From the Department of Medicine, Solna
Karolinska Institutet, Stockholm, Sweden

Chronic inflammatory disease and its treatment during pregnancy

Gabriella Bröms

Karolinska Institutet

Stockholm 2015

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Published by Karolinska Institutet.
Printed by AJ E-print AB

ISBN 978-91-7549-891-1

Centrum för läkemedelsepidemiologi, Institutionen för medicin, Solna

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Gabriella Bröms

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Kugelbergsalen, R2:U1,Karolinska universitetssjukhuset, Solna

Fredagen den 5 juni 2015 kl 09.00

Huvudhandledare:
Docent Helle Kieler
Centrum för läkemedelsepidemiologi
Institutionen för medicin, Solna
Karolinska institutet

Bihandledare:
Docent Fredrik Granath
Enheten för klinisk epidemiologi
Institutionen för medicin, Solna
Karolinska institutet

Docent Olof Stephansson
Enheten för klinisk epidemiologi
Institutionen för medicin, Solna och
Institutionen för kvinnors och barns hälsa
Karolinska institutet

Opponent:
Professor Sonia Hernández Díaz
Department of Epidemiology
Harvard School of Public Health

Betygsnämnd:
Docent Solveig Nordén Lindeberg
Institutionen för kvinnors och barns hälsa
Uppsala universitet

Docent Anastasia Nyman Iliadou
Institutionen för medicinsk epidemiologi och biostatistik, Karolinska institutet

Docent Michael Eberhardson
Institutionen för klinisk forskning och utbildning, Södersjukhuset, Karolinska institutet

Stockholm 2015

You don't have to have it all figured out to move forward.

-Unknown

Abstract

The decision to have children is often coupled with varying degrees of apprehension. Women with chronic disease often worry about how the disease itself or its treatment will affect pregnancy and the fetus. The aim of this thesis was to add to the current knowledge concerning pregnancy and birth outcomes in chronic inflammatory disease.

First, we studied pregnancy and delivery complications in women with Crohn's disease and ulcerative colitis, the main types of inflammatory bowel disease (IBD). By using register data, we constructed a proxy model for disease activity, categorizing women according to (i) no activity, (ii) stable disease and (iii) flaring disease. Compared to women without IBD, women with Crohn's disease and ulcerative colitis more often delivered by emergency and elective cesarean sections. Women with ulcerative colitis had a higher risk of venous thromboembolism during pregnancy, which seemed to be the highest in women with flaring disease.

In the second study, we assessed risks of adverse birth outcomes in women with Crohn's disease and ulcerative colitis and their infants, by diagnosis and by the disease activity proxy model. Compared to women without IBD, women with Crohn's disease and ulcerative colitis more often gave birth preterm, particularly those with flaring disease and with thiopurine treatment during pregnancy. Small for gestational age and stillbirth were more common for women with Crohn's disease, and were also related to flaring disease.

The third study focused on anti-tumor necrosis factor (anti-TNF) treatment and birth defects, a relationship which has not been well-studied. Anti-TNF is used to treat IBD and other chronic inflammatory disease such as rheumatoid arthritis, ankylosing spondylitis, psoriasis and psoriatic arthritis. We included all infants to women with these diseases in Sweden and Denmark and determined their anti-TNF treatment status in early pregnancy. Infants of the general population were included for a frame of reference for descriptive purposes, while formal comparisons were limited to the women with chronic inflammatory disease. The distribution of birth defects in all three groups was similar and ventricular septal defect, atrial septal defect, congenital hydronephrosis and hypospadias were the most common. Rates for corrective surgery were also similar. Comparing infants to women with chronic inflammatory disease, with and without anti-TNF treatment, the risk of any birth defect or defect of a particular organ-system was slightly but imprecisely increased, and an association could not be determined.

In the fourth study, we identified all live-born singleton cases of preterm birth as cases, and births occurring at a later gestational age as their controls, among women with IBD. We found that significant disease activity and treatment with thiopurines or anti-TNF predicted preterm birth. The study illustrated the challenges of confounding by indication. Some misclassification of disease activity was likely not completely avoided, leading to residual confounding and making it impossible to assess the effects of disease activity and immunosuppressive treatment separately. However, weighing the risks of relapsing disease against those of drug treatment, disease activity seems more important to avoid.

List of scientific papers

I. **Complications from inflammatory bowel disease during pregnancy and delivery**
Gabriella Bröms, Fredrik Granath, Marie Linder, Olof Stephansson, Maria Elmberg and Helle Kieler
Clinical Gastroenterology and Hepatology 2012;10:1246–1252

II. **Birth outcomes in women with inflammatory bowel disease: Effects of disease activity and drug exposure**
Gabriella Bröms, Fredrik Granath, Marie Linder, Olof Stephansson, Maria Elmberg and Helle Kieler
Inflammatory Bowel Diseases 2014;20:1091–1098

III. **Anti-TNF treatment and the risk of birth defects**
Gabriella Bröms, Fredrik Granath, Anders Ekbom, Karin Hellgren, Lars Pedersen, Henrik Toft Sørensen and Helle Kieler
Manuscript submitted for publication

IV. **Preterm birth in women with inflammatory bowel disease – the association with disease activity and drug treatment**
Gabriella Bröms, Fredrik Granath, Olof Stephansson and Helle Kieler
Manuscript

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Abbreviations

5-ASA	5-aminosalicyte
Anti-TNF	Anti-tumor necrosis factor treatment
ARTIS	Anti-Rheumatic Therapy in Sweden
ATC	Anatomical Therapeutic Chemical classification
BMI	Body mass index
CD	Crohn's disease
CI	Confidence interval
EUROCAT	The European Surveillance of Congenital Anomalies
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
ICD-10	ICD, 10th version
NCSP	Nordic Classification of Surgical Procedures
OR	Odds ratio
PsoReg	The Swedish Registry for Systemic Psoriasis Treatment
SGA	Small for gestational age
SSZ	Sulfasalazine
TNF	Tumor necrosis factor
UC	Ulcerative colitis

1 Introduction

One of life's major decisions is the decision to try to conceive and have children, which is often coupled with varying degrees of apprehension. For women with chronic inflammatory disease, the consequences of the disease itself and the related drug treatment for the pregnancy, and the child in particular, add to the concerns. Some may abstain from treatment, even if it means risking their own health, and others may refrain from having children due to the fear of affecting their own or the offspring's health negatively.

Due to ethical considerations, studies of adverse effects of drugs generally do not include pregnant women. Instead, knowledge regarding intrauterine exposure relies on results from animal studies and observational studies in pregnant women. As a result, the knowledge of how drug exposure affects pregnancy and birth outcomes often remains limited in general, and takes a long time to acquire.[1,2]

The studies in this thesis were conducted with the aim to contribute to the yet limited knowledge concerning the effects of chronic inflammatory disease and its treatment during pregnancy. Emerging data suggest that the course of pregnancy and parturition shares features with the pathological inflammation of chronic inflammatory disease, and how treatment directed towards the inflammation affects the interplay remains largely unknown.

1.1 Chronic inflammatory disease

Inflammation is an immune system response that involves immune cells and small signaling proteins called cytokines. One of the main purposes of inflammation is to eradicate foreign pathogens such as bacteria. Through well-coordinated signaling, inflammation is involved in eliminating the initial cause of cell injury, clearing out damaged tissues while stimulating tissue repair. In chronic inflammatory disease, such as Crohn's disease and ulcerative colitis (collectively defined inflammatory bowel disease, IBD), rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis, the coordination is lost. The result is an unwarranted inflammatory response, often characterized by relapse-remission cycles with flares of increased activity. The causes of the abnormal activation of the immune system is not entirely clear, but genetic and environmental factors are most likely involved.

Chronic inflammatory disease may affect women in their reproductive years. The highest incidence of IBD is between 20 and 40 years of age, with diagnoses peaking earlier in the interval for Crohn's disease and later for ulcerative colitis, with no prominent sex variation.[3-5] The peak onset of rheumatoid arthritis occurs at a later age, but predominantly affects women.[6] In contrast, ankylosing spondylitis affects more men than women, but usually presents before the age of 45.[7] The majority of psoriasis patients present before 40 years of age and if arthritic symptoms prompting a diagnosis of psoriatic arthritis appear, it occurs about 10 years after the first skin lesions.[8]

Inflammatory bowel disease

Ulcerative colitis and Crohn's disease share many characteristics, although there are also significant differences. Ulcerative colitis only affects the colon, causing continuous mucosal inflammation that starts in the rectum and extends proximally (Figure 1.1). Lesions of Crohn's disease may present anywhere along the gastro-intestinal tract, in a discontinuous pattern of often deeper, granulomatous inflammation that may be transmural.[9,10] Crohn's disease is prone to cause intestinal strictures, and may penetrate tissues causing abscesses and fistulae, a problem often affecting the perianal area.[11] Patients with Crohn's disease and ulcerative colitis may present with diarrhea, blood and mucus in stool, tenesmuses and urgency to empty bowels. Systemic inflammatory response with fever and weight loss is a sign of severe flaring disease. Up to a third of patients are affected by extraintestinal manifestations, most frequently arthropathies and mucocutaneous lesions.[12] Abdominal pain is a frequent symptom of both Crohn's disease and ulcerative colitis, which along with pain from extraintestinal manifestations affect the quality of life for many patients.[13] The diagnoses rest on criteria-based symptoms, biochemical markers, radiological findings and macro- and microscopic inspection of the intestinal mucosa by endoscopy.[14,15] Because of similarities between Crohn's disease and ulcerative colitis, about 10% of patients will typically be reclassified to the other.[16,17] The relapse-remitting disease course may be monitored with clinical indexes such as the Harvey Bradshaw index and the Crohn's Disease Activity Index for Crohn's disease, and the Simple Clinical Colitis Activity index for ulcerative colitis.[18-20] These do, however, not necessarily correspond well to endoscopic disease activity.[21] There are no specific biochemical markers and general inflammatory markers such as C-reactive protein and fecal calprotectin do not always mirror endoscopically assessed disease activity.[21]

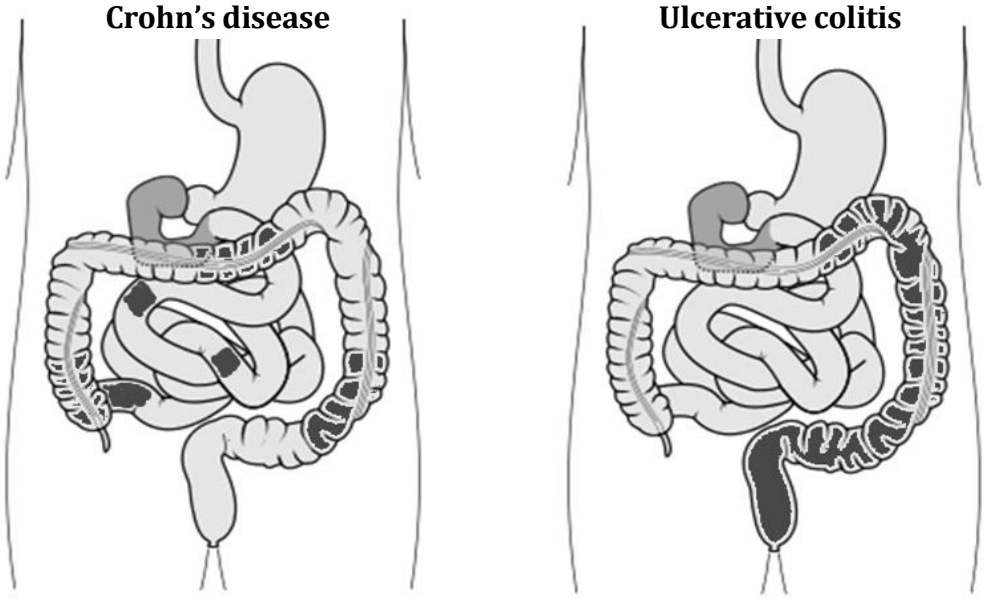

Figure 1.1 Schematic illustration of the localization of inflammation (dark color). Adapted from Remesz.[22]

Current knowledge suggests that the intestinal inflammation develops because of unwarranted immune responses to the microbial flora in genetically susceptible individuals.[23] Several genetic susceptibility loci have been identified in patients with IBD, many of them shared by Crohn's disease and ulcerative colitis. Other loci are specific to either Crohn's disease or ulcerative colitis, supporting that these two variants of IBD are separate entities.[24] Many of the loci code for proteins included in the mucosal barrier function and proteins in the innate and adaptive immune systems. The mucosal barrier is the first line of defense against microbes and consists of epithelial cells that seal off the submucosal space by being connected to each other with tight junctions. In addition, specialized cells, such as Goblet cells and Paneth cells within the epithelial cell layer, excrete mucus that is anti-microbial. In ulcerative colitis and Crohn's disease, changes in the barrier function and intestinal permeability have been observed, thereby likely allowing the translocation of luminal antigens such as those of the microbial flora to the submucosal space.[25-27] In homeostatic conditions, microbe antigens are constantly being presented to T-cells, a group of cells that belong to the adaptive immune system, in the submucosal space. The result of the translocation of microbial antigens is a well-balanced response of, on the one hand effector T-cells that promote inflammatory activity, and on the other, regulatory T-cells that suppress inflammation.[28] In IBD, the balance in the response is lost, resulting in excessive immune activation and chronic inflammation, mediated by cytokines, among them tumor necrosis factor (TNF).[9,11,29]

In IBD mouse models, mice that are genetically susceptible do not develop intestinal inflammation when raised in a bacteria-free environment, pointing out the interplay of genetic and environmental factors in IBD pathogenesis.[30] Also, although familial IBD is one of the most important risk factors for developing the disease, only 5-15% of patients report having an affected first-degree relative.[31,32] The risk for children with one parent with IBD to develop the same is, however, increased by 2-13 times, and even more for those with two affected parents.[33,34]

In a recent Swedish study, the national prevalence of IBD was reported at 0.65%.[35] The epidemiology of IBD may mirror its multifactorial pathogenesis. The highest incidence is reported in Northern Europe and North America and IBD is more common in industrialized than in non-industrialized countries and more common in urban than in rural areas.[4,36,37] There is an increasing global incidence today, partially pertaining to emerging IBD populations in Asia and in second-generation immigrants in Europe, which implies an association with changing lifestyles and behavior.[4,38,39] Several studies have observed that smoking is an important factor for IBD, increasing the risk of Crohn's disease, while being protective against active ulcerative colitis, making smoking cessation a deceitful trigger for the latter.[40,41]

A report published in 1933 stated that 16 out of the 21 (76%) enrolled patients with acute presentation of ulcerative colitis died within one year, and one study reported a 15% and 5% mortality rate during the 1940s and the 1950s, respectively.[42,43] From the 1950s, medical and surgical treatment has evolved, and specialist centers now report a mortality rate below 1%.[44]

Rheumatoid arthritis, ankylosing arthritis, psoriatic arthritis and psoriasis

Rheumatoid arthritis is marked by symmetrical, peripheral polyarthritis, due to an inflammatory response that affects joints in the hands, feet, and wrists in particular. Similarly, ankylosing spondylitis involves inflammation of the spinal joints. Psoriasis is an inflammatory skin disease, most commonly featuring plaque-type lesions on elbows, knees and scalp. Out of patients with psoriasis, up to 30% will also develop psoriatic arthritis, in which, in addition to skin lesions, inflammation predominantly affects joints in the hands and in the spine.[45,46] The pathogeneses of rheumatoid arthritis, ankylosing spondylitis, psoriasis and psoriatic arthritis seem to be as multifactorial as for ulcerative colitis and Crohn's disease with genetic predisposition, reactivity to external pathogens and inappropriate activation of the immune system involved in the process.[47-50] Of the inflammatory cytokines that mediate the inflammatory response, TNF is central to chronic inflammatory disease.[51]

1.2 Treatment of chronic inflammatory disease

The treatment of chronic inflammatory disease aims at subduing the inflammatory response. The various substances that can achieve the anti-inflammatory effect have in common that they inhibit the activity of the immune system, although for many of them, the exact mechanism remains elusive (Table 1.1). The main draw-back with immunosuppressive treatment is the increased risk of infection arising from the manipulation of the immune system.

It is believed that corticosteroids act by entering into immune cells to inhibit genes that code for pro-inflammatory cytokines, among them TNF.[53] Corticosteroids are very effective in subduing inflammation. However, long-term use should be avoided because of adverse effects such as metabolic disorders and osteoporosis.[54] Instead, corticosteroids are typically used initially, or when the inflammatory activity increases in a flare. Patients are started on high-dose corticosteroids that are tapered continuously, and maintenance therapy with some other immunosuppressive treatment is started if considered necessary according to the risk of relapse.[55-58]

Treatment used for maintenance of remission includes 5-aminosalicylates (5-ASA) and sulfasalazine, thiopurines (azathioprine and 6-mercaptopurine), methotrexate and cyclosporine. Sulfasalazine is composed of aminosalicylate and the antibiotic sulfapyridine, while 5-ASA consists of only aminosalicylate. The effect of thiopurines is exerted by disrupting the production of DNA in gene sequences, resulting in prevented clonal expansion of lymphocytes.[59] Methotrexate also affects DNA by hindering purine production.[60]

The history of chronic inflammatory disease treatment is filled with groundbreaking discoveries. In the 1930s, Dr Philip S. Hench observed that pregnancy and jaundice had beneficial effects on rheumatoid arthritis and set out to identify the substance exerting the effect.[61] Following years of determined basic science and clinical research, he was awarded the Nobel Prize in Medicine and Physiology in 1950 together with Dr E C Kendall and Dr T Reichstein for the discovery of corticosteroids.

Table 1.1 Proposed pharmacodynamics of selected drugs used to treat chronic inflammatory disease

Substance	Introduced	Characteristics and effects
Systemic corticosteroids	1940s	Act on the glucocorticoid receptor, a transcription factor that can change gene expression via nuclear factor NF-κB, promoting anti-inflammatory cytokines and inhibiting pro-inflammatory cytokines, i.e. TNF, thus down-regulating immune response.[53]
Sulfasalazine 5-ASA	1930s	Act on the PPARγ-receptor and nuclear factor NF-κB through which pro-inflammatory cytokines are stimulated, among them TNF.[62]
Methotrexate	1940s	Folic acid analog, inhibits the conversion of an essential co-factor in DNA synthesis, repair, RNA synthesis and cell division, which is rapid in immune system cells.[63]
Thiopurines	1960s	Azathioprine and 6-mercaptopurine are converted analogs of guanin, interfering with DNA, RNA and protein synthesis.[59]
Cyclosporine	1970s	Antibiotic. Disrupts T-cell activation by inhibiting genes that code for cytokines, among them TNF.[64]
Anti-TNF drugs	1990s	Specifically directed at cytokine TNF. Neutralize soluble TNF, point out membrane-bound TNF for cytotoxic cells and complement which in turn can induce cell death of inflammatory cells.[65]

Characteristics of anti-TNF drugs

Substance	Introduced	Characteristics	Indications
Infliximab	1999	Chimeric IgG antibody, part human, part mouse	CD, UC, RA, PsA, PsO, AS
Etanercept	2000	Fusion of TNF-receptor and Fc-part of IgG antibody	RA, PsA, PsO, AS
Adalimumab	2003	Human monoclonal IgG antibody	CD, UC, RA, PsA, PsO, AS
Certolizumab-pegol	2009	Pegylated Fab-part of IgG antibody	RA
Golimumab	2009	Human monoclonal IgG antibody	UC, RA, PsA, AS

Selection based on the most common drugs used for IBD, list not complete. Year of introduction and indications for anti-TNF substances defined by year of approval and therapeutic area by the European Medical Agency.[66]
CD - Crohn's disease, UC - ulcerative colitis, RA - Rheumatoid arthritis, PsA - psoriatic arthritis, PsO - psoriasis, AS - ankylosing spondylitis

The introduction of anti-TNF treatment in the late 1990s has been a significant addition to the available treatment regimens of chronic inflammatory disease and has also added valuable insight in disease pathogenesis.[67] Designed to specifically counteract TNF, which is central to chronic inflammation, anti-TNF treatment currently includes five substances: infliximab, adalimumab, etanercept, certolizumab-pegol and golimumab (Table 1.1 and Figure 1.2). Despite their common target, their effects also differ. Etanercept is effective for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis, but not for Crohn's disease or ulcerative colitis.[67,68] Common for all anti-TNF substances is that their indication depends on disease severity, and they are generally indicated in moderate to severe disease.[66]

One of the earliest treatment options for ulcerative colitis was sulfasalazine. Dr Nanna Svartz, a Karolinska institutet researcher and doctor, played a significant role in its development in the 1930s and 1940s. Later, she went on to become the first female professor appointed in Sweden.

In the guidelines of the European Crohn's and Colitis Organization, immunosuppressive treatment including anti-TNF is recommended for patients with Crohn's disease with early debut, need of systemic corticosteroids at debut, steroid-refractory, perianal or extensive disease, after colonic surgery or in case of early or frequent relapse.[56] Similarly, immunosuppressive treatment for ulcerative colitis is recommended for extensive disease, early or frequent relapse and steroid-dependent or steroid-refractory disease.[57] Another consideration before anti-TNF treatment is its cost-effectiveness since the substances are expensive. In 2014, the European patents for infliximab and etanercept ran out, paving the way for biosimilars, drugs that mimic structures and characteristics of the anti-TNF substances. This may in time lower the costs and may make anti-TNF available for a broader segment of patients.[69]

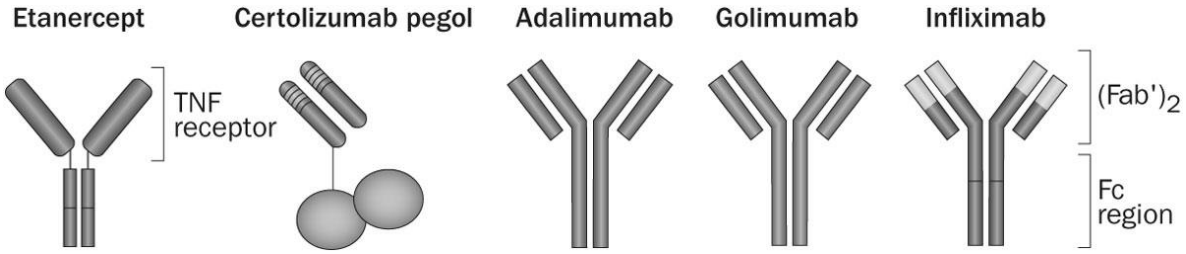

Figure 1.2 Anti-TNF substances, van Schouwenburg al.[70] Reprinted with permission from Nature Publishing group. ©

When medical treatment is not enough to avert the inflammatory activity, surgical treatment may be required. For ulcerative colitis, colectomy with ileo-rectal anastomosis, ileo-anal pouch anastomosis or ileostomy are the main options.[9] With the target organ removed, the inflammatory process is eliminated. For Crohn's disease, local debilitating complications may be removed in bowel resections.[11] However, the disease may relapse in other sites.

1.3 Pregnancy

Pregnancy implicates a significant change in physiology for the woman. Homeostasis is shifted to make the body ready to nourish and protect the fetus throughout gestation. This includes changes in hemostasis to prevent hemorrhage and changes in the immune system to allow the semi-allogenic fetus to thrive within. Pregnancy may be considered an inflammatory state, and shares some immunological processes with chronic inflammatory disease.[71-73] Both implantation and parturition involve localized physiological inflammation.[73] Interestingly, the inflammatory component of implantation and parturition have also been considered possible targets for fertility treatment and for delaying parturition. The inhibitory effects of anti-TNF treatment has been reported to increase success of fertility treatment in humans and to prolong pregnancy in mice.[74-76]

The key to maternal tolerance of the semi-allogenic fetus has not been completely elucidated. Lately, more attention has been drawn toward regulatory T-cells that surveil the immune system for immune cells that might attack the fetus, suppressing their response and promoting a successful pregnancy.[77] Reduced levels of regulatory T-cells have indeed been associated with spontaneous abortion and infertility.[78] This is of particular interest in chronic inflammatory disease, where reduced levels of regulatory T-cells and the abundance of their counterpart effector T-cells may explain the unwarranted inflammatory response.[79,80]

1.4 Pregnancy complications

Several pro-coagulant factors are increased in pregnancy, while plasma fibrinolytic activity is reduced.[81] During delivery, the increased coagulability is vital to prevent exsanguination after the placenta has separated from the uterus. A disadvantage of the physiological adjustments towards hypercoagulation is an increased risk of venous thromboembolism. Data from Sweden and Denmark present a rate of venous thromboembolism during pregnancy, including deep vein thrombosis and pulmonary embolism, ranging from 1.0-1.3 per 1000 births.[82,83] The highest risk is seen in the post-partum period, specifically the six weeks following delivery. Venous thromboembolism is a leading cause of maternal death in high-income countries, including Sweden, where it causes 1-2 deaths per 100,000 live-births.[84-87] Fortunately, only a minimal fraction of venous thromboembolism cases are fatal.[88] Inflammation has been associated with thromboembolism, and non-pregnant as well as pregnant patients with IBD have an increased risk of thrombotic events compared to healthy controls.[89-94] Maternal age, smoking, obesity, hospitalization and cesarean section are risk factors for venous thromboembolism in connection with pregnancy.[95] When appropriate according to the assessment of risk factors, prophylactic treatment may be started. Low molecular weight heparin is the first choice of prophylaxis. Although bleeding and heparin-induced thrombocytopenia are infrequent adverse reactions, the treatment is generally considered safe and efficient during pregnancy.[96,97]

Preeclampsia is characterized by the onset of hypertension and albuminuria after the 20th week of gestation and affects approximately 3% of women who give birth in Sweden.[98] With acute maternal complications, such as eclampsia, stroke, liver hemorrhage and rupture, pulmonary edema, acute renal failure and death, and fetal complications such as preterm birth, intrauterine growth restriction and stillbirth, it is a leading cause of morbidity and mortality for mother and fetus.[99]

Placental abruption means that the placenta completely or partially separates from the uterus wall prior to delivery. Signs may be vaginal antepartum hemorrhage and abdominal pain. Preeclampsia, placental abruption and intrauterine growth restriction may be grouped to the collective term ischemic placental disease.[100] Although the etiology is incompletely understood, a common biological pathway involving poor placentation, with cell dysfunction, infection and inflammation, is suspected, and a dysfunctional immune response towards the fetus, or lack of maternal tolerance as described earlier, may be involved.[101] The major symptoms in ischemic placental disease

may be mostly on the maternal side, as in preeclampsia, or the fetus may be more affected, resulting in intrauterine growth restriction.[102]

A higher risk of preeclampsia has been linked to rheumatoid arthritis which could be explained by an exaggerated response to the inflammatory stress of pregnancy and that the inflammatory disease further amplifies the response.[103] Again, TNF plays a pivotal role in the inflammatory balance, and increased levels of TNF have been associated with both preeclampsia and rheumatoid arthritis.[103,104] However, ulcerative colitis and Crohn's disease have not been associated with preeclampsia.[93,105]

1.5 Mode of delivery

Parturition through vaginal delivery happens following increased contractility of the uterus, dilatation of the cervix and rupture of the membranes, in all of which inflammatory signaling seems important, although the physiology is not fully understood.[106] After being mostly inactive during pregnancy, the uterine myometrium starts to contract, coinciding with the release of pro-inflammatory cytokines. When collagen cross-linking in the extracellular matrix is lost, the cervix softens in order to be able to dilate. Increased expression of cytokines, among them TNF, results in dissolution of extracellular matrix components and membrane rupture.[107]

When the progression of delivery fails, there are several examples of intervening procedures used in clinical practice today. Parturition may be promoted by medical induction, intensifying the contractility of the uterus with amniotomy or oxytocin administration, or may be mechanistically facilitated by use of forceps or vacuum extraction. Cesarean section may be performed if considered necessary according to maternal or fetal factors. Although in most cases not a complicated procedure, the risk of re-hospitalization is increased when delivery is by cesarean section.[108] Cesarean section has been linked to increased risks of childhood inflammatory disease, including IBD, possibly explained by the fact that the infant is not as exposed to the maternal microbial flora in the birth canal when birth is by cesarean section compared to by vaginal delivery.[109]

1.6 Birth outcomes

Normal gestational age of human pregnancy has been estimated to 281-284 days, depending on if estimation is by ultrasound or counting days from last menstrual period.[110] Preterm birth is defined by birth at a gestational age of less than 37 weeks (259 days), as proposed by the World Health Organization in the 1970s.[111] Being born before 37 weeks is associated with significant morbidity, both in the short- and long-term perspective, with risks inversely related to gestational age.[112,113] The prevalence of preterm birth in Sweden is around 5-6% and about 80% of those infants are born late preterm, i.e. in week 34-36.[114] Risk factors for preterm birth include family history, previous preterm birth, maternal age, short inter-pregnancy interval, smoking and multiple gestation.[115]

Because of different etiologies, spontaneous preterm birth and medically induced preterm birth are often considered separately. With spontaneous onset, the process

begins with premature labor or with preterm premature rupture of the membranes.[116] Medical induction resulting in preterm birth is often due to a combination of maternal and fetal indications, such as preeclampsia, intrauterine growth restriction and fetal distress.[117]

Low birth weight is defined as a birth weight below 2500 g. This measure is a crude estimate of fetal growth with the limitation that it does not take gestational age into account. An infant born preterm is expected to have a lower birth weight than an infant born at term, without being growth restricted. Instead, small for gestational age (SGA), in which birth weight is adjusted for sex and gestational age, may be used as measure. SGA is usually defined relative to the general population, as adjusted weight in the lower 10th percentile or below 2 standard deviations of the mean. SGA may be a better indicator of intrauterine growth restriction than low birth weight, though still affected by other factors as well, such as short stature in parents and asymmetrical growth. SGA has been associated with adverse outcomes such as stillbirth, neonatal death, respiratory disease and neurodevelopmental disorders.[118,119]

Stillbirth is defined as fetal death late in pregnancy, before or during labor. However, the gestational week from which fetal death is classified as stillbirth and not miscarriage varies between countries and over time.[120] Risk factors for stillbirth include infection, smoking, poor nutritional status, birth defects and placental disorders such as preeclampsia and placental abruption.[120] The majority of cases are classified as unexplained, and half of these are stillbirths with a fetus that is SGA, thus linking stillbirth to placental dysfunction and possibly to ischemic placental disease.[120]

The Apgar score, developed by Virginia Apgar in 1953, is used to assess infant status just after birth.[121] It includes five separate assessments each earning 0, 1 or 2 points, later described in the following mnemonic: A for appearance, P for pulse, G for grimace, A for activity and R for respiration. In Sweden, Apgar scores within the first minute after birth, at five minutes and at ten minutes are systematically recorded. Apgar scores may predict adverse outcome and Apgar score below 7 at five minutes denotes a frequently used cut-off when studying risks of neonatal mortality and morbidity.[122]

In neonatal hyperbilirubinemia, increased levels of bilirubin are seen in infant blood due to a greater production and slower metabolism early in life. Although hyperbilirubinemia in the majority of cases is a normal physiological reaction, excessive amounts of bilirubin can cause neurological disorders.[123] Preterm infants have higher levels than term infants, and the level at which therapeutic phototherapy is indicated differs.[124] Preterm infants are also at higher risk to present with hypoglycemia, because of a higher demand of glucose per time unit, smaller stores of glycogen and a less effective metabolism to convert other nutrients to glucose than infants born at term.[125] SGA, preterm birth and maternal diabetes are risk factors for hypoglycemia.[126]

1.7 Birth defects

Birth defects or congenital abnormalities, are defined as structural abnormalities that are present at birth.[127] Birth defects are a heterogeneous group of conditions, affecting different organs and functions. The heterogeneity poses a challenge for research. First, the definition and classification of different entities is not clear-cut, and various have been used in studies, making comparisons of results difficult.[128] The European Surveillance of Congenital Anomalies (EUROCAT), a European collaborative register, uses the classification of the International Classification of Diseases (ICD).[129] Here, subgroups of defects are formed based on the organ system the defect has occurred in. Second, not all defects may be considered when reporting a prevalence. Birth defects are often divided into major and minor depending on their severity. Many studies exclude minor defects, because of their supposed lesser relevance, but also because of the lesser probability of these being reported. Studies may also exclude chromosomal defects, e.g. Down syndrome. Third, most birth defects are detected during the neonatal period, but some may be diagnosed later, adding significance to the follow-up time used. Consequently, the prevalence of birth defects in Sweden has been reported to be between 1.5% in the Swedish Malformation Register and 4.5% in register-based studies using data from the Medical Birth Register and the Patient Register, depending on the definition.[130-132] Another challenge in teratology is that some induced malformations will also cause spontaneous abortion, and prevalence estimates are principally limited to assessment of completed pregnancies that have resulted in live- or stillbirth.[128]

For the majority of birth defects, 65-70%, the etiology remains unknown. Around 20% are genetic, 3-5% chromosomal or cytogenetic and 3-4% are attributed to maternal morbidity such as rubella, cytomegalovirus, HIV and diabetes.[133-135] Merely 2-3% are suggested to be caused by environmental or medical teratogens.[135] Each defect is in most cases extremely rare, and identifying associations between potential teratogens and specific birth defects in observational studies is difficult.[136] Consequently, data confirming teratogenicity were considered sufficient for only a small minority of drugs whose use is not recommended in pregnancy by the US Food and Drug Administration.[2]

It is important but challenging to consider the plausibility of a potential association between drug exposures and birth defects. During pregnancy, the embryo, which is to later become the fetus, is varyingly vulnerable. The first weeks of gestation (15-60 days after conception) are considered particularly susceptible to harmful effects, although there is some variability.[137] The dose of the exposure, which may depend on potential of placental transfer, genetic or gestational factors of metabolism, are of importance when considering biological plausibility.[135]

One of the incentives for the Nordic medical birth registers was the 1960s discovery that thalidomide, *Neurosedyn*, a sedative and hypnotic drug, could cause limb defects in the offspring if taken by pregnant women. It was reported that 50% of infants that were exposed during a certain critical period of embryogenesis were affected.[138] Thalidomide is still used today to treat leprosy and multiple myeloma and, in exceptional cases, Crohn's disease, probably exerting its effect through TNF-inhibition.[139]

1.8 Chronic inflammatory disease and its treatment during pregnancy

Inflammatory bowel disease and pregnancy

In a case series report published in the *New England Journal of Medicine* in 1952, Patterson et al. discussed the advisability of pregnancy in women with ulcerative colitis coming to the following conclusion: [140]

> *"Pregnancy that occurs during an inactive stage of ulcerative colitis is usually well tolerated. Pregnancy in a patient who is having mild and moderately active symptoms may produce variable effects. In some patients there is marked improvement; in others there is definite aggravation. If possible, pregnancy should be delayed until the colitis is quiescent, but in the majority of our patients, once it occurred, regardless of symptoms, the pregnancy was carried to term with viable children. Ulcerative colitis that develops during pregnancy is an extremely virulent disease and may be fatal."*

It is remarkable that the rationality of the conclusion still holds today, after decades of research. However, the question of causality between adverse pregnancy outcome and IBD remains unanswered. Also, since the report, medical management has improved greatly, and fatality in active disease is no longer of great concern. Instead, knowledge about the effects of medical treatment is warranted.

It seems women with IBD have fewer children than women in general, however, with a few exceptions, fertility does not seem to be decreased.[141] One study published in 1986 of fertility in Crohn's disease, which included a questionnaire, reported significant infertility, but as the authors pointed out, curiously 23% of women with Crohn's disease had been advised to avoid or terminate pregnancy, compared to 8% in the comparison group.[142] Instead, several studies, also based on questionnaires, to women with IBD have reported that the childlessness is voluntary to the greater part.[143,144] Women affirm concerns for heritability of the diagnosis, exacerbations of the disease and teratogenicity of treatment.[145-147] All studies concluded that women's views seemed exaggerated compared to the existing knowledge about pregnancy and IBD, and that women should be better informed by their treating doctor.[143] Decreased fertility, i.e. failure to conceive within one year, has, however, been observed for women that have undergone ileo-anal pouch anastomosis.[148,149] Recent data points to a reduced risk if the procedure is performed laparoscopically.[150]

Once pregnant, women with Crohn's disease have a similar risk of relapsing with flares during pregnancy as do non-pregnant women in the same time period.[151-154] For women with ulcerative colitis, however, more frequent relapsing has been observed in the first and second trimesters and post-partum in a recent prospective study.[155] Maternal pregnancy complications have not been extensively studied in IBD. An increased risk of venous thromboembolism has been reported among women hospitalized during pregnancy in one study.[93] In two other studies, aggregates of different pregnancy complications were associated with IBD, but the studies lacked power to draw conclusions about separate complications.[105,156]

Vaginal delivery is generally recommended for women with IBD. However, perianal tears acquired during delivery may affect fecal continence and bowel function. Current

knowledge is divergent regarding whether vaginal delivery is a risk factor for fecal incontinence in women with IBD.[157,158] In women with already altered pelvic anatomy and bowel function, after ileo-anal pouch surgery in particular, cesarean section may be indicated.[159,160] Active perianal disease in Crohn's disease does motivate cesarean delivery, and may predict severe perianal laceration if delivery is vaginal.[161,162] Several studies have reported an approximately doubled frequency of cesarean section in women with IBD.[131,163,164]

The most consistently reported increased risks for adverse birth outcomes for women with IBD are for preterm birth (Table 1.2).[131,141,163,165-171] Some studies have not reported this association, the majority of them were restricted by small numbers.[105,156,172-174] One crossover study from Denmark that did not report an overall risk of preterm birth, included pregnancies of women that had not yet been diagnosed in the analysis.[175] When only considering women after diagnosis, the risk was substantially increased, strongly supporting an association. Two studies reported an increased risk of preterm birth for Crohn's disease, but not for ulcerative colitis.[141,176] That these studies included fewer cases of ulcerative colitis than Crohn's disease, while the latter is actually less common of the two, suggests that apart from the limited size of the studies, women may have been misrepresented. Yet another study of limited size reported the opposite, with ulcerative colitis but not Crohn's disease being associated with preterm birth.[177]

It has long been suspected that disease activity affects the birth outcomes in women with IBD. Eight studies included assessment of disease activity based on clinical data from medical charts. Three of them indicated that disease activity strengthened the association,[156,169,173] while three did not.[105,166,172] The remaining two studies did not control for disease activity in the formal analyses.[167,177] Two other large studies including data from Denmark and Sweden used register data to assess disease activity as defined by previous hospital admission, surgery and disease duration, and disease activity was indeed associated with preterm birth.[131,163]

Drug treatment was controlled for in three of the listed studies in Table 1.2. One found that treatment with a combination of immunosuppressive drugs increased the risk of preterm birth in ulcerative colitis.[172] The other two did not report significant effects of drug treatment.[105,166] Two Danish studies focused on disease activity and drug treatment among women Crohn's disease separately and found a non-statistically significant association between disease activity and preterm birth. The association between preterm birth and thiopurine treatment was, however, clear.[178,179]

The risk of stillbirth for women with IBD has been studied previously with inconclusive results, mostly due to the rarity of the event. Two Danish population-based studies published in 2000 reported elevated, but imprecise risk estimates for ulcerative colitis and Crohn's disease, respectively.[170,175] In a meta-analysis published in 2007, no association was reported.[164] Since then, two large studies including the Danish and Swedish populations have reported no increased risks of stillbirth for Crohn's disease or ulcerative colitis.[131,163] In four studies, cases were too few to analyze risk ratios, although in two of them, frequencies were doubled compared to the comparison group and in the other two, a single case of stillbirth occurred in women with Crohn's disease, but there

Table 1.2 Selected observational studies reporting risk of preterm birth in women with IBD compared to women without IBD

Study	Diagnosis	Setting	IBD n/N	Comparison n/N	OR	95% CI	Treatment	Disease activity
Baird et al. 1990[141]	CD	NC, USA	21/84	27/273	3.2	1.6 - 6.1		Disease duration
	UC		6/41	27/273	2.4	0.8 - 6.9		
Bengtson et al. 2010[166]	IBD	S East Norway	23/119	47,970/479,693	2.2	1.4 - 3.4	Included in analyses	Activity in medical charts
Bortoli et al. 2011[172]	CD	12 European countries	13/145	11/145	0.9	0.4 - 2.1	Included in analyses	Activity indices and surgery in medical charts
	UC		12/187	14/187	1.0	0.4 - 2.4		
Bush et al. 2004[156]	IBD	NY, USA	13/116	5,640/56,398	NC,NS	-	Presented, not included in analyses	Activity indices and surgery in medical charts
Dominitz et al. 2002[176]	CD	WA, USA	23/155	93/1308	2.3	1.4 - 3.8	-	-
	UC		11/107	93/1308	1.5	0.8 - 2.9		
Elbaz et al. 2005[167]	IBD	Negev, Israel	25/127	47/508	2.0	1.2 - 3.5	-	Activity in medical charts
Fedorkow et al. 1989[173]	IBD	Alberta, Canada	17/98	12/98	1.5	0.7 - 3.3	-	Activity in medical charts
Fonager et al. 1998[170]	CD	Denmark	37/510	144/3018	1.6	1.1 - 2.3	-	-
Kornfeld et al. 1997[168]	IBD	Sweden	47/756*	10,270/239,017	1.5	1.1 - 2.0	-	-
			14/756†	2,471/239,017	1.8	1.1 - 3.1		
Lin et al. 2010[165]	UC	Taiwan	23/196	98/1,568	1.9	1.2 - 3.1	-	-
Mahadevan et al. 2007[105]	IBD	Northern CA, USA	28/308	36/274	NC,NS	-	Included in analyses	Activity and surgery in medical charts
Norgard et al. 2000[175]	UC	Denmark	82/1523	415/9042	1.2	0.9 - 1.5	-	Disease duration
Oron et al. 2012[169]	IBD	Tikva, Israel	10/75	12/225	NC, S	-	Presented, not included in analyses	Activity and surgery in medical charts
Porter et al. 1986[177]	CD	Oxford	6/38	6/76	NC, NS	-	Presented, not included in analyses	Activity in medical charts
	UC		7/44	6/88	NC, S	-		
Raatikainen et al. 2011[174]	IBD	Kuopio, Finland	12/135	2,352/38,285	1.2	0.6 - 2.5	Presented, not included in analyses	-
Stephansson et al. 2010[163]	CD	Sweden & Denmark	209/2,377‡	45,639/869,202	1.8	1.5 - 2.1	-	Previous surgery
			40/2,377§	8067/869,202	1.9	1.4 - 2.5		
Stephansson et al. 2011[131]	UC	Sweden & Denmark	235/2,637‡	45,613/868,942	1.8	1.5 - 2.1	-	Hospitalization, surgery, disease duration
			32/2,637§	8,075/868,942	1.4	1.0 - 2.0		

*IBD - inflammatory bowel disease. CD - Crohn's disease. UC - ulcerative colitis. OR - odds ratio. CI - confidence interval. NC - not calculated. NS - p >0.05 in comparison. S - p ≤0.05 in comparison. *Week 33-36. †Week <33. ‡Week 32-36. §Week <32. Numbers have been rounded to a single decimal.*

were no cases in the comparison group.[105,167,172,180]

Fetal growth restriction as measured by low birth weight and SGA have been reported for women with Crohn's disease and ulcerative colitis.[131,141,163,165] In contrast, some studies have not been able to confirm this finding.[164,172] The divergence may pertain to different selection of included women, were one study showing no association may have been influenced by the low prevalence of women with active IBD in the study.[172] The magnitude of the association in general seems to be similar in Crohn's disease and ulcerative colitis, at around 30% increase, but some studies have implied a stronger association between Crohn's disease than ulcerative colitis and fetal growth restriction.[131,156,163,176] It is possible that poor maternal nutritional status which is frequent in women with IBD and a determinant of SGA, contributes to the association between IBD and fetal growth restriction.[181,182]

Chronic inflammatory disease and risk of birth defects

Despite the difficulties in studying birth defects in observational studies because of their rarity, attempts have been made. For ulcerative colitis, at least two studies have reported increased risks of birth defects.[176,183] The mechanism and biological plausibility of inflammatory disease having a teratogenic effect have not been well-described. It has been hypothesized that the changes in the level of nuclear transcription factor NF-κB, which is both stimulated by and triggers the production of TNF, may alter cellular proliferation and apoptosis, leading to birth defects.[184] However, recently, large population-based studies in Norway, Denmark and Sweden reported no association between birth defects and either ulcerative colitis, Crohn's disease or rheumatoid arthritis.[131,163,185] Drug treatment was not taken into account in these studies. A recent study of the risk of birth defects in IBD reported no increased risks whether treated with 5-ASA, corticosteroids or thiopurines or not.[186]

Early studies on corticosteroid exposure during pregnancy reported an increased risk of cleft-palate defects in mice.[187] An association with cleft-palate defects and corticosteroids in humans has been observed in some studies[188,189] but in two large studies, refuted, since.[190,191] Sulfasalazine and 5-ASA are generally considered safe, as supported by a meta-analysis in 2008.[192] Folic acid supplements are recommended for women treated with sulfasalazine since a decreased intestinal absorption of folic acid has been observed.[193] A biologically plausible teratogenic effect of thiopurines has been presented, as they affect DNA synthesis and repair in dividing cells. However, results in observational studies have been contradictory. One study found risks of birth defects after thiopurine exposure to be similar to those reported in women with IBD but without thiopurine treatment.[194] Two Nordic studies found imprecise increased risks.[132,178] The conceived studies on thiopurine treatment during pregnancy were included in a meta-analysis that could not determine any association between thiopurines and birth defects.[195] Methotrexate is considered to have teratogenic effects based on case reports recently summarized in a review article and is contraindicated during pregnancy.[196]

Anti-TNF treatment and risk of birth defects

As they were only recently introduced, there is a particular lack of data on anti-TNF substances and birth defects. In terms of biological plausibility of a teratogenic effect of anti-TNF treatment, placental transfer is important. It is known that IgG antibodies may cross the placenta by facilitated transport starting from the second trimester and the transport increases during the remainder of the pregnancy.[197] Consequently, infliximab, etanercept and adalimumab have been detected in cord blood at delivery.[198-200] Certolizumab-pegol, lacking the required Fc component required for placental transport, is theoretically prevented from placental transport in late pregnancy However, reports of IgG transfer into embryonic tissue at 4 weeks and separate reports of low levels of certolizumab-pegol detected in cord blood suggest yet unidentified mechanisms for placental transport.[198,201] Thus, placental transfer of anti-TNF substances in the first trimester, during organogenesis, cannot be completely ruled out.

One study reported on an association between anti-TNF treatment and the co-occurring defects of the VACTER-L association (vertebral anomalies, anal atresia, cardiac effect, trachea-esophageal defects, renal defects and limb defects), but the study, based on the US Food and Drug Administration database of reported adverse events, was hampered by recall bias and lack of comparison group.[202] Other studies have been more reassuring regarding birth defects, although small in size.[203-205] Preliminary results from the TREAT (Crohn's Therapy, Resource, Evaluation, and Assessment Tool) registry for patients with Crohn's disease, and the PIANO (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes) register for women with IBD indicate no increased risks of birth defects.[206,207] A very recent study of 485 exposed pregnancies in a European multi-center study reported increased risks of major birth defects.[208] Recruitment was made from spontaneous telephone inquiries made to teratology information services and interview follow-ups, which may result in selection bias.

2 Objectives

The overall objective of this thesis was to add to the knowledge of the effects of chronic inflammatory disease and its treatment on pregnancy and birth outcomes.

Specific objectives

1. To assess the association between IBD and pregnancy complications.
2. To assess the association between IBD and adverse birth outcomes.
3. To assess the risk of birth defects in infants to women with chronic inflammatory disease treated with anti-TNF in early pregnancy.
4. To assess the relationship between preterm birth, disease activity and drug treatment for IBD.

3 Material and methods

An overview of the material and methods used in this thesis is presented in table 3.1.

3.1 Setting

The studies included in this thesis were all set in Sweden, with study III also comprising data from Denmark. Both countries have long-standing traditions of keeping records of their inhabitants and individual data has been collected for centuries. The second half of the 20th century saw the parallel development of the Swedish and Danish national health registers that have provided data for numerous epidemiological studies. The unique personal identification number can be used to merge data from various registers and from medical charts so that study subjects can be followed from the antenatal period, via birth and on to health care visits and drug prescriptions later in life, and finally to records of their causes of death. In Sweden and Denmark alike, healthcare is public and equally accessible to all residents. In addition, reporting to the registers is mandatory for healthcare providers, promoting high coverage. With almost complete coverage, study populations can be selected in an essentially non-biased manner.

3.2 Data sources

Birth registers

The Swedish Medical Birth Register contains data on more than 99% of all births in Sweden from 1973 and onwards.[209] Women and their infants are linked in the register. Data are prospectively collected and entered through structured forms filled out by midwives and physicians throughout pregnancy, delivery and the neonatal period. Information on reproductive history, smoking, maternal comorbidity according to ICD codes, drug treatment by Anatomical Therapeutic Chemical classification (ATC), height and weight are recorded at the first visit to antenatal care, typically at the end of the first trimester. From then on, information regarding changes in drug treatment, comorbidity and occurrence of pregnancy complications are continuously added to the forms. At birth, mode of delivery and measures of gestational age, birth weight and height, SGA and Apgar score at 1, 5 and 10 minutes are recorded. Estimation of gestational age and start of pregnancy are primarily based on ultrasound examination, which is offered to all women, and carried out in the majority of women, in early second trimester. When ultrasound measurements are missing, gestation is estimated based on first day of last menstrual period.

Previously, pregnancies ending in the delivery of a stillborn infant before 28 weeks of gestation were not entered in the Swedish Medical Birth Register. In July 2008, this time limit was lowered to 22 weeks of gestation. Spontaneous and induced abortions before 22 weeks are therefore not represented in the register.

The Danish Medical Birth Register was established in 1968 and computerized in 1973. It has many features that are similar to its Swedish equivalent regarding recorded data on pregnancy, delivery and neonatal period. [210,211] Stillbirth is recorded from 22 weeks.

Table 3.1 Overview of studies included in the thesis

	Study I	Study II	Study III	Study IV
Design	Cohort	Cohort	Cohort	Case-control
Population	All births to women with IBD and 5 matched births to women without IBD in Sweden	All births in Sweden	All births in Denmark and Sweden	All preterm births to women with IBD, and an equal number of control births in Sweden
Number	12,956; 857 CD, 1304 UC, 10,885 non-IBD	470,110; 1220 CD, 1833 UC, 467,057 non-IBD	1,272,424; 683 exposed to anti-TNF	476; 237 cases, 239 controls
Comparison	IBD versus non-IBD	IBD versus non-IBD	Anti-TNF treatment versus no anti-TNF treatment	IBD; preterm versus later gestational age
Data sources	- Medical Birth Register - Patient Register - Prescribed Drug Register	- Medical Birth Register - Patient Register - Prescribed Drug Register - Medical charts for validation	- Danish and Swedish birth registers - Patient registers - Prescribed drug registers - ARTIS - PsoReg	- Medical Birth Register - Patient Register - Prescribed Drug Register - Medical chart review
Time of data collection	October 2006 - December 2009	July 2006 - December 2010	Denmark: January 2004 - December 2012 Sweden: July 2006 – December 2012	July 2006 - December 2010
Outcomes	Risk estimates for: Hypertension Gestational diabetes Thrombosis Antepartum hemorrhage Induced delivery Instrumental delivery Planned cesarean delivery Emergency cesarean delivery Postpartum hemorrhage	Risk estimates for: Preterm delivery Spontaneous preterm delivery Low birth weight SGA Low APGAR at 5 min Stillbirth Hypoglycemia Hyperbilirubinemia	Risk estimates for: Birth defects; in general and by organ-system subgroup	Risk estimates for exposures: Reproductive history Comorbidity Disease history Disease activity Drug treatment

IBD - inflammatory bowel disease. CD - Crohn's disease. UC - ulcerative colitis.

Patient registers

The Swedish Patient Register contains records of in-patient care visits with almost complete coverage since 1987 and reporting of out-patient care visits has been mandatory since 2001.[212] However, the coverage in the out-patient register is lower, in general around 80%, mostly due to failure to report visits in private health care.[212] Similarly, the Danish Patient Register was started in 1977 with in-patient health care and

public out-patient health care was added in the 90s.[213] Although private health care givers are also obliged to report, coverage is lower for out-patient care.[214] Each visit or a period of hospitalization is recorded in the patient registers with a list of the patient's main diagnosis and any supplemental diagnoses according to ICD codes and surgical procedures according to the Nordic Classification of Surgical Procedures (NCSP) at discharge. As of 1994 in Denmark and as of 1998 in Sweden, the 10th version of ICD (ICD-10) has been used. Visits to primary care centers are not entered into the national patient registers, limiting the validity for diagnoses that are typically managed out of hospital, such common infections.

Prescribed drug registers

The Swedish Prescribed Drug Register was established in July 2005, and holds records of all filled prescriptions, whether coming from primary or specialist care, by ATC codes and date of filling.[215] Denmark has recorded prescription data in an equivalent register since 1994.[216] Medications for continuous treatment are typically prescribed to last for three months. Some patients will still fill their prescriptions irregularly. This creates a challenge in studying maintained drug treatment, as the next prescription may be filled earlier or later than anticipated. Another pitfall is the lack of data on the indication for which the drug has been prescribed.

ARTIS and PsoReg

In study III, we studied treatment with anti-TNF drugs. Some of these drugs, infliximab in particular, which requires intravenous administration, are given in-hospital. Therefore, only some of the treatment can be identified through prescriptions in the Swedish Prescribed Drug Register.[215] To make data more complete, we added information from disease-specific quality registers ARTIS (Anti-Rheumatic Therapy in Sweden) and PsoReg (The Swedish Registry for Systemic Psoriasis Treatment). ARTIS was set up in 1999 with the aim to monitor biologic therapy in rheumatoid arthritis patients.[217] With time, and extended indications for the biologics, patients with ankylosing spondylitis and psoriatic arthritis have also been included. In 2015, the coverage of anti-TNF treatment as compared to the Prescribed Drug Register was estimated at 95% for rheumatoid arthritis and 86% for ankylosing spondylitis and psoriatic arthritis.[218] Infliximab was not included in the comparison because of the expected incompleteness of its representation in the Prescribed Drug Register, but it is likely that the results can be extrapolated to infliximab also. PsoReg was set up in 2007 to monitor psoriasis and psoriatic arthritis patients, following the approval to treat psoriatic disease with biologics in 2004.[219] The register is nationwide and reported a coverage of 65% in 2013.[220]

Medical charts

In study IV, medical charts were collected to obtain information on clinical features of IBD in a selection of pregnant women. Heads of department of obstetrics, gastroenterology and internal medicine nationwide were approached to get permission to extract information from the charts. The collection of data was successful, and covered 96.7% of the identified births.

3.3 Study population

All women and singleton infants recorded in the Swedish Medical Birth Register constituted the study population for studies I, II and IV. For study III, singleton, as well as multiple gestation, births in the Swedish and Danish birth registers were included. Some women gave birth more than once, and each set of pregnancy, birth and infant was considered separately. The studies extended over different time periods. For Sweden, three studies started on July 2006 in order to get complete coverage of maternal drug treatment in the Prescribed Drug Register at least one year before delivery. Study I started in October 2006 to have data on maternal drug treatment 6 months before conception. In all studies, pregnancy was studied in sections of 90-day periods. We defined a "trimester 0" as the 90 days leading up to start of pregnancy as defined by ultrasound examination or last menstrual period. Trimester 1 and 2 were defined as the two following 90-day periods leading up to trimester 3. Trimester 3 could be either shorter or longer than 90 days, and always ended on the date of delivery. For the small minority of births occurring before 26 weeks, there was no third trimester to study.

3.4 Study I and study II

Study I and study II included all births to women with Crohn's disease and ulcerative colitis from October 2006 to December 2009 and from July 2006 to December 2010, respectively. The other main difference in study design was the comparison group. In study I, the comparison group was composed by including five births to women without IBD and matched to the births by women with IBD. Matching factors were maternal age, parity and year and month of the delivery. In study II, all 467,057 births to women without IBD were included for comparison.

Diagnoses and disease activity of Crohn's disease and ulcerative colitis

Diagnoses of Crohn's disease and ulcerative colitis were defined as the corresponding ICD-10 codes recorded either in the Patient Register or in the Medical Birth Register. The ICD-10 codes are listed in Table 3.2. To be defined as diagnosed with IBD, we required either one in-patient discharge diagnosis, two out-patient diagnoses, or one out-patient diagnosis followed by a drug prescription of sulfasalazine, 5-ASA, thiopurine or anti-TNF. The majority of women were identified with the first two criteria. Some women had been diagnosed with both Crohn's disease and ulcerative colitis, in which case, the latest recorded diagnosis was used.

Table 3.2 ICD-10 codes used for diagnoses of chronic inflammatory disease

Diagnosis	ICD-10
Crohn's disease	K50 (+M074, M091 in study III)
Ulcerative colitis	K51 (+M075, M092 in study III)
Rheumatoid arthritis	M05-06
Psoriatic arthritis	L405, M070-M073, M090
Psoriasis	L40 (not L405)
Ankylosing spondylitis	M45

A proxy model for disease activity, presented in Box 3.1, was constructed with the available register data according to exposures in trimester 0-3. In the analyses, women in each disease activity category were compared to women without IBD.

In study II, we presented a validation study of the disease activity proxy model. From obtained copies of medical charts, clinical data on disease activity for a subset of 88 women who gave birth between July and December 2006 was compared to the proxy model. To be eligible, they had records of either at least one in-patient visit or two or more out-patient visits because of IBD during pregnancy, implying flaring disease.

Box 3.1 Disease activity proxy model based on register data

Flaring disease	Prescription of systemic corticosteroids Prescription of rectal treatment following endoscopic examination In-patient main discharge diagnosis of IBD Surgical procedure related to IBD
Maintenance treatment	Treatment with sulfasalazine, 5-ASA, thiopurine or anti-TNF
Inactive disease	No treatment, in-patient discharge diagnosis, maintenance treatment or surgery

Outcomes study I

Hypertensive disorders included gestational hypertension, pre-eclampsia and eclampsia. Gestational diabetes was defined by the specific ICD-10 code, to avoid inclusion of women with pregestational diabetes. Venous thromboembolism included pulmonary embolism, deep vein thrombosis, portal vein thrombosis and cerebral venous sinus thrombosis. For this outcome, the risk in the post-partum period was also assessed. Antepartum hemorrhage included both unspecified bleeding and placental abruption. For delivery complications, we studied start of delivery by induction and ending of delivery by instrumental delivery, planned or emergency cesarean section. Postpartum hemorrhage was defined as hemorrhage >1000 ml or unspecified bleeding followed by blood transfusion. Perianal tear was defined by ICD-10 codes for 3rd and 4th degree tears.

Outcomes study II

Preterm birth was defined as delivery before 37 weeks of gestation. Spontaneous preterm birth meant those starting with either labor or rupture of the membranes as recorded in the Medical Birth Register. Premature rupture of the membranes was also assessed. Low birth weight was defined as a birth weight of less than 2500 g. Small for gestational age was assessed in relation to the entire birth cohort by the lower 90th percentile and below 2 standard deviations. Low Apgar score was defined by a score of 7 or lower at 5 minutes. The prevalence of stillbirth was assessed, and stillbirth was defined as fetal death after 28 weeks of gestation between 2006 and June 2008. From July 2008

the gestational age limit was set to 22 weeks of gestation. Hypoglycemia and hyperbilirubinemia were also assessed.

3.5 Study III

In this study, we included all infants that were born between January 2004 and December 2012 in Denmark and between July 2006 and December 2012 in Sweden. The study start for Denmark was set to January 2004 because we assumed that after a few years of availability, anti-TNF would be used in pregnancy not only in extraordinary cases. All data were managed at Karolinska institutet with the permission from the Danish Data Protection Agency and our Danish collaborators.

Anti-TNF treatment and diagnoses of chronic inflammatory diagnoses

We identified women that had been treated with anti-TNF from (i) the Swedish and Danish prescribed drug registers, (ii) the Swedish Medical Birth Register, (iii) the Danish Patient Register and (iv) the Swedish disease-specific registers ARTIS and PsoReg. The diagnoses according to ICD-10 codes as presented in Table 3.2 leading to anti-TNF treatment were extracted from the same sources and the Swedish Patient Register, with most women identified in the patient registers. Similarly, women diagnosed with chronic inflammatory disease and not exposed to anti-TNF were identified. For patients diagnosed with more than one chronic inflammatory disease, the latest diagnosis was used. For the few women where more than one disease was recorded at the last visit during pregnancy, we used the following hierarchy: Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and finally psoriasis. In addition to infants to women with chronic inflammatory disease, we included infants of the general population as a frame of reference for descriptive purposes.

Outcomes

Information on infants concerning diagnoses of major birth defects was obtained from the birth registers and the patient registers, following the infants up to one year of age. Birth defects were assessed as any major birth defect, and birth defects by 12 organ system subgroups according to EUROCAT classification (Table 3.3). The prevalence was reported for infants to women with anti-TNF treatment, infants to women with chronic inflammatory disease without anti-TNF treatment and for infants of the general population. Hospital visits and surgery procedures according to NCSP, specific to the observed cases of birth defects were reported. Formal risk comparisons were limited to infants to women with chronic inflammatory disease.

Table 3.3 Organ system subgroups for birth defects

Nervous system	Cleft, lip, palate	Limbs
Eye, ear, head and neck	Digestive system	Musculoskeletal system
Cardiovascular system	Genital organs	Chromosomal
Respiratory system	Urinary organs	Other

3.6 Study IV

From study II, we selected the 246 live-born singleton preterm births among women with IBD between July 2006 and December 2010 to conduct a case-control study and assess risk factors for preterm birth. The cases were randomly matched by maternal age in years, parity (primiparous/multiparous) and IBD diagnosis (Crohn's disease/ulcerative colitis) to controls who were women with IBD and who had not yet given birth at the gestational age that the case preterm birth occurred. Medical charts of 96.3% cases and 97.2% controls were obtained and scrutinized.

Exposures

From the Medical Birth Register, we obtained information on maternal smoking in early pregnancy and body mass index (BMI) in kg/m2. We also determined previous preterm birth and short inter-pregnancy interval in multiparous women. Maternal comorbidity was defined by diagnoses recorded in the Patient Register and included hypertension, diabetes and other chronic inflammatory disease. We also identified women who had undergone surgery related to IBD at some time before pregnancy, perianal disease during pregnancy and in-patient visits for IBD during pregnancy. Infections during pregnancy were studied by recorded diagnoses in the Patient Register and in medical charts, and by antibiotic prescriptions. Prescriptions of any antibiotic, as well as by subclass, were assessed.

Contrary to study I and II, we relied on medical chart data, and not register data, to assess disease activity in the three months before pregnancy (trimester 0) and the three trimesters of pregnancy. Disease activity was assessed in three levels; (i) inactive disease defined as two or fewer bowel movements daily, no blood/pus in stools, no abdominal pain or systemic symptoms, (ii) mild activity, between three or four bowel movements daily, and/or blood or pus in stools, and/or mild abdominal pain less than daily, no systemic symptoms such as fever or weight loss, or (iii) moderate to severe, or *significant*, activity, more than four bowel movements daily, and/or blood or pus daily, and/or abdominal pain either severe or daily, with or without systemic symptoms such as fever or weight loss. The rationale for this categorization of disease activity was adapted from previous Danish studies on IBD.[179] In charts with no specific information on disease activity, women were considered as having no disease activity. For a random sample of 21 charts, a double entry of records was performed by a trained research nurse who also graded the disease activity. The grading by the two independent assessors were compared and found to be in agreement. Combining data from registers and medical charts, we determined extension of inflammatory disease, for UC proctosigmoiditis/proctitis versus other, and for CD small bowel inflammation versus other, and treatment with systemic corticosteroids, local corticosteroids and 5-ASA, systemic 5-ASA, sulfasalazine, thiopurines and anti-TNF.

3.7 Statistical analyses

Logistic regression

In all the included studies, we used logistic regression to assess associations. Regression analysis can be used to study the association between variables. In binary logistic regression, the dependent variable is dichotomous in two mutually exclusive levels (case/non-case, or exposed/unexposed). We can predict the odds of being a case based on the values of the independent variables, which can be of any type; dichotomous, categorical and continuous. To model a linear relationship, the dependent variable is transformed by the logit function. The results of logistic regression are presented as odds ratios (OR) for which confidence intervals (CI) may be estimated. It is generally appreciated that when the outcome is rare (prevalence <10%), the OR approximates the risk ratio, which is a more intuitive measure to interpret the difference between populations. In case-control studies, the risk ratio cannot be estimated, as the prevalence in the population is not known.

Logistic regression can be unconditional or conditional. The latter is used to maintain the inter-strata integrity in the analysis of data where groups or pairs have been matched, as in a case-control study. A potential draw-back in conditional regression is that data can be excluded from analysis if there are missing data regarding the included variable, making the strata uninformative.

Study I and II

In study I and II, the exposure of interest was IBD (1/0), with Crohn's disease and ulcerative colitis considered separately. In study I, the unexposed had been matched by maternal age, parity and year and month of birth, while study II included all women without IBD, un-matched. Subanalyses by disease activity levels were also performed. Apart from crude analyses, adjustments were made for maternal age (13-24, 25-34 (reference) and ≥35 years), parity (primiparous/multiparous), smoking (yes/no), BMI (≤19, 20-24 (reference), 25-29, ≥30) and maternal comorbidity (yes/no). Since some women gave birth more than once and these births were therefore correlated, analyses were additionally performed using the generalized estimation equation, though not altering the results.

In sensitivity analyses in study II, we restricted the analysis to include only stillbirths after 28 weeks. Risk of hypoglycemia was adjusted for SGA and risk of hyperbilirubinemia adjusted for preterm birth. In subanalyses, timing of flare was defined as early, i.e. trimester 0 or first trimester, late, i.e. second or third trimester, or both and stratification by thiopurine exposure in stable and flaring disease was performed.

Study III

The exposure in study III was defined as anti-TNF treatment in trimester 0 or 1 (yes/no). The prevalence of any major birth defect and birth defects by organ system subgroup were presented for infants to women exposed to anti-TNF, infants to women with chronic inflammatory disease but no anti-TNF treatment and infants of the general population.

The prevalence of hospital visits and surgery specific to the birth defect were presented for the most common defects. In logistic regression analyses, the anti-TNF treated were compared to untreated women with chronic inflammatory disease. Apart from crude analyses, two additional models were constructed, the first adjusting for maternal disease (Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis) and country (Sweden, Denmark). In the second model, adjustments were also made for maternal age (13-24, 25-34 (reference) and ≥35 years), parity (primiparous/multiparous), BMI (≤19, 20-24 (reference), 25-29, and ≥30) and multiple gestation (singleton/multiple). In two separate sensitivity analyses, we excluded infants with preterm birth and included only infants to women who had records of being treated in the first trimester, respectively.

Study IV

Being a case, i.e. preterm birth, or control, i.e. birth at a later gestational age than the matched case, to a woman with IBD, formed the dependent variable in study IV. Since cases had been matched to controls, conditional logistic regression was used. Conditional strata were constructed by maternal age (13-24, 25-34 and ≥35 years), parity (primiparous/multiparous), IBD diagnosis (Crohn's disease/ulcerative colitis) and case gestational week at birth. ORs for pregestational factors smoking (yes/no), BMI (13-19, 20-24, 25-29 (reference), 30-34, 30+), previous preterm birth (yes/no), short inter-pregnancy interval (yes/no) and any comorbidity (yes/no), were presented in crude and in mutually adjusted analyses. ORs for IBD-related factors, such as extension of ulcerative colitis, extension of Crohn's disease, perianal disease, in-patient visit for IBD, highest disease activity (no activity, mild activity, significant activity) and timing of significant disease activity (no, early, late, early and late in pregnancy) were estimated. Adjusted ORs were then calculated through mutual adjustments for the disease-related factors and for previous preterm birth and comorbidity. Likewise, risks of preterm birth in association with treatment with systemic corticosteroids (yes/no), timing of treatment with systemic corticosteroids (early, late or early and late in pregnancy) and maintenance therapy (no, 5-ASA, sulfasalazine or local corticosteroids, thiopurines or anti-TNF) were assessed, adjusted by previous preterm birth and comorbidity.

Six groups of combinations of disease activity and treatment were identified and assessed according to their probability of being a case: (i) No or mild disease activity, 5-ASA, sulfasalazine, local corticosteroids or no treatment, (ii) No or mild disease activity, systemic corticosteroids, (iii) No or mild disease activity, thiopurine or anti-TNF treatment, (iv) Significant disease activity, 5-ASA, sulfasalazine, local corticosteroids or no treatment, (v) Significant disease activity, systemic corticosteroids and (vi) Significant disease activity, thiopurine or anti-TNF treatment. Subanalyses were performed for spontaneous preterm birth, medically indicated preterm birth, birth between gestational weeks 22-33 and birth between gestational weeks 34-36.

3.8 Ethical considerations

Studies on pregnancy and birth outcomes including birth defects are practically only possible to perform in an observational setting. An alternative to limit confounding could

be randomized studies, but they are in principal ethically questionable for studies of pregnant women.

In Sweden and Denmark in general, patient consent should be obtained when using individual data in research. In disease-specific register such as ARTIS and PsoReg, the patients have consented to being included in the registers. However, inclusion of individual data in the national registers does not require consent. Instead, one could say that the government has approved consent on behalf of the population, based on the notion that the potential benefits for the population outweigh the risks for the individual. An approval from one of the six regional ethical review boards in Sweden can endorse that national register data be accessed for research, after an evaluation of the soundness and importance of the research. In Denmark, an ethical approval is not required for register studies. However, the handling of data must be approved by the Data Protection Agency in both Sweden and Denmark.

Typically, register data are delivered to the research institution with unidentifiable sequence numbers. When medical chart data are needed, the personal identification number is also included, requiring more rigorous security since data can be identified. In this study, all data were handled by the unidentifiable sequence numbers and presented in aggregate analyses to minimize the violation of personal integrity.

The studies in this thesis were approved by the ethical review board at Karolinska institutet, record numbers 2006/889-31, 2007/1391-32, 2008/631-32.

4 Results

4.1 Study I

During the study period, 787 women with Crohn's disease gave birth to 847 singletons. The corresponding figures for ulcerative colitis were 1,209 women and 1,304 singletons and for women without IBD, 10,773 and 10,805. According to our disease activity proxy model, 26% of women with Crohn's disease and 37% of women with ulcerative colitis had flaring disease during pregnancy. We found that 13 % of women with ulcerative colitis received their first recorded diagnosis during pregnancy. The majority of women with Crohn's disease (56%) and ulcerative colitis (43%) were first diagnosed ≥5 years prior to the studied pregnancy.

Women with ulcerative colitis had increased risks of venous thromboembolism, with a crude OR of 3.4 (95% CI: 1.4-8.2), and 3.8 (95% CI: 1.5-9.4), after adjusting for smoking, BMI and maternal comorbidity (Table 4.1). The risks were the highest for women with flaring disease, although small numbers rendered this analysis imprecise, crude OR 20.2 (95% CI: 2.3-180), adjusted OR 25.0 (95% CI: 2.5-250). An increased risk of antepartum hemorrhage was observed for women with Crohn's disease with adjusted OR of 1.7 (95% CI: 1.1-2.5), which was the strongest for women with no activity.

Table 4.1 Pregnancy and delivery complications for women with Crohn's disease and ulcerative colitis

Crohn's disease (CD)	CD N (%)		Non-CD N (%)		Crude OR CD versus non-CD	Adjusted OR CD versus non-CD
	857	(100)	4,285	(100)		
Antepartum hemorrhage	36	(4.2)	107	(2.5)	1.7 (1.2 - 2.5)	1.7 (1.1 - 2.5)
Venous thromboembolism	3	(0.4)	12	(0.3)	1.3 (0.4 - 4.4)	1.3 (0.4 - 4.5)
Emergency cesarean delivery	93	(10.9)	324	(7.6)	1.5 (1.1 - 1.9)	1.5 (1.2 - 1.9)
Elective cesarean delivery	169	(19.7)	402	(9.4)	2.4 (2.0 - 2.9)	2.3 (1.9 - 2.8)
Ulcerative colitis (UC)	**UC N (%)**		**Non-UC N (%)**		**Crude OR UC versus non-UC**	**Adjusted OR UC versus non-UC**
	1,304	(100)	6,520	(100)		
Antepartum hemorrhage	47	(3.6)	195	(3.0)	1.2 (0.9 - 1.7)	1.1 (0.9 - 1.6)
Venous thromboembolism	8	(0.6)	12	(0.2)	3.4 (1.4-8.2)	3.8 (1.5 - 9.4)
Emergency cesarean delivery	136	(10.4)	514	(7.9)	1.4 (1.1 - 1.7)	1.4 (1.1 - 1.7)
Elective cesarean delivery	246	(18.9)	569	(8.7)	2.4 (2.1 - 2.9)	2.4 (2.1 - 2.9)

Among women with Crohn's disease and ulcerative colitis, around 30% had cesarean delivery (Table 4.1). Around 2/3 of those were elective. Crohn's disease and ulcerative colitis precipitated very similar observed risks, the adjusted ORs for emergency cesarean delivery and elective cesarean section were 1.5 (95% CI: 1.2-1.9) and 2.3 (95% CI: 1.9-2.8) for Crohn's disease and 1.4 (95% CI: 1.1-1.7) and 2.4 (95% CI: 2.1-2.9) for ulcerative colitis. However, when considering disease activity, women with Crohn's disease and

ulcerative colitis differed slightly. For women with Crohn's disease, emergency cesarean section was more common among those with flaring disease, OR 2.4 (95% CI: 1.5-3.8), whereas for ulcerative colitis, the highest risk of elective cesarean section was observed in women with no activity, OR 3.2 (95% CI: 2.4-4.3). When adjusting for previous surgery, the OR for elective cesarean section in women with ulcerative colitis and no activity was attenuated, OR 1.8 (95% CI: 1.3-2.5). We found no increased risks of hypertensive disorders, thyroid disease, gestational diabetes, postpartum hemorrhage, induced delivery, instrumental vaginal delivery or perianal tears grade 3 and 4 with any of the IBDs.

4.2 Study II

We included 1,220 singleton births to 1,026 women with Crohn's disease and 1,833 births to 1,492 women with ulcerative colitis (Table 4.2). All 467,057 births to women without ulcerative colitis or Crohn's disease occurring during the study period constituted the comparison group. Women with Crohn's disease and ulcerative colitis were less often under 25 years of age, and women with ulcerative colitis less often reported smoking, while 10 % of women with Crohn's disease reported smoking.

Table 4.2 Maternal characteristics of women with IBD compared with the general population

	Ulcerative colitis N (%)		Crohn's disease N (%)		General population N (%)	
	1,833	(100)	1,220	(100)	467,057	(100)
Maternal age at birth						
≤24years	143	(7.8)	131	(10.7)	68,592	(14.7)
25-34 years	1,256	(68.5)	813	(66.6)	296,334	(63.5)
≥35 years	434	(23.7)	276	(22.6)	102,128	(21.9)
Missing		-		-	3	
Parity						
Primiparous	827	(45.1)	545	(44.7)	210,404	(45.1)
Multiparous	1,006	(54.9)	675	(55.3)	256,653	(54.9)
Smoking in 1st trimester						
Non-smoker	1,703	(92.9)	1,058	(86.7)	416,556	(89.2)
Smoker	59	(3.2)	122	(10.0)	31,043	(6.7)
Missing	71	(3.9)	40	(3.3)	19,458	(4.2)

Among women with Crohn's disease, 45% had no activity, 28% had stable disease and 26% had flaring disease, for ulcerative colitis the proportions were 30%, 34% and 36%, respectively. Of the 438 women who gave birth more than once, 66% had similar disease activity as in the previous pregnancy. For the validation of the disease proxy model, 109 women were eligible for chart review, and we were able to collect medical charts of 88

women, corresponding to a response rate of 81%. When comparing the proxy model with medical charts, the sensitivity was 83% and the specificity was 81% (Table 4.3).

Table 4.3 Validation of disease activity model

	Medical charts		
Disease activity model	**No activity**	**Flaring disease**	
No or stable disease	29	9	*Sensitivity: 43/52 = 83%*
Flaring disease	7	43	*Specificity: 29/36 = 81%*

Risks of preterm birth were similar for women with Crohn's disease and ulcerative colitis, and did not change after adjustments for maternal age, parity, smoking, BMI and maternal comorbidity, ORs 1.7 (95% CI: 1.3-2.1) for Crohn's disease and 1.8 (95% CI: 1.5-2.1) for ulcerative colitis. Risks were slightly lower for spontaneous preterm birth, but still elevated. The highest risks for preterm birth and for spontaneous preterm birth were found among those with flaring disease. Analyses of low birth weight exhibited a similar pattern with risks for Crohn's disease in general at adjusted OR 1.9 (95% CI: 1.5-2.4) and for ulcerative colitis, OR 1.6 (95% CI: 1.3-2.0). For flaring ulcerative colitis, the risk estimate for low birth weight in the adjusted analysis was doubled, and for CD, tripled. Women with Crohn's disease had increased risks of having infants that were SGA at 2 SD, with the highest risks among those with flaring disease.

Increased risks of low 5-minute Apgar score and hypoglycemia were observed for women with flaring Crohn's disease, adjusted OR 2.2 (95% CI: 1.2-3.9) and 2.4 (95% CI: 2.4-4.0). In subanalysis adjusting for SGA, the risk for hypoglycemia was only slightly lower, OR 2.0 (95% CI: 1.1-3.5). We found a slight increase for hyperbilirubinemia in women with ulcerative colitis, which did not persist when adjusting for preterm birth. Adjusting may not have been the best option here, since preterm birth and SGA may be considered mediators of the outcome. Stratification might have been more informative. The risk of stillbirth was increased for women with Crohn's disease, with increasing risk estimates across disease activity groups to an adjusted OR in flaring disease of 4.5 (95% CI: 1.7-12), based on 11 cases among Crohn's disease, of which 4 had flaring disease.

For women with ulcerative colitis or with Crohn's disease, the risks of adverse birth outcomes were, with some exceptions, higher when flares occurred in late pregnancy. The highest risks were in women with flares in both early and late pregnancy. In general, women with flares and also treated with thiopurines had the highest risks of preterm birth and SGA. The influence of thiopurines on risks of preterm birth seemed to be independent of disease activity as higher risks were found both among women with stable disease and those with flaring disease. The forest plots in Figures 4.1 and 4.2 illustrate the estimated risks for preterm birth in different subgroups, by disease activity and thiopurine treatment. The overall estimates for Crohn's disease and ulcerative colitis are were of high precision, while smaller subgroups yielded wide, imprecise confidence intervals.

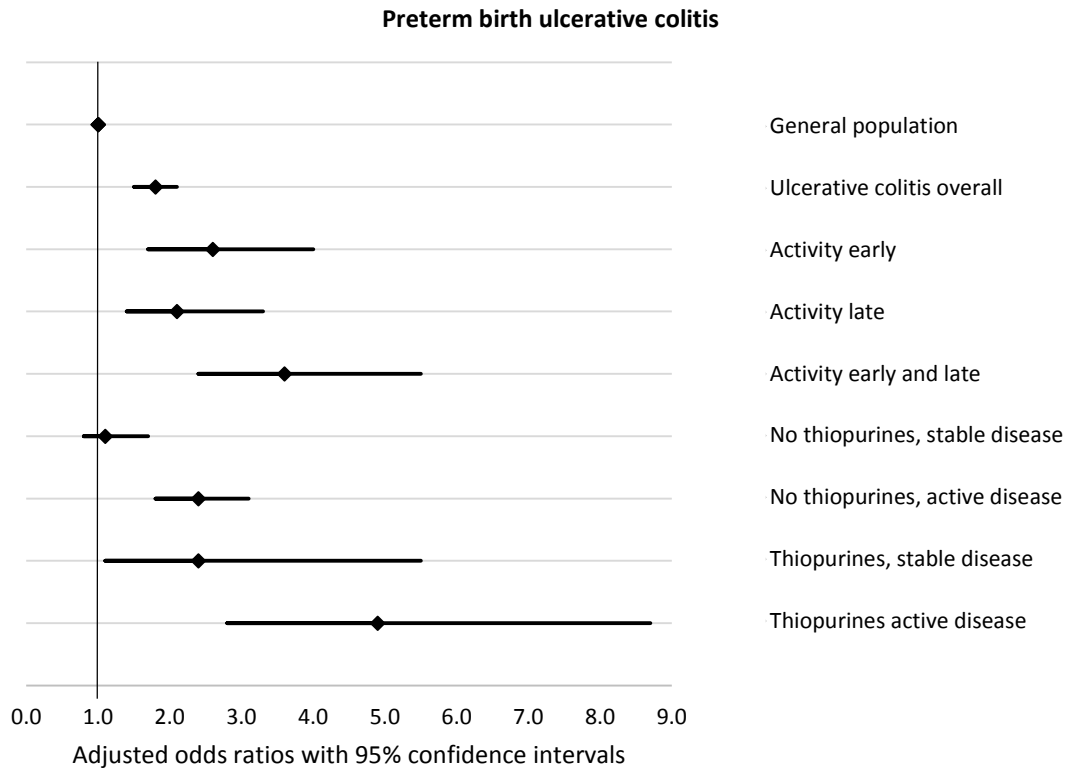

Figure 4.1 Adjusted odds ratios of preterm birth by disease activity and thiopurine treatment in women with ulcerative colitis.

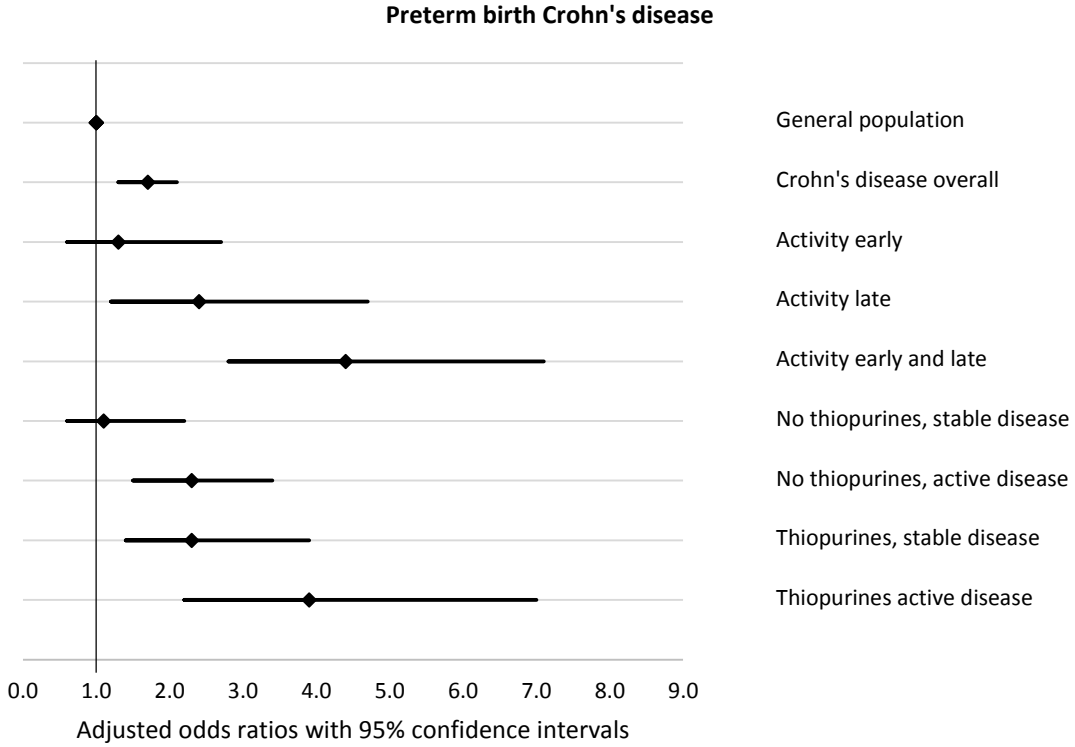

Figure 4.2 Adjusted odds ratios of preterm birth by disease activity and thiopurine treatment in women with Crohn's disease.

Activity early - activity in the 90 days before pregnancy or the first trimester. Activity late - activity in the second or third trimester. Thiopurine treatment - treatment at any time during pregnancy.

Study III

There were 1,272,424 eligible infants born during the study period in Sweden and Denmark. We identified 683 whose mothers had been treated with anti-TNF in trimester 0 or in the first trimester. Maternal rheumatoid arthritis was the most common indication for anti-TNF treatment, 51% (Table 4.4).

Among infants to women with anti-TNF treatment, 43 had at least one birth defect. Overall, the prevalence of birth defects was higher for infants born to women with anti-TNF treatment (6.3%) and for infants born to women with chronic inflammatory disease but no anti-TNF treatment (4.7%), than in the general population (4.2%). Cardiovascular, genital, and urinary defects were the most commonly reported, with similar patterns in the three groups. The most common defects after anti-TNF treatment were ventricular septal defect, atrial septal defect, congenital hydronephrosis and hypospadias and distributions of defects were generally similar between anti-TNF treatment and chronic inflammatory disease without anti-TNF. Hospital visits and surgery recorded for a specific defect diagnosis and for any diagnosis were also comparable. None of the infants with atrial septal defect, congenital hydronephrosis or hypospadias born to women with anti-TNF treatment had organ-specific surgery during the first year of life.

Table 4.4 Chronic inflammatory disease diagnoses, anti-TNF substances and birth defects

		Anti-TNF N (%)	Chronic inflammatory disease N (%)	Any birth defect*	OR (95% CI)†
Chronic inflammatory disease diagnosis	Rheumatoid arthritis	349 (51.1)	3727 (17.3)	31 (6.7)	1.4 (1.0-2.1)
	Psoriatic arthritis	38 (5.6)	911 (4.2)		
	Ankylosing spondylitis	40 (5.9)	777 (3.6)		
	Psoriasis	31 (4.5)	5529 (25.7)		
	Ulcerative colitis	54 (7.9)	6352 (29.5)	12 (5.3)	1.2 (0.6-2.1)
	Crohn's disease	171 (25.0)	4253 (19.7)		
Anti-TNF substance	Any	683 (100)	21,549 (100)	43 (6.3)	1.3 (0.9-1.8)
	Etanercept	344 (50.4)	-	24 (7.0)	1.5 (0.9-2.3)
	Infliximab	156 (22.8)	-	9 (5.8)	1.3 (0.6-2.5)
	Adalimumab	161 (23.6)	-	9 (5.6)	1.2 (0.6-2.3)
	Certolizumab	2 (0.3)	-	1 (50.0)	-
	Golimumab	4 (0.6)	-	0 (0.0)	-
	Combinations	16 (2.3)	-	-	-

**Prevalence of any birth defect among infants to women treated with anti-TNF*

† Adjusted odds ratios compared to women with chronic inflammatory disease without anti-TNF treatment

The estimated OR for any birth defect was 1.3 (95% CI: 0.9-1.8) when comparing infants to women treated with anti-TNF and infants to the untreated women with chronic inflammatory disease, adjusting for country, chronic inflammatory diagnoses, maternal age, parity, smoking, BMI and multiple birth. The adjusted ORs for cardiovascular, genital and urinary organs were 1.6 (95% CI: 0.9-2.6), 1.8 (95% CI: 0.7-3.7) and 2.2 (95% CI: 0.9-4.7), respectively. Restricting the analysis to IBD only, the OR for any birth defect was 1.2 (95% CI: 0.6-2.1) and for other diseases 1.4 (95% CI: 1.0-2.1). Restricting the analyses to those with treatment according to the first trimester only, attenuated the risk estimates birth defects, while excluding preterm birth did not change results. Adjusting for treatment with systemic corticosteroids, methotrexate, other anti-inflammatory treatment, antidiabetics, and anticonvulsants had only minor effects.

4.3 Study IV

The distribution of available charts by department was similar for cases and controls: gastroenterology/internal medicine and obstetrics (43.5 versus 39.3%), obstetrics only (43.5 versus 49.4%) and gastroenterology/internal medicine only (13.0 versus 11.3%). The proportion of women that had been prescribed antibiotics during pregnancy were similar, even when considering different subclasses of antibiotics. Records of infection according to the Patient Register and medical charts were more common for cases.

Comparing data on drug treatment from medical charts and the Prescribed Drug Register as a dichotomous variable, the agreement was high for maintenance treatment. Of the 90 women that reported treatment with thiopurines in the medical charts, 92% had filled prescriptions of the same and 87% continued treatment in both early and late pregnancy. For systemic corticosteroids, 124 reported treatment at some time, while 81 % of them had filled prescriptions. Of those treated with systemic corticosteroids, 52% were treated in both early and late in pregnancy. Eight of the 15 women treated with anti-TNF were found only in the medical chart review, and not in the Prescribed Drug Register. All of these were infliximab treatment.

Previous preterm birth was associated with preterm birth cases. Short inter-pregnancy interval and comorbidity were not predictors of preterm birth, though the risk estimate for diabetes was high, adjusted OR 3.4 (95% CI: 0.6-19.8). Previous surgery for IBD or extension of ulcerative colitis were not related to preterm birth, though extension into the sigmoideum/rectum only was nearly significantly protective. Small bowel Crohn's disease was more common among preterm birth cases, OR 2.9 (95% CI: 1.1-7.3).

Mild activity as the highest assessed disease activity was not associated with preterm birth, while significant disease activity was, OR 2.2 (95% CI: 1.4-3.5). Significant disease activity both in early and late pregnancy seemed particularly important, with an OR of 4.8 (95% CI: 2.1-10.9). The OR for systemic corticosteroid treatment both early and late in pregnancy was 2.3 (95% CI: 1.2-4.2) and for thiopurine or anti-TNF treatment (immunosuppressive treatment), 2.9 (95% CI: 1.6-5.0), while treatment with 5-ASA, SSZ or local corticosteroids were not associated with preterm birth cases. For 5-ASA, SSZ and thiopurines, treatment was generally continued throughout pregnancy, and stopping or starting treatment was uncommon. For anti-TNF, however, nine out of 13 treated cases

and the two treated controls stopped treatment early in pregnancy. Two cases continued to the second trimester, and only one case was treated in the third trimester. Seven of the nine cases and one of the two controls who discontinued anti-TNF treatment had relapses after discontinuing the drug treatment. Three women were started on anti-TNF due to steroid-refractory disease activity in the second trimester.

We analyzed the association between preterm birth and the six groups of combinations of disease activity and treatment, as described in section 3.6, The analyses pointed out an association between preterm birth and immunosuppressive treatment, especially with significant disease activity (OR 12.8 95% CI: 3.7-44.7), but also a weaker association with immunosuppressive treatment without significant disease activity (OR 95% CI: 1.9 95% CI: 1.0-3.4) (Figure 4.2). The highest risks were in association with spontaneous preterm birth and preterm birth in week 34-36.

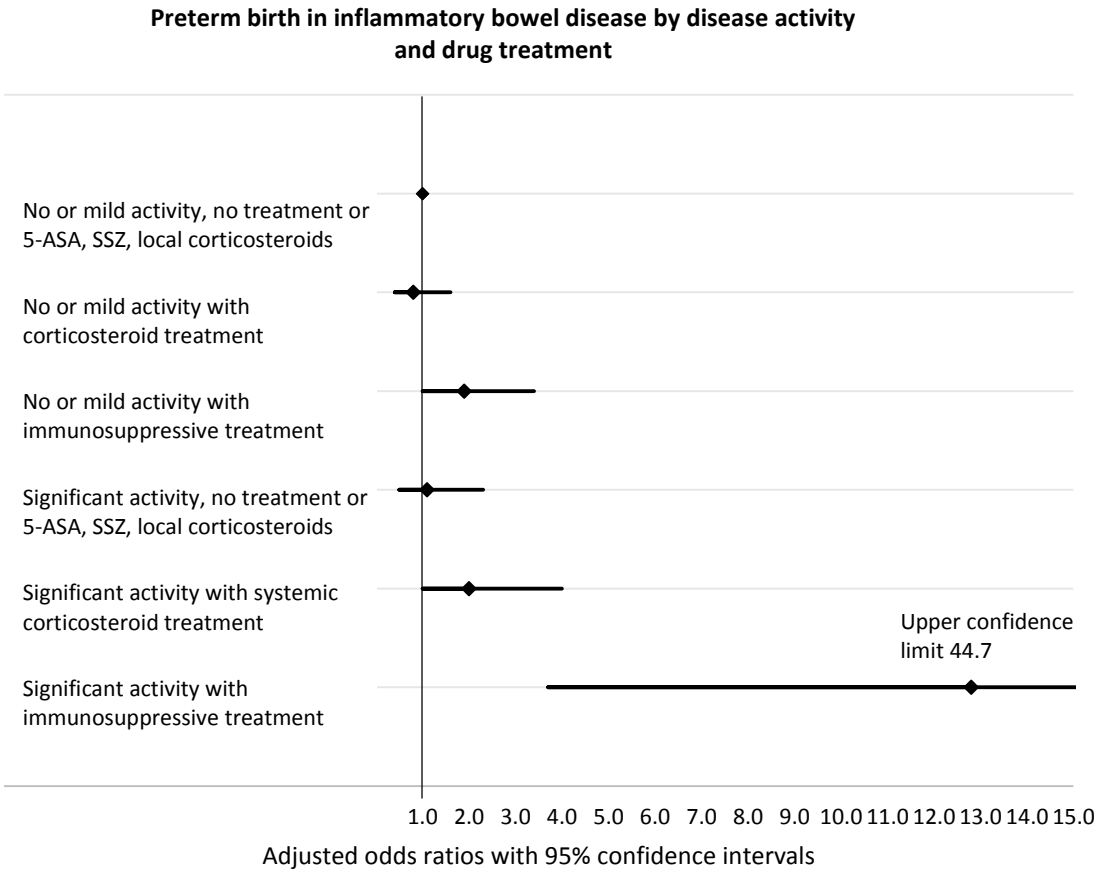

Figure 4.3 Adjusted odds ratios by disease activity/treatment group, comparing cases of preterm birth and their controls among women with IBD. SSZ – sulfasalazine. Significant activity - moderate to severe disease activity as assessed in medical charts, at any time during pregnancy. Immunosuppressive treatment – treatment with thiopurines or anti-TNF at any time during pregnancy.

5 Methodological considerations

5.1 Study design

It is nearly impossible to conduct a study with immaculate validity while still being efficient. The study design has to be contemplated so that it suits the particular research question in the best possible way. In a classical cohort study design, a study population is identified and followed over time. The included individuals are grouped by exposure status and rates of predefined outcomes are assessed. It is possible to study the effect of an exposure on multiple outcomes. This type of study is often time-consuming and costly, and if an outcome is rare, a very large sample size is needed. Also, if followed over time, subjects may be lost to follow up, creating a problem of validity. We used a cohort study design in study I, II and III. However, some features in the studies deviate from the classical definition of a cohort. In all studies, we included pregnancies that had resulted in either a live or stillborn infant. In a classical cohort study, all initiated pregnancies would be followed from start to finish. Most women only notice that they are pregnant a few weeks into pregnancy. In order to accomplish an inclusion of all pregnancies, women would have to be followed closely and repeatedly clinically, which was not possible in the register-based setting that we had chosen.

In the first study, we selected five matches for each birth in women with IBD for comparison, while we in the second study included all births in the entire Swedish population comparison. Selecting five matches is a way to make the study design more effective while still maintaining precision. However, when the outcome is rare, as for venous thromboembolism in study I, few cases among IBD and in the comparison group contributed to the analyses, which affected the precision. Birth defects as studied in study III are not uncommon as a group, but each birth defect is very uncommon. We needed a large sample to study birth defects and therefore included both Swedish and Danish data. To be able to statistically ascertain an estimated OR of 1.3, we would need approximately twice as many treated to anti-TNF as we included in the study. Data may need to be collected for years longer, which would delay important information concerning the safety of anti-TNF when used during pregnancy.

In case-control studies, a number of cases with the outcome are compared to a selected number of controls without the outcome. Compared to cohort studies, case-control studies are more efficient. Rare outcomes and a wide range of exposures can be studied. However, incidence or risk of outcome cannot be measured. We used a case-control design in study IV where the aim was to study risk factors for preterm birth among women with IBD. By choosing this design, we limited the time-consuming medical chart review to cases and an equal number of controls and at the same time made sure that we had sufficient statistical power to assess the most commonly occurring risk factors.

5.2 Validity and precision

External validity describes the generalizability of the study and if results can be applied to a setting other than the one used in the study. Since the studies in this thesis were population-based, including all births, there is no question of whether or not they are generalizable to the Swedish population, and in study III also the Danish population.

Indeed, the high coverage in the national registers leave only around 1-2% of the population out of the studies. However, in studies I, II and IV, only singletons were included, limiting the generalizability for multiple gestation births. Whether or not the results can be transferred to other populations depend upon, whether the exposures vary in different settings. For chronic inflammatory diagnoses, the treatment regimen is constantly evolving, and the indication for anti-TNF treatment, for example, may change over time. The reluctance to treat pregnant women is assumingly the greatest when a substance is new.

Internal validity describes how reliable the results of the study are. With limited internal validity, external validity is also limited. An optimized study design aims at reducing the effect of selection bias, information bias and confounding, the main threats to validity.

Selection bias

Selection bias may occur if the probability of being included in the study is influenced by the exposure or outcome of interest. In studies I, II and III, the population-based design limits this issue, since practically everyone is included, regardless of association with the exposure or outcome.

An issue in studying birth outcomes arises when trying to define the cohort. Births are only entered into the birth registers if they have completed a certain length of gestation. In this perspective, this is when inclusion in the cohort happens. For stillbirth, these cases were only recorded in the birth registers in Sweden after 28 weeks and 22 weeks before and after July 2008, respectively, and in Denmark after 22 weeks. However, exposures that have taken place before inclusion are still considered. This may result in a "healthy-fetus" bias, where only the fetuses well enough to complete more than half of pregnancy are selected. For study III in particular, the potential teratogenic effects of anti-TNF that are studied may in the worst case have resulted in terminated pregnancies that were not possible to include in the study, underestimating adverse effects. However, placental transfer is limited before the second trimester, and interestingly, there have indeed been reports of anti-TNF even decreasing the risk of spontaneous abortion. If women with IBD are at higher risk of 1st trimester termination of pregnancy, which has been not well examined, it may be that the included offspring are healthier than would have been if all embryos had been included at an early stage in pregnancy. For example, if the effect of disease activity in early pregnancy contributes to pregnancy loss, the observed risk estimate for disease activity in early pregnancy on preterm birth would be lower than the true value. Aiming at studying all initiated pregnancies would, however, be a difficult undertaking. Some women may not even be aware of having been pregnant when termination occurs.

Selection bias is often of concern in case-control studies, in which efforts should be made to select controls that are representative of the population under study. Sometimes, matching is done in order to select cases and controls that are similar regarding matching factors. However, the effects on the outcome of variables that have been matched for cannot be evaluated, and there is a risk of over-matching, where effects of one exposure of interest is consumed by a matching variable. Also matching may create a bias if

controls after matched selection are less similar to the population they are derived from. In study IV, comparisons were made with controls that were matched by maternal age, parity and IBD diagnosis, which could make the control group less similar to the entire group of women with IBD that had given birth if the distribution of the matching variables differ.

Information bias

Information bias occurs when assessment of exposure or outcome is incorrect. The main exposure, IBD and other chronic inflammatory diagnoses, was determined from diagnoses recorded in the national health registers. For studies I, II and IV, a strict definition was used for IBD, where we required a repeated diagnosis or one diagnosis followed by treatment. In the Swedish-Danish collaboration in study III, the definition was less strict, requiring only one diagnosis. Consequently, the group of women with IBD was 20% larger in study III than if the stricter criteria would have been used. For studies I, II, IV, the women classified as having IBD may represent a segment of the disease group with more active disease. However, it is also more likely that that the stricter criteria increased specificity, excluding those with a single and thus, more uncertain diagnosis.

Information bias may be non-differential or differential, depending on if misclassification of exposure or outcomes occurs in both comparison groups or not. Missing data creates differential misclassification if data are missing to a higher degree in one group than the other. Missing data may also been result in assumed non-exposure or non-occurring outcome, when in fact, the occurrence was just not reported.

Many of the outcomes used in this thesis are assessed by standard procedures in connection with birth, such as birth weight, gestational age and SGA, and are likely similarly classified for infants to women with and without IBD. For maternal complications, the detection rate may be influenced by the number of visits to antenatal care. A diagnosis of chronic inflammatory disease may also lead to a referral to specialist antenatal care. If women with disease are more regularly seen and more often examined by specialists, complications may be detected earlier or more frequently. However, all women are invited to regular check-ups in the final weeks of pregnancy, whether in specialist care or in regular antenatal care.

For birth defects, it is possible that greater surveillance of pregnancies in women with anti-TNF treatment led to detection of less prominent or less severe defects, thus overestimating the risks. This is supported by the rate of corrective surgery in the first year of life, which was similar or even lower for cases that had been detected among infants to women treated with anti-TNF and cases among women with and without chronic inflammatory disease.

Drug treatment was assessed mainly by filling of prescriptions. Some patients may fill prescriptions, but not adhere to the regimen. This would overestimate the use, possibly diluting the assessed risks of drug treatment. In study IV, we could compare the assessment of drug exposure as filled prescriptions and as reported by the women in medical charts. For thiopurine treatment, 92% of the women that had reported treatment in medical charts, also filled prescriptions, adding to the reliability of the data. That 87%

were treated through early and late pregnancy, indicating uninterrupted treatment, justifies the use of a dichotomous variable for thiopurines. Treatment with systemic corticosteroids was more complicated since they are typically prescribed to be tapered and prescriptions are filled irregularly. Women may already have pills from old prescriptions at home to start on, if disease activity relapses. Although timing of systemic corticosteroid treatment was complicated, 82% that reported treatment with systemic corticosteroids also filled prescriptions.

In study III, data on treatment with intravenously administered infliximab were obtained from the prescribed drug registers when recorded, and from the disease-specific registers ARTIS and PsoReg in Sweden. In the absence of data from disease-specific registers for women with IBD, some of the infliximab-treated among them may have been misclassified as women without anti-TNF treatment. This was a lesser issue in Denmark, where administration of infliximab is recorded in the Patient Register. Accordingly, we found that half of the women treated with anti-TNF in study IV were not found in the Swedish Prescribed Drug Register. A national disease-specific register for IBD, Swibreg, is currently gaining in coverage, and is likely to fill the infliximab gap, as well as add data on clinical details, in future studies.[221]

In studies I and II, disease activity may have been misclassified, since it was indirectly measured using a register data proxy model. In comparison with medical charts, the disease activity proxy model had high specificity and sensitivity. However, from the results in study IV, it was implied that the assessment model for disease activity may have been inadequate because clinical details were lacking in medical charts and the categorization of symptoms and activity not sufficiently agile to account for different disease phenotypes. In data analyses, the results were inconsistent for the effects of disease activity and drug treatment. Since medical charts were collected after the exposure and outcome, we could not influence whether all the information we needed was included in the medical charts or not. Some misclassification of disease activity could not be avoided, but is not expected to be differential, since clinical details were recorded when the outcome of preterm birth was not yet known. A typical issue in case-control studies is recall bias. If information is recorded after the outcome, subjects affected by the outcome are likely to distort exposure information. Recall bias was not an issue in study IV, since medical charts were authored prospectively.

Confounding

A confounder is a variable that is associated with both the exposure and the outcome, but is not an intermediate in the causal pathway. A confounder may distort the association between exposure and outcome, either decreasing or increasing its strength. For example, smoking is a confounder when studying the effect of ulcerative colitis activity on the risk of preterm birth. Smoking protects against disease activity in ulcerative colitis, but also contributes to preterm birth. We found that women with Crohn's disease and ulcerative colitis were less often below 25 years of age. Since older maternal age is associated with several adverse pregnancy and birth outcomes, it is important to consider age when assessing the association between IBD and pregnancy and birth outcomes.

Confounders may be considered and addressed in study design in several different ways, and matching is an example of reducing confounding. In the analyses, the confounder can be handled with stratification, where smokers and non-smokers would be analyzed separately. It may also be addressed by including it in a regression model. Stratification may be more intuitive, but has limitations when there are many confounders, as this would yield an ungraspable amount of strata. Adjusted logistic regression is also limited by study power if there are many confounders. For example, when studying a rare event such as venous thromboembolism as in study I, having a larger comparison group would have added power to the adjusted analysis.

A prerequisite for having the possibility to control for confounders is adequate data on them. For example, even though the national health registers include almost the entire population, there may be confounders that could have been considered, if the information were available. Also, many of the confounders for which we do have data, are assessed at a single point in time. For smoking, we used data as recorded at the first antenatal visit, usually taking place in the first trimester. Some women may have given up smoking later pregnancy, reducing the effect of smoking.

We adjusted for *a priori* selected confounders associated with both chronic inflammatory disease and with the adverse pregnancy and birth outcomes. In addition to smoking, maternal age and parity were added to the model. BMI has been found to affect birth outcomes both when low and high, possibly pertaining to imbalanced metabolism and inflammation.[222] In addition, other inflammatory diseases have also been associated with adverse birth outcomes, and may coincide with the diseases under study and we adjusted for other inflammatory comorbidity.

Confounding by indication

An issue that is often a limitation in pharmacoepidemiological studies is confounding by indication. An indication for treatment always precedes the actual treatment, possibly with the exceptions of primary preventive treatment, contraception and vaccinations. That disease activity and drug treatment are allocated to the same subjects, complicates the assessment of the effects of each separately. Confounding by indication was present in all of the included studies and was the focus of study IV. We were not able to completely disentangle the effects of disease activity and drug treatment, since the strongest effect on preterm birth was seen in women who had both significant disease activity and immunosuppressive treatment. In study III, the distribution of chronic inflammatory disease differed between the women with anti-TNF treatment from those without anti-TNF. If the risk of birth defects differs for the diagnoses, this may distort the results. We adjusted for maternal diagnosis in the analyses and presented analyses stratified by IBD/non-IBD.

Random error

Systematic error such as bias and confounding would remain even if the study is increased in size or repeated in another setting. Random errors are instead chance findings that would not necessarily be repeated if the same study was performed several times. Random error can be limited by increasing the study size and thereby increasing

precision. Statistical analyses are used to evaluate the chance of random error. The confidence interval of 95% has been arbitrarily set and denotes that if the test were to be repeated 100 times, the confidence interval would include the correct value in 95 of those tests. Any result should always be contemplated in light of its strength and statistical significance, but also by its biological plausibility, its potential dose-response effect, its consistency in subanalyses and other studies, and the temporality of exposure and outcome. Also, the risk that a result is due to random error increases by the number of performed statistical tests.

6 Findings and implications

6.1 Inflammatory bowel disease and pregnancy complications (Study I)

Few studies on maternal pregnancy complications in women with IBD had been conducted when the study was performed. The previous studies mainly focused on outcomes related to the infant. We observed and almost 4-fold increased risk of venous thromboembolism in women with ulcerative colitis, which indicates that the already increased risk of thromboembolism from pregnancy is aggravated by inflammation, as supported by previous studies.[93,94,223] The association between inflammation and thromboembolism also suggests that with higher inflammatory disease activity, the risk of venous thromboembolism also increases. Consequently, European and American guidelines alike recommend prophylactic treatment with low molecular weight heparins in non-pregnant patients with IBD that are hospitalized.[224-226] We found that the risk estimate for venous thromboembolism was considerably higher for women with ulcerative colitis that had active disease during pregnancy. Accordingly, prophylactic treatment should be considered for these women, particularly if other risk factors are present.[227]

The question of recommended mode of delivery for patients with IBD is not uncomplicated. The body of knowledge implies that vaginal delivery can be recommended in the absence of active disease, perianal disease and previous ileo-anal pouch surgery.[227] Although we lacked data on the indication leading to cesarean section, some of the women in our study may have had cesarean sections without any of these complicating factors. Two thirds of the cesarean sections among women with IBD were elective, which implies a well-reflected decision, rather than emergency procedures.

In our study, 13% of women with ulcerative colitis were first diagnosed during pregnancy. It may be that pregnancy triggered ulcerative colitis or worsened previous symptoms so that the diagnosis of ulcerative colitis was recorded in the charts. A recent study reported that women with ulcerative colitis were more prone to relapse during pregnancy than non-pregnant women with ulcerative colitis when followed for an equal period of time, which may indicate that pregnancy promotes disease activity in ulcerative colitis.[155] More frequent contacts with healthcare during pregnancy, leading to detection, is also possible.

6.2 Inflammatory bowel disease and birth outcomes (Study II and IV)

It has been acknowledged for decades that women with IBD have increased risks of adverse birth outcomes and preterm birth in particular.[227] Disease activity during pregnancy and drugs used for the treatment of IBD may affect the observed association. However, the separate effects of each are not easily studied.

Our results on the risk of preterm birth for women with Crohn's disease and ulcerative colitis were consistent with previous studies and suggested an almost doubled risk.[131,163,164] In the attempt to further characterize the disease-specific risk factors for preterm birth, we used two different approaches to assess the effects of disease activity and drug treatment. In study II, register data were used to construct a proxy model for

disease activity, partly based on drug treatment. In study IV, we instead collected data on disease activity and drug treatment from medical charts. It was clear that using either method, there were no increased risks of preterm birth in the absence of disease activity and immunosuppressive treatment during pregnancy. The majority of patients belonged to this category.

Congruently in both study II and IV, disease activity in both early and late pregnancy was strongly associated with preterm birth. The combination of both immunosuppressive treatment and disease activity was a strong predictor of preterm birth. Some of the findings in study IV were contradictory, implying issues with the disease activity assessment. Significant disease activity with no treatment or treatment with 5-ASA, sulfasalazine or local corticosteroids only was not associated with preterm birth. Systemic corticosteroid treatment predicted preterm birth only when data suggested that significant disease activity was present, and immunosuppressive treatment yielded a doubled risk estimate even without significant activity. Together, this implies that the data on disease activity as recorded in the medical charts may have been inadequate. In accordance with study IV, thiopurine treatment in stable disease in study II yielded doubled risks of preterm birth, while thiopurine treatment with active disease during pregnancy as assessed by register data yielded even higher risks.

Assessing maintenance treatment as dichotomous variables does not take into account if the treatment is discontinued during treatment. In the event that treatment was discontinued, increased disease activity may have been the result, and is one possible explanation to the association between thiopurines and preterm birth. The majority of women did, however, report continuous treatment with thiopurines in pregnancy. For anti-TNF treatment, discontinuation was more frequent, and some of the women were indeed started on treatment because of increased disease activity during pregnancy.

Immunosuppressive treatment implies a more complicated disease course, assuming that the indication for treatment was in line with clinical recommendations from the European Crohn's and Colitis Organization.[56,57] With this in mind, the risks associated with thiopurines in study II and immunosuppressive treatment (thiopurines and anti-TNF) in study IV, may be due to unmeasured disease severity and not the drug treatment.

However, an effect of immunosuppressive treatment *per se* cannot be ruled out, particularly as the strongest association was observed for spontaneous preterm birth. Infection increases the risk of spontaneous preterm birth.[228] Thiopurines and anti-TNF increase the susceptibility to infections with their effects on the immune system and it is possible that they interfere with the immunological process of spontaneous onset of labor.[229,230] In study IV, the cases of preterm birth had more often than controls been diagnosed with infections. However, cases and controls had similar distributions of antibiotic prescriptions, even when considering different subgroups of antibiotics. Although we did not have data on in-hospital administration of antibiotics, the antibiotic prescriptions data may imply that infection was not a mediator between immunosuppressive treatment and preterm birth. However, even if the effects of immunosuppressive treatment would be independent of disease activity, it is important to note that ceasing treatment may lead to increased activity, which may result in a risk

higher than the doubled risk observed for immunosuppressive treatment in the absence of disease activity.

The characteristics of preterm birth in women with IBD have not been well-described previously. In study I, we observed that cesarean sections, elective in particular, were more common in women with IBD. In study IV, medically indicated preterm birth was not associated with either immunosuppressive treatment or disease activity separately, but was associated when both were present. In addition, preterm birth between weeks 22-33 was not associated with immunosuppressive treatment in case of no or mild disease activity, which is reassuring. Although preterm birth in week 34-36 has been associated with slightly increased risks of morbidity and mortality, there is a clear declining gradient with higher gestational age.[113]

We found elevated risks of SGA and stillbirth for women with Crohn's disease, in particular when the disease had been flaring during pregnancy. Fetal growth, which can be assessed as SGA is a major determinant of stillbirth risk.[231] Infection is also an important risk factor for stillbirth and bowel inflammation and immunosuppressive treatment may increase the susceptibility to infection.[120,229,230] Stillbirth is a rare event, but altogether this may warrant closer surveillance of women with Crohn's disease during pregnancy and delivery, particularly in active disease or when a fetus has been estimated as SGA.

6.3 Anti-TNF treatment and birth defects (Study III)

We found a risk estimate of 1.3 for any major birth defect in infants to women who had been treated with anti-TNF in early pregnancy, which was not statistically significant. The lack of precision may be ascribed to relatively few exposed and too few cases with birth defects.

We included the prevalence of major birth defects in the general population for a frame of reference for descriptive purposes. Comparisons were limited to the chronic inflammatory disease comparator in order to control for the impact of the underlying condition and the potential surveillance bias. However, we lacked data on disease severity, which may still lead to residual surveillance bias as anti-TNF treatment is indicated for women with a more complicated disease course.

As for infants to women with chronic inflammatory disease without anti-TNF treatment and for infants in the general population, the most commonly observed birth defects for infants to women treated with anti-TNF were ventricular septal defect, atrial septal defect, hydronephrosis and hypospadia. Also, the number of hospital visits and corrective surgical procedures for these outcomes were similar between infants to women with chronic inflammatory disease whether treated with anti-TNF or not and with the general population. If anything, the infants to women with anti-TNF treatment with birth defects required surgery less often.

7 Conclusions

- Women with IBD give birth by cesarean section more often than women without the disease, particularly by elective cesarean section. Active disease for women with Crohn's disease and previous bowel surgery for women with ulcerative colitis increased the risks of cesarean section.
- Women with ulcerative colitis had an almost quadrupled risk of venous thromboembolism compared to women without disease and active disease seemed to increase the risk substantially. The number of events was small in the disease activity subanalysis and the results should be cautiously interpreted.
- Women with Crohn's disease and ulcerative colitis had an almost doubled risk of preterm birth. Quiescent disease and treatment typically used for mild disease rendered risks equal to the general population and significant disease activity and immunosuppressive treatment during pregnancy denoted particularly increased risks.
- Due to the close relationship between disease activity and drug treatment, disentangling the effects of disease activity and drug treatment on outcomes proved difficult and confounding by indication could not be completely avoided.
- Infants to women with Crohn's disease were more often affected by neonatal morbidity and stillbirth than women without the disease. The highest risks of stillbirth were observed in active disease.
- Anti-TNF treatment was not found to be associated with birth defects. The most commonly occurring birth defects were ventricular septal defects, atrial septal defects, congenital hydronephrosis and hypospadia. The cases of birth defects among infants to women who had been exposed to anti-TNF treatment necessitated surgery and hospital care no more often than infants to other women.

8 Future perspectives

The results in the studies included in this thesis give rise to questions, among them:

Could prospectively collected clinical data with continuously reported changes in disease activity and drug treatment during pregnancy, such data in the Swedish IBD-register, add clinical details that would help to assess the effect of disease activity and drug treatment separately?

Given that IBD increases the risk of adverse birth outcomes, do adverse birth outcomes predict a future diagnosis of IBD?

Does being born by cesarean section to a woman with IBD increase the already elevated risks pertaining to heritability?

Does disease activity in other chronic inflammatory disease affect birth outcomes?

Does anti-TNF treatment affect birth outcomes other than birth defects, such as preterm birth and SGA?

Does the immunosuppression of anti-TNF treatment lead to increased risks of infections in neonates?

9 Sammanfattning på svenska

Beslutet att skaffa barn innebär ofta ett visst mått av osäkerhet och oro inför eventuella svårigheter och komplikationer som kan uppstå. För kvinnor med kronisk inflammatorisk sjukdom kommer därtill särskilda överväganden för hur sjukdomen i sig och de läkemedel som används för att behandla sjukdomen påverkar graviditeten och det ofödda barnet. Denna avhandling består av fyra arbeten vars gemensamma syfte var att få mer kunskap att kunna använda i konsultationer med kvinnor i just denna situation.

Kroniska inflammatoriska sjukdomar

Kroniska inflammatoriska sjukdomar har gemensamt en oönskad inflammatorisk process i vissa organ, för de inflammatoriska tarmsjukdomarna Crohns sjukdom och ulcerös kolit – tarmarna, för reumatoid artrit – kroppens leder, för ankyloserande spondylit – ryggens leder, för psoriasisartrit – hud och leder, och slutligen psoriasis – huden. Inflammatorisk tarmsjukdom (IBD) drabbar ungefär 0.7% av Sveriges befolkning och en ungefär lika stor andel drabbas av reumatoid artrit. Några procent har psoriasis, medan ankyloserande spondylit och psoriasisartrit är mer ovanliga. Gemensamt är att de alla kan drabba kvinnor i barnafödande ålder, i IBD insjuknar de flesta mellan 20-40 års ålder. Orsaken till den oönskade inflammatoriska processen, som består i en aktivering av det immunologiska systemet, är ännu oklar, men man har visat att både genetik och miljö sannolikt spelar roll.

Behandling av kroniska inflammatoriska sjukdomar

Den inflammatoriska process som sjukdomarna har gemensamt gör att läkemedlen i respektive behandlingsarsenal överlappar. Under 1900-talets senare hälft gjordes flera framsteg som haft stor betydelse för prognos och välbefinnande hos dessa patienter. Ett av de första läkemedlen som kunde börja användas var kortison, som imiterar kroppens egna anti-inflammatoriska hormon. Alla svarar dock inte på kortison, och biverkningarna av långtidsbehandling är stora, med ökad risk för ämnesomsättningsrubbningar och benskörhet. Istället använder man ofta i långtidsbehandling immundämpande läkemedel som angriper de immunologiska celler som står för den inflammatoriska processen. Ett annat stort framsteg inom läkemedelsbehandling för kroniska inflammatoriska sjukdomar kom i slutet av 90-talet. Man lyckades ta fram substanser som verkade hämmande specifikt på de signalsubstanser som de immunologiska cellerna producerar. En central signalsubstans är tumor necrosis factor, TNF.

Kroniska inflammatoriska sjukdomar och graviditet

Tre av delstudierna inkluderade kvinnor med IBD och deras nyfödda. Man vet sedan tidigare att dessa kvinnor har en ökad risk för att föda för tidigt, och vissa studier har även visat en ökad risk för låg födelsevikt i förhållande till graviditetsvecka. Att födas för tidigt och att vara liten för tiden innebär båda en ökad risk för sjuklighet tidigt och sent i livet, med infektioner, lungsjukdom, cirkulationsstörningar och ögonskador i späd ålder och en ökad risk för utvecklingsstörningar och hjärt-kärlsjukdom senare i livet. För kvinnan själv vet man att förlossningen oftare blir med kejsarsnitt och att risken för att drabbas av blodpropp är högre än för andra gravida kvinnor. Mycket pekar på att hur

aktiv sjukdomen är under graviditeten spelar stor roll för hur det går under graviditet och förlossning, men man har inte kunnat skilja på hur sjukdom och läkemedel påverkar, då dessa i regel samvarierar. Det saknas särskilt tillförlitlig information om nyaste preparaten, som TNF-hämmarna. När ett nytt preparat introduceras är en vanlig oro att det skulle kunna orsaka missbildningar. Detta studeras i första hand i djurstudier, där någon sådan effekt inte kunnat ses för TNF-hämmarna. Att de sedan används under mänsklig graviditet utan dokumentation för deras säkerhet, grundar sig i att man vägt risken och nyttan mot varandra, och funnit ett oundgängligt behov av behandling hos modern.

I Sverige har man en tradition av att föra hälsoregister för att kunna utforska befolkningens hälsa och sjuklighet. I Medicinska födelseregistret, Patientregistret, Läkemedelsregistret och i kvalitetsregister kan man följa den svenska befolkningens graviditeter, förlossningar, sjukvårdsbesök och uthämtade läkemedelsrecept på individuell nivå. Varje individs personnummer gör att data från de olika registren kan länkas. Viktigt att påpeka är att data från registren normalt lämnas ut avidentifierade för forskning, med ett löpnummer som ersatt personnumret. Detta för att värna om den personliga integriteten.

Studie I

Den första studien fokuserade på moderns komplikationer under graviditeten. Alla kvinnor som diagnosticerats med IBD och som fött barn under perioden oktober 2006 till december 2010 inkluderades. Kvinnor utan IBD användes som jämförelse. Det saknas data om kliniska detaljer i registren. För att försöka bedöma sjukdomsaktiviteten under graviditeten tog vi istället fram en modell baserad på data i registren. Sjukdomsaktiviteten indelades i tre nivåer; inaktiv obehandlad sjukdom, inaktiv sjukdom med behandling och aktiv sjukdom. Resultaten visade att 30% av kvinnor med Crohns sjukdom och ulcerös kolit genomgick kejsarsnitt, jämfört med 17% i jämförelsegruppen. Vad gäller sjukdomsaktivitet skilde sig de båda sjukdomarna åt, då det var aktiv Crohns sjukdom, men inaktiv ulcerös kolit, som stod för den större delen av kejsarsnitten i respektive sjukdomskategori. Valet att göra ett kejsarsnitt kan bero på olika saker och oftast utförs kejsarsnitt för att inte riskera moderns eller barnets hälsa. Vi saknade information om vad besluten för kejsarsnitt grundade sig på och för kvinnor med IBD kan även andra faktorer relaterade till sjukdomen spela roll. Hänsyn tas ofta till att bevara avföringskontinensen och tidigare tarmoperationer kan också påverka beslutet. När vi i analyserna tog hänsyn till tidigare operationer hos kvinnor med ulcerös kolit minskade sambandet mellan tarmsjukdomen och kejsarsnitt. Vi såg också att kvinnor med ulcerös kolit hade en ökad risk för blodpropp. Blodpropp innebär ett stopp i blodflödet, och drabbar oftast blodkärlen i benen, men en propp kan också fastna i lungorna vilket kan vara ett livshotande tillstånd. Blodpropp är ovanligt och det var få kvinnor som drabbades i vår studie, majoriteten av dem hade dock aktiv sjukdom. Av denna anledning rekommenderas att man överväger blodförtunnande behandling under graviditeten hos dessa kvinnor, särskilt om även andra riskfaktorer för blodpropp finns.

Studie II

I den andra studien utökade vi studiepopulation och inkluderade även födslar under 2010. Vi använde samma modell för att fastställa sjukdomsaktivitet som i den första studien. Kvinnor med Crohns sjukdom och ulcerös kolit hade en nästan dubblerad risk för tidig förlossning, och risken ökade ytterligare med aktiv sjukdom, särskilt om sjukdomen hade varit aktiv i graviditetens senare del. Att stå på behandling med immundämpande läkemedel höjde också risken för tidig födsel. För barn till kvinnor med Crohns sjukdom såg vi ökade risker för sjuklighet under nyföddhetstiden, och en 4 gånger högre risk för dödfödsel om modern hade haft aktiv sjukdom under graviditeten. Dödfödsel är lyckligtvis mycket ovanligt, och drabbade 0.3% i jämförelsegruppen jämfört med 0.9% i gruppen med Crohns sjukdom. Sammanfattningsvis finns det anledning att noggrant övervaka graviditeter hos kvinnor med aktiv IBD.

Studie III

I Studie III undersökte vi riskerna för missbildningar hos barn till kvinnor som behandlats med TNF-hämmare precis före eller under graviditetens första tre månader. Under graviditetens första del anläggs alla organ och fostrets utveckling är som mest sårbar för yttre faktorer. För att få tillräckligt många behandlade kvinnor, inkluderade vi förutom kvinnor med IBD även annan kronisk inflammatorisk sjukdom som också behandlas med TNF-hämmare; reumatoid artrit, ankyloserande spondylit, psoriasisartrit och psoriasis. Dessutom inkluderades både svenska och danska kvinnor och deras nyfödda. Vi fann 683 barn vars mödrar hade behandlats med TNF-hämmare och jämförde dem med 21 549 barn till kvinnor med kronisk inflammatorisk sjukdom utan TNF-hämmarbehandling. Båda dessa grupper hade jämfört med övriga befolkningen en något högre andel av missbildningar. I jämförelsen mellan TNF-behandlade och obehandlade kvinnor med kronisk inflammatorisk sjukdom kunde vi inte påvisa någon ökad risk för missbildningar, även om resultaten pekade på att vi hade för få fall i studien för att tillförlitligt kunna bedöma risker. Biologiskt sett är det osannolikt att ett ämne skulle orsaka flera typer av skilda missbildningar. Vi undersökte därför missbildningar grupperade efter drabbat organsystem. Inte heller här kunde vi påvisa någon skillnad. Även om missbildningar förekommer hos ungefär 4-5% av de nyfödda barnen är specifika missbildningar mycket ovanliga. De vanligaste missbildningarna hos barn till kvinnor med TNF-hämmarbehandling var defekter i hjärtats skiljevägg, defekter i pojkar urinrörsmynning och avflödeshinder från njurar, vilket också speglar fördelningen av missbildningar bland nyfödda generellt. Genom att studera hur ofta de drabbade barnen hade besökt sjukhus och behövt genomgå operationer under det första levnadsåret, kunde vi se att fallen bland TNF-hämmarbehandlade sannolikt inte utgjordes av mer komplicerade fall än övriga. Med tanke på att kvinnor med kronisk inflammatorisk sjukdom hade ökad risk för missbildningar, vare sig de blivit behandlade med TNF-hämmare eller inte, kan det vara så att dessa kvinnor och deras barn är mer övervakade, och missbildningar upptäcks oftare och tidigare i livet.

Studie IV

För att studera riskfaktorer för tidig födsel hos kvinnor med IBD mer detaljerat inkluderade vi de fall av för tidig födsel som vi funnit i studie II i en fall-kontrollstudie, där vi också inhämtade information från journaler. Varje fall jämfördes med en kvinna med IBD som kontroll och som fött barn senare i graviditeten. Vi samlade in medicinska journaler som förts under varje graviditet och skattade sjukdomsaktivitet baserat på kliniska uppgifter. Syftet var att försöka skilja ut om sjukdomsaktivitet eller läkemedelsbehandling spelade större roll för den för tidiga födseln. Det var svårt, även med den mer detaljerade informationen från journaler, att gradera sjukdomsaktiviteten och resultaten var inte entydiga. Starkast kopplat till för tidig födsel var det att ha haft både en aktiv sjukdom och immundämpande läkemedel under graviditeten. Kvinnor som behandlas med immundämpande läkemedel är de som är mest sjuka och det behöver därför inte vara behandlingen i sig som är orsaken till att dessa kvinnor har ökad risk att föda för tidigt. Kopplingarna var starkare till spontan förlossningsstart. Kopplingarna var också starkare till födsel i vecka 34-36, vilket är bra i det hänseendet att så sen för tidig födsel i alla fall är bättre än att födas före vecka 34. Samlat pekar resultaten på att det är önskvärt att söka minimera sjukdomens aktivitet under graviditeten, även om det innebär att man måste fortsätta med behandling med immundämpande läkemedel.

10 Acknowledgements

There are so many people that have contributed to the fact that this thesis is now in print, and I am outrageously grateful. Words are not enough, and thoughts difficult to gather at this stage, but I will try with these:

My main supervisor Helle Kieler, for being tirelessly supportive and patient with me, even though I sometimes deliver at a later minute than you would prefer. Thank you for taking me on. Your skillful, warm and thoughtful guidance is an inspiration.

My co-supervisor Fredrik Granath, for always having your door open and finding the time to explain and explain again, even when I say I won't stay long and it is obviously a lie.

My co-supervisor Olof Stephansson, for being constantly present, although not always in person, to reply to questions sooner than I could wish for and for always being so encouraging.

My co-authors, Anders Ekbom, Maria Elmberg, Karin Hellgren, Marie Linder, Lars Pedersen and Henrik Toft Sørensen, for lending your expertise and all that you have contributed to my work and progress.

All my colleagues at Centre for Pharmacoepidemiology/Unit of Clinical Epidemiology, including:

Anders Ekbom and Johan Askling, for setting the pleasant and inspiring tone at Eugeniahemmet, letting me be a part of it, and all the thoughtful advice along the way.

Early morning coffee (and tea) drinkers, Michael Fored, Thomas Frisell, Maria Altman and Anna-Karin Edstedt Bonamy; I learn something about research and life every day, while starting the day with laughter.

Sven Cnattingius, for putting my worries into perspective in the midst of my thesis writing. Ola Olén, for interesting IBD discussions and last-minute writing advice. Jonas Ludvigsson, for the spontaneous e-mails with tips on articles to read through the years. Johan Reutfors, Robert Bodén, Elizabeth Arkema, Lena Brandt, Bengt Haglund and Ina Anveden Berglind, for your always considerate encouragement.

Camilla Byström, for impeccable work helping to track down and then keep track of hundreds of medical charts. Ulrika Undén, Monica Rundgren, Lillemor Melander and Eva Willis, for never failing to answer any question I might come up with, and fast. Farzad Hedayaty and Samir Hussin, for keeping everything up and running, especially when my laptop perished last summer.

Past and present fellow doctoral students Lina Forssell, Madeleine Svensson, Adina Welander, Anna Westerlund, Jonas Eriksson, Lena Eriksson, Charlotte Elvander, Elina Salonen, Tobias Svensson, Lotta Ekstrand, Louise Scheen, Hjalmar Wadström, John Svensson, Carl-Martin Pethrus, Lingjing Chen, Henrik Benoni, Anna Sandström, Miriam Qvarnström, Katarina Remaeus, Arvid Nordenskjöld, Fredrik Baecklund, and the rest of the T2/T3 crew, for superb company even in the most frustrating of research moments. Annica Bergendal, for your fab pep-talks and a lot of laughter.

Departments of internal medicine, gastroenterology and obstetrics and gynecology across the land for granting access to the medical charts used in the studies.

Anna Abrahamsson, for awakening my interest in gastroenterology back in medical school. Mattias Lissing and Rebecca Undén Göransson, for my first positions as a junior doctor in internal medicine. I just might stay in the field.

My brilliant friends and fellow researchers Viveca Gyberg and Helena Nordenstedt, for taking the time to read, discuss and prepare me for what is to come, keeping the hotline open at all times and for monitoring my blood glucose level throughout.

Lars Öhrmalm, for broadening my research interests in our shared projects, and for always overstating my skills.

Anne Elwin, Johanna Eknert, Maria Horwitz, Christine Toll, Johan Ejerhed, Teresa Herlin, Logan Werry and Calle Unckel, for making sure I didn't burn out during this process.

All my dear friends, for cheering me on. Frankly, in this last stage of writing I am too afraid of forgetting, so I will refrain from mentioning. I am lucky to have you in my life.

My parents Birgitta and Per-Olov, for all the love and encouragement, you are true role models. Per Oscar, Pernilla, Cecilia and Paula for while being family, you are the best friends I could possibly have. And thank you for expanding the support team with your fabulous families!

I also want to acknowledge Janssen, supporters of *Exposure to REMICADE® (Infliximab) during Pregnancy in Patients with Inflammatory Bowel Disease, Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Psoriasis: A Review and Analysis of Birth Outcomes from the Swedish, Danish, and Finnish Medical Birth Registers,* a post-marketing study commissioned by the European Medicines Agency, from which a part of this thesis was developed.

11 References

1. Shields KE, Wiholm BE, Hostelley LS, Striano LF, Arena SR, Sharrar RG. Monitoring outcomes of pregnancy following drug exposure: a company-based pregnancy registry program. *Drug Saf.* 2004;27(6):353-367.

2. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. *American journal of medical genetics. Part C, Seminars in medical genetics.* Aug 15 2011;157C(3):175-182.

3. Loftus EV, Jr., Sandborn WJ. Epidemiology of inflammatory bowel disease. *Gastroenterology clinics of North America.* Mar 2002;31(1):1-20.

4. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology.* Jan 2012;142(1):46-54 e42; quiz e30.

5. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV, Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology.* Oct 2010;139(4):1147-1155.

6. Kvien TK, Uhlig T, Odegard S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. *Annals of the New York Academy of Sciences.* Jun 2006;1069:212-222.

7. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. *Rheumatology.* Apr 2014;53(4):650-657.

8. Queiro R, Tejon P, Alonso S, Coto P. Age at disease onset: a key factor for understanding psoriatic disease. *Rheumatology.* Jul 2014;53(7):1178-1185.

9. Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet.* Nov 3 2012;380(9853):1606-1619.

10. Feakins RM. Ulcerative colitis or Crohn's disease? Pitfalls and problems. *Histopathology.* Feb 2014;64(3):317-335.

11. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet.* Nov 3 2012;380(9853):1590-1605.

12. Ott C, Scholmerich J. Extraintestinal manifestations and complications in IBD. *Nature reviews. Gastroenterology & hepatology.* Oct 2013;10(10):585-595.

13. Schirbel A, Reichert A, Roll S, et al. Impact of pain on health-related quality of life in patients with inflammatory bowel disease. *World journal of gastroenterology : WJG.* Jul 7 2010;16(25):3168-3177.

14. Van Assche G, Dignass A, Panes J, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *Journal of Crohn's & colitis.* Feb 2010;4(1):7-27.

15. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *Journal of Crohn's & colitis.* Dec 2012;6(10):965-990.

16. Moum B, Ekbom A, Vatn MH, et al. Inflammatory bowel disease: re-evaluation of the diagnosis in a prospective population based study in south eastern Norway. *Gut.* Mar 1997;40(3):328-332.

17. Henriksen M, Jahnsen J, Lygren I, et al. Change of diagnosis during the first five years after onset of inflammatory bowel disease: results of a prospective follow-up study (the IBSEN Study). *Scandinavian journal of gastroenterology.* Sep 2006;41(9):1037-1043.

18. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet.* Mar 8 1980;1(8167):514.

19. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut.* Jul 1998;43(1):29-32.

20. Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology.* Mar 1976;70(3):439-444.

21. Falvey JD, Hoskin T, Meijer B, et al. Disease Activity Assessment in IBD: Clinical Indices and Biomarkers Fail to Predict Endoscopic Remission. *Inflammatory bowel diseases.* Mar 3 2015.

22. Remesz O. Tractus intestinalis duodenum. 2007. http://commons.wikimedia.org/wiki/File:Tractus_intestinalis_duodenum.svg. Accessed 2015-04-16.

23. Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. *World journal of gastroenterology : WJG.* Jan 7 2014;20(1):91-99.

24. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* Nov 1 2012;491(7422):119-124.

25. Soderholm JD, Olaison G, Peterson KH, et al. Augmented increase in tight junction permeability by luminal stimuli in the non-inflamed ileum of Crohn's disease. *Gut.* Mar 2002;50(3):307-313.

26. Zeissig S, Burgel N, Gunzel D, et al. Changes in expression and distribution of claudin 2, 5 and 8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn's disease. *Gut.* Jan 2007;56(1):61-72.

27. Heller F, Florian P, Bojarski C, et al. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroenterology.* Aug 2005;129(2):550-564.

28. Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. *Nature.* Jun 16 2011;474(7351):298-306.

29. Neurath MF. Cytokines in inflammatory bowel disease. *Nature reviews. Immunology.* May 2014;14(5):329-342.

30. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature.* Jul 26 2007;448(7152):427-434.

31. Halme L, Paavola-Sakki P, Turunen U, Lappalainen M, Farkkila M, Kontula K. Family and twin studies in inflammatory bowel disease. *World journal of gastroenterology : WJG.* Jun 21 2006;12(23):3668-3672.

32. Moller FT, Andersen V, Wohlfahrt J, Jess T. Familial Risk of Inflammatory Bowel Disease: A Population-Based Cohort Study 1977-2011. *The American journal of gastroenterology.* Mar 24 2015.

33. Orholm M, Fonager K, Sorensen HT. Risk of ulcerative colitis and Crohn's disease among offspring of patients with chronic inflammatory bowel disease. *The American journal of gastroenterology.* Nov 1999;94(11):3236-3238.

34. Bennett RA, Rubin PH, Present DH. Frequency of inflammatory bowel disease in offspring of couples both presenting with inflammatory bowel disease. *Gastroenterology.* Jun 1991;100(6):1638-1643.

35. Busch K, Ludvigsson JF, Ekstrom-Smedby K, Ekbom A, Askling J, Neovius M. Nationwide prevalence of inflammatory bowel disease in Sweden: a population-based register study. *Alimentary pharmacology & therapeutics.* Jan 2014;39(1):57-68.

36. Ekbom A, Helmick C, Zack M, Adami HO. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. *Gastroenterology.* Feb 1991;100(2):350-358.

37. Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nature reviews. Gastroenterology & hepatology.* Mar 3 2015.

38. Thia KT, Loftus EV, Jr., Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *The American journal of gastroenterology.* Dec 2008;103(12):3167-3182.

39. Li X, Sundquist J, Hemminki K, Sundquist K. Risk of inflammatory bowel disease in first- and second-generation immigrants in Sweden: a nationwide follow-up study. *Inflammatory bowel diseases.* Aug 2011;17(8):1784-1791.

40. Beaugerie L, Massot N, Carbonnel F, Cattan S, Gendre JP, Cosnes J. Impact of cessation of smoking on the course of ulcerative colitis. *The American journal of gastroenterology.* Jul 2001;96(7):2113-2116.

41. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clinic proceedings.* Nov 2006;81(11):1462-1471.

42. Hardy TL, Bulmer E. Ulcerative Colitis: A Survey of Ninety-Five Cases. *British medical journal.* Nov 4 1933;2(3800):812-815.

43. Edwards FC, Truelove SC. The Course and Prognosis of Ulcerative Colitis. *Gut.* Dec 1963;4:299-315.

44. Jakobovits SL, Travis SP. Management of acute severe colitis. *British medical bulletin.* 2005;75-76:131-144.

45. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Annals of the rheumatic diseases.* Mar 2005;64 Suppl 2:ii14-17.

46. Ficco HM, Citera G, Cocco JA. Prevalence of psoriatic arthritis in psoriasis patients according to newer classification criteria. *Clinical rheumatology.* Oct 2014;33(10):1489-1493.

47. Haroon M, Fitzgerald O. Pathogenetic overview of psoriatic disease. *The Journal of rheumatology. Supplement.* Jul 2012;89:7-10.

48. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. *Annals of the rheumatic diseases.* Mar 2005;64 Suppl 2:ii30-36.

49. Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. *Lancet.* Feb 21 2009;373(9664):659-672.

50. Reveille JD, Arnett FC. Spondyloarthritis: update on pathogenesis and management. *The American journal of medicine.* Jun 2005;118(6):592-603.

51. Van Hauwermeiren F, Vandenbroucke RE, Libert C. Treatment of TNF mediated diseases by selective inhibition of soluble TNF or TNFR1. *Cytokine & growth factor reviews.* Oct-Dec 2011;22(5-6):311-319.

52. Nuti F, Civitelli F, Cucchiara S. Long-term safety of immunomodulators in pediatric inflammatory diseases. *Paediatric drugs.* Oct 2014;16(5):343-352.

53. Spies CM, Bijlsma JW, Burmester GR, Buttgereit F. Pharmacology of glucocorticoids in rheumatoid arthritis. *Current opinion in pharmacology.* Jun 2010;10(3):302-307.

54. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacology & therapeutics.* Oct 2002;96(1):23-43.

55. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Annals of the rheumatic diseases.* Mar 2014;73(3):492-509.

56. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *Journal of Crohn's & colitis.* Feb 2010;4(1):28-62.

57. Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *Journal of Crohn's & colitis.* Dec 2012;6(10):991-1030.

58. Gossec L, Smolen JS, Gaujoux-Viala C, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Annals of the rheumatic diseases.* Jan 2012;71(1):4-12.

59. Sahasranaman S, Howard D, Roy S. Clinical pharmacology and pharmacogenetics of thiopurines. *European journal of clinical pharmacology.* Aug 2008;64(8):753-767.

60. Dogra S, Mahajan R. Systemic methotrexate therapy for psoriasis: past, present and future. *Clinical and experimental dermatology.* Aug 2013;38(6):573-588.

61. Hench PS. Effect of Jaundice on Rheumatoid Arthritis. *British medical journal.* Aug 20 1938;2(4050):394-398.

62. Whittle BJ, Varga C. New light on the anti-colitic actions of therapeutic aminosalicylates: the role of heme oxygenase. *Pharmacological reports : PR.* May-Jun 2010;62(3):548-556.

63. Visentin M, Zhao R, Goldman ID. The antifolates. *Hematology/oncology clinics of North America.* Jun 2012;26(3):629-648, ix.

64. Kruh J, Foster CS. Corticosteroid-sparing agents: conventional systemic immunosuppressants. *Developments in ophthalmology.* 2012;51:29-46.

65. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacology & therapeutics.* Feb 2008;117(2):244-279.

66. European public assessment reports "Cimzia", "Enbrel", "Humira", "Remicade", "Simponi". European Medicines Agency; 1995-2015.

http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=Diseases.Immune+System+Diseases.Autoimmune+Diseases&treeNumber=&currentCategory=Arthritis%2C+Rheumatoid&searchGenericType=generics. Accessed 2015-04-26.

67. Sfikakis PP. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. *Current directions in autoimmunity.* 2010;11:180-210.

68. Sandborn WJ, Hanauer SB, Katz S, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology.* Nov 2001;121(5):1088-1094.

69. Kay J, Smolen JS. Biosimilars to treat inflammatory arthritis: the challenge of proving identity. *Annals of the rheumatic diseases.* Oct 2013;72(10):1589-1593.

70. van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nature reviews. Rheumatology.* Mar 2013;9(3):164-172.

71. Nasef NA, Ferguson LR. Inflammatory bowel disease and pregnancy: overlapping pathways. *Translational research : the journal of laboratory and clinical medicine.* Jul 2012;160(1):65-83.

72. Guleria I, Sayegh MH. Maternal acceptance of the fetus: true human tolerance. *Journal of immunology.* Mar 15 2007;178(6):3345-3351.

73. Romero R, Gotsch F, Pineles B, Kusanovic JP. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. *Nutrition reviews.* Dec 2007;65(12 Pt 2):S194-202.

74. Winger EE, Reed JL. Treatment with tumor necrosis factor inhibitors and intravenous immunoglobulin improves live birth rates in women with recurrent spontaneous abortion. *American journal of reproductive immunology.* Jul 2008;60(1):8-16.

75. Winger EE, Reed JL, Ashoush S, Ahuja S, El-Toukhy T, Taranissi M. Treatment with adalimumab (Humira) and intravenous immunoglobulin improves pregnancy rates in women undergoing IVF. *American journal of reproductive immunology.* Feb 2009;61(2):113-120.

76. Holmgren C, Esplin MS, Hamblin S, Molenda M, Simonsen S, Silver R. Evaluation of the use of anti-TNF-alpha in an LPS-induced murine model. *Journal of reproductive immunology.* Jul 2008;78(2):134-139.

77. Betz AG. Immunology: Tolerating pregnancy. *Nature.* Oct 4 2012;490(7418):47-48.

78. Somerset DA, Zheng Y, Kilby MD, Sansom DM, Drayson MT. Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset. *Immunology.* May 2004;112(1):38-43.

79. Bettini M, Vignali DA. Regulatory T cells and inhibitory cytokines in autoimmunity. *Current opinion in immunology.* Dec 2009;21(6):612-618.

80. Sakaguchi S, Miyara M, Costantino CM, Hafler DA. FOXP3+ regulatory T cells in the human immune system. *Nature reviews. Immunology.* Jul 2010;10(7):490-500.

81. Bremme KA. Haemostatic changes in pregnancy. *Best practice & research. Clinical haematology.* Jun 2003;16(2):153-168.

82. Virkus RA, Lokkegaard EC, Bergholt T, Mogensen U, Langhoff-Roos J, Lidegaard O. Venous thromboembolism in pregnant and puerperal women in Denmark 1995-2005. A national cohort study. *Thrombosis and haemostasis.* Aug 2011;106(2):304-309.

83. Lindqvist P, Dahlback B, Marsal K. Thrombotic risk during pregnancy: a population study. *Obstetrics and gynecology.* Oct 1999;94(4):595-599.

84. James AH. Pregnancy and thrombotic risk. *Critical care medicine.* Feb 2010;38(2 Suppl):S57-63.

85. Samuelsson E, Hellgren M, Hogberg U. Pregnancy-related deaths due to pulmonary embolism in Sweden. *Acta obstetricia et gynecologica Scandinavica.* 2007;86(4):435-443.

86. Bodker B, Hvidman L, Weber T, et al. Maternal deaths in Denmark 2002-2006. *Acta obstetricia et gynecologica Scandinavica.* 2009;88(5):556-562.

87. Hogberg U, Innala E, Sandstrom A. Maternal mortality in Sweden, 1980-1988. *Obstetrics and gynecology.* Aug 1994;84(2):240-244.

88. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *Journal of thrombosis and haemostasis : JTH.* Apr 2008;6(4):632-637.

89. Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. *Gut.* Jul 2011;60(7):937-943.

90. Fox EA, Kahn SR. The relationship between inflammation and venous thrombosis. A systematic review of clinical studies. *Thrombosis and haemostasis.* Aug 2005;94(2):362-365.

91. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet.* Feb 20 2010;375(9715):657-663.

92. Magro F, Soares JB, Fernandes D. Venous thrombosis and prothrombotic factors in inflammatory bowel disease. *World journal of gastroenterology : WJG.* May 7 2014;20(17):4857-4872.

93. Nguyen GC, Boudreau H, Harris ML, Maxwell CV. Outcomes of obstetric hospitalizations among women with inflammatory bowel disease in the United States. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* Mar 2009;7(3):329-334.

94. Lee JJ, Pope JE. A meta-analysis of the risk of venous thromboembolism in inflammatory rheumatic diseases. *Arthritis research & therapy.* 2014;16(5):435.

95. Virkus RA, Lokkegaard E, Lidegaard O, et al. Risk factors for venous thromboembolism in 1.3 million pregnancies: a nationwide prospective cohort. *PloS one.* 2014;9(5):e96495.

96. Duhl AJ, Paidas MJ, Ural SH, et al. Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. *American journal of obstetrics and gynecology.* Nov 2007;197(5):457 e451-421.

97. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood.* Jul 15 2005;106(2):401-407.

98. Roberts CL, Ford JB, Algert CS, et al. Population-based trends in pregnancy hypertension and pre-eclampsia: an international comparative study. *BMJ open.* Jan 1 2011;1(1):e000101.

99. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet.* Aug 21 2010;376(9741):631-644.

100. Ananth CV. Ischemic placental disease: a unifying concept for preeclampsia, intrauterine growth restriction, and placental abruption. *Seminars in perinatology.* Apr 2014;38(3):131-132.

101. Roberts JM. Pathophysiology of ischemic placental disease. *Seminars in perinatology.* Apr 2014;38(3):139-145.

102. Parker SE, Werler MM. Epidemiology of ischemic placental disease: a focus on preterm gestations. *Seminars in perinatology.* Apr 2014;38(3):133-138.

103. Redman CW, Sargent IL. Preeclampsia and the systemic inflammatory response. *Semin Nephrol.* Nov 2004;24(6):565-570.

104. Haider S, Knofler M. Human tumour necrosis factor: physiological and pathological roles in placenta and endometrium. *Placenta.* Feb 2009;30(2):111-123.

105. Mahadevan U, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology.* Oct 2007;133(4):1106-1112.

106. Gomez-Lopez N, Vega-Sanchez R, Castillo-Castrejon M, Romero R, Cubeiro-Arreola K, Vadillo-Ortega F. Evidence for a role for the adaptive immune response in human term parturition. *American journal of reproductive immunology.* Mar 2013;69(3):212-230.

107. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. *Science.* Aug 15 2014;345(6198):760-765.

108. Lydon-Rochelle M, Holt VL, Martin DP, Easterling TR. Association between method of delivery and maternal rehospitalization. *JAMA : the journal of the American Medical Association.* May 10 2000;283(18):2411-2416.

109. Sevelsted A, Stokholm J, Bonnelykke K, Bisgaard H. Cesarean section and chronic immune disorders. *Pediatrics.* Jan 2015;135(1):e92-98.

110. Kieler H, Axelsson O, Nilsson S, Waldenstrom U. The length of human pregnancy as calculated by ultrasonographic measurement of the fetal biparietal diameter. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology.* Nov 1995;6(5):353-357.

111. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. *Acta obstetricia et gynecologica Scandinavica.* 1977;56(3):247-253.

112. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet.* Jan 19 2008;371(9608):261-269.

113. Shapiro-Mendoza CK, Lackritz EM. Epidemiology of late and moderate preterm birth. *Seminars in fetal & neonatal medicine.* Jun 2012;17(3):120-125.

114. Morken NH, Kallen K, Hagberg H, Jacobsson B. Preterm birth in Sweden 1973-2001: rate, subgroups, and effect of changing patterns in multiple births, maternal age, and smoking. *Acta obstetricia et gynecologica Scandinavica.* Jun 2005;84(6):558-565.

115. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* Jan 5 2008;371(9606):75-84.

116. Voltolini C, Torricelli M, Conti N, Vellucci FL, Severi FM, Petraglia F. Understanding spontaneous preterm birth: from underlying mechanisms to predictive and preventive interventions. *Reproductive sciences.* Nov 2013;20(11):1274-1292.

117. Wong AE, Grobman WA. Medically indicated--iatrogenic prematurity. *Clinics in perinatology.* Sep 2011;38(3):423-439.

118. Ray JG, Urquia ML. Risk of stillbirth at extremes of birth weight between 20 to 41 weeks gestation. *Journal of perinatology : official journal of the California Perinatal Association.* Nov 2012;32(11):829-836.

119. Pallotto EK, Kilbride HW. Perinatal outcome and later implications of intrauterine growth restriction. *Clinical obstetrics and gynecology.* Jun 2006;49(2):257-269.

120. Smith GC, Fretts RC. Stillbirth. *Lancet.* Nov 17 2007;370(9600):1715-1725.

121. Apgar V. A proposal for a new method of evaluation of the newborn infant. *Current researches in anesthesia & analgesia.* Jul-Aug 1953;32(4):260-267.

122. Moster D, Lie RT, Irgens LM, Bjerkedal T, Markestad T. The association of Apgar score with subsequent death and cerebral palsy: A population-based study in term infants. *The Journal of pediatrics.* Jun 2001;138(6):798-803.

123. Morioka I, Iwatani S, Koda T, Iijima K, Nakamura H. Disorders of bilirubin binding to albumin and bilirubin-induced neurologic dysfunction. *Seminars in fetal & neonatal medicine.* Nov 26 2014.

124. Wallenstein MB, Bhutani VK. Jaundice and kernicterus in the moderately preterm infant. *Clinics in perinatology.* Dec 2013;40(4):679-688.

125. Mitanchez D. Glucose regulation in preterm newborn infants. *Hormone research.* 2007;68(6):265-271.

126. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. *The Journal of pediatrics.* Nov 2012;161(5):787-791.

127. Corsello G, Giuffre M. Congenital malformations. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* Apr 2012;25 Suppl 1:25-29.

128. Kalter H. Teratology in the 20th century: environmental causes of congenital malformations in humans and how they were established. *Neurotoxicology and teratology.* Mar-Apr 2003;25(2):131-282.

129. EUROCAT Guide 1.4: Instructions for the Registration of Congenital Anomalies. *EUROCAT Central Registry* 2013; http://www.eurocat-network.eu/content/EUROCAT-Guide-1.4-Section-3.3.pdf. Accessed April 12, 2015.

130. Hjern A. Children's health: Health in Sweden: The National Public Health Report 2012. Chapter 2. *Scandinavian journal of public health.* Dec 2012;40(9 Suppl):23-41.

131. Stephansson O, Larsson H, Pedersen L, et al. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. *Inflammatory bowel diseases.* Mar 2011;17(3):795-801.

132. Cleary BJ, Kallen B. Early pregnancy azathioprine use and pregnancy outcomes. *Birth defects research. Part A, Clinical and molecular teratology.* Jul 2009;85(7):647-654.

133. Kalter H, Warkany J. Congenital malformations (second of two parts). *The New England journal of medicine.* Mar 3 1983;308(9):491-497.

134. Finnell RH. Teratology: general considerations and principles. *The Journal of allergy and clinical immunology.* Feb 1999;103(2 Pt 2):S337-342.

135. Brent RL. Environmental causes of human congenital malformations: the pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. *Pediatrics.* Apr 2004;113(4 Suppl):957-968.

136. Strom BL, Hennessy S, Kimmel SE, Ebook Library. Pharmacoepidemiology. 5th ed. Chicester: Wiley; 2011:1 online resource (977 p.).

137. Shiota K. Variability in human embryonic development and its implications for the susceptibility to environmental teratogenesis. *Birth defects research. Part A, Clinical and molecular teratology.* Aug 2009;85(8):661-666.

138. Lenz W. Malformations caused by drugs in pregnancy. *American journal of diseases of children.* Aug 1966;112(2):99-106.

139. Plamondon S, Ng SC, Kamm MA. Thalidomide in luminal and fistulizing Crohn's disease resistant to standard therapies. *Alimentary pharmacology & therapeutics.* Mar 1 2007;25(5):557-567.

140. Patterson M, Eytinge EJ. Chronic ulcerative colitis and pregnancy. *The New England journal of medicine.* May 1 1952;246(18):691-694.

141. Baird DD, Narendranathan M, Sandler RS. Increased risk of preterm birth for women with inflammatory bowel disease. *Gastroenterology.* Oct 1990;99(4):987-994.

142. Mayberry JF, Weterman IT. European survey of fertility and pregnancy in women with Crohn's disease: a case control study by European collaborative group. *Gut.* Jul 1986;27(7):821-825.

143. Tavernier N, Fumery M, Peyrin-Biroulet L, Colombel JF, Gower-Rousseau C. Systematic review: fertility in non-surgically treated inflammatory bowel disease. *Alimentary pharmacology & therapeutics.* Oct 2013;38(8):847-853.

144. Manosa M, Navarro-Llavat M, Marin L, Zabana Y, Cabre E, Domenech E. Fecundity, pregnancy outcomes, and breastfeeding in patients with inflammatory bowel disease: a large cohort survey. *Scandinavian journal of gastroenterology.* Apr 2013;48(4):427-432.

145. Mountifield R, Bampton P, Prosser R, Muller K, Andrews JM. Fear and fertility in inflammatory bowel disease: a mismatch of perception and reality affects family planning decisions. *Inflammatory bowel diseases.* May 2009;15(5):720-725.

146. Marri SR, Ahn C, Buchman AL. Voluntary childlessness is increased in women with inflammatory bowel disease. *Inflammatory bowel diseases.* May 2007;13(5):591-599.

147. Selinger CP, Eaden J, Selby W, et al. Inflammatory bowel disease and pregnancy: lack of knowledge is associated with negative views. *Journal of Crohn's & colitis.* Jul 2013;7(6):e206-213.

148. Cornish JA, Tan E, Teare J, et al. The effect of restorative proctocolectomy on sexual function, urinary function, fertility, pregnancy and delivery: a systematic review. *Diseases of the colon and rectum.* Aug 2007;50(8):1128-1138.

149. Lepisto A, Sarna S, Tiitinen A, Jarvinen HJ. Female fertility and childbirth after ileal pouch-anal anastomosis for ulcerative colitis. *The British journal of surgery.* Apr 2007;94(4):478-482.

150. Beyer-Berjot L, Maggiori L, Birnbaum D, Lefevre JH, Berdah S, Panis Y. A total laparoscopic approach reduces the infertility rate after ileal pouch-anal anastomosis: a 2-center study. *Annals of surgery.* Aug 2013;258(2):275-282.

151. Bortoli A, Saibeni S, Tatarella M, et al. Pregnancy before and after the diagnosis of inflammatory bowel diseases: retrospective case-control study. *Journal of gastroenterology and hepatology.* Apr 2007;22(4):542-549.

152. Reddy D, Murphy SJ, Kane SV, Present DH, Kornbluth AA. Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. *The American journal of gastroenterology.* May 2008;103(5):1203-1209.

153. Nielsen OH, Andreasson B, Bondesen S, Jacobsen O, Jarnum S. Pregnancy in Crohn's disease. *Scandinavian journal of gastroenterology.* Sep 1984;19(6):724-732.

154. Nielsen OH, Andreasson B, Bondesen S, Jarnum S. Pregnancy in ulcerative colitis. *Scandinavian journal of gastroenterology.* Sep 1983;18(6):735-742.

155. Pedersen N, Bortoli A, Duricova D, et al. The course of inflammatory bowel disease during pregnancy and postpartum: a prospective European ECCO-EpiCom Study of 209 pregnant women. *Alimentary pharmacology & therapeutics.* Sep 2013;38(5):501-512.

156. Bush MC, Patel S, Lapinski RH, Stone JL. Perinatal outcomes in inflammatory bowel disease. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* Apr 2004;15(4):237-241.

157. Ong JP, Edwards GJ, Allison MC. Mode of delivery and risk of fecal incontinence in women with or without inflammatory bowel disease: questionnaire survey. *Inflammatory bowel diseases.* Nov 2007;13(11):1391-1394.

158. Norton C, Dibley LB, Bassett P. Faecal incontinence in inflammatory bowel disease: associations and effect on quality of life. *Journal of Crohn's & colitis.* Sep 1 2013;7(8):e302-311.

159. Remzi FH, Gorgun E, Bast J, et al. Vaginal delivery after ileal pouch-anal anastomosis: a word of caution. *Diseases of the colon and rectum.* Sep 2005;48(9):1691-1699.

160. Polle SW, Vlug MS, Slors JF, et al. Effect of vaginal delivery on long-term pouch function. *The British journal of surgery.* Nov 2006;93(11):1394-1401.

161. Ilnyckyji A, Blanchard JF, Rawsthorne P, Bernstein CN. Perianal Crohn's disease and pregnancy: role of the mode of delivery. *The American journal of gastroenterology.* Nov 1999;94(11):3274-3278.

162. Hatch Q, Champagne BJ, Maykel JA, et al. Crohn's disease and pregnancy: the impact of perianal disease on delivery methods and complications. *Diseases of the colon and rectum.* Feb 2014;57(2):174-178.

163. Stephansson O, Larsson H, Pedersen L, et al. Crohn's disease is a risk factor for preterm birth. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* Jun 2010;8(6):509-515.

164. Cornish J, Tan E, Teare J, et al. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut.* Jun 2007;56(6):830-837.

165. Lin HC, Chiu CC, Chen SF, Lou HY, Chiu WT, Chen YH. Ulcerative colitis and pregnancy outcomes in an Asian population. *The American journal of gastroenterology.* Feb 2010;105(2):387-394.

166. Bengtson MB, Solberg IC, Aamodt G, et al. Relationships between inflammatory bowel disease and perinatal factors: both maternal and paternal disease are related to preterm birth of offspring. *Inflammatory bowel diseases.* May 2010;16(5):847-855.

167. Elbaz G, Fich A, Levy A, Holcberg G, Sheiner E. Inflammatory bowel disease and preterm delivery. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* Sep 2005;90(3):193-197.

168. Kornfeld D, Cnattingius S, Ekbom A. Pregnancy outcomes in women with inflammatory bowel disease--a population-based cohort study. *American journal of obstetrics and gynecology.* Oct 1997;177(4):942-946.

169. Oron G, Yogev Y, Shcolnick S, et al. Inflammatory bowel disease: risk factors for adverse pregnancy outcome and the impact of maternal weight gain. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* Nov 2012;25(11):2256-2260.

170. Fonager K, Sorensen HT, Olsen J, Dahlerup JF, Rasmussen SN. Pregnancy outcome for women with Crohn's disease: a follow-up study based on linkage between national registries. *The American journal of gastroenterology.* Dec 1998;93(12):2426-2430.

171. Lin K, Martin CF, Dassopoulos T, et al. Pregnancy outcomes amongst mothers with inflammatory bowel disease exposed to systemic corticosteroids: results of the PIANO registry (vol 146, pg S1, 2014). *Gastroenterology.* Nov 2014;147(5):1186-1186.

172. Bortoli A, Pedersen N, Duricova D, et al. Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003-2006. *Alimentary pharmacology & therapeutics.* Oct 2011;34(7):724-734.

173. Fedorkow DM, Persaud D, Nimrod CA. Inflammatory bowel disease: a controlled study of late pregnancy outcome. *American journal of obstetrics and gynecology.* Apr 1989;160(4):998-1001.

174. Raatikainen K, Mustonen J, Pajala MO, Heikkinen M, Heinonen S. The effects of pre- and post-pregnancy inflammatory bowel disease diagnosis on birth outcomes. *Alimentary pharmacology & therapeutics.* Feb 2011;33(3):333-339.

175. Norgard B, Fonager K, Sorensen HT, Olsen J. Birth outcomes of women with ulcerative colitis: a nationwide Danish cohort study. *The American journal of gastroenterology.* Nov 2000;95(11):3165-3170.

176. Dominitz JA, Young JC, Boyko EJ. Outcomes of infants born to mothers with inflammatory bowel disease: a population-based cohort study. *The American journal of gastroenterology.* Mar 2002;97(3):641-648.

177. Porter RJ, Stirrat GM. The effects of inflammatory bowel disease on pregnancy: a case-controlled retrospective analysis. *British journal of obstetrics and gynaecology.* Nov 1986;93(11):1124-1131.

178. Norgard B, Pedersen L, Christensen LA, Sorensen HT. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. *The American journal of gastroenterology.* Jul 2007;102(7):1406-1413.

179. Norgard 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. *The American journal of gastroenterology.* Sep 2007;102(9):1947-1954.

180. Molnar T, Farkas K, Nagy F, et al. Pregnancy outcome in patients with inflammatory bowel disease according to the activity of the disease and the medical treatment: a case-control study. *Scandinavian journal of gastroenterology.* Nov 2010;45(11):1302-1306.

181. Rocha R, Santana GO, Almeida N, Lyra AC. Analysis of fat and muscle mass in patients with inflammatory bowel disease during remission and active phase. *The British journal of nutrition.* Mar 2009;101(5):676-679.

182. Campbell MK, Cartier S, Xie B, Kouniakis G, Huang W, Han V. Determinants of small for gestational age birth at term. *Paediatric and perinatal epidemiology.* Nov 2012;26(6):525-533.

183. Norgard B, Fonager K, Pedersen L, Jacobsen BA, Sorensen HT. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. *Gut.* Feb 2003;52(2):243-247.

184. Dennery PA. Effects of oxidative stress on embryonic development. *Birth defects research. Part C, Embryo today : reviews.* Sep 2007;81(3):155-162.

185. Norgaard M, Larsson H, Pedersen L, et al. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. *Journal of internal medicine.* Oct 2010;268(4):329-337.

186. Ban L, West J, Abdul Sultan A, Dhalwani NN, Ludvigsson JF, Tata LJ. Limited risks of major congenital anomalies in children of mothers with coeliac disease: a population-based cohort study. *BJOG : an international journal of obstetrics and gynaecology.* Oct 7 2014.

187. Fraser FC, Walker BE, Trasler DG. Experimental production of congenital cleft palate: genetic and environmental factors. *Pediatrics.* Apr 1957;19(4 Part 2):782-787.

188. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. *Teratology.* Jul 1998;58(1):2-5.

189. Carmichael SL, Shaw GM, Ma C, et al. Maternal corticosteroid use and orofacial clefts. *American journal of obstetrics and gynecology.* Dec 2007;197(6):585 e581-587; discussion 683-584, e581-587.

190. Hviid A, Molgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* Apr 19 2011;183(7):796-804.

191. Skuladottir H, Wilcox AJ, Ma C, et al. Corticosteroid use and risk of orofacial clefts. *Birth defects research. Part A, Clinical and molecular teratology.* Jun 2014;100(6):499-506.

192. Rahimi R, Nikfar S, Rezaie A, Abdollahi M. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. *Reproductive toxicology.* Feb 2008;25(2):271-275.

193. Halsted CH, Gandhi G, Tamura T. Sulfasalazine inhibits the absorption of folates in ulcerative colitis. *The New England journal of medicine.* Dec 17 1981;305(25):1513-1517.

194. Francella A, Dyan A, Bodian C, Rubin P, Chapman M, Present DH. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. *Gastroenterology.* Jan 2003;124(1):9-17.

195. Akbari M, Shah S, Velayos FS, Mahadevan U, Cheifetz AS. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. *Inflammatory bowel diseases.* Jan 2013;19(1):15-22.

196. Hyoun SC, Obican SG, Scialli AR. Teratogen update: methotrexate. *Birth defects research. Part A, Clinical and molecular teratology.* Apr 2012;94(4):187-207.

197. Simister NE. Placental transport of immunoglobulin G. *Vaccine.* Jul 28 2003;21(24):3365-3369.

198. Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* Mar 2013;11(3):286-292; quiz e224.

199. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. *The American journal of gastroenterology.* Jan 2009;104(1):228-233.

200. Berthelsen BG, Fjeldsoe-Nielsen H, Nielsen CT, Hellmuth E. Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. *Rheumatology.* Nov 2010;49(11):2225-2227.

201. Gurevich P, Elhayany A, Ben-Hur H, et al. An immunohistochemical study of the secretory immune system in human fetal membranes and decidua of the first trimester of pregnancy. *American journal of reproductive immunology.* Jul 2003;50(1):13-19.

202. Carter JD, Ladhani A, Ricca LR, Valeriano J, Vasey FB. A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. *The Journal of rheumatology.* Mar 2009;36(3):635-641.

203. Katz JA, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. *The American journal of gastroenterology.* Dec 2004;99(12):2385-2392.

204. Schnitzler F, Fidder H, Ferrante M, et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflammatory bowel diseases.* Sep 2011;17(9):1846-1854.

205. Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, Ornoy A. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. *Reproductive toxicology.* Jan 2014;43:78-84.

206. Lichtenstein G, Feagan B, Cohen R, et al. Pregnancy Outcomes in Patients with Crohn's Disease Treated with Infliximab: Results from the TREAT (TM) Registry. *American Journal of Gastroenterology.* Oct 2013;108:S521-S521.

207. Mahadevan U, Martin CF, Sandler RS, et al. PIANO: A 1000 Patient Prospective Registry of Pregnancy Outcomes in Women With IBD Exposed to Immunomodulators and Biologic Therapy. *Gastroenterology.* May 2012;142(5):S149-S149.

208. Weber-Schoendorfer C, Oppermann M, Wacker E, et al. Pregnancy outcome after TNF-alpha inhibitor therapy during the first trimester: a prospective multicentre cohort study. *British journal of clinical pharmacology.* Mar 25 2015.

209. Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. *Scandinavian journal of social medicine.* Jun 1990;18(2):143-148.

210. Langhoff-Roos J, Krebs L, Klungsoyr K, et al. The Nordic medical birth registers--a potential goldmine for clinical research. *Acta obstetricia et gynecologica Scandinavica.* Feb 2014;93(2):132-137.

211. Kristensen J, Langhoff-Roos J, Skovgaard LT, Kristensen FB. Validation of the Danish Birth Registration. *Journal of clinical epidemiology.* Aug 1996;49(8):893-897.

212. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC public health.* 2011;11:450.

213. Erlangsen A, Fedyszyn I. Danish nationwide registers for public health and health-related research. *Scandinavian journal of public health.* Mar 10 2015.

214. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scandinavian journal of public health.* Jul 2011;39(7 Suppl):30-33.

215. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiology and drug safety.* Jul 2007;16(7):726-735.

216. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic & clinical pharmacology & toxicology.* Feb 2010;106(2):86-94.

217. Simard JF, Arkema EV, Sundstrom A, et al. Ten years with biologics: to whom do data on effectiveness and safety apply? *Rheumatology.* Jan 2011;50(1):204-213.

218. Wadstrom H, Eriksson J, Neovius M, Askling J, On Behalf Of The Artis Study G. How good is the coverage and how accurate are exposure data in the Swedish Biologics Register (ARTIS)? *Scandinavian journal of rheumatology.* Nov 7 2014:1-7.

219. Schmitt-Egenolf M. PsoReg--the Swedish registry for systemic psoriasis treatment. The registry's design and objectives. *Dermatology.* 2007;214(2):112-117.

220. Socialstyrelsen. PsoReg (Register för Systembehandling av Psoriasis). 2013. http://www.socialstyrelsen.se/register/registerservice/nationellakvalitetsregister/psoregregisterforsystembehandl. Accessed 2015-04-27.

221. Ludvigsson JF, Myrelid P. [Swibreg--a new version of national IBD registry]. *Lakartidningen.* Nov 4-12 2009;106(45):3014-3015.

222. Sen S, Iyer C, Meydani SN. Obesity during pregnancy alters maternal oxidant balance and micronutrient status. *Journal of perinatology : official journal of the California Perinatal Association.* Feb 2014;34(2):105-111.

223. Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thrombosis and haemostasis.* Mar 2001;85(3):430-434.

224. Van Assche G, Dignass A, Reinisch W, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *Journal of Crohn's & colitis.* Feb 2010;4(1):63-101.

225. Van Assche G, Dignass A, Bokemeyer B, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. *Journal of Crohn's & colitis.* Feb 2013;7(1):1-33.

226. Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of G. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *The American journal of gastroenterology.* Mar 2010;105(3):501-523; quiz 524.

227. van der Woude CJ, Ardizzone S, Bengtson MB, et al. The Second European Evidenced-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease. *Journal of Crohn's & colitis.* Nov 26 2014.

228. Oliver RS, Lamont RF. Infection and antibiotics in the aetiology, prediction and prevention of preterm birth. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology.* Nov 2013;33(8):768-775.

229. Frei P, Biedermann L, Nielsen OH, Rogler G. Use of thiopurines in inflammatory bowel disease. *World journal of gastroenterology : WJG.* Feb 21 2013;19(7):1040-1048.

230. Murdaca G, Spano F, Contatore M, et al. Infection risk associated with anti-TNF-alpha agents: a review. *Expert opinion on drug safety.* Apr 2015;14(4):571-582.

231. Smith GC. Predicting antepartum stillbirth. *Clinical obstetrics and gynecology.* Sep 2010;53(3):597-606.