduction to the research area, (ii) a description and discussion of data sources and methods, (iii) the main results based on the eight publications and a discussion of the results in relation to the existing literature, (iv) a discussion of methodological considerations, and (v) concluding remarks and suggestions for future studies.

This thesis uncovers new aspects of the association between chronic inflammatory bowel disease (IBD) and adverse birth outcomes. For more than fifty years ulcerative colitis (UC) and Crohn's disease (CD) have been suspected to increase the risk of adverse birth outcomes, but the magnitude of a possible harmful influence of UC and CD has not been clarified. Possible causes of adverse birth outcomes in women with UC and CD remains unknown but may be related to factors such as the underlying disease itself, disease activity, and/or anti-inflammatory drug therapy. The literature has shown an obvious lack of appropriate data to illuminate, specifically, a possible impact of anti-inflammatory drug therapy and disease activity during pregnancy on the risk of adverse birth outcomes.

It is of crucial importance to clarify new aspects regarding UC, CD, drug therapy, and disease activity in order to minimize the risk of adverse birth outcomes. Only this will ensure that clinical decisions are evidence based and guided according to the best possible recommendations for treatment and surveillance of pregnant women with IBD. As the process for this thesis has proceeded the relevance of the issue has become still clearer, and although our knowledge about the issue has improved, many questions still remain unanswered, and new important issues continue to surface.

MEASURING BIRTH OUTCOMES

During the last decades, one of the issues in the literature has been how to define adverse birth outcome most appropriately. Some have argued that the most important birth outcome is a combined measure counting different outcome entities, e.g., "success pregnancy" (live born children with no major congenital abnormalities [CAs]) versus "unsuccessful pregnancies" (1), "successful outcome " (healthy child, premature or full term) versus "failure outcome" (2), "normal" versus "abnormal outcomes" (children with prematurity and low birth weight [LBW] and respiratory distress) (3) or "fetal complication" (children with LBW, prematurity, stillbirth, CAs) versus "no fetal complications "(4,5). Thus, these combined measures for birth outcomes have been used in several papers and reported in papers published as late as in 2003 and 2004 (1,2). Most investigators have, however, realized that specific focus on selected single birth outcome variables (such as gestational age or birth weight) gives valuable information because of the ability to consider specific attendant complications according to child morbidity and mortality.

Since the 1970s, preterm birth (delivery before 37 completed weeks of gestation (6)) and LBW (birth weight less than 2 500 g (6)) have often been standard outcome

measures in studies of reproductive outcomes. However, LBW as a definition for pathological fetal growth is not useful, because LBW children represent a mix of neonates whose growth is suboptimal, neonates delivered early, and neonates that are small for genetic reasons (7). Therefore, LBW is most often studied according to stages of gestation or supplemented by measure of intrauterine growth retardation (IUGR). IUGR is strongly associated with neonatal morbidity and mortality and indicates that the growth potential of the fetus has not been reached (8-10), but since the growth potential of a fetus is unknown in most situations, it is difficult to define pathological intrauterine growth. Thus, several measures of IUGR have been suggested, e.g. based on Ponderal Index (PI), birth weight below the 10th percentile of weight for gestational age or more than two standard deviations below the mean, crown-to-heel length, or head circumference/abdominal circumference ratio (7,10-16). None of these measures are ultimate, e.g., children with a birth weight below the 10th percentile will not necessarily be growth retarded, and some with birth weight above the 10th percentile may be growth retarded, because they were genetically predisposed to having a higher birth weight than they had. In the studies of this thesis we used the measurement "LBW at term" (birth weight < 2 500 g and ≥ 37 weeks of pregnancy) as the combination of these attributes suggests that the child remains small despite adequate time for growth to have occurred (6,7). Studying CAs is a special challenge as each individual type of CA is rare, with the most common in the order of 1/1000 live births (7). Such a measure of 'prevalence at birth' suggests problems in obtaining accurate epidemiologic measures. The etiologic events that generate structural CAs typically occur within the first 3-8 weeks post conception (17), but the recognition of CAs may not occur until later in pregnancy, at the time of birth, in early childhood, later in life, or CAs may never be recognized. Thus, after initiation of a CA, subsequent events such as spontaneous abortion, prenatal diagnosis and induced abortion, or survival of the fetus to birth will affect the degree to which 'prevalence at birth' differs from the incidence.

Measures of specific adverse birth outcomes are of major importance according to the need for immediate in-hospital treatment after birth and short term evaluation of the health of a child, but they seem also to be important in a long term perspective. In the short term perspective preterm birth has been found to be the most important single cause of perinatal mortality and morbidity (18-24); preterm birth accounting for 75% of perinatal mortality (22,23). Likewise, LBW is one of the main predictors of child mortality and morbidity (6,23,24), and perinatal mortality rate among growth-restricted children is 10-20 times the rate among appropriate-for-gestational-age children (10). In a long term perspective, DJ Barker and colleagues have suggested that several diseases of adult life (including coronary heart disease, hypertension, and type 2 diabetes) originate from impaired intrauterine growth and development (25-27); and some follow-up studies have reproduced these findings (28). These diseases in adulthood may thus be consequences of "programming", whereby an insult at a critical, sensitive period of early life has permanent effects on structure, physiology, and metabolism.

Based on these considerations, we focused on the prevalence of specific birth outcomes in children of IBD patients, i.e., birth weight, LBW, LBW at term, preterm birth, stillbirth and CAs. Consequently, we did not examine issues regarding infertility, abortions, or diseases diagnosed in later life among children born by women with IBD.

Birth outcomes in women with IBD

The first case-series that suspected UC and CD to influence the birth outcomes emerged in the 1950s - 1970s (29-34), and more followed in the subsequent years (Enc., Table 5). During the last decades numerous studies have focused on the birth outcomes in women with IBD. Most of these studies have been observations from case-series in women with UC (30,31,35-40) and CD (32,33,36,38,39,41-44). Other, more methodologically sound studies have suffered from important limitations, i.e., inability to control sufficiently for confounders and inability to distinguish between patients with UC or CD in the analyses (Enc., Table 1, 3 and 4). The latter might be of crucial importance because of indications of differential risk of adverse birth outcomes depending on the nature of underlying disease, i.e., UC or CD. Until the end of the 1990s, only two large epidemiological studies existed (45,46). One study focused on the risk of adverse birth outcome in women with CD (45), and the other on women with IBD (patients with UC and CD could not be separated in the analyses) (46). Despite the limited amount of evidence, the main attitude in the 1990s was that women with IBD had an increased risk for preterm birth and LBW; and that CD had a greater impact on birth outcomes than UC.

PHARMACOEPIDEMIOLOGY AND PREGNANCY

Therapeutic drug treatment during pregnancy remains an issue of special clinical challenge because most drugs cross the placenta to the fetal circulation. Rapid cell growth and extremely complicated cell differentiation, makes a fetus much more vulnerable to drug adverse effects than a neonate, child or adult; and particular attention should be paid to drugs used during organogenesis, i.e. between the third and eighth week after conception, and during the rapid fetal growth stage in the third trimester (17,47).

Drug use during pregnancy may be of concern because it can lead to fetal death, CAs, functional disorders, reduced fetal growth, or a change in organ programming. As a result of the thalidomide disaster (48,49), most attention has been given to the possible teratogenic effects of drugs, but information is also needed on other reproductive outcomes.

The potential impact of most drugs during pregnancy on reproductive outcomes has not been clarified since drugs are not tested in pregnant women before they are released on the market. Knowledge on specific drug effects on the fetus is usually limited to the experiences from animal studies – studies, whose results often cannot be extrapolated to humans. Therefore, the underlying influence of drug therapy on different reproductive outcomes, according to mechanisms and critical periods, are still not clarified. Consequently, clinical decisions on pharmacotherapy during pregnancy are most often based on evidence from observational studies that might be vulnerable to different kinds of bias and problems with statistical precision due to low prevalence of adverse birth outcomes. Because clinical experimental studies are not carried out on pregnant women, the need of observational studies in this area of research has increased and has caused implementation of epidemiological methods in the area of pharmacological research.

Pharmacoepidemiology and birth outcomes in women with IBD

Questions about the safety of drug therapy during pregnancy become even more crucial when women are not only pregnant, but also have chronic diseases like IBD that might need intense and continuous medical treatment. In patients with IBD, pharmacotherapy may be required to control disease activity before conception, and/or to maintain remission and/or to treat flare-ups during pregnancy. Clinicians and patients are both aware of a potential harmful effect of drug therapy, and thus the safety of drug therapy for IBD during pregnancy remains of important clinical concern.

Knowledge of the safety of anti-inflammatory agents is mainly assessed from the results of animal studies, anecdotal reports, and clinical experience in other disorders. However, conclusions drawn for IBD patients from these methods must take into consideration the difficulties extrapolating animal data to humans, distinguishing the effects of drug therapy from the underlying condition for which it is required, and the impact of concurrent medications. Since the 1980s, several investigators have tried to illuminate the association between drug therapy during pregnancy and birth outcomes in women with UD and CD (1,2,4,5,35,37,43,50-53) (Enc., Table 2). The main limitations of these studies are lack of estimation of the risk of separate birth outcomes (1,2,4,5,35,37,43,51), and lack of appropriate control for confounders (4,5,35,37,43,50,51,53). In conclusion, only very little available evidence exists regarding the use of therapeutics in pregnant women with IBD.

The association between pharmacotherapy and adverse birth outcomes in women with IBD had not earlier been examined in population-based settings – most likely due to lack of appropriate data. Pregnant women with IBD often have complex patterns of drug therapy, i.e., changing types of anti-inflammatory drugs during pregnancy, varying drug doses, several drugs at the same time, and/or drug free intervals; it is, therefore extremely difficult to record accurate clinical details - even after review of medical records. In register-based dataset it is also impossible to collect detailed drug information covering all aspect of drug therapy during pregnancy; and as in other register-based research we were left with the challenge to use the available data with conscientiousness and in respect to their limitations.

Because of the increasing demand of observational studies on drug safety during pregnancy we examined the association between anti-inflammatory drug therapy and adverse birth outcomes.

DISEASE ACTIVITY AND BIRTH OUTCOMES IN WOMEN WITH IBD

In the literature it is often discussed whether adverse birth outcomes in women with IBD are related to disease activity or the medications used to treat it (54-58). The exact role of disease activity is, however, controversial, and the critical role of disease activity has not been clarified in epidemiological studies (54,55,58).

Similar to the lack of studies on a possible influence of drug therapy on reproductive outcomes in women with IBD, only very sparse data exist on a possible impact of disease activity (case-series (37,42,43) and small studies with no estimation of the risk of specific outcomes and no confounder control (3,5,59)). Like information on drug therapy, it is very difficult to collect sufficiently detailed data on disease activity during pregnancy in large unselected cohorts of women with IBD. No routinely collected data include information on disease activity, and therefore population-based registries or other secondary data are of limited value when it comes to clinical details. Information on disease activity has to be collected through prospective recording, questionnaires/interviews, or through review of medical records; but such collection of detailed data on disease activity in large cohorts of pregnant women with IBD demands considerable resources. Still, several problems may arise: (i) The definition of disease activity may not be unambiguous; (ii) data on disease activity has to be recorded according to each trimester or gestational age to assess the exact role of disease activity, and (iii) the degree of disease activity may vary between trimesters and within trimesters. Because disease activity during pregnancy is closely related to drug therapy it is not very useful to analyze the association between disease activity and adverse birth outcome unless concomitant data on drug therapy is recorded; and such details on both disease activity and drug therapy by each trimester only calls for further resources.

AIM

In this thesis I have examined the hypothesis of an association between women with UC and CD and adverse birth outcomes, together with the hypothesis of an association between anti-inflammatory drug treatment and adverse birth outcomes.

The included publications are referred to by Roman numerals, and cover the following areas:

Studies on women with UC

I examined the hypothesis of an association between UC and the risk of adverse birth outcomes (study I), and the risk of specific CAs in children born by women with UC (study II).

Pharmacoepidemiological studies (including women with UC and CD)

I examined the hypothesis of an association between the use of sulfasalazine during pregnancy and the risk of CAs (study III), the use of 5-amonosalicylic acid (5-ASA) during pregnancy and the risk of adverse birth outcomes (study IV), and the use of azathioprine (AZA)/6-mercaptopurine (6-MP) during pregnancy and the risk of adverse birth outcomes (study V). I also examined the risk of CAs in children fathered by men treated with AZA/6-MP before conception (study VI).

Studies on women with CD

I examined the association between CD and the risk of adverse birth outcomes within cohorts of CD women classified according to type of drug therapy during pregnancy (study VII), and the hypothesis of an association between disease activity and the risk for adverse birth outcomes in women with CD (study VIII).

These studies were approved by the Danish Data Protection Agency (record no. 1994-1200-556, 2004-41-4231, 1995-1200-362, 1995-1200-362, and 2003-41-3554).

2. MATERIAL AND METHODS

This thesis consists of eight studies, based on

(i) a Danish nationwide cohort of births by UC women with data obtained from the Danish National Hospital Discharge Registry (HDR) and the Danish Medical Birth Registry (MBR) (Study I),

(ii) a population-based case-control data set from Hungary (the Hungarian Case Control Surveillance of Congenital Abnormalities [HCCSCA]) on women with UC (Study II),

(iii) a population-based case-control data set from Hungary (HCCSCA) on women exposed to sulfasalazine during pregnancy (Study III),

(iv) a Danish cohort of women who took up prescriptions for 5-ASA during pregnancy with data obtained from the population-based prescription registry in the North Jutland County, the HDR, and MBR (Study IV),

(v) a Danish cohort of women who took up prescriptions for AZA/6-MP during pregnancy with data obtained from the population-based prescription registry in the North Jutland County, the HDR, and the MBR (Study V),

(vi) a Danish cohort of fathers who took up prescriptions for AZA/6-MP before conception with data obtained from the prescription registry in North Jutland County, the HDR, and the MBR (Study VI),

(vii) a Danish nationwide cohort of births by CD women categorized according to maternal therapeutic drug use during pregnancy with data obtained from the HDR, the MBR, and the nationwide prescription database (Study VII),

(viii) a Danish cohort of births by CD women in the North Jutland County with data obtained from the HDR, the MBR, and through review of all medicals records (Study VIII).

In all studies, accurate record linkage between registries was made by the unique civil registration number (CPR), which includes date of birth and sex. The CPR is given by the Central Population Registry, which has assigned the 10-digit number to all residents of Denmark since 1 April 1968 (60).

COHORT STUDIES (STUDY I, IV, V, VI, VII, VIII)

Exposure and unexposure assessment

In study I, women were enrolled to the exposed cohort if they had a discharge diagnosis of UC between January 1, 1977 and December 31, 1992, and we noted the first time the diagnosis was recorded in the HDR. We assumed that the first registration of UC in the HDR was the time of UC diagnosis. To reduce the risk of misclassification of type of IBD, any woman, who at any time had been diagnosed with CD, was excluded from the exposed cohort. Based on this a total of 5 787 UC women were identified from 1977 to 1992. Only birth data from 1982 to 1992 were used due to differences in coding procedures and missing reports in the MBR before 1982. The 5 787 UC women had 1 531 single births in the study period from 1982 to 1992 (Table 1). The unexposed cohort comprised births that were randomly selected in the MBR, after matching for date of birth of the child and county of residence (Table 1).

Table 1. Age of individuals in the study cohorts. Women with ulcerative colitis were identified in the Danish National Registry of Patients

	Births to women with ulcerative colitis (N=1531)*	Births to controls (N=9092)*
Age at the time of delivery, number (%)		
< 25 years	291 (19.0)	2740 (30.1)
25-29 years	667 (43.6)	3717 (40.9)
30-34 years	409 (26.7)	1951 (21.5)
≥35 years	164 (10.7)	684 (7.5)
Mean age at the time of delivery, years	28.4	27.2

* Representing 1015 women with ulcerative colitis and 9045 controls

Study IV and V were based on all births between 1 January 1991 and 31 December 2000 in the North Jutland County, and mother exposure assessment in pregnancy (5-ASA in study IV and AZA/6-MP in study V) was determined according to linkage to the population-based Pharmacoepidemiological Prescription Database of North Jutland. The drug data are transferred to the prescription database from the accounting system maintained by the pharmacies and includes the patient's CPR, the type of drug prescribed according to the anatomical therapeutic chemical (ATC) classification system, and the date of the prescription. The database contains data on prescribed drugs from the whole county since 1 January 1991. The drug exposure in study IV and V was identified according to the ATC classification system and the date of the prescription (Appendix for ATC codes).
In Study IV and V women were classified according to the stage of gestation (based on ultrasound or last menstrual period) at which they had taken up prescriptions for 5-ASA and AZA/6-MP: 1) the 'early pregnancy' group comprised women who had taken up prescriptions from 30 days before conception to the end of first trimester (N=60 for 5-ASA, N=9 for AZA/6-MP) and 2) the 'entire pregnancy' group comprised women who had taken up prescriptions during the entire pregnancy (N=88 for 5-ASA, N=10 for AZA/6-MP) (Table 2 and 3). The underlying maternal diseases of exposed women were UC or CD in study IV and UC, CD, or autoimmune diseases in study V. The 'early pregnancy' group was used to examine the risk of CAs because this is the period during which the organs are especially vulnerable to teratogenic exposure, and women exposed in the 'entire pregnancy' group were used to examine other birth outcomes. Unexposed cohorts constituted different cohorts of births by women who had not taken the drug under study during pregnancy: (i) births by women who had not been prescribed any kind of reimbursed medicine from three months before conception to the end of pregnancy (Study IV and V) (Table 2 and 3), (ii) births by all pregnant women, apart from those treated with the drug under study from three months before conception to the end of pregnancy (thereby allowing use of other drugs among controls) (Study IV and V), and (iii) births by women treated with the drug under study outside pregnancy, i.e. more than three months before or after pregnancy (IBD control group in study IV), and more than three months before pregnancy (diseased controls with IBD or autoimmune disorders in study V). Due to the limited number of AZA/6-MP exposed in study V we had no opportunity to make sub-analysis on IBD patients only.

Table 2. The 5-ASA study. Age of individuals in the study cohorts

		Exposed to 5-aminosalicylic acid*		Unexposed**
		1st trimester or 30 days before pregnancy (N=60)	During pregnancy (N=88)	(N=19 418)
Mother's age (year)	Mean (SD)	30.1 (4.8)	30.7 (4.4)	28.7 (4.7)
	Range	21-42	21-42	13-47

* Represents 52 women exposed during the first time period, 74 during the second time period and, 16 486 different unexposed women
** No prescribed drugs from three months before conception to the end of pregnancy

Table 3. AZA/6-MP Study. Age of individuals in the study cohorts

		Pregnancies exposed to azathioprine or 6-mercaptopurine *		Unexposed**
		1st trimester or 30 days before pregnancy (N=9)	During the entire pregnancy (N=10)	(N=19 418)
Mother's age (years)	Mean (SD)	26.7 (4.8)	27.7 (5.3)	28.7 (4.7)
	Range	21-35	21-35	13-47

* Represents 9 different women exposed during the 1st trimester or 30 days before pregnancy, and 9 different women exposed during the entire pregnancy
** No prescribed drugs from three months before conception to the end of pregnancy. Represents 16 486 different unexposed women

Study VI included data on all women in the North Jutland County who, between 1 January 1991 and 31 December 2001, had a live born singleton child. The fathers to the birth cohort were identified from the Central Population Registry. Exposure assessment was determined by linkage to the population-based Pharmacoepidemiological Prescription Database of North Jutland thereby identifying all fathers who, at any time before conception of their child, had filed prescriptions for AZA/6-MP (N=54). The exposed fathers had different underlying diseases; 35.2% were transplant recipients, 31.5% had IBD, 14.8% had skin diseases, 13.0% had rheumatic diseases/connective tissue diseases, and a few had other diseases. The unexposed cohort comprised all fathers, who had never taken AZA or 6-MP before the time of conception, in the birth cohort (N=57.195).

Study VII was based on a nationwide cohort of live born and singleton births by CD women who had never been registered in the HDR with a diagnosis of UC. The women with CD were classified according to type of anti-inflammatory drug exposure used from the time of conception until the end of the third trimester. Data on drug exposure derived from the nationwide registration of prescribed drugs. All Danish pharmacies are equipped with computerized accounting systems through which data are sent directly to the nationwide prescription database, with key information on prescriptions for refundable drugs (61). Data are available from 1995, and complete from 1996, and thus births by CD women were included if the deliveries occurred in the period of 1 January 1996–31 December 2003. Three exposed subcohorts were assessed according to anti-inflammatory drug use in pregnancy:
1) "5-ASA/sulfasalazine group", N=179 (prescription of 5-ASA [local or systemic] or sulfasalazine from the time of conception until the end of the third trimester, but no use of steroids or AZA/6-MP);
2) "steroid group", N=73 (prescription of steroids [local or systemic] and 5-ASA/sulfasalazine [local or systemic] - or steroids alone – from the time of conception until the end of the third trimester, with no use of AZA/6-MP);
3) "AZA/6-MP group", N=20 (prescription of AZA/6-MP [alone, or in combination with 5-ASA/sulfasalazine or steroids] from the time of conception until the end of the third trimester).
The unexposed cohort constituted pregnancies with no maternal prescriptions for 5-ASA, steroids, or AZA/6-MP, from 30 days before conception until the end of the third trimester (Table 4).

Table 4. Characteristics for women with Crohn's Disease according to drug use during pregnancy

	Reference group (N=628)	*5-ASA/ sulfasalazine group (N=179)*	*Steroid group (N=73)*	*AZA/6-MP group (N=20)*
Age at time of delivery, in years				
Mean (SD)	29.4 (4.3)	29.6 ((4.5)	28.7 (4.0)	28.2 (4.7)
Hospital admissions, each of ≥ 2 days duration, for CD during pregnancy. Number (%)				
≥ 2	19 (3.0)	10 (5.6)	25 (34.2)	2 (10%)
Duration of CD at the time of giving birth				
< 5 years with CD, number (%)	300 (47.8)	97 (54.2)	42 (57.5)	10 (50.0)
≥ 5 years with CD, number (%)	328 (52.2)	82 (45.8)	31 (42.5)	10 (50.0)

Study VIII was based on children by CD women in the population of the North Jutland County from 1 January 1977 to 31 December 2005. The validity of the CD diagnosis was validated through review of the medical records, and all live born children to women diagnosed with CD prior to the delivery were enrolled. Despite a study period of 29 years, the number of CD births was modest (N=163). Exposure assessment was determined by the degree of disease activity during pregnancy in accordance with earlier investigators classification of disease activity (62-64). Review of all medical records were thus made to classify the pregnancies according to: (i) inactive disease defined as two or fewer bowel movements per day and absence of blood/pus in the stools, no abdominal pains and no systemic symptoms such as fever or weight loss, (ii) low activity defined as more than two and no more than four bowel movements per day and/or blood or pus in the stools and/or mild abdominal pain less than daily, no systemic symptoms such as fever or weight loss, (iii) moderate-high activity defined as more than four bowel movements daily and/or passage of blood or pus daily and/or abdominal pains either severe or daily, with or without systemic symptoms such as fever or weight loss. For each pregnancy, the degree of disease activity was evaluated according to each trimester. The study included 157 births (by 108 CD women) for analyses. Pregnancies with low or moderate-high disease activity at any time during pregnancy constituted the exposed cohort (N=71), and pregnancies with inactive CD constituted the unexposed cohort (N=86) (Table 5). The main purpose of reviewing medical records was to collect data on disease activity, but also data on other details that are not available in routinely collected data registries (date of the début of symptoms of CD, date of CD diagnosis, fulfilled diagnostic criteria for CD, extent of gastrointestinal lesions, and use of anti-inflammatory drugs, vitamins and other kind of drugs during pregnancy by each trimester). Anti-inflammatory drugs were classified according to the ATC classification system (Appendix for ATC codes). Through the review process we also evaluated whether the women seemed to comply with the therapeutic drug treatment.

Table 5. Characteristics and birth outcomes for women with Crohn's Disease according to disease activity during pregnancy

	Births to women with Crohn's disease (108 women)	
	Pregnancies with disease activity during pregnancy (N=71)	Pregnancies without disease activity during pregnancy (N=86)
Mean age at the time of delivery, years (SD)	29.1 (4.1)	29.9 (4.4)
Disease location in pregnancy, n (%)		
small bowel	16 (22.5)	12 (14.0)
large bowel	19 (26.8)	31 (36.1)
Ileocolitis	29 (40.9)	31 (36.1)
missing information	7 (9.9)	12 (14.0)
Duration of CD at the time of birth, n (%)		
< 5 years with CD	39 (54.9)	29 (33.7)
≥ 5 years with CD	32 (45.1)	57 (66.3)
Smoking during pregnancy, n (%)		
Yes	25 (35.2)	42 (48.8)
No	38 (53.5)	37 (43.0)
missing information	8 (11.3)	7 (8.1)
Drug use at some time during pregnancy, n (%)		
5-ASA (local or systemic)	22 (31.0)	16 (18.6)
systemic steroid	12 (16.9)	4 (4.7)
local steroid	7 (9.9)	1 (1.2)
Sulfasalazine	12 (16.9)	5 (5.8)
immunosuppressive drugs	7 (9.9)	6 (7.0)
Vitamins	48 (67.6)	51 (59.3)
Other	23 (32.4)	15 (17.4)

Outcome assessment

The main birth outcomes studied were:

- Birth weight (study I, IV, V, VII, and VIII)
- LBW (birth weight < 2500 g (6,65)) (study I, IV, V, VII, and VIII)
- Preterm birth (birth before 37 completed weeks of pregnancy (6)) (study I, IV, V, VII, and VIII)
- LBW at term (birth weight < 2500 g with a gestational age ≥ 37 weeks of pregnancy (6)) (study I, VII, and VIII)
- PI (birth weight in g x 100 / birth length in cm^3) (study I)
- Stillbirths (late fetal death, i.e., fetal loss beyond 20 weeks of gestation (66,67)) (study I and IV)
- Perinatal mortality (number of stillbirths and deaths during the first week) (study I and V)
- CAs (study IV, V, VI, VII, and VIII).

Most outcome data were obtained from the MBR. Data on CAs were obtained from the MBR and HDR. The MBR only includes information on whether a child is born with a CA, while the HDR gives information on the date for the diagnosis of CA and the type of CA according to International Classification of Diseases (ICD) 8 and ICD10 (Appendix for ICD codes). Because of their low validity, discharge diagnoses of congenital dislocation of the hip and undescended testis were excluded as CA in all relevant studies (68).

The PI is a frequently used measurement for a baby's weight for height, i.e. the baby's Body Mass Index (corresponding to the body mass index in adults). A malnourished baby with a low birth weight relative to length has a low PI (11,13,15). In study I this measurement was used to support the analyses of LBW at term to estimate the risk of IUGR.

In Denmark, stillborn children are not given a CPR, and therefore, information on stillborn children was not included in all registries. We were therefore only allowed to study stillborn children, and to estimate perinatal mortality, in some of our studies (study I, IV, and V).

Analyses

In studies I, IV, V, VI, VII, and VIII contingency tables for the main study variables were constructed, and the relative risk estimates (prevalence odds ratio, [OR]), with 95 percent confidence intervals (95% CI) were computed). Logistic regression analyses were used to compute relative risk estimates for adverse birth outcomes (LBW, LBW at term, preterm birth, stillbirth, perinatal mortality, and CAs) associated with the exposure of interest, and to adjust for potential confounders. The exposure of interest was UC in study I, 5-ASA in study IV, maternal use of AZA/6-MP in study V, paternal use of AZA/6-MP in study VI, maternal use of 5-ASA/sulfasalazine in CD women in study VII, maternal use of steroid in CD women in study VII, maternal use of AZA/6-MP in CD women in study VII, and disease activity in CD women in study VIII. When estimating the relative risk of CAs, logistic regression models were used according to the 'early pregnancy' group in study IV, V and VII, and the 'entire pregnancy' group was used when estimating the risk of the other birth outcomes. Every pregnancy was included in the analyses as an independent event. In study VIII, in a sub-analysis including only the first pregnancy by each woman, the relative risk estimates were estimated.

Stratified analyses were both performed to reveal effect modification but also to enable presenting results according to identified effect modifiers. In study I, stratified ana-

lyses were performed according to the time of birth in relation to the first hospitalization for UC (into strata of births occurring before the time of UC diagnosis, births within 0-6 months after UC diagnosis, 6-12 months after diagnosis, and more than 12 months after diagnosis). In study IV, stratified analyses were performed according to the use of steroid during pregnancy as a proxy for disease activity and according to the type of underlying disease (UC or CD).
The additional risks (prevalence among the drug exposed – prevalence among the unexposed), with 95% CI, were calculated in study VII according to LBW at term, preterm birth, and CAs.

CASE CONTROL STUDIES (STUDY II AND III)

Cases and controls
The Hungarian Congenital Abnormality Registry (HCAR) was founded in 1962 and is now a valuable national-based registry of cases with CAs (69,70). The registry includes 90% of all major CAs between 1980 and 1996 in Hungary, and reporting of malformed fetuses, stillborns, and live born children is compulsory in Hungary for physicians, mainly obstetricians and pediatricians. Furthermore, autopsy was obligatory for all child deaths and usual in stillborn fetuses; and the pathologists sent a copy of the autopsy report to the HCAR. Pregnancies that terminated during the second trimester due to antenatal diagnosis of fetal defects were also evaluated. The HCCSCA was established covering the study period of 1980-1996. Cases with CAs were selected from the HCAR, excluding children with mild defects (congenital dislocation of the hip based on the Ortolani click, congenital inguinal hernia, and hemangioma), syndromes of known origin (e.g. chromosome disorders), and minor anomalies (e.g. umbilical hernia, hydrocele). At the time of conducting study II a total of 22,843 children with CAs belonged to the HCCSCA, and at the time for running study III a total of 22,865 children with CAs were included (i.e., through continuing validation procedures a few cases were excluded from the case group from 2001-2003). The aim was for each case to select two neonate children without CAs as controls, matched according to sex, birth week, and district of parents' residence from the national birth registry of the Central Statistical Office, Hungary. For some cases, two controls could not be obtained and only one was included. A total of 38,151 population controls were selected to the HCCSCA.

Exposure information
A post-paid questionnaire with an explanatory letter and list of diseases and drugs was mailed to the parents immediately after the selection of cases and controls. The mothers were asked to fill out a structured questionnaire, which included ten parts (e.g., information on the children's diagnosis of CA, sex, birth weight, gestational age, demographic data, year and outcome of previous pregnancies, family history of CA, family planning, complications during pregnancy, chronic underlying maternal diseases, acute maternal diseases during pregnancy by gestational month, and medication taken during the study pregnancy by gestational month). To standardize the answers, the mothers were asked to read the enclosed list of diseases and drugs before they replied. All mothers were asked to send the antenatal care logbook, which is a written record of diseases and drugs given by obstetricians to treat pregnancy-related diseases (70,71).

Study II included information on maternal UC exposure from the HCCSCA in cases and controls (among cases N=71 with UC and N=22,722 without UC, among controls N=95 with UC and N=38,056 without UC) (Table 6). Information on the mothers' underlying UC disease was based on both self-reported data and antenatal logbook information, and all identified women with UC were diagnosed before pregnancy. We had no information on disease severity during pregnancy. However, no hospitalization due to UC occurred during pregnancy. Information was also included on maternal age at the time of delivery, birth order, use of sulfasalazine during pregnancy, and use of other drugs during pregnancy. The drug of choice for treatment of UC in Hungary during the study period was sulfasalazine.

Table 6. Basic characteristics for cases and controls according to ulcerative colitis (UC)

	Cases		Controls	
	Without UC (n=22,772)	With UC (n=71)	Without UC (n=38,056)	With UC (n=95)
Maternal age at delivery (yr)				
Mean age (SD)	25.5 (5.5)	25.7 (5.4)	25.5 (5.3)	25.9 (5.0)
Maternal age (yr) [n (%)]				
<25	10,941 (48.0)	32 (45,1)	17,899 (47.0)	38 (40.0)
25-29	7,061 (31.0)	23 (32.4)	12,507 (32.9)	35 (36.8)
>29	4,770 (21.0)	16 (22.5)	7,650 (20.1)	22 (23.2)
Birth order [n (%)]				
Parity = 1	13,867 (60.9)	47 (66.2)	22,701 (59.7)	42 (44.2)
Parity ≥ 2	8,905 (39.1)	24 (33.8)	15.355 (40.3)	53 (55.8)
Use of sulfasalazine [n (%)]				
Yes	13 (0.1)	4 (5.6)	16 (0.04)	10 (10.5)
No	22,759 (99.9)	67 (94.4)	38,040 (99.9)	85 (89.5)

Study III included information on maternal sulfasalazine exposure from the HCCSCA in cases and controls (among cases N=17 with sulfasalazine exposure and N=22,848 without, among controls N=26 with sulfasalazine exposure and N=38,125 without) (Table 7). The trimester of exposure provided information on maternal use of sulfasalazine and was based on both self-reported use and logbook information. The sulfasalazine was given orally with a recommended dose per day of 4-8 g. All women treated with sulfasalazine had UC or CD, apart from one control woman.

Table 7. Study Groups according to sulfasalazine exposure and type of congenital abnormalities (CAs) among cases

	Sulfasalazine exposure at some time during pregnancy		Total
Study groups	No.	%	No.
Controls	26	0.07	38151
Isolated CAs			
Cleft lip ± palate	2	0.15	1369
Cardiovascular CAs	2	0.04	4467
Clubfoot	3	0.12	2420
Other isolated CAs	8	0.05	13045
Multiple CAs	2	0.13	1564
Total	17	0.07	22865

Analyses

In studies II and III contingency tables were made for the main study variables, and the OR with 95% CI for CA was estimated overall and for selected CAs. We used logistic regression analyses to compute relative risk estimates for CAs associated with the exposure of interest (UC in study II, sulfa-salazine in study III), and to adjust for potential confounders.

3. RESULTS, INCLUDING DISCUSSION OF EXISTING LITERATURE

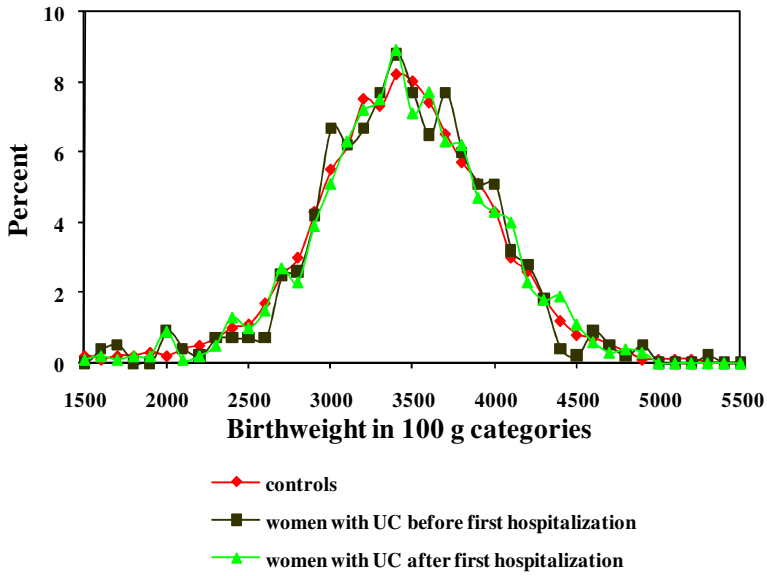
Results of the studies are given according to the aim of the thesis in the following three main headings: Studies on women with UC, pharmacoepidemiological studies (including women with UC and CD), and studies on women with CD.

STUDIES ON WOMEN WITH UC

I examined the hypothesis of an association between UC and the risk of adverse birth outcomes (study I), and the risk of specific CAs in children born by women with UC (study II).

In study I we found that the mean birth weight of neonates to UC mothers was virtually the same as that of neonates in the control group (3 457 g [lower-upper quartiles 3 140-3 820] and 3 438 g [lower-upper quartiles 3 100-3 800] respectively). Figure 1 shows that the distribution of birth weight in neonates of women with UC was the same as that of neonates in the control group, even after stratification for time of birth in relation to the first hospitalization for UC.

Figure 1



After adjusting for confounders we found no increased risk of LBW or IUGR for neonates born to women with UC (Table 8 and 9) neither for births occurring before nor after first hospitalization for UC. The results of IUGR were supported by analyses of PI as we found no decrease in PI for neonates born to women with UC (neither before nor after the first hospitalization), compared with controls.

We found a threefold increased risk (OR=3.4, 95% CI 1.8-6.4) of preterm birth for neonates born in the period of 0-6 months after a woman was hospitalized for UC for the first time; except for this period, we found no significant increased risk of preterm birth (Table 8). The analyses of stillbirths and perinatal mortality had limited statistical precision because of few events. From 1982 to the end of 1992 we found 1.0% (16/1531) perinatal deaths in the neonates of UC women, and 0.7% (60/9092) among the controls. Among women with UC, the adjusted risk of stillbirths and perinatal mortality was OR=1.9 (95% CI=1.0-4.0) and OR=1.7 (95% CI=0.9-3.0), respectively.

Table 8. Crude and adjusted odds ratios (OR) for low birth weight and preterm birth according to ulcerative colitis (UC) and stratified for time of birth in relation to the first hospitalization for UC

	UC: Events/Total (%)	Controls: Events/Total (%)	OR (crude) (95% CI)	Adjusted OR* (95% CI)
LBW				
Overall	70/1527 (4.6)	419/9071 (4.6)	1.0 (0.8-1.3)	0.8 (0.6-1.2)
Before first hospitalization	25/568 (4,4)	419/9071 (4.6)	1.0 (0.6-1.4)	0.9 (0.5-1.6) †
0-6 months after first hospitalization	8/87 (9.2)	419/9071 (4.6)	2.1 (1.0-4.4)	0.7 (0.2-2.2) †
6-12 months after first hospitalization	3/52 (5.8)	419/9071 (4.6)	1.3 (0.4-4.1)	1.1 (0.2-5.6) †
>1 yr after first hospitalization	34/820 (4.1)	419/9071 (4.6)	0.9 (0.6-1.3)	0.8 (0.5-1.3) †
Preterm				
Overall	82/1523 (5.4)	415/9042 (4.6)	1.2 (0.9-1.5)	1.2 (0.9-1.5) ‡
Before first hospitalization	23/566 (4.1)	415/9042 (4.6)	0.9 (0.6-1.4)	0.9 (0.6-1.3) ¶
0-6 months after first hospitalization	12/87 (13.8)	415/9042 (4.6)	3.3 (1.8-6.2)	3.4 (1.8-6.4) ¶
6-12 months after first hospitalization	3/52 (5.8)	415/9042 (4.6)	1.3 (0.4-4.1)	1.3 (0.4-4.1) ¶
>1 yr after first hospitalization	44/818 (5.4)	415/9042 (4.6)	1.2 (0.9-1.6)	1.2 (0.9-1.7) ¶

LBW=birth weight less than 2500 g. Preterm birth=gestational age less than 37 weeks. 95%CI=95% confidence limits.
* Adjusted for gestational age (32 wk or less, 33-36 wk, 37-41 wk, and 42 wk or more), mother's age (<25 yr, and 25-29 yr, 30 yr or more), and parity (first delivery or one or more previous deliveries) in a logistic regression model
† and adjusted for calendar period (1982-1985, 1986-1989, and 1990-1992)
‡ not adjusted for gestational age
¶ not adjusted for gestational age, but for calendar period

Table 9. Crude and adjusted odds ratios (OR) for intrauterine growth retardation according to ulcerative colitis (UC) and stratified for time of birth in relation to the first hospitalization for UC

	UC: Events/Total (%)	Controls: Events/Total (%)	OR (crude) (95% CI)	Adjusted OR* (95% CI)
IUGR, overall	19/1439 (1.3)	151/8618 (1.8)	0.8 (0.5-1.2)	0.7 (0.5-1.2)
IUGR, before first hospitalization	7/543 (1.3)	151/8618 (1.8)	0.7 (0.3-1.6)	0.7 (0.3-1.5)†
IUGR, after first hospitalization	12/896 (1.3)	151/8618 (1.8)	0.8 (0.4-1.4)	0.8 (0.4-1.4)†

95%CI=95% confidence limits. IUGR=Intrauterine Growth Retardation (birth weight <2500 g with a gestational age ≥37 wk).
* Adjusted for mother's age (<25 yr, and 25-29 yr, 30 yr or more), and parity (first delivery or one or more previous deliveries) in a logistic regression model
† and adjusted for calendar period (1982-1985, 1986-1989, and 1990-1992)

In study II we found no significantly increased overall risk of CAs in children born to women with UC (adjusted for parity, mothers' age and use of sulfasalazine and other drugs during pregnancy OR=1.3, 95% CI=0.9-1.8). However, we found an increased risk of some selected CA's (Table 10) – limb deficiencies (OR=6.2, 95% CI=2.9-13.1), obstructive urinary CA's (OR=3.3, 95% CI=1.1-9.5), and multiple CA's (OR=2.6, 95% CI=1.3-5.4). After reviewing the components in the nine children with multiple CA's we found no characteristic pattern.

Table 10. Adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for selected congenital abnormalities (CAs) in children born to women with ulcerative colitis (UC)

	Total	With UC	%	OR*	95% CI
Controls	38,151	95	0.25	Referent	
Cases with isolated CAs					
Limb deficiencies	548	8	1.46	6.2	2.9-13.1
Polysyndactyly**	1,744	3	0.17	0.7	0.2-2.2
Neural tube defects**	1,202	4	0.33	1.4	0.5-3.8
Cardiovascular CAs	4,479	12	0.27	1.1	0.6-2.1
Clubfoot	2,424	5	0.21	0.8	0.3-2.0
Cleft lip ± palate	1,374	4	0.30	1.1	0.4-3.0
Hypospadias**	3,038	7	0.23	1.0	0.5-2.1
Undescended testis	2,051	4	0.20	0.8	0.3-2.3
Obstructive CAs of the urinary tract	502	4	0.80	3.3	1.1-9.5
Cases with multiple CAs	1,349	9	0.70	2.6	1.3-5.4

* adjusted for maternal age (< 25 years, 25-29 years, and 30 years or more), birth order (first delivery or one or more previous deliveries), use of sulfasalazine (as a dichotomous variable), and use of other drugs during pregnancy (as a dichotomous variable) in a logistic regression model

** not possible to adjust for use of sulfasalazine during pregnancy

Studies on women with UC and the existing literature

Since the 1980s several epidemiologic studies have been conducted to investigate the association between UC and adverse birth outcomes (1,4,5,46,59,72-77,77-79) (Enc., Table 1). When comparing our findings with the results of others we bring into discussion only those English language studies that made analysis separately on UC; keeping in respect that UC and CD are two different diseases with distinct pathophysiology, complications, and course of disease. Furthermore, only the studies that include a comparison group (i.e., excluding case-series) are discussed.

Regarding analyses on specifically UC patients, the data set in study I is still the largest study so far, published in the area of adverse birth outcomes. Our results as regards LBW support the findings of Porter and Stirrat (73), Dominitz JA et al. (76) and Ludvigsson JF et al. (75), analyzing 44, 107, and 26 UC pregnancies respectively. On the other hand Schade et al. (72) found a significantly increased risk of LBW children among UC women in the crude analysis (four children with LBW in 12 deliveries by UC women), but there was no adjustment for gestational age, and in fact half of the children were born preterm. In several other studies the risk of LBW was not specifically estimated (4,5,74,77).

The finding of no increased risk of IUGR for neonates born (before or after the first hospitalization) of UC women was new and important; and our analyses on PI supported the finding of no increased risk of IUGR. One other study has later examined the risk of IUGR in neonates by UC women, also without finding a significantly increased risk (76). This has later been confirmed by joint analyses of the two studies (76,80) in a meta-analysis from 2007 (81).

Our overall result of an increased risk of preterm birth is in accordance with other studies (73-75,77,78). We found a more than threefold increased risk of preterm birth when the first hospitalization for UC took place during pregnancy, but no increased risk of preterm birth in pregnancies occurring before diagnosis of UC. Thus, we could not confirm the high proportion of preterm births before the onset of symptoms, reported by Baird et al. (74), and our result is in accordance with the study by Bortoli et al. suggesting no difference in preterm birth between UC and controls (79). The recent meta-analysis on birth outcomes in UC pregnancies found an OR=1.34 (95 CI%=1.09-1.64) for preterm birth, but data and analyses were not separated regarding to time of birth in relation to début of UC (81). The finding of an increased risk of preterm birth in the meta-analysis could thus be blurred by differential risks of preterm birth according to time span between birth and début of UC as indicated in our study. Additionally, the meta-analysis indicated that the increased risk of preterm birth was probably not due to induced preterm deliveries, as the risk of caesarean section was not significantly increased.

Two, very small studies have reported on perinatal mortality in children of UC women, and no cases of perinatal deaths were observed (72,73). However, in view of the limited number of deliveries in these studies (44 and 16 respectively), one would not expect any deaths to occur. Our study is the largest to date, but still we have estimates with very low statistical precision.

Only two other studies have estimated the overall risk of CAs. Dominitz et al. found a nearly fourfold increased risk (OR=3.8, 95% CI=1.5-9.8) in children by UC women (76), and Bortoli et al. found no increased risk of CAs after comparing UC births by CD births (79). However, the study by Dominitz et al. might have overestimated the risk due to inclusion of chromosomal disorders (76). Our study, based on Hungarian data, is the only study so far on the risk of selected CAs in children born to UC women, and our finding of an increased risk of limb deficiencies, obstructive urinary CA's, and multiple CAs can therefore not be compared to other studies.

PHARMACOEPIDEMIOLOGICAL STUDIES (INCLUDING WOMEN WITH UC AND CD)

I examined the hypothesis of an association between use of sulfasalazine during pregnancy and the risk of CAs (study III), the use of 5-ASA during pregnancy and the

risk of adverse birth outcome (study IV), and the use of AZA/6-MP during pregnancy and the risk of adverse birth outcome (study V). Furthermore, I examined the risk of CAs in children fathered by men treated with AZA/6-MP before conception (study VI).

In **study III** we found no significantly increased overall risk of CAs in children born to women exposed to sulfasalazine during pregnancy (adjusted for mothers' age, parity, acute and chronic maternal diseases, and use of other drugs; OR=1.2, 95% CI=0.6-2.1, Table 11). Regarding the analyses of the prevalence of selected CAs, the OR was approximately two-fold increased for cleft lip ± palate, clubfoot and multiple CAs, but none of the associations were statistically significant.

Table 11. Adjusted odds ratios (OR) with 95% confidence interval (95% CI) for congenital abnormalities (CAs) after sulfasalazine treatment according to gestational age at treatment

	Entire pregnancy				Total
Study groups	No.	%	OR*	95% CI	No.
Controls	26	0.07	Referent		38151
Isolated CAs					
Cleft lip ± palate	2	0.15	2.1	0.5-9.0	1369
Cardiovascular CAs	2	0.04	0.7	0.2-2.8	4467
Clubfoot	3	0.12	2.0	0.6-6.5	2420
Other isolated CAs	8	0.05	1.0	0.4-2.1	13045
Multiple CAs	2	0.13	1.8	0.4-7.7	1564
Total	17	0.07	1.2	0.6-2.1	22865

* Adjusted for maternal age, birth order, maternal diseases, and other drug use

In **study IV** the adjusted ORs for stillbirths, preterm birth, CAs, and low birth weight in women who took up prescriptions for 5-ASA drugs during pregnancy were 6.4 (95% CI=1.7-24.9), 1.9 (95% CI=0.9-3.9), 1.9 (95% CI=0.7-5.4) and 1.2 (95% CI=0.4-3.3) respectively (Table 12). In a sub-analysis we included only those cases of CAs in 5-ASA exposed women that could be confirmed by review of the hospital records and found thereafter no increased risk of CAs (OR=0.9, 95% CI=0.2-3.8). After stratification for concomitant use of steroids (as a surrogate of disease activity) we found that the risk of stillbirth increased further, but statistically with very imprecise estimate (OR=20.4, 95%CI=3.4-122.9).
Our main results thus indicated an increased risk of stillbirth and preterm birth, and no substantial increased risk of LBW or CAs. After stratification for type of underlying disease, the increased risks of stillbirth and preterm birth were found only in UC patients (Table 13).
When we used the IBD control group, i.e. women who took up prescriptions for 5-ASA drugs before or after, but not during the pregnancy, we still found an increased risk of preterm birth (OR=2.0, 95% CI=0.8-5.0) and stillbirth (OR=7.1, 95% CI=0.2-205.1) - although not statistically significant.

Table 12. Adjusted odds ratios (OR), with 95% confidence intervals (CI), for birth outcome in patients treated with 5-aminosalicylic acid (5-ASA) in pregnancy

	Treated with 5 ASA (overall)	
	Events/total (%)	OR ‡ (95% CI)
LBW *	4/88 (4.6)	1.2 (0.4-3.3)
Preterm birth**	8/88 (9.1)	1.9 (0.9-3.9)
Stillbirth	3/88 (3.4)	6.4 (1.7-24.9)
CAs †	4/60 (6.7)	1.9 (0.7-5.4)

* LBW=birth weight less than 2500 g. ** Preterm birth=gestational age less than 37 weeks
† CAs=congenital abnormalities. Different exposure window when examining congenital malformations (exposed in the period 30 days before conception to the end of first trimester)
‡ Adjusted for mother's age (below 25 years, 25-29 years, and 30 years or more), parity (1 or more than 1), smoking (yes/no) in a logistic regression model. LBW and stillbirths also for gestational age (32 weeks or less, 33-36 weeks, and 37 weeks or more)

Table 13. Adjusted odds ratios (OR), with 95% confidence intervals (CI), for birth outcome in patients treated with 5-aminosalicylic acid (5-ASA) in pregnancy, stratified by type of underlying disease (Crohn's disease [CD] or ulcerative colitis [UC])

	Patients with CD treated with 5-ASA		Patients with UC treated with 5-ASA	
	Events/total (%)	OR‡ (95% CI)	Events/total (%)	OR‡ (95% CI)
LBW *	1/23 (4.3)	0.9 (0.1-6.7)	3/65 (4.6)	1.4 (0.4-4.3)
Preterm birth**	1/23 (4.3)	0.8 (0.1-5.6)	7/65 (10.8)	2.4 (1.1-5.3)
Stillbirth	0/23 (0.0)	-	3/65 (4.6)	8.4 (2.0-34.3)
CAs†	1/18 (5.6)	1.5 (0.2-11.4)	3/42 (7.1)	2.1 (0.7-6.9)

* LBW=birth weight less than 2500 g. ** Preterm birth=gestational age less than 37 weeks
† CAs=congenital abnormalities. Different exposure window when examining congenital malformations (exposed in the period 30 days before conception to the end of first trimester)
‡ Adjusted for mother's age (below 25 years, 25-29 years, and 30 years or more), parity (1 or more than 1), smoking (yes/no) in a logistic regression model. LBW and stillbirths also for gestational age (32 weeks or less, 33-36 weeks, and 37 weeks or more)

In **study V** the number of AZA/6-MP exposed pregnancies was limited during a study period of 10 years. Among 11 different exposed women, six had UC or CD (55%) and the other underlying diseases were vasculitis, myasthenia, glomerulonephritis, nephritis and aggressive autoimmune hepatitis. We found a significantly increased risk of preterm birth, perinatal mortality, and CAs when using the main control group (Table 14), and similar results when using the second control group that allowed use of other drugs apart from AZA/6-MP during pregnancy. After using the third control group, comprising women with similar diseases to the exposed (women who used AZA/6-MP before pregnancy, but not three months before pregnancy or during pregnancy), the adjusted risk estimates remained increased (Table 15), but none were significantly increased.
Our main results suggest that the use of AZA/6-MP during pregnancy may be associated with an increased risk of preterm birth, perinatal mortality, and CAs. The results, however, turned out not to be statistically significant, and the magnitude of the relative risk estimates declined, when we used the control group of women with the same type of underlying diseases as the exposed. This suggests that the risk of adverse birth outcome is influenced by the underlying disease itself or factors related to the disease.

Table 14. Adjusted odds ratios (OR) for birth outcome in women treated with azathioprine (AZA) or 6-mercaptopurine (6-MP) during pregnancy, using the main control of women who had not been prescribed any kind of medicine from three months before conception to the end of pregnancy

	Outcome/total (%)		
	AZA/6-MP exposed pregnancies	control pregnancies	OR ** (95% confidence interval)
LBW H	3/10 (30.0)	844/19418 (4.4)	3.8 (0.4-33.3)
Preterm birth I	3/10 (30.0)	1062/19418 (5.5)	6.6 (1.7-25.9)
Perinatal mortality	1/10 (10.0)	109/19418 (0.6)	20.0 (2.5-161.4)
CAs*	2/9 (22.2)	711/19418 (3.7)	6.7 (1.4-32.4)

H LBW=birth weight less than 2500 g. I Preterm birth=gestational age less than 37 weeks.
* CAs=congenital abnormalities. Different exposure window when examining congenital abnormalities (exposed in the period 30 days before conception to the end of first trimester)
** Adjusted for mother's age (below 25 years, 25-29 years, and 30 years or more), parity (1 or more than 1), and smoking (yes/no) in a logistic regression model. LBW also for gestational age (continuous variable)

Table 15. Adjusted odds ratios (OR) for birth outcome in women treated with azathioprine (AZA) or 6-mercaptopurine (6-MP) during pregnancy, using a control group of women treated with AZA/6-MP before pregnancy but not during pregnancy

	Outcome/total (%)		
	AZA/6-MP exposed pregnancies	Diseased controls	OR ** (95% confidence interval)
LBW [H]	3/10 (30.0)	6/30 (20.0)	2.3 (0.4-13.6)
Preterm birth [I]	3/10 (30.0)	6/30 (20.0)	2.8 (0.4 - 19.4)
Perinatal mortality	1/10 (10.0)	1/30 (3.3)	3.2 (0.2 - 56.9)
CAs*	2/9 (22.2)	1/30 (3.3)	7.7 (0.6-102.1)

H LBW=birth weight less than 2500 g. I Preterm birth=gestational age less than 37 weeks
* CAs=congenital abnormalities. Different exposure window when examining congenital abnormalities (exposed in the period 30 days before conception to the end of first trimester)
** Adjusted for mother's age (below 25 years, 25-29 years, and 30 years or more), parity (1 or more than 1), and smoking (yes/no) in a logistic regression model. LBW also for gestational age (continuous variable)

In **study VI** we found an increased risk of CAs (OR=1.8, 95% CI=0.7-5.0) in children fathered by men treated with AZA/6-MP before conception (Table 16).
In the exposed group, all cases of CAs were reviewed in the medical records. The types of malformations were: i) polysyndactylia; ii) esophagus atresia; iii) hydronephrosis and megaloureter; and iv) ventricular septal defect. All cases of CAs were among male children. For children with CAs whose fathers were treated with AZA, the time interval between the father's last prescription for AZA until the time of conception was 9 to 38 months. Three of the men treated with AZA/6-MP, who subsequently fathered a child with CA, were renal transplant recipients, while the fourth had skin disease. None had IBD. After an evaluation of the type of other paternal drug exposure before conception and maternal drug exposure during pregnancy for exposed cases of CAs, we had no reason to believe that use of other therapeutic drugs had confounded the association. The type and amount of data did not allow us to consider the possible influence of the type of underlying paternal disease or disease activity.

Table 16. Crude and adjusted odds ratio (OR), with 95% confidence interval (CI), for congenital abnormalities in children fathered by men treated with azathioprine (AZA) or 6-mercaptopurine (6-MP) before conception

	AZA/6-MP exposed pregnancies, Number (%)	Control pregnancies Number (%)	Crude OR (95% CI)	OR* (95% CI)
Congenital abnormalities	4/54 (7.4)	2,334/57,195 (4.1)	1.9 (0.7-5.2)	1.8 (0.7-5.0)

*Adjusted for mother's age (below 25 years, 25-29 years and 30 years or more), parity (1 or more than 1), maternal smoking (yes/no), and gender of the child in a logistic regression model
Hosmer-Lemeshow model control: *P*=0.51

Pharmacoepidemiological studies and the existing literature

Since 1980, several studies on anti-inflammatory drug exposure (sulfasalazine, 5-ASA, AZA/6-MP) in IBD patients and birth outcome have been published (1,2,4,5,35,37,43,50-53,82) (Enc., Table 2); and the existing literature on drug therapy, relevant for this thesis, is distributed on sulfasalazine (4,5,35,37,43), 5-ASA (1,50,51), and AZA/6-MP (1,2,52,53,82). Several studies have thus been published on the safety of anti-inflammatory drug therapy, but many studies are hampered by no external control groups, no estimation of the specific birth outcomes, and no confounder control.

According to our data on CAs after ***sulfasalazine*** exposure in pregnancy we have no sound epidemiological designed studies to compare our results with. There are no other published studies examining the prevalence of selected CAs after sulfasalazine exposure. In the beginning of the 1980s five studies were published including some information on CAs after sulfasalazine exposure (4,5,35,37,43), but all studies were without estimation of the risk of CAs and without confounder control. Only the study from 1980 by Willoughby and Truelove (37) indicates an increased teratogenic risk after sulfasalazine exposure. In this study three cases of CAs were found in neonates born to 54 sulfasalazine exposed women and none among 50 unexposed women.

The suggestion of an increased risk of stillbirth in the ***5-ASA*** study, particularly in patients with UC, is new. After reviewing the hospital records of the stillbirths in 5-ASA exposed women, however, we found no specific pattern in the cause of death. The risk of stillbirth was not esti-

mated in the studies by Moskovitz et al. (1), Diav-Citrin et al. (50), or Marteau et al. (51); and previous studies suggesting an association between patients with IBD and an increased risk of stillbirth included no data on drug use (45,46,80). In our analysis of women who had taken up prescriptions for 5-ASA and steroids (as a surrogate of disease activity) the risk of stillbirth increased further, and this may actually indicate the importance and the disadvantage of disease activity.
The increased risk of preterm birth after 5-ASA exposure during pregnancy has been indicated in other studies (50,51). A new aspect is, however, that the finding of an increased risk of preterm birth does only apply to 5-ASA exposed women with UC. The risk of preterm birth was also increased using IBD patients as controls, which may indicate that use of 5-ASA plays a role for the outcome, but an alternative explanation is that the apparent effect of 5-ASA is confounded by disease activity.
The finding of no substantially increased risk of LBW or CAs after use of 5-ASA drugs during pregnancy is in agreement with other findings (50,51).

In study V we suggested an increased risk of CAs, perinatal mortality and preterm birth after ***maternal AZA/6-MP*** exposure in pregnancy, but we also found an effect of the underlying disease, since the relative risk estimates of perinatal mortality and preterm birth declined when we used the control group of women with the same type of underlying diseases as the exposed. Nearly all human data on the safety of AZA/6-MP had come from pregnancies in organ transplant recipients; mainly case reports and case series. At the time of conducting study V the evidence of safety of AZA/6-MP in IBD pregnancies were indeed very limited; restricted to two case-series of two and 14 women exposed during pregnancy (83,84), and results from a case-control study which had been presented in abstract form only (85).
Study V was published in 2003 and based on 1991-2000 data from one county in Denmark. In 2007 I co-authored a nationwide study by Langagergaard et al. (52), based on national data from 1996-2001. Therefore, some of the exposed pregnancies in study V are also included in the study by Langagergaard et al. (52). As regards preterm birth the result was supported by the study by Langagergaard et al. (52). Goldstein et al. found increased risks of CAs, preterm birth, LBW and stillbirth, like the findings in study V and in the study by Langagergaard et al. (52) using the population controls. A large national study from Sweden has recently supported the findings of increased risk of CAs (OR=1.41, 95% CI=0.98-2.04), preterm birth (OR=3.6, 95% CI=2.8-4.5) after AZA exposure during pregnancy (82). It is important to notice that they still found increased risk of CAs and preterm birth when women with IBD were used as controls (82).

Most studies have centered upon female patients taking AZA/6-MP during pregnancy, and the literature is very slow-growing regarding the outcomes of pregnancies when the male partner is or has been treated with a potential harmfully agent (86). Only one other study with a control group has estimated the specific risk of CAs after ***paternal 6-MP exposure*** (87). In that study, Rajapakse et al. found an increased risk of CAs in children fathered by men treated with 6-MP for IBD, compared with fathers who had never been treated with 6-MP (87). They found two cases of CAs in children fathered by men treated with 6-MP, and both fathers were treated with 6-MP within three months of conception (87). Based on our observations according to the time period between last prescription of AZA/6-MP and the time of conception, our data may indicate a possible more long-term effect. However, a single prescription of AZA/6-MP may include a very large number of tablets providing treatment for long periods; thus, based on only prescription data, we cannot be certain as to how many months the fathers were actually exposed before conception. The type of underlying diseases in the AZA-exposed fathers, who had children with CAs, may in fact indicate a permanent use of AZA. Based on these arguments, our finding of a possible more long-term effect of AZA/6-MP should be interpreted with extreme caution. Spermatogenesis in humans takes 70-90 days and a causative effect, given the ≥ 9 months hiatus between prescription and conception, is mainly speculative. Animal studies have indicated cytogenetic toxicity in early premeiotic and meiotic germ cell (88,89), but we lack human data (90).

STUDIES ON WOMEN WITH CD

I examined the association between CD and the risk adverse birth outcome within cohorts of CD women classified according to the type of drug therapy during pregnancy (study VII), and the hypothesis of an association between disease activity and the risk for adverse birth outcome in women with CD (study VIII).

In **study VII** the birth outcome in CD women were studied in sub-cohorts according to therapeutic drug treatment during pregnancy.
For *CD births in the 5-ASA/sulfasalazine group*, we found increased relative risks of LBW and LBW at term, but none were significantly increased (Table 17). The additional risk of LBW at term was very small (0.8%, 95% CI=-1.2-3.2).
For *CD births in the steroid group*, the adjusted relative risk of preterm birth was 1.4 (95% CI=0.6-3.3), with 'disease activity' (at least two admissions, each of ≥2 days duration) as the most important confounder (Table 17). The risk difference indicated that, compared to the reference group, users of steroids had an additional risk of preterm birth of 5.8% (95% CI=-2.0%-13.6%). We found no increased relative risk of LBW at term or of CAs.
For *CD births in the AZA/6-MP group*, the adjusted relative risk of preterm birth was 4.2 (95% CI=1.4-12.5), with 'disease activity' as the most important confounder (Table 17). The risk differences indicated that, compared to the reference group, users of AZA/6-MP had an additional risk of preterm birth of 18.5% (95% CI=-0.1%-37.6%).
The relative risk of CAs was 2.9 (95% CI=0.9-8.9), and the additional risk of bearing children with CAs was 9.7%, 95% CI=-4.3%-23.6%). The discharge diagnoses of CAs, among children whose mothers were exposed to AZA/6-

MP, were cataracta congenital, encephalocele occipitalis, malformations congenitae musculi sternocleidomastoidei, and malformations congenitae aliae cutis.

Table 17. Crude and adjusted relative risk (RR), with 95 % confidence interval (95% CI), for birth outcomes in women with Crohn's disease (CD) in the 5-ASA/sulfasalazine group, steroid group, and AZA/6-MP group, compared to the reference group (no drug use for CD)

	CD pregnancies with use of **5-ASA/sulfasalazine** Outcome/total (%)	CD pregnancies in the reference group Outcome/total (%)	RR (95% CI)	RR § (95% CI)
LBW *	7/179 (3.9)	31/628 (4.9)	0.8 (0.3-1.8)	1.7 (0.6-4.8)
Preterm birth †	7/179 (3.9)	41/628 (6.5)	0.6 (0.3-1.3)	0.5 (0.2-1.2)
LBW at term	4/179 (2.2)	9/628 (1.4)	1.6 (0.5-5.3)	1.9 (0.6-6.4)
CAs‡	9/157 (5.7)	36/628 (5.7)	1.0 (0.5-2.1)	1.0 (0.5-2.1)
	CD pregnancies with use of **steroid** Outcome/total (%)	CD pregnancies in the reference group Outcome/total (%)	RR (95% CI)	RR § (95% CI)
LBW *	5/73 (6.9)	31/628 (4.9)	1.4 (0.5-3.8)	1.1 (0.2-5.7)
Preterm birth †	9/73 (12.3)	41/628 (6.5)	2.0 (0.9-4.3)	1.4 (0.6-3.3)
LBW at term	1/73 (1.4)	9/628 (1.4)	1.0 (0.1-7.9)	0.9 (0.1-7.1)
CAs‡	2/48 (4.2)	36/628 (5.7)	0.7 (0.2-3.1)	0.7 (0.2-3.2)
	CD pregnancies with use of **AZA/6-MP** Outcome/total (%)	CD pregnancies in the reference group Outcome/total (%)	RR (95% CI)	RR § (95% CI)
LBW *	3/20 (15.0)	31/628 (4.9)	3.4 (0.9-12.2)	0.4 (0.0-4.1)
Preterm birth†	5/20 (25.0)	41/628 (6.5)	4.8 (1.7-13.8]	4.2 (1.4-12.5)
LBW at term	0/20 (0)	9/628 (1.4)	-	-
CAs‡	4/26 (15.4)	36/628 (5.7)	3.0 (1.0-9.1)	2.9 (0.9-8.9)

* LBW=birth weight less than 2500 g. Preterm birth=gestational age less than 37 weeks ‡ A different exposure window was used when examining CAs (exposed in the period 30 days before conception to the end of first trimester)
§ LBW adjusted for mother's age (continuous variable), parity (1 or more than 1), gestational age (continuous variable), and disease activity (<2 or ≥2 admissions, of at least 2 days of duration for CD during pregnancy) in a logistic regression model. LBW at term adjusted for mother's age, and parity. Preterm birth and congenital abnormalities adjusted for mother's age, parity, and disease activity

In **study VIII,** of live born children to CD women, 55% (N=86) of the mothers had inactive disease during pregnancy and 45% (N=71) had low or moderate-high disease activity. In all trimesters women with low activity were mainly treated with 5-ASA, and in those with moderate-high activity 5-ASA and systemic steroid. Immunosuppressive drugs were only used by few women in all trimesters.
The adjusted relative risk of preterm birth was more than two-fold increased (2.4, 95% CI=0.6-9.5) in women with low or moderate-high disease activity during pregnancy, compared to women without activity; and we found no increased risk of LBW, LBW at term or CAs (Table 18). We also found that approximately 14% of enrolled CD women had moderate-high disease activity in first, second, and third trimester; and in analyses of birth outcomes in women with the highest degree of activity (moderate-high at some time during pregnancy), compared to women with inactive disease, the relative risk of preterm birth increased to OR=3.4 (95% CI=1.1-10.6), and still we found no increased risk of LBW, LBW at term, or CAs (1.1, 95% CI=0.3-4.0; 0.9, 95% CI=0.1-8.5; and 0.4, 95% CI=0.0-3.9 respectively).
In sub-analyses we restricted to the pregnancy first recorded by each woman, but the risk estimates were virtually unchanged.

Table 18. Crude and adjusted odds ratios (OR) for low birth weight (LBW), LBW at term, preterm birth, and congenital abnormalities (CAs) in Crohn's disease (CD) women with disease activity during pregnancy, compared to women with inactive disease

	CD pregnancies with disease activity Outcome/total§ (%)	CD pregnancies with no disease activity Outcome/total§ (%)	Crude OR (95% confidence interval)	Adjusted OR ¶ (95% confidence interval)
LBW*	4/69 (5.8)	8/83 (9.6)	0.6 (0.2-2.0)	0.2 (0.0-2.6) **
LBW at term†	1/62 (1.6)	3/77 (3.9)	0.4 (0.0-4.0)	0.4 (0.0-3.7)
Preterm birth‡	8/70 (11.4)	6/82 (7.3)	1.6 (0.5-5.0)	2.4 (0.6-9.5)
CAs	3/71 (4.2)	5/86 (5.8)	0.7 (0.2-3.1)	0.8 (0.2-3.8)

* LBW=birth weight less than 2500 g. † LBW among children born at term (≥ 37 weeks of gestation). ‡ Preterm birth=gestational age less than 37 weeks
§ missing data are excluded from total numbers

¶ adjusted for mother's age (continuous variable), parity (1 or more than 1), maternal smoking during pregnancy (yes/no), use of drugs during pregnancy (5-ASA, local or systemic steroid or immunosuppressive drugs, yes/no), disease duration of CD (< 5 years, ≥ 5 years) and calendar period of birth (1977-85, 1986-95, and 1996-2005) in a logistic regression model.
** also adjusted for gestational age (continuous variable)

Studies on women with CD and the existing literature
Since the 1980s several epidemiologic studies have been conducted to investigate the association between CD and adverse birth outcomes (3,4,45,73-79;91) (Enc., Table 3), but several studies did not estimate the risk of specific birth outcomes (3,4,73,77,91). It is most often reported that children born to CD women have increased risk of preterm birth (45,73-76,78,79) and LBW (45,75,76,79) when compared to controls in the general population. However, the epidemiological studies, addressing the risk of specific birth outcomes in women with CD, did not examine an effect of disease activity per se, on birth outcomes (45,74-76,78,79) – or a possible impact of therapeutic drug therapy. Also in the most recent and comprehensive meta-analysis by Cornish et al. (81) neither disease activity nor therapeutic drug therapy was analyzed as confounders (92).
Study VII is the first study to combine the power of a dataset containing national discharge diagnoses of CD, outpatient visits, and national birth data combined with a national prescription database (92). The most worrisome results are the increased risks of preterm birth and CAs among CD women prescribed AZA/6-MP during pregnancy. The result must, however, be interpreted with caution as we have only a proxy measurement of disease activity - estimating that 6% had disease activity during pregnancy. The proxy measurement of disease activity may mainly include those with the most severe disease activity, which in our proxy measurement are those who need hospital admission.
Study VIII is the first epidemiological study of the risk of adverse birth outcome in CD women with disease activity during pregnancy, compared to the outcome in CD women with no activity; and in which a concomitant effect of drug therapy and other confounders have been taken into consideration. The evidence for a possible role of disease activity in determining different birth outcomes has been restricted to case-series (37,42,43), and a few small studies with no estimation of the risk of specific outcomes and no possibility of confounder control (3,5,59). Study VIII provides some evidence for the role of disease activity in determining birth outcomes, and our data might be especially useful because we have also considered a possible impact of concomitant drug therapy. Although we do have problems with low statistical precision, these first data on the impact of disease activity in CD pregnancies suggest that disease activity contributes only to an increased risk of preterm birth.

4. METHODOLOGICAL DISCUSSION

CHOICE OF STUDY DESIGNS

In this area of research, on birth outcomes in women with IBD and a possible influence of drug therapy, randomized trials cannot be performed and are not proper due to ethics. Most of the studies in this thesis were designed as cohort studies (study I, IV, V, VI, VII, VIII), which are generally considered less prone to distortion than even well-conducted case-control studies (93). Cohort design reduces the probability of selection and information bias. Despite the virtual completeness of the cohorts (established in a population-based fashion), the completeness of follow-up, and outcome data in high-quality national administrative registries, some possible limitations need considerations.

Methodologically, pharmacoepidemiological research has considerable requirements for the amount and quality of data – e.g., with respect to the challenge of estimating the risk of rare specific types of CAs (94). Such studies of teratogenesis require special attention as CAs cannot be regarded as a single homogenous outcome, because exposure to a teratogen does not uniformly increase the rates of all CAs, but rather tends to increase the rates of selected CAs (94). Since cohort studies can only detect considerable increases in the risk of specific defects, most cohort studies are limited in their ability to provide assurance of safety. Cohort studies of limited size, however, may still be valuable, because such studies may i) examine the development and incidence of many different CAs over time, ii) give suggestions for the magnitude of possible positive associations for CAs, iii) record prospective information on drug exposure before the diagnostic process of CAs, and iv) record a precise time of drug exposure according to gestational age. Therefore, when cohort studies of a limited size are used, we cannot expect to see CAs belonging to the same organ systems. Such a finding, suggesting that all CAs belong to the same organ system or to one specific type of CA in a cohort study, would require an extremely strong teratogenic potential – maybe even a stronger potential than was seen for thalidomide in the past (48). Such a teratogenic potential is not expected. Therefore, ideally, studies of specific rather than overall rates of CAs should be performed, and that is most rationally done in case-control designs (study II and III).

COHORT STUDIES

Establishment of cohorts
Persons who enter an exposed cohort must have the factor investigated, and our population-based approach dictates us to include all possible exposed in a nationwide or countywide fashion. A population-based approach is possible in Denmark due to free access to a tax supported health care system and because of a unique availability of county and nationwide registries. The HDR records more than 99% of all hospital discharges for somatic diseases (95), and we had access to the obligatory registration from Danish hospitals since 1977 and all

outpatient visits since 1994. In addition, we had access to data on out-patient drug prescriptions since 1 January 1995 from the nationwide prescription database, maintained by the Danish Medicine Agency. We used these unique Danish possibilities to identify women with UC or CD, and to identify cohorts of women who were given therapeutic drugs in pregnancy.
The completeness of diagnoses of UC and CD in the HDR have been examined in a Danish study using the pathology system as a reference standard (96) – showing that of all patients, with a confirmed diagnosis of CD or UC, 94% were included in the HDR (96). In the studies of this thesis, only women who have been hospitalized or have been out-patients were included in the exposed cohorts, and thus some women with IBD may not have been included if they were diagnosed and treated solely by the general practitioner. However, we expect that the vast majority of IBD patients are included because general practitioners by principal rule refer the patient to hospital for exact IBD diagnosis, treatment, and surveillance.
Our pharmacoepidemiological cohort studies were based on complete prescription databases (county- or nationwide) because of the computerized accounting systems sending key data directly to the prescription databases. Using the CPR, we were able to obtain the prescription history of each woman diagnosed with the disease under study, and could classify the time of drug prescription according to gestational age. The prescription databases do not include data on over-the-counter sale, but all the drugs under study in this thesis are available only by prescription in Denmark.
In one study (study VIII) the cohort establishment in CD women was based on review of hospital journals according to disease activity. This classification was carefully carried out by each trimester and based on well-defined criteria for disease activity (62-64).

Due to our well-organized Danish national registries, we were able to use different kinds of unexposed cohorts, i.e., i) randomly selected national births (after matching) from the MBR, ii) all births in a county except for those whose mother took up drug prescriptions in pregnancy iii) births by women with no therapeutic drug use during pregnancy, iv) births by women with no use of the drug under study during pregnancy, but allowing use of other kinds of therapeutic drugs, v) births by women with similar diseases as the exposed, i.e. women using the drug under study, but outside pregnancy. In each study, one or more of these different unexposed cohorts were compared to the exposed cohort to illuminate different kinds of aspects, i.e., a possible influence of an underlying disease.

Selection bias
Our population-based (county- and nationwide), register-based, cohort studies prevent selection bias produced by differential patient recruitment as in hospital-based studies and incomplete follow-up.

Misclassification of exposure
In epidemiological studies, risk estimates, close to unity may indicate non-differential misclassification of the exposure – a misclassification of exposure that is unrelated to the occurrence of outcome. In our register-based studies, very detailed measurements of exposure are usually impossible to assess, and some misclassification of exposure may occur. As for the vast majority, misclassification of our exposure is unrelated to the outcome, and in our studies with two exposure levels such a misclassification will bias the risk estimates towards the null hypothesis. This means that, if a non-differential misclassification is severe, it will tend to produce estimates of the effect that are diluted, or closer to the no-effect than the actual effect. In our studies, this would obviously be a problem as the studies in that case would not assess the real effect of the exposure (giving false reassuring results).
We have more reasons to believe that there is no major misclassification of the diagnoses of UC and CD. Firstly, in study I, VII and VIII we minimized the risk of misclassification of diagnoses of UC and CD by excluding those with both discharge diagnoses of UC and CD according to their discharge history (taking diagnoses of both diseases as an indication of diagnostic uncertainty). Secondly, the validity of diagnoses was examined in a Danish study, and the overall validity of the CD diagnosis in the HDR was 97% and for UC 90% (96). Most patients with CD and UC were diagnosed at specialized departments, and when diagnosed here the validity of UC diagnosis increased to 94% (96). Thirdly, in study VIII the diagnosis of CD was validated by review of the medical records.
One of the strengths in the pharmacoepidemiological studies is that the exposure measurements are based on prescriptions and not on recall, as drug exposure based on self-reported use may lead to severe recall bias or under-ascertainment (97). The used data from the prescription databases are of high quality as a result of direct computerized transfer of information when a prescribed drug is dispensed at a pharmacy. However, we used redeemed drugs as a proxy measurement of drug intake. A prescribed drug, even if it is redeemed, need not be taken, or it may be taken by someone else; but a patient noncompliance, regarding drug use, would tend to underestimate our risk estimates. There are more arguments for a possible non-differential misclassification to be faint: i) there is no over-the-counter sale of the drugs under study, ii) the patients have paid for part of the costs for the drugs, which increases the likelihood of compliance, and probably most importantly iii) these chronically sick patients have a high incentive for daily medication for symptom-relieve. Prescription databases have thus been found to be of great value for drugs prescribed for serious diseases that need continuous treatment (47), such as UC and CD.
While collecting data on disease activity in study VIII, the registrar was blinded for the birth outcome, preventing an influence of the score for disease activity when knowing the birth outcome.

Misclassification of outcome

In these register-based studies the outcome data were obtained independently of the hypotheses investigated, and independently of exposure measurement preventing differential misclassification of the outcome measurement.

Outcome data from the MBR are reported of high quality (98-100), and valid for birth weight, birth complications, and parity (99,100). Data on gestational age have been found less valid because the MBR recorded gestational age longer (by one week) than in the medical records, and the distribution of discrepancies in gestational age was the same whether the birth was term or preterm (100). However, this misclassification is probably non-differential between exposed and unexposed pregnancies.

Regarding CAs, detailed information was obtained from the HDR, and the predictive value and completeness has been calculated as 88.2% and 89.9% which makes general surveillance and epidemiological research on CAs acceptable (68).

A non-differential misclassification of our binary outcome measurements cannot be ruled out, but in most situations such misclassification is independent of other errors producing bias toward the null (93).

CASE CONTROL STUDIES

Establishment of cases and controls

The thalidomide catastrophe (48) prompted two Hungarian pediatricians to suggest a registration of cases with CAs. This lead, in 1962, the Ministry of Health to order an obligatory notification of all CAs by physicians, and the HCAR was established – the first national-based CA registry in the world (69). Due to the enormous work with continuous evaluation of all CA cases, Dr. Andrew E. Czeizel was given the head functions of the HCAR in the National Institute of Public Health; and thanks to his dedicated effort, the HCAR became a huge success. The case-control data set from Hungary is unique for several reasons (69,70,101,102): i) it is population-based, ii) cases and controls are drawn from an ethnically homogeneous population (European Caucasian) decreasing the possibility for influence of etiological and phenotypic heterogeneity and increasing the generalizability, iii) it includes 90% of all major CAs between 1980 and 1996, iv) cases include malformed live born children diagnosed to the age of one year, malformed stillborn fetuses, and selectively terminated malformed fetuses after antenatal diagnoses, v) due to the large number of cases it is possible to divide CAs into 25 CA groups for analyses, vi) matched controls are drawn from the national birth registry of the Central Statistical Office in Hungary, vii) detailed information on exposure according to gestational age, and viii) detailed information on several confounders.

Selection bias

The particular susceptibility of case-control studies to selection bias arises because of the need to obtain samples of both cases and controls. Unless each sample is obtained without regard to exposure, the results may be biased (103). The case-control studies (study II and III) are population-based, which reduces the possibility of selection bias as cases and controls derive from the same source population and exposure histories of controls are more likely to reflect those of persons without the disease of interest. However, exposure data were only available for 85% of cases and 69% for controls (70,102). District nurses visited and questioned non-respondent case families, but were not allowed to contact non-respondent population controls, because the Ethics Committee in Hungary considered this to be disturbing to the parents of healthy children. Some influence of selection bias can therefore not be ruled out if the selection was associated with the exposure. However, in a sample, 200 population control families with no response were visited and questioned, and the occurrence and distribution of drug use during pregnancy did not differ from the pattern of control pregnant women who responded (102).

Misclassification of exposure

Self-reported information on exposure may lead to recall bias – resulting in either an under- or overestimation of the true OR (47,71). If mothers of children with CAs were more liable to remember accurate exposure information than mothers with healthy children, there was a risk of overestimating the risk of CAs. However, in study II and III some conditions speak against a strong influence by recall bias: i) we did not see a general increased risk of selected CAs, ii) the magnitude of some of the associations, iii) exposure data were not only collected from questionnaires but also from the antenatal care logbooks (including written records of recommendations from the obstetricians). A study on the role of recall bias has been carried out within the HCCSCA (71). This study showed that recall bias was mainly present for drugs used for short periods, that severe or visible CAs did not appear to be more conducive to recall bias than other abnormalities, and that the case-control surveillance system may cause spurious associations with biased ORs up to a factor of 1.9 (71).

The advantage of the Hungarian data in study III was that exposure information was not only based on self-reported information, and that the medical therapy examined was long-lasting therapy for chronic disease. Therefore, we do not believe that severe information bias has influenced our results, but some influence can not entirely be ruled out.

Misclassification of outcome

A misclassification of CAs can virtually be ruled out because all cases of CAs were carefully reviewed and validated, based on a pathogenetically oriented classification (69). To improve the validity of CA diagnoses, medical records of diagnoses of CAs were reviewed by the HCCSCA headquarter (70). Some minor misclassification though may have occurred depending on the CA type (69); but any misclassification of the outcome is

most probably non-differential leading to bias towards the null.

CONFOUNDING

Birth outcomes in women with UC or CD

When examining birth outcomes in women with IBD several aspects have to be taken into consideration. One should consider not only the impact of an effect of the disease itself (UC or CD) on the risk of adverse birth outcome, but ideally also a possible confounder impact of therapeutic drug use according to gestational age, disease activity during pregnancy, other personal related factors (e.g., age, smoking, comorbidity), and socioeconomic factors. No population-based dataset covers all these varieties of information, and therefore our analyses can, of course only to some degree, estimate 'true' associations. Nevertheless, a possible impact of therapeutic drug treatment and disease activity will be discussed, since these aspects have drawn most attention in the last decades (54,92). Therapeutic drug use and disease activity are often closely related, and these two aspects are difficult, or maybe impossible, to separate. Use of drugs during pregnancy might be mapped at least to some degree of details, but the assessment of disease activity in pregnancy may be difficult for more reasons. Continuous details on disease activity are very difficult to map during months of gestation – the response in disease activity after introduction of new therapeutic drugs/changes in doses/new combinations of drug therapies etc. Furthermore, women with IBD may consider abdominal pain and/or altered bowel movements as a flare of the disease, instead of a possible consequence of pregnancy; and indexes used for scores of disease activity (e.g., CD Activity Index (104)), used in most therapeutic studies, have not been developed for pregnant women.

Therapeutic drug treatment during pregnancy may reflect a need for control of ongoing disease activity, and in that case an impact of disease activity should be taken into account. Therefore, in the most recent study on birth outcome in women with CD (study VII), disease activity was considered by use of a proxy measurement (hospital admissions due to CD). We might not, however, have controlled perfectly for an effect of disease activity in that study. Disease activity (the proxy measurement) was found to be an important confounder for the risk of preterm birth (decreasing the relative risk estimate after adjustment); and if we underestimated the proportion of women with disease activity due to a relatively strict proxy measurement, we might have overestimating the risk of preterm birth in study VII.

In the evaluation of the risk of adverse birth outcome in women with UC and CD several confounders were considered. We considered the influence of the following confounders: parity (study I, II, VII, VIII), mothers age at the time of delivery (study I, II, VII, VIII), gestational age (study I, VII, VIII), use of drugs (study II, VII, VIII), calendar period (study I, VIII), proxy measurement of disease activity (VII), smoking in pregnancy (VIII), and disease duration (VIII). Some factors were left out of the final models because they had little or no influence (marital status in study I, smoking, calendar period, duration of CD at the time of giving birth, and maternal chronic diseases in study VII).

In study II, the drug of choice for treatment of UC in Hungary was sulfasalazine, and in the study period, drug treatment with AZA/6-MP was not used for IDB treatment in Hungary. Therefore, our results on CAs cannot be confounded by use of AZA/6-MP. On the other hand, some influence by disease severity during pregnancy cannot entirely be ruled out. Severe disease activity was, however, not a major problem as no hospitalizations due to UC occurred during pregnancy. With respect to tobacco and alcohol use as possible confounders in study II, the former has not been identified as an independent risk factor for limb deficiencies, obstructive urinary CAs, or multiple CAs, and it is questionable whether alcohol consumption could be a confounder in some of these associations (105-107).

Theoretically, many other factors could be considered. Preterm birth, for instance, is thought to be a syndrome initiated by multiple mechanisms and an increasing number of factors are thought to interact to cause preterm birth (22,24,108), but in general, there is a lack of clear understanding of the pathophysiology and lack of understanding of how potential factors interact (22,108). Many maternal or fetal characteristics have been associated with preterm birth, including maternal demographic characteristics, nutritional status, pregnancy history, present pregnancy characteristics, psychological characteristics, adverse behaviors, infection, uterine contractions and cervical length, and biological and genetic markers (22,23). Equally, a variety of potential risk factors have been suggested as regards LBW; sociodemographic factors (e.g., ethnicity, social-economic level), maternal medical disorders before pregnancy (e.g., hypertension, glucose metabolism disorders), risks of current pregnancy (e.g., gestational diabetes, maternal nutrition, placental causes), health care, environmental and behavior risks (6,10,23). In our analyses of preterm birth and LBW, we had no possibility to determine whether some of these factors could be confounders.

In conclusion, the most critical aspect regarding confounder adjustment in the studies on birth outcomes in women with UC or CD is probably the relative lack of very detailed information on therapeutic drug intake (e.g., drug dose) and concomitant details on disease activity.

Birth outcomes after therapeutic drug exposure

In the pharmacoepidemiological studies on the use of 5-ASA, sulfasalazine and AZA/6-MP during pregnancy we have similar considerations of the influence of confounders. To minimize the impact of different underlying diseases, treated with a specific drug, it is most appropriate to study the associations within sub-cohorts of women with the same underlying disease. Whenever possible, sub-analyses were made according to different underlying diseases (study V). However, for various reasons such distinctions were not always possible: i) the

type of underlying disease could not be determined based on discharge diagnoses – and therefore based on our best assumption (study VI and VII), ii) no access to further details on the type of underlying disease (study IV), and iii) the number of exposed women did not allow stratification for the type of underlying disease (study VI and VII).
An influence of other confounders was also considered. Smoking was considered whenever possible (study III, V, VI, VII), and so was parity (study III, IV, V, VI, VII), mothers' age at the time of delivery (study III, IV, V, VI, VII), gestational age (study III, V, VI, VII), use of other potentially harmful drugs (study IV, V, VI, VII), and comorbidity (study III, IV).
Most of the methodological comments on other possible confounders for different adverse birth outcomes were addressed in the previous section.
The most critical aspect regarding confounder adjustment in the studies on birth outcome after therapeutic drug exposure is probably the lack of detailed information on drug dose, co-medication, disease activity, and that sub-analyses could not always be performed according to the type of underlying disease.

CHANCE

The possibility that positive results obtained in a study are due to chance can never be excluded. It has become customary to attach special significance to P values falling below 0.05 (1 in 20), because it is generally agreed that a chance less than 1 in 20 is a small enough risk of being wrong. Regarding the risk of chance findings of the studies in this thesis i) the conducted studies were all based on a priori hypotheses, ii) the assessment of the role of chance was "estimation" as the statistical method (instead of "hypothesis testing and P values") to estimate that range of values that were likely to include the true value, and thereby assessing the CI giving information about statistical power, and iii) the 95% CI gave the information that the true value was most likely to be close to the point estimate, less likely to be near the outer limits of the interval, and could (5 times out of 100) fall outside these limits altogether. When making many sub-group analyses, problems with multiple comparisons may arise. In our studies, however, analyses were based on a priori hypotheses, and the associations under study were not examined according to hypotheses to be accepted or rejected on the basis of P values, but, on the contrary, on estimation with attended CI (109).

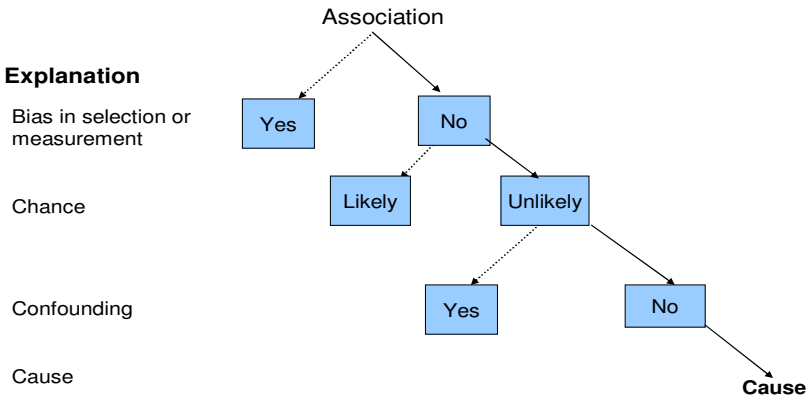
Analyses

The types of analyses are described in the Material and Method section, and here I will add only a few general comments. Most clinical phenomena, as examined in the studies of this thesis, are the results from many variables acting together in complex ways. Most of the studies in this thesis were performed as simple analyses to get insight in the relationships by first doing stratified analyses and to reveal possible effect modification. Modeling, however, has become an essential part and regular feature of modern analyses in clinical epidemiological studies; and there is no other way to adjust for or to include many variables at the same time. We included confounders in the models based on the "change-in-estimate" method (93), and generally, before possible confounder variables were included in the model, we performed stratified analyses. The "change-in-estimate" method makes the analyst able to decide the cut-off for what constitutes an important change in the estimate, based on a biological rational. In some situations a change of more than 5% might be considered important and relevant, and in other situations only a 10% change is considered important. In the studies of this thesis, confounders were generally included if accounting for a change of 10% or more. This technique for selecting confounders is in contrast to other methods where statistical tests are used to select confounders. Hosmer-Lemeshow tests for model controls were used for assessing the fit of logistic regression models (110).

CAUSALITY

In clinical medicine, it is not possible to prove causal relationships beyond any doubt, because the understanding of the relationships is based on empiric evidence and at least theoretically, it is possible that new evidence could change our understanding (109). A postulated cause-and-effect relationship should be examined in as many different ways as possible, and this usually means that several studies must be performed to build evidence for or against cause. Not all associations are causal, and figure 2 outlines other reasons for association that must be excluded. Therefore, one has to consider if an apparent association is real or merely an artifact of the study because of bias, random variation, or confounding.

Figure 2. Association and cause



From Fletcher and Fletcher: Clinical Epidemiology - the essentials

When considering a possible causal relationship, the strength of the research design used to establish the relationship is an important piece of evidence. The best evidence for a cause-and-effect relationship comes from well-conducted randomized trials. Well-conducted cohort studies are the second best design, because they can be performed in a way that minimizes biases. Especially in areas of research, like this, where randomized trials are not available, several features increase the likelihood that an association is causal. The British statistician Austin Bradford Hill proposed a set of features that should be sought when deciding whether a relationship is causal (111). With some modification to observational studies these criteria include: Temporality, strength, dose-response, reversibility, consistency, biologic plausibility, specificity, and analogy. The individual criteria are not all of equal weight; and he also stated that none of the standards can bring indisputable evidence for or against the cause-and-effect and none can be required as sine qua non (111). Some of the Hill features have already been discussed in relation to the studies in this thesis – temporality, consistency, and specificity.

As regards plausible biological mechanisms for adverse birth outcome in women with IBD, different explanations exist. It is not surprising that women with IBD might have a greater risk of adverse birth outcome – caused by factors related to the underlying chronic disease itself, disease activity, or the medication used. More pathophysiological mechanisms, related to the *disease itself*, have been proposed; increased intestinal permeability, vascular abnormalities, infectious agents, abnormal immunologic response, auto-antibodies, abnormal absorption of antigens and pro-inflammatory molecules. Furthermore, some degree of malnutrition might be seen in patients with CD; and if the fetus suffers during stages of maternal malnutrition (proteins and calories) evidence from animal studies support the findings of an increased risk of adverse birth outcome (112-115).

There are more biological arguments for women with *disease activity* to be subject to preterm birth compared to women with inactive disease. This also implies that factors related to disease activity might be crucial for the risk of preterm birth. The exact underlying biological mechanisms, which may have impact on preterm birth, are mainly speculative. However, there is hardly any doubt that inflammatory mediators play an important role in the control of myometrial function during labor (18,54). Such mediators (e.g., plasminogen activators and proinflammatory cytokines) may thus be involved in tissue remodeling of the uterus during labor (18), and thereby facilitate cervical dilatation and passage of the fetus. Furthermore, leukocyte products may stimulate uterine contractions by facilitating the production of uterotonic prostaglandins (18). It is also possible that active disease stimulates preterm birth as a result of nutritional deficiency.

Related to the causation of adverse birth outcome after use of *medical agents* several plausible biological mechanisms exist, and a possible role of sulfasalazine and AZA/6-MP will be mentioned.

Sulfasalazine is composed of 5-ASA joined to sulfapyridine by an azo-linkage, and is broken down in the colon into its component parts. Sulfasalazine and its metabolite, sulfapyridine, readily cross the placenta, and the fetal concentrations are approximately the same as the maternal concentrations (116-118). Sulfapyridine has a bilirubin-displacing ability, and, furthermore, it acts as a competitive inhibitor of the enzyme dihydropteroate synthase in the folate metabolism (119,120); this may lead to deficiency of dihydrofolate and tetrahydrofolate, which are needed for the biosynthesis of DNA and RNA bases (guanine, adenine, thymine). It is generally believed that folate deficiency may result in impaired mitoses, cell death, and subsequent CAs for a subset of pregnant women (121).

After absorption, AZA, an inhibitor of purine metabolism, is rapidly converted in the liver into a number of metabolites, including the active metabolite 6-MP (122-124). There are no data to suggest that AZA and 6-MP

have different efficacy profiles, and both drugs are usually discussed together with regard to their efficacy and safety (125,126). Both drugs cross the placenta, and amounts of 6-MP can be measured in fetal blood (58,123,126). In theory, the fetus is protected from the adverse effects of AZA in early pregnancy as its liver lacks the enzyme, inosinate pyrophosphorylase, that converts AZA to its active metabolites, and only trace amounts of its metabolites are detected in fetal serum (58,127,128). Maternal AZA/6-MP treatment during pregnancy is clearly teratogenic in animals, at doses similar to or greater than those used in humans, with CAs like cleft palate, hydrocephalus, limb deficiencies, skeletal defects, and ocular anomalies (58,90,129-131). Furthermore, supported by animal and human data (on renal transplant recipients only), the use of AZA in pregnancy may be related to IUGR (58,130,132,133). The mechanisms by which AZA and 6-MP or their metabolites induce teratogenicity are not known (90). Two mechanisms have been proposed: 1) inhibition of nucleic acid synthesis, or 2) alteration of maternal zinc metabolism (90). Numerous in vivo and in vitro studies have demonstrated that 6-MP is incorporated into the nucleic acids of human and other mammalian cells, and that this incorporation is the key mechanism of cytotoxicity (90). Zinc is essential to many enzyme systems that influence DNA and RNA synthesis, and cell division and proliferation. In rats, maternal zinc deficiency can produce fetal CAs very similar to those caused by maternal treatment with 6-MP; and therefore, it has been suggested that the teratogenic effect of 6-MP may be mediated through embryonic zinc deficiency (90).
The mechanisms of teratogenicity and mutagenicity, and the risks associated with them, are distinct. Teratogenisis occurs when an initially normal embryo or fetus is damaged while it is developing, usually by an exposure that the mother sustains while she is pregnant; and teratogenicity affects many cells of the developing organism. Furthermore, the severity of teratogenic effects increase with the dose and the number of cells affected. In contrast, mutation results from DNA damage within a single cell. Germ cell mutations occur when there is damage to the DNA of the sperm or oocyte. If an individual is conceived from a sperm or oocyte containing a mutation, the mutation will be copied into every cell of that individual's body. Only a single event is required for mutation to occur and a potential mutagenic risk may therefore exist at any dose. Because AZA/6-MP interferes with nucleic acid synthesis, treatment with these drugs might produce germ cell mutations as well as teratogenic effects (90). Mutations that occur in the germ cells of a treated parent could result in chromosomal abnormalities or a new dominant disease in children who are conceived. Such effects would be more likely to occur after treatment of a man than of a woman because DNA synthesis in oogenesis is restricted to embryonic and fetal life. Mutation of germ cell precursors could also occur during embryogenesis (associated with treatment of the mother during pregnancy), but any chromosomal abnormalities or new dominant diseases produced would occur in her grandchildren, not in her children. AZA/6-MP have found to be mutagenic in various mammalian in vitro and in vivo assays (89,134,135); and damage occurred in the early stages of spermatogenesis, mainly affecting the late differentiating spermatogonia and early spermatocytes (90). The mechanisms behind a possible paternal drug effect on birth outcome may thus include: i) genetic or chromosomal damage of the spermatocytes; ii) drugs or metabolites in seminal fluid that might have an impact on sperm maturation and/or a direct effect on the uterus; iii) a systemic effect of the drug or metabolites on the female herself by absorption through the vaginal mucosa (90,136,137).

5. CONCLUDING REMARKS AND FUTURE STUDIES

WHAT DOES THIS THESIS CONTRIBUTE OF KNOWLEDGE?

Exceeding the studies included in my previous PhD thesis, this thesis provides new evidence on the following subjects: i) the risk of selected CAs in children of women with UC, ii) pharmacoepidemiological studies on the risk of adverse birth outcome after maternal AZA/6-MP exposure in pregnancy, and the risk of CAs in children fathered by men treated with AZA/6-MP before conception, iii) the risk of adverse birth outcome in women with CD according to type of anti-inflammatory drug treatment in pregnancy (sulfasalazine/5-ASA, steroids or AZA/6-MP), and iv) the impact of disease activity in women with CD on adverse birth outcome.

THE BURDEN OF PREGNANCY-RELATED CHALLENGES AMONG IBD PATIENTS

The risk of adverse birth outcome in women with IBD, and aspects of the safety of anti-inflammatory drug therapy, will remain an issue of significant importance for clinicians (e.g., gastroenterologists, obstetricians and neonatologists). For decades, neither the frequency of IDB has declined nor the frequency of adverse birth outcome. The incidence of both CD and UC is increasing in Denmark as in many other countries worldwide (138-140); and despite improvement in many health indicators, the rate of preterm birth has not decreased over the last three decades (22,23). On the contrary, the preterm rate has increased in most industrialized counties, e.g., in the USA from 9.5% in 1981 to 12-13% (22), and in Europe and other developed countries reported rates are generally 5-9% (22).
Besides the challenges of increasing incidence of IBD and certain adverse birth outcomes, there is a continuous need of knowledge of the safety of anti-inflammatory therapy. The latter applies to both medical agents that have been used for decades (those agents studied in this thesis but also ciprofloxacin, metronidazole, and cyclosporine) and for new biological agents more recently introduced (e.g., Infliximab (54,141)). Therapeutic drug treatment, and developing guidelines for the use of medications in pregnancy, poses unique challenges. According to the American's Food and Drug Administration sulfasalazine, mesalzine (5-ASA), olsalazine (5-ASA), and AZA/6-MP are classified as Pregnancy Category B, B,

C and D drug, respectively (142) (Enc., Table 6) –a classification based on available evidence of the safety of drugs used in pregnancy. Overall, the absence of randomized control trials limits the conclusion that can be drawn and maintains the controversy on therapeutic drug treatment in pregnancy.

STUDIES ON WOMEN WITH UC

Our results on birth outcomes in women with UC were mainly reassuring as we did not find an increased risk of LBW, IUGR or overall increased risk of CAs (summary in table 19). We did find an increased risk of preterm birth, if the birth occurred in the period of 0-6 months after establishing the diagnosis of UC. This increased risk might perhaps be explained by disease activity around the time for making the UC diagnosis. We also found an increased risk of some selected CAs (e.g., limb deficiencies and obstructive urinary CAs). These associations have not been examined in other studies, and the findings need to be clarified or confirmed in future studies. Our results regarding stillbirth and perinatal mortality suffered from low statistical precision due to few events, and no conclusions can be made.
To illuminate further details on birth outcome in women with UC it is necessary to establish larger cohorts of women, and most valuable would be data from a prospective pregnancy registry (including details on therapeutic drug treatment and disease activity). Thus, the current problem in assessing more detailed results is restricted to lack of appropriate data.

PHARMACOEPIDEMIOLOGICAL STUDIES (INCLUDING WOMEN WITH UC AND CD)

Regarding exposure to ***sulfasalazine*** during pregnancy our results were reassuring as we did not find significantly increased overall relative risk of CAs; and also the analyses of the prevalence of selected CAs showed no significantly increased risks (summary in table 19).

Our results on birth outcomes in women exposed to ***5-ASA*** during pregnancy were mainly reassuring as we did not find significantly increased relative risk of LBW, IUGR or overall increased risk of CAs (summary in table 19). Our data suggested a significantly increased relative risk of preterm birth and stillbirth in UC women who took up prescriptions for 5-ASA, compared to pregnant women who had not been prescribed any kind of reimbursed medicine in pregnancy. The risks of preterm birth and stillbirth were still increased after comparing to IBD controls not taking 5-ASA in pregnancy. More data are needed to determine whether 5-ASA actually plays a role for the risk of preterm birth or stillbirth in women with UC – or the positive associations found in our study are influenced by confounding by disease activity, especially.

Our results after ***maternal AZA/6-MP*** use in pregnancy suggested increased relative risks of preterm birth, CAs, and perinatal mortality (summary in table 19) – also after using controls with similar underlying diseases.

These were the first data from a controlled observational study on exposed IBD patients, and similar findings have recently been reported in a Swedish nationwide study suggesting an increased risk of preterm birth, CAs, and LBW. The main disadvantage of our study, and the Swedish study, is probably the lack of adjustment for disease activity; and it is difficult to rule out that some of the associations may be confounded. From study VIII, however, we learned that disease activity is not necessarily an important confounder since disease activity had virtually no influence on the risk of CAs.

As regards the risk of CAs, maternal AZA/6-MP treatment during pregnancy is clearly teratogenic in animals, and given the animal data one must assume that some risk exists with chemotherapeutic doses of AZA/6-MP in early pregnancy. Based on the available human data a teratogenic effect of AZA/6-MP cannot be ruled out; but the data, although limited, suggest that the risk of CAs is not great. Still, the evidence of the reproductive safety of AZA/6MP exposure in IBD pregnancies is limited; and to improve the quality of the results we need large unselected cohorts of AZA/6-MP exposed women for whom detailed information on drug therapy, co-medication, disease activity, and other relevant confounders exists. Accurate prescription registries can be used, as used in Danish and Swedish studies, but the information must be supported by review of the medical records to obtain information on clinical details. A chart review of this magnitude would, however, be a monumental task. Therefore, alternatively, adverse birth outcomes would be better examined by a prospective pregnancy registry. Very little is known about potential long-term health consequences, and therefore, an appropriate focus for future research is long-term studies of children born after parent exposure to AZA/6-MP before or during pregnancy. Thus, still less has been reported as to whether AZA/6-MP given to mothers at any point prior to, but not during, pregnancy can present a risk to the fetus (90,143). Such studies could very well be conducted in the Scandinavian countries because we are able to study long-term events in our registries.

Regarding preconceptional ***paternal use of AZA/6-MP*** we found an increased risk of CAs, although not significant (table 19). Because AZA/6-MP interferes with nucleic acid synthesis, treatment with these drugs might produce germ cell mutations as well as teratogenic effects; and both AZA and 6-MP have been found to be mutagenic in various mammalian. The number of reported children conceived by men treated with AZA/6-MP is far too small to draw conclusions regarding a possible mutagenic effect; and large populations are required to detect even a small increase in germ cell mutation. The limited data available suggest that the risk of CAs associated with preconceptional treatment with AZA/6-MP is likely to be increased only slightly, if at all.

STUDIES ON WOMEN WITH CD

In CD women with the highest degree of disease activity during pregnancy, the risk of preterm birth was significantly increased (table 19).
Furthermore, our overall results showed that the risk of adverse birth outcome in CD women varied according to therapeutic drug treatment in pregnancy (summary in table 19). The results on sulfasalazine/5-ASA and steroids were reassuring regarding the risk of LBW, LBW at term, preterm birth, and CAs. The most worrisome results were a four-fold significantly increased risk of preterm birth and a threefold increased risk of CAs (not significantly increased) among CD women prescribed AZA/6-MP in pregnancy. In the analyses of CD women we found that disease activity was an important confounder in the association between AZA/6-MP and preterm birth; and if we have underestimated the proportion of women with disease activity, we may not have fully adjusted for an impact of disease activity – thereby overestimating the risk of preterm birth. A similar argument can hardly be applied to the relative risk of CAs, as disease activity showed virtually no confounding effect on the association between AZA/6-MP and CAs in CD women.
To illuminate further details on birth outcomes in women with CD (according to the impact of therapeutic drug treatment and disease activity) it is necessary to establish larger cohorts of CD women, e.g., in a prospective pregnancy registry. The current problem in assessing more detailed results on birth outcome in women with CD is related to lack of data on large unselected cohorts for whom detailed information on e.g. disease activity and drug therapy exists.

COUNSELING THE PREGNANT PATIENT

Until prospective, unbiased information arrives, the best advice is to recognize the limitations of our knowledge and carefully counsel each individual patient on the potential risks of IBD and its therapies during pregnancy. In all cases, therapy has to be individually assessed as to the potential risks of the fetus versus the therapeutic benefit. Categorized as a D drug by the American's Food and Drug Administration, the association between the use of AZA/6-MP during pregnancy and the risk of CAs has drawn the most attention. Women of reproductive age, who must be treated with AZA/6-MP, should be advised about a potential teratogenic and mutagenic risk of these drugs. However, a woman's risk giving birth to a child with CAs will also depend on her state of health, underlying disease, other potentially adverse exposures, pregnancy, and family history. An individual's risk should also be presented with reference to the background risk of CAs that attends every pregnancy, but because of her illness, the background risk for a woman who requires treatment with AZA/6-MP will probably be higher than the 3-5% that is usually quoted for the general population.
In general, pregnancies in women who require AZA/6-MP and/or other anti-inflammatory drug treatment require careful, coordinated perinatal and medical care. Detailed fetal ultrasound examination can be used to screen for many serious CAs and also to monitor fetal growth. Despite the potential risks associated with anti-inflammatory drug treatment in pregnancy, such drugs enable some chronically ill women to have healthy children.

Table 19. A table of the main results of the studies included in the thesis. The conclusions are given according to the outcome after analyses in logistic regression models, and the word "risk" refers to a relative risk estimate

	Birth outcome					
	LBW	LBW at term (IUGR)	Preterm birth	CAs (overall)	Selected CAs	Stillbirth/ perinatal mortality
Exposure of interest						
Women with UC	no increased risk	no increased risk	significantly increased risk in special period	no significantly increased risk	significantly increased risk of some CAs	
Sulfasalazine				no significantly increased risk	no significantly increased risk	
5-ASA	no significantly increased risk	no increased risk	significantly increased risk in UC women	no significantly increased risk		significantly increased risk in UC women
Maternal AZA/6-MP	no significantly increased risk		significantly increased risk	significantly increased risk		significantly increased risk
Paternal AZA/6-MP				no significantly increased risk		
Women with CD + 5-ASA / sulfasalazine	no significantly increased risk	no significantly increased risk	no increased risk	no increased risk		
Women with CD + steroid	no increased risk	no increased risk	no significantly increased risk	no increased risk		
Women with CD + AZA / 6-MP	no increased risk	no increased risk	significantly increased risk	no significantly increased risk		
Disease activity in CD women	no increased risk	no increased risk	significantly increased risk	no increased risk		

6. SUMMARY

The clinical epidemiological studies included in this thesis fall into three parts. The first part includes studies on birth outcome in women with ulcerative colitis. The second part includes pharmacoepidemiological studies on birth outcome after anti-inflammatory drug therapy in pregnancy, including patients with ulcerative colitis and Crohn's disease. The third part (and the latest publications) includes birth outcome in women with Crohn's disease; and the methods of cohort establishment in these studies are developed and improved due to the knowledge gathered from conducting the earlier studies.

The birth outcomes in women with ***ulcerative coli*tis** are examined in a nationwide, Danish, cohort of women based on data from the Danish National Hospital Discharge Registry and the Danish Medical Birth Registry, and within a Hungarian case-control data set. Our data suggest

- Significantly increased risk of preterm birth when women give birth 0-6 months after establishment of the diagnosis. It is considered whether the increased risk may be influenced by disease activity around the time of establishing the diagnosis.
- No increased risk of giving birth to children with low birth weight, intrauterine growth retardation or congenital abnormalities (evaluated overall).
- Significantly increased risk of some selected congenital abnormalities (limb deficiencies, obstructive urinary and multiple congenital abnormalities). No other studies have examined the risk of selected congenital abnormalities in children born by women with ulcerative colitis.

The pharmacoepidemiological studies on birth outcomes after use of anti-inflammatory drug therapy in pregnancy, including women with ulcerative colitis and Crohn's disease, are based on data from the Hungarian case-control data set, a countywide Danish prescription Database, the Danish National Hospital Discharge Registry, the Danish Medical Birth Registry, and review of selected medical records.
After exposure to ***sulfasalazine*** during pregnancy our data suggest

- No significantly increased overall relative risk of congenital abnormalities and no significantly increased risks of selected congenital abnormalities.

After exposure to ***5-aminosalicylic aci***d during pregnancy our data suggest

- No significantly increased relative risk of low birth weight, intrauterine growth retardation or congenital abnormalities (evaluated overall).
- A significantly increased relative risk of preterm birth and stillbirth in ulcerative colitis women, compared to women with no prescription of reimbursed medicine in pregnancy – and also after comparing with women with chronic inflammatory bowel disease not taking 5-aminosalicylic acid during pregnancy. It is not clear whether these associations are causal or influenced by confounding by disease activity in particular.

After ***maternal*** exposure to ***azathioprine/6-mercaptopurine*** during pregnancy our data suggest

- An increased relative risk of preterm birth, congenital abnormalities, and perinatal mortality – also after using controls with similar underlying diseases.

It is difficult to rule out an influence of uncontrolled confounding. These were the first published data from a controlled observational study on exposed women with chronic inflammatory bowel disease.

After preconceptional ***paternal*** use of ***azathioprine/6-mercaptopurine*** our data suggest

- An increased risk of congenital abnormalities, although not significantly increased.

The birth outcomes in women with ***Crohn's disease*** are examined in nationwide sub-cohorts classified according to type of anti-inflammatory drug exposure during pregnancy, and based on data from the Danish National Hospital Discharge Registry, the nationwide Danish Prescription Database and the Danish Medical Birth Registry. Furthermore, birth outcomes are examined in Crohn's disease women with disease activity during pregnancy, based on data from review of hospital records, the Danish National Hospital Discharge Registry and the Danish Medical Birth Registry. Our data suggest

- The risk of adverse birth outcomes in women with Crohn's disease varies according to the type of anti-inflammatory drug therapy in pregnancy.
- Reassuring results according to low birth weight, intrauterine growth retardation, preterm birth and congenital abnormalities after use of sulfasalazine/5-aminosalicylic acid or steroids.
- Worrisome findings of a significantly increased risk of preterm birth and an increased risk of congenital abnormalities (not significantly increased) after prescription of azathioprine/6-mercaptopurine during pregnancy.
  Some residual confounding by disease activity may have been left in the analyses of preterm birth.

In Crohn's disease women with disease activity during pregnancy our data suggest

- A significantly increased relative risk of preterm birth in women with the highest degree of disease activity during pregnancy.
- Disease activity does not seem to increase the risk of low birth weight, intrauterine growth retardation or congenital abnormalities.

This study is the first epidemiological study of the risk of adverse birth outcomes in Crohn's disease women with disease activity during pregnancy, compared to women with no activity during pregnancy, and in which confounders have been taken into consideration.

Exceeding the studies included in my previous PhD thesis, this thesis provides new evidence on the following subjects: i) the risk of selected congenital abnormalities in children of women with ulcerative colitis, ii) pharmacoepidemiological studies on the risk of adverse birth outcome after maternal azathioprine/6-mercaptopurine exposure in pregnancy, and the risk of congenital abnormalities in children fathered by men treated with azathio-

prine/6-mercaptopurine before conception, iii) the risk of adverse birth outcome in women with Crohn's disease according to type of anti-inflammatory drug treatment in pregnancy (sulfasalazine/5-aminosalicylic acid, steroids or azathioprine/6-mercaptopurine), and iv) the impact of disease activity in women with Crohn's disease on adverse birth outcome.

We learned from the studies in this thesis that the traditional way of reporting birth outcome in women with chronic inflammatory bowel disease, i.e. without having valid information on the type of underlying disease, concurrent therapeutic drug treatment and disease activity, is of limited value. The studies show that the risk of specific adverse birth outcome in women with ulcerative colitis and Crohn's disease depends on several factors including the time of birth in relation the début of disease, the type of underlying disease (ulcerative colitis or Crohn's disease), the type of anti-inflammatory drug treatment during pregnancy, and the degree of disease activity during pregnancy. At the same time one also has to realize that the existing evidence is still limited, especially in the field of reproductive safety after therapeutic drug treatment during pregnancy and possible effects of preconceptional therapeutic drug exposure.

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7. APPENDIX

Codes in ICD-8:
ulcerative colitis - 563.19 and 569.04
Crohn's disease - 563.01
CAs - 740.00-759.99
diabetes mellitus - 249.xx and 250.xx
epilepsy - 345.xx
cirrhosis/alcoholic liver disease - 571.xx and 303.xx

Codes in ICD-10:
Crohn's disease - K50.X
ulcerative colitis - K51.0, K51.1, K51.2, and K51.3
CAs - Q0.00-Q99.9
diabetes mellitus - E10-E14
epilepsy - G40 and G41
cirrhosis/alcoholic liver disease - F10, K70, K72-74, and K76

Prescriptions were identified according to ATC-codes:
A07E C02 mesalazine
A07E C03 olsalazine
A07E C01 sulfasalazine
H02A B06 prednisolone
H02A B07 prednisone
A07E A01 prednisolone
A07E A02 hydrocortisone
A07E A06 budesonide
L04A X01 azathioprine
L01B B02 6-mercaptopurine

8. ENCLOSURES: TABLE 1-6

Table 1. Birth outcome in women with ulcerative colitis (UC), an overview of the literature.

Included are English language studies that i) cover results according to the birth outcome after maternal diagnoses of UC, ii) include the specific outcome that are under study in this thesis (birth weight [BW], low birth weight [LBW], intrauterine growth retardation [IUGR], preterm birth, mortality, and congenital abnormalities [CAs]). Case-series are excluded. Included are studies that use internal comparisons within a cohort

Author, country, publication year	**Design**	**Separate analyses on UC pregnancies**	**Number of exposed UC pregnancies Number of controls**	**Risk estimates for adverse birth outcomes given?**	**Adjustment for confounders?**	**Most important results and conclusions**	**Comments**
Bortoli A et al (79) Italy, 2007	Cohort	Yes	67 live births by diagnosed UC women. 204 control births by women with other diseases than IBD. Collected information on disease activity and therapy but do not use this information according to birth outcomes.	Not for UC births compared to controls	No model adjustment.	Birth weight of neonates born to UC women was identical to that of neonates born to controls. Preterm: OR**=1.2 CAs: 3/67 (4.7%) in UC births and no CAs among controls. Disease activity at conception: 17/85 (20,0%). In pre-diseased pregnancies: no increased risk of preterm birth.	Risk of severe recall bias. All information on birth outcome, disease activity and treatment given by interviews in 1995-96 among births occurring form 1943-1996. No adjustment for drug therapy or disease activity. Data on birth outcomes not shown according to disease activity or drug therapy.
Elbaz G et al (78) Israel, 2005	Cohort	Yes, but only regarding preterm birth	79 UC pregnancies 508 non-IBD pregnancies	Yes	No model adjustment	Preterm: OR=2.0 (1.0-3.8)	No adjustment for drug therapy, disease activity or other confounders (e.g., age, parity, smoking, gestational age).
Bush MC et al (77) USA, 2004	Cohort	Yes	53 UC pregnancies Controls: 63 CD pregnancies	No	No	Compared to CD pregnancies: increased risk of preterm birth and LBW	No confounder adjustment for drug therapy, disease activity or other confounders.
Nørgård B et al (144) Denmark, 2003	Case control study	Yes	Cases: 22843, and 71 had mothers with UC. Controls: 38151, and 95 had mothers with UC.	Yes	Yes	CAs: OR*=1.3 (0.9-1.8) The risk of selected CAs was given. Increased risk of Limb deficiencies – OR*=6.2 (2.9-13.1) Urinary CAs – OR*=3.3 (1.1-9.5) Multiple CAs – OR*= 2.6 (1.3-5.4).	Adjusted for maternal age, parity, use of sulfasalazine and use of other drugs. More data are needed to determine whether the association between UC and certain selected CAs is causal or in influenced by bias.
Dominitz JA et al (76) USA, 2002	Cohort	Yes	107 UC pregnancies 1308 non-IBD controls	Yes	Yes	LBW: OR* = 1.1 (0.4-3.4) Preterm birth: OR* = 1.0 (0.4-2.5) IUGR: OR*= 1.7 (0.8-3.8) CAs: OR*=3.8 (1.5-9.8)	Confounder adjustment. No ability to adjust for drug therapy or disease activity.

Ludvigsson JF et al (75) Sweden, 2002	Cohort	Yes	26 UC births 10373 non-CD births	Yes	Yes in models.	LBW: OR*=1.60 (0.17-14.41) Preterm birth: OR*=1.82 (0.42-7.81)	Little sample size (exposed UC births), and imprecise risk estimates. No adjustment for drug therapy, or disease activity.
Nørgård B et al (80) Denmark, 2000	Cohort	Yes	1531 UC pregnancies 9092 non-UC controls	Yes	Yes in models.	BW, mean: UC 3458g (3438g in controls) LBW: OR* = 0.8 (0.6-1.2) IUGR: OR* = 0.7 (0.5-1.2) Preterm birth: OR*= 1.2 (0.9-1.5) Stillbirth: OR*= 1.9 (1.0-4.0) Perinatal mortality: OR*= 1.7 (0.9-3.0)	Large population-based study. No adjustment for smoking, drug therapy, or disease activity.
Baird DD et al (74) USA, 1990	Cohort	Yes	41 UC pregnancies 216 non-UC controls	Yes	Yes	Preterm: OR = 2.4* (0.8-6.9)	No adjustment for drug therapy, or disease activity.
Porter RJ et al (73) England, 1986	Cohort	Yes	44 UC pregnancies 88 non-UC controls (matched on age and parity)	No	Matching variables, no models	BW, mean: No significant difference was found Preterm birth: *OR** = 2.6* CAs: One among UC births No cases of perinatal deaths	No adjustment for drug therapy or disease activity.
Schade RR et al (72) USA, 1984	Cohort	Yes	16 UC pregnancies 103,881 control pregnancies	Yes	No	Increased risk of LBW:OR= 5.6 (1.45-21.74) No cases of perinatal deaths	Very few exposed (UC pregnancies). No confounder adjustment, not even for gestational age.

CD = Crohn's disease. UC= ulcerative colitis. OR = unadjusted odds ratio. OR* = adjusted odds ratio. OR** = OR not given in the paper, but a crude OR can be calculated from the figures in the paper. 95% CI = 95% confidence interval.

Table 2. Anti-inflammatory maternal drug exposure (AZA/6-MP, 5-ASA, sulfasalazine) in IBD patients and birth outcome, an overview of the literature.
Included are English language studies that i) cover results according to the birth outcome after specified anti-inflammatory drug exposure in IBD patient, ii) include the specific outcome that are under study in this thesis (birth weight [BW], low birth weight [LBW], intrauterine growth retardation [IUGR], preterm birth, mortality, and congenital abnormalities [CAs]). Case-series are excluded. Included are studies that use internal comparisons within a cohort

Author, country, publication year	**Design**	**Separate analyses on UC/CD pregnancies**	**Type of drug exposure Number of exposed Number of controls**	**Risk estimates for adverse birth outcomes given?**	**Adjustment for confounders?**	**Most important results and conclusions**	**Comments**
Cleary BJ et al (82)	Cohort	No	**AZA/6-MP** 476 exposed to AZA in	Yes	Yes, in models	CAs (control group 1): overall OR*= 1.41 (0.98-2.04)	Population-based large study from Sweden.

Sweden, 2009			first trimester (77% had IBD). Controls: 1) births without AZA exposure between 1995-2007, N= 1.180.974. 2) IBD group with other treatment than AZA in pregnancy, N=1739.			Ventricular/atrial septal defects: OR*= 3.18 (1.45- 6.04) CAs (control group 2): Only AZA exposed IBD patients OR*= 1.42 (0.93-2.18) Only AZA exposed IBD patients, compared to control group 2: Preterm birth – OR*= 1.57 (1.13-2.23) LBW - OR*=1.37 (0.99-2.01) SGA – OR*=1.38 (0.85-2.23)	Exposure information is solely from early pregnancy (first trimester). Estimates adjusted for year of birth, maternal age, parity, smoking, and BMI. The increased risk of adverse pregnancy outcomes did NOT disappear when women with similar underlying diseases were used as controls. No adjustment for disease activity.
Goldstein JH et al (53) Israel, Canada and Europe, 2007	Cohort	No	**AZA/6-MP** 189 women exposed to AZA. 230 control women (no IBD patients) taking drugs – but not AZA.	Yes	Only the estimate for CAs (and not presented in the paper)	CAs: RR=1.2 (0.4-3.7) Preterm birth: RR=4.0 (2.0-8.1) LBW: RR=3.8 (2.0-7.2) Stillbirth: RR=3.9 (0.4-38.3)	No confounder adjustment for the specific birth outcomes. Outcome data were collected from the mothers and not from medical records. Unknown number of cases lost for follow up.
Langagergaard Vet al (52) Denmark, 2007	Cohort	No	**AZA/6-MP** 76 AZA exposed pregnancies Controls: 1) Population controls – no prescriptions for medication 2) Controls with AZA treatment outside pregnancy	Yes	Matched by year/month of birth, and county. Stratification and pooled Mantel-Haenszel estimates.	Using controls with similar kind of disease: CAs; RR=1.1 (0.5-2.9) LBW at term; RR=1.7 (0.3-8.7) Preterm birth; RR=1.9 (1.1-3.3) Preterm birth, spontaneous; RR= 1.1 (0.5-2.6) Preterm birth, induced; RR=4.6 (1.7-12.0) Using population controls, the estimates were generally higher. The results suggest that adverse birth outcomes were cause by the underlying disease rather than by use of AZA/6-MP.	National databases. No confounder data on smoking, alcohol and co-medication.
Nørgård B et al (145) Denmark, 2003	Cohort	No	**AZA/6-MP** Exposed pregnancies: In all 10 AZA/6-MP pregnancies. 6 women had UC/CD	Yes	Yes	LBW: OR*=3.8 (0.4-33.3) Preterm birth: OR*= 6.6 (1.7- 25.9) Perinatal mortality: OR*=20.0 (2.5-161.4) CAs: OR*=6.7 (1.4-32.4)	Small number of exposed. No adjustment for disease activity.

			(55%). Controls: 1) 19418 (no drug use during pregnancy) 2) pregnancies were women had been treated with AZA/6MP before pregnancy			Still increased risk estimates after using the control group of women with similar diseases to the exposed, but none significantly increased.	
Francella A et al (2) US, 2003	Cohort	No	**AZA/6-MP** 55 IBD pregnancies exposed to 6-MP before or during pregnancy, and 69 control pregnancies with use of 6-MP after pregnancy	No	Only age	OR (successful outcome)=0.85 (0.47-1.55) – adjusted for age and female parent affected. Successful outcome: defined as a healthy child (premature or full term) 6-MP before or during pregnancy appears to be safe.	No analyses according to different birth outcomes. Use of 'successful' versus 'failure' outcome. No models used for different birth outcomes.
Moskovitz DN et al (1) Canada, USA 2004	Cohort, with internal control group.	No	**5-ASA, AZA/6-MP** 113 IBD patients with 207 conceptions. At some time during pregnancy: 100 on 5-ASA 49 on prednisone 101 on 6-MP/AZA 27 on metronicazole 18 on ciprofloxacin 2 on cyclosporine 85 no use (reference)	No	Only the association between 5-ASA and 'success pregnancy' is analysed in model (adjustment for age and other drugs)	OR (successful pregnancy in 5-ASA exposed) = 0.8 (adjusted for age, and use of other drugs) None of the drugs (5-ASA, metronidazol, ciprofloxacin, prednisone, 6.MP, AZA, cyclosporine) appeared to be associated with poor pregnancy outcomes.	Specific birth outcome not analysed. Considerations of effect of dose. One mixed group – 'success pregnancy' (live birth with no major CA). No adjustment for disease activity or other confounders.
Nørgård B et al (146) Denmark, 2003	Cohort	Joined analyses, and separately on UC and CD	**5-ASA** 60 pregnancies exposed to 5-ASA in the 1st trimester or 30 days before pregnancy 88 pregnancies exposed to 5-ASA during pregnancy. Controls: 1) 19.418 not exposed (no 5-ASA, no IBD) 2) IBD controls not on 5-ASA during pregnancy	Yes	Yes	No substantial increased risk of CAs or LBW. Increased risk of preterm birth (OR*= 2.4 (1.1-5.3)) and stillbirth (OR*=8.4 (2.0-34.3)) in UC patients. Sub-analyses, proxy for disease activity (use 5-ASA + steroid): Stillbirth - OR*=20.4 (3.4-122.9)	No adjustment for disease activity. The risk of preterm birth and stillbirth was still increased after using the IBD controls (taking into account the influence of underlying disease). In sub-analyses used proxy measure for disease activity (steroid treatment).

			(N=243)				
Diav-Citrin O et al (50) Canada, 1998	Cohort	No	**5-ASA** 165 5-ASA exposed IBD pregnancies (146 with 1. trimester exposure). 165 controls from 'Motherisk database' (matched on smoking and alcohol consumption)	Yes	No other than matching variables	No increased risk of CAs. Preterm birth: 1.5 (1.2-2.0) Significantly lower BW for exposed, compared to controls. Overall: 5-ASA does not represent a major risk Sub-analyses: 5-ASA exposed with activity in pregnancy had lower gestational age than 5-ASA exposed with inactive disease (38.8 weeks versus 39.6).	No models used and no confounder control except for the matching variables. The risk of preterm birth and CAs among 5-ASA exposed not adjusted for disease activity.
Marteau P et al. (51) France, 1998	Cohort, internal comparison	No	**5-ASA** 123 pregnancies exposed to 5-ASA, divided into low-dose and high-dose groups of 5-ASA use.	No	No	5-ASA in safe at doses ≤ 2g/day, and probably also a dose of 3 g/day. 4 cases of CAs in 126 foetuses (3.1%) – similar to the general population. Risk of preterm birth and IUGR was 9.5% - and significantly higher (13%) in women on large doses of 5-ASA.	No models used and no confounder control.
Nørgård B et al (147) Denmark, 2001	Case control study	No	**Sulfasalazine** Cases: 22865 - and 17 had mothers exposed to sulfasalazine. Controls: 38151 - and 26 had mothers exposed to sulfasalazine.	Yes	Yes	CAs: OR*=1.2 (0.6-2.1) The risk of selected CAs was given.	The study lack statistical power to identify even a moderate increase in prevalence of selected CAs. Adjusted for maternal age, parity, maternal diseases and other drug use.
Baiocco PJ et al (5) USA, 1984	Cohort	Yes, partly	**Sulfasalazine** 18 sulfasalazine exposed 101 untreated IBD pregnancies Statistics from the general population.	No	No	In sulfasalazine exposed: no CAs or stillbirths. The frequency of fetal complication (including preterm birth, stillbirth, CAs) in treated patients was higher than in the general population, but was not higher than in untreated IBD patients. Disease activity in 43% of treated patients whose pregnancies ended in fetal complications. Thus, disease activity might be more risky than drug treatment.	No risk estimates given for different birth outcomes. No confounder control.
Nielsen OH et		Only CD	**Sulfasalazine**	No	No	Prematurity, stillbirths and abortions	No risk estimates, and no con-

al (43) Denmark, 1984			Internal comparison: 24 sulfasalazine exposed compared with 63 unexposed			were not more prevalent among exposed compared to unexposed. No CAs among live born children.	founder control.
Nielsen OH et al (35) Denmark, 1983	Cohort, internal comparison	Only UC	**Sulfasalazine** Internal comparison: 46 sulfasalazine exposed compared with 88 unexposed	No	No	1 CA among sulfasalazine exposed and 2 CAs in unexposed. Prematurity and stillbirths were not more prevalent among exposed compared to unexposed.	No risk estimates, and no confounder control.
Mogadam M et al (4) USA, 1981	Cohort, internal comparison	Yes, partly	**sulfasalazine** Internal comparison: Treated (172 UC, 115 CD) versus not treated (137 UC, 107 CD). 102 exposed to sulfasalazine and 245 unexposed pregnancies.	No	No	Sulfasalazine exposed experienced no more complications (LBW, prematurity, abortion, CAs) than untreated IBD group. Two stillbirths in 102 sulfasalazine exposed compared to 1 in 245 untreated.	No risk estimates, and no confounder control.
Willougby CP and Truelove SC (37) England, 1980	Cohort, internal comparison	Only UC	**Sulfasalazine** Internal comparison among UC women: Women on remission at time of conception – 49 exposed pregnancies compared to 77 unexposed. Women with activity – 54 exposed compared to 50 unexposed.	No	No	Sulfasalazine had probably no harmful effect on pregnancy outcome, although 3 CAs in 54 exposed pregnancies with disease activity in pregnancy. Adverse birth outcome (CAs, abortions, stillbirths) was probably due to severity of UC rather than to the effect of medical therapy.	No risk estimates, and no confounder control. No considerations regarding LBW or preterm birth.

CD = Crohn's disease. UC= ulcerative colitis. OR = unadjusted odds ratio. OR* adjusted odds ratio. 95% CI = 95% confidence interval

Table 3. Birth outcome in women with Crohn's disease (CD), an overview of the literature

Included are English language studies that i) cover results according to the birth outcome after maternal diagnoses of CD, ii) include the specific outcome that are under study in this thesis (birth weight [BW], low birth weight [LBW], intrauterine growth retardation [IUGR], preterm birth, mortality, and congenital abnormalities [CAs]). Case-series are excluded. Included are studies that use internal comparisons within a cohort

Author, country, publication year	**Design**	**Separate analyses on CD pregnancies**	**Number of exposed CD pregnancies. Number of controls**	**Risk estimates for adverse birth outcomes given?**	**Adjustment for confounders?**	**Most important results and conclusions**	**Comments**
Nørgård B et al (148) Denmark, 2007	Cohort	Yes	CD pregnancies classified according to prescriptions for CD medication: 5-ASA group/ sulfasalazine (N=179) Steroids (N=73) AZA/6-MP (N=20) References (no medication) (N=628)	Yes	Yes	5-ASA group/ sulfasalazine: LBW: OR*=1.7 (0.6-4.8) LBW at term: OR*= 1.9 (0.6-6.4) An additional risk of LBW at term of 0.8% (-1.2-3.2%). No increased risk of preterm birth or CAs Steroid group: Preterm: OR*=1.4 (0.6-3.3) An additional risk of preterm birth of 5.8% (-2.0-13.6%). No increased risk of LBW at term or CAs AZA/6-MP group Preterm: OR*=4.2 (1.4-12.5) CAs: OR*=2.9 (0.9-8.9) An additional risk of preterm birth of 18.5% (-0.1-37.6%), and of CAs 9.7% (-4.3-23.6%). No increased risk of LBW or LBW at term.	The risk of LBW, LBW at term, preterm birth and CAs is estimated for each drug group in CD women. Estimates adjusted for maternal age, parity, gestational age and a proxy measurement of disease activity.
Nørgård B et al (149) Denmark, 2007	Cohort	Yes	Births by women with CD. CD pregnancies with disease activity (low or moderate-high) during pregnancy: 71 CD pregnancies with no disease activity during pregnancy: 86	Yes	Yes	Preterm: OR*=2.4 (0.6-9.5) No increase risk estimates for LBW, LBW at term or CAs. Sub-analysis: Risk of preterm birth in those with the highest degree of activity compared to those without disease activity OR*= 3.4 (1.1-10.6)	Adjusted for maternal age, parity, maternal smoking, use of therapeutic drugs in pregnancy, disease duration, and calendar period. Restricting analyses to the pregnancy first recorded by each woman did not alter the results.
Bortoli A et al (79) Italy, 2007	Cohort	Yes	28 live births by diagnosed CD women. 204 control births by women with other diseases	Not for CD births compared to controls	No model adjustment.	Birth weight of neonates born to CD women was significantly lower that that of neonates born to controls, mean 2964 g and 3273, respectively.	Risk of recall bias. All information on birth outcome, disease activity and treatment given by interviews in 1995-96 among

			than IBD. Collect information on disease activity and therapy but do not use this information according to birth outcomes.			Preterm: OR**=1.7 CAs: 2/28 (7.4%) in CD births and no CAs among controls. Disease activity at conception: 6/36 (16.7%)	births occurring form 1943-1996. No adjustment for drug therapy or disease activity. Data on birth outcomes not shown according to disease activity or drug therapy.
Elbaz G et al (78) Israel, 2005	Cohort	Yes, but only regarding preterm birth	48 CD pregnancies 508 non-IBD pregnancies	Yes	No model adjustment	Preterm: OR=2.6 (1.2-5.6)	No adjustment for drug therapy, disease activity or other confounders (e.g., age, parity, smoking, gestational age).
Bush MC et al (77) USA, 2004	Cohort	Yes	63 CD pregnancies Controls: 53 UC pregnancies	No	No	Compared to UC pregnancies: no increased risk of preterm birth, LBW or SGA	No confounder adjustment for drug therapy, disease activity or other confounders.
Dominitz JA et al (76) USA, 2002	Cohort	Yes	155 CD pregnancies 1308 non-IBD controls	Yes	Yes	LBW: OR* = 3.6 (2.2-5.9) Preterm birth: OR*= 2.3 (1.4-3.8) IUGR: OR*= 2.3 (1.3-3.9) CAs: OR*=2.1 (0.8-5.6)	Good statistical analyses and confounder adjustments. No ability to adjust for drug therapy or disease activity. In subanalyses restriction to first recorded birth by each mother: unchanged results.
Ludvigsson JF et al (75) Sweden, 2002	Cohort	Yes	13 CD births 10386 non-CD births	Yes	Yes in models.	LBW: OR*=3.1 (0.1-73.5) Preterm birth: OR*=2.6 (0.3-20.5)	Little sample size of exposed (CD births), and very imprecise risk estimates. No adjustment for drug therapy, or disease activity.
Moser MAJ et al (91) Canada, 2000	Cohort	Yes	65 CD pregnancies (quiescent at the start of pregnancy). 65 non-CD control pregnancies.	No.	No, but matched for maternal age smoking, and gestational age.	BW, mean: 3150g (3500g for controls) IUGR: 24.6% (1.5% for controls), i.e. OR** = 20.9 CAs: OR** =1	Small sample size. No adjustment for drug therapy or disease activity.
Fonager K et al (45) Denmark, 1998	Cohort	Yes	510 CD pregnancies 3018 non-CD control births	Yes	Yes in models	BW, mean: CD 3274 g and 3419 g for controls LBW: OR* = 2.4 (1.6-3.7) Preterm birth: OR*= 1.6 (1.1-2.3) Stillbirth: OR*= 2.0 (0.5-7.0) Perinatal mortality: OR*= 0.8 (0.2-2.5) CD or its treatment may influence fetal growth.	Large population-based study and good quality of statistical analyses. No adjustment for smoking, drug therapy, or disease activity.

Baird DD et al (74) USA, 1990	Cohort	Yes	84 CD pregnancies 216 non-CD controls	Yes	Yes	Preterm: OR = 3.2* (1.6-6.1)	No adjustment for drug therapy, or disease activity.
WoolfsonK et al (3) Canada, 1990	Cohort	Yes	78 CD pregnancies Internal comparisons according to disease activity and drug use, e.g., at conception: - 8 with active disease, and 13 inactive. - 36 with no medication and 26 on medication	No	No	Patients with active disease at conception or during the pregnancy had more abnormal outcomes (including LBW, preterm, respiratory distress) compared with those with inactive disease. Drug use at conception did not unfavorable affect the pregnancy outcome (LBW, preterm, respiratory distress).	Small study. The drug group comprising most CD women was 13 women receiving steroids. Specific birth outcome not estimated. No risk estimates and no confounder control.
Porter RJ et al (73) England, 1986	Cohort	Yes	38 CD pregnancies 76 non-CD controls (matched on age and parity)	No	Matching variables, no models	BW, mean: No significant difference was found Preterm birth: *OR** = 2.2* CAs: No CAs in CD births	No adjustment for drug therapy or disease activity.
Mogadam M et al (4) USA, 1981	Cohort	Yes, partly	Internal comparison: Treated (172 UC, 115 CD) versus not treated (137 UC, 107 CD).	No	No	CD: Treated group experienced more complications (LBW, preterm, stillbirth, CAs) than untreated IBD group.	No risk estimates, and no confounder control. Adverse pregnancy outcomes only given as one mixed group (fetal complications).

CD = Crohn's disease. UC= ulcerative colitis. OR = unadjusted odds ratio. OR* = adjusted odds ratio. OR** = OR not given in the paper, but a crude OR can be calculated from the figures in the paper. 95% CI = 95% confidence interval

Table 4. Birth outcome in women with chronic inflammatory bowel disease (IBD), an overview on the literature.
Included are English language studies that i) cover results according to the birth outcome after maternal diagnoses of IBD, ii) include the specific outcome that are under study in this thesis (birth weight, low birth weight [LBW], intrauterine growth retardation [IUGR], preterm birth, mortality, and congenital abnormalities [CAs]). Case-series are excluded. Included are studies that use internal comparisons within a cohort

Author, country, publication year	**Design**	**Separate analyses on UC or CD pregnancies**	**Number of exposed IBD pregnancies. Number of controls.**	**Risk estimates for adverse birth outcomes given?**	**Adjustment for confounders?**	**Most important results and conclusions**	**Comments**
Bortoli A et al (79) Italy, 2007	Cohort	IBD	95 births by IBD women. 204 control births by women with other diseases than IBD. Collect information on disease activity and therapy but do not use this information according to birth outcomes.	Yes	No model adjustment	Birth weight of neonates born to IBD women was similar to that of controls. Preterm: OR=1.4 (0.5-3.4) CAs: OR=25.8 (1.4-471.2)	Risk of severe recall bias. All information on birth outcome, disease activity and treatment given by interviews in 1995-96 among births occurring form 1943-1996. No adjustment for drug therapy or disease activity. Data on birth outcomes not shown according to disease activity or drug therapy.
Elbaz et al (78) Israel, 2005	Cohort	IBD	127 IBD pregnancies 508 non-IBD pregnancies	Yes	No model adjustment	Preterm: OR=2.2 (1.3-3.8) LBW: OR=2.1 (not given) No increased risk of perinatal mortality or CAs.	No adjustment for drug therapy, disease activity or other confounders (e.g., age, parity, smoking, gestational age).
Bush et al (77) USA, 2004	Cohort	IBD	116 IBD pregnancies 56.398 controls without IBD	No	No	No increased risk of LBW, IUGR or preterm birth. Sub-analyses: 22 pregnancies with activity versus 94 without activity – increased risk of LBW and preterm birth in those with activity.	No adjustment for drug therapy, disease activity or other confounders (e.g., age, parity, smoking, gestational age). Sub-analyses not adjusted for drug therapy or other confounders.
Kornfeld et al (46) Sweden, 1997	Cohort	IBD	756 IBD pregnancies. 239,017 non-IBD controls	yes	Yes, in models.	LBW: OR*=1.6 (1.1-2.3) Preterm: OR*= 1.5 (1.1-2.0) SGA: OR*= 1.4 (0.9-2.0) Stillbirth: *OR** = 1.6*	No adjustment for drug therapy or disease activity.
Federkow et al (59) Canada, 1989	Cohort	IBD	98 IBD pregnancies. 196 none-IBD control pregnancies (matched on age, parity, sex of neo-	No	Not in models, matching on some study variables	BW,mean: 3097g for IBD, 3283 g for controls Preterm: *OR** = 3.2* Stillbirth: *OR** = 0.7*	No adjustment for disease activity. In sub-analyses regarding an impact of drugs and disease activity: No confounder control.

			nates, and year of delivery)			CAs: *OR** = 4.1* SGA: *OR**= 2.1* Sub-analyses in IBD pregnancies: Pharmacotherapy and disease activity may be predictors for preterm birth and SGA.	

CD = Crohn's disease. UC= ulcerative colitis. OR = unadjusted odds ratio. OR* = adjusted odds ratio. OR** = OR not given in the paper, but a crude OR can be calculated from the figures in the paper. 95% CI = 95% confidence interval

Table 5. Birth outcome in women with ulcerative colitis (UC) and Crohn's disease (CD), case-series
Included are studies that i) cover results according to the birth outcome after maternal diagnoses of UC or CD, and ii) include the specific outcome that are under study in this thesis (birth weight [BW], low birth weight [LBW], small for gestational age [SGA], preterm birth, mortality, and congenital abnormalities [CAs])

Case-series	UC or CD	Number of pregnancies	Main conclusion
Morales M (44) 2000	CD patients	35 pregnancies	Active CD during pregnancy is risk factor for abnormal pregnancy outcome.
Marteau P (51) 1998	UC and CD patients	123 5-ASA exposed pregnancies	Low dose 5-ASA does not influence the risk of CAs. 103 born at term without CAs, and 5 with CAs.
Hudson M (36) 1997	UC and CD patients	135 CD pregnancies 161 UC pregnancies	Classified according to disease activity and birth outcomes. At conception women with active disease were as likely to have normal full-term pregnancy as those in remission.
Rogers RG (41) 1995	CD patients	17 CD women	3 children with LBW, and two were born premature and with IUGR.
Habal FM (39) 1993	UC and CD patients	In all 19 5-ASA exposed pregnancies	18 pregnancies ended in full term deliveries. No CAs, and no with LBW.
Nilsen OH (43) 1984	CD patients	109 pregnancies (76 children delivered)	Increased risk of preterm birth and spontaneous abortion, but was due to women with active disease at the time of conception and women who had undergone bowel resection during pregnancy.
Baiocco PJ (5) 1984	UC and CD patients	147 IBD pregnancies.	Prematurity: 5.4% Stillbirth: 1.3% CAs: 2.7%
Khosla R (42) 1984	CD patients	88 pregnancies	56 normal live births. Patients in remission at the time of conception had a normal pregnancy.
Nilsen OH (35) 1983	UC patients	173 pregnancies (136 delivered children)	Women with active disease at the start of pregnancy had greater risk of spontaneous abortion and premature delivery.
Levy N (40) 1981	UC patients	60 pregnancies	UC does not interfere with the outcome of pregnancy.
Willoughby CP (37) 1980	UC patients	216 pregnancies	Disease activity and drug treatment are taken into consideration. Active disease may decrease the risk of normal child.
Homan WP (33) 1976	CD patients	42 CD pregnancies	Outcomes of pregnancies are reassuring.
De Dombal FT (32) 1972	CD patients	60 pregnancies in 40 CD women	Most pregnancies went normally to term.
McEwan HP (31) 1972	UC patients	50 pregnancies	One stillbirth and no neonatal deaths.
De Dombal FT (30) 1965	UC patients	107 pregnancies	83% had full term normal delivery. 3% had CAs. 2% were stillborn.
Crohn BB (34) 1956	UC patients	150 pregnancies	Classified according to debut of UC/disease activity. Number of abortions, and stillbirths reported.
Crohn BB (29) 1956	CD patients	84 CD pregnancies	Among three patients in whom the onset of CD coincided with the pregnancy there were no full-term pregnancies

Table 6. The American's Food and Drug Administration (FDA) – Pregnancy Categories

FDA Pregnancy Category	Interpretation
A	Controlled studies in animals and women have shown no risk in the first trimester, and possible fetal harm in remote
B	Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnancy women, or animal studies have shown an adverse effect that was not confirmed in women in the first trimester
C	No controlled studies in humans have been performed an animal studies have shown adverse events, or studies in humans and animals are not available; give if potential benefit outweighs the risk
D	Positive evidence of fetal risk is available, but the benefits may outweighs the risk if life-threatening or serious disease
X	Studies in animals or humans show fetal abnormalities; drug contraindicated