OPTIMIZING CARE FOR PREGNANT WOMEN WITH INFLAMMATORY BOWEL DISEASE

ALISON DE LIMA

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		Prof.dr. M.P. Peppelenbosch
Copromotor	:	Dr. Z. Zelinkova-Detkova

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CHAPTER 1

GENERAL INTRODUCTION, AIMS AND THESIS OUTLINE

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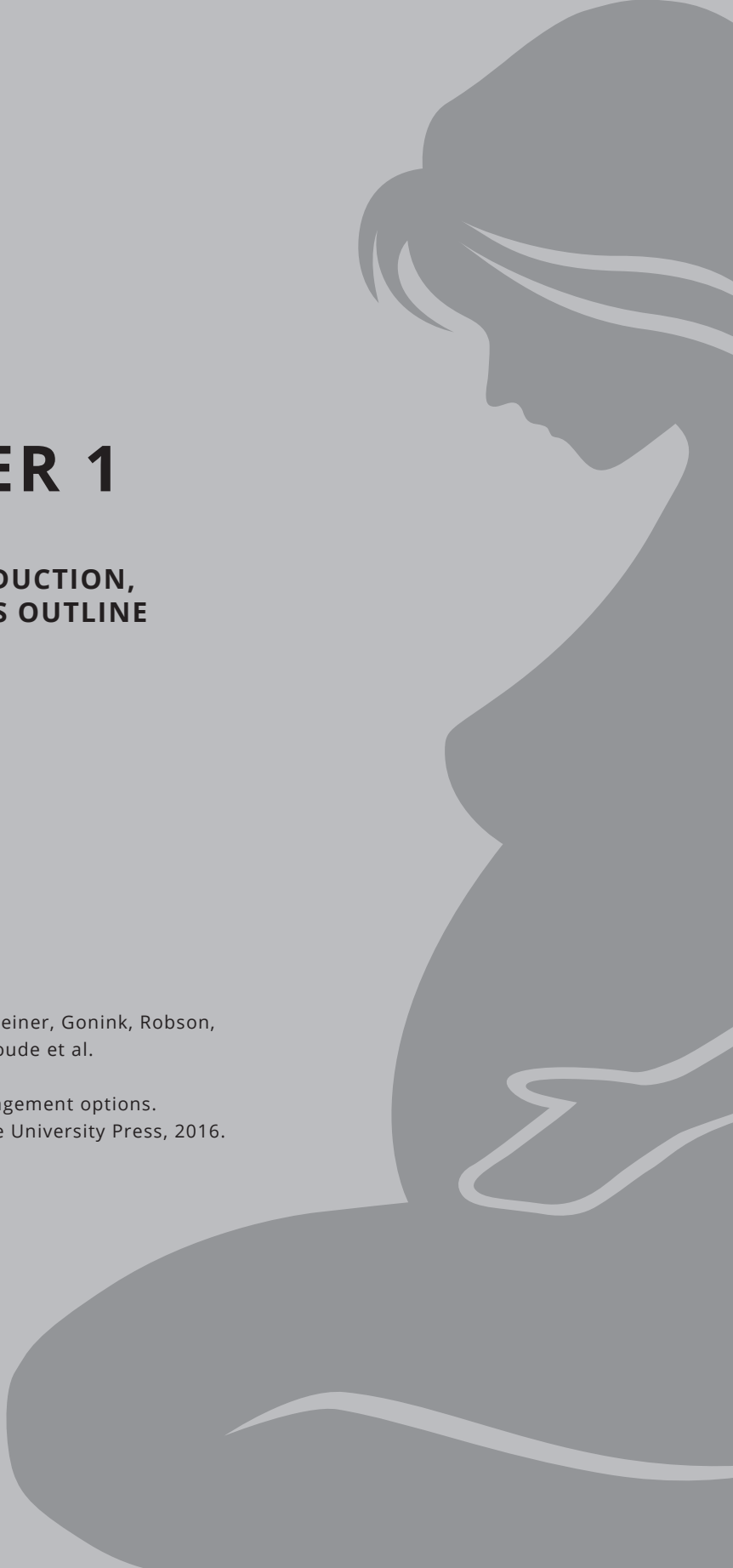

GENERAL INTRODUCTION

Inflammatory bowel diseases (IBD), commonly referring to Crohn's disease (CD) and ulcerative colitis (UC), are chronic, debilitating, relapsing and remitting inflammatory conditions of the gastrointestinal tract. The disease is incurable and many patients are bound to lifelong maintenance medication to keep the disease in remission. Symptoms of IBD include abdominal pain, fatigue, diarrhea, nausea and vomiting, fever and weight loss. Typically, IBD is diagnosed at a young age, as approximately 50% of IBD patients are diagnosed before the age of 35 [1]. Therefore, fertility and reproduction are important clinical considerations in the treatment of IBD patients.

HISTORICAL BACKGROUND

Samuel Wilks was the first to refer to the chronic inflammatory condition of the colon as ulcerative colitis in 1859, although it is uncertain if he is the first to have described the disease. The first case report of ulcerative colitis coinciding with pregnancy stems from 1909 [2].

The phenomenon 'regional ileitis' was first described in a case series in 1932 by Gordon Oppenheimer, Leon Ginzburg and Burril Crohn [3]. As scientific journals used to arrange authors in alphabetical order, the disease was named after Crohn, even though he was still a resident at that time. Crohn's disease during pregnancy was first described in literature in 1946 [4].

IBD AND PREGNANCY

Whereas it is known that in autoimmune conditions such as rheumatoid arthritis and multiple sclerosis, pregnancy has an ameliorating effect on the disease course [5, 6], this phenomenon is not observed in pregnant women with IBD. In the mid twentieth century disease relapse rates during pregnancy were even reported to be as high as 90% [7]. Luckily, nowadays relapse rates during pregnancy are lower and most pregnancies in women with quiescent inflammatory bowel disease will be uncomplicated [8-10]. However, IBD is associated with adverse pregnancy course and adverse pregnancy outcomes [11-15]. Disease activity at time of conception and during pregnancy is associated with a higher rate of spontaneous abortion, preterm delivery and low birth weight (LBW) [9, 16, 17]. This indicates the necessity of maintaining remission with the continuation of medication. In addition, disease activity increases the risk for thrombo-embolic events and emergency caesarian delivery [18]. As disease remission at conception is favorable for both maintaining remission during pregnancy and for child outcome, treatment strategy should therefore be part of preconception advice in females with IBD [19].

DIAGNOSTIC TESTS DURING PREGNANCY

Monitoring disease activity during pregnancy may be difficult if exclusively clinical parameters are used. Pregnancy itself can be accompanied by gastrointestinal complaints and correctly differentiating between these 'physiological' complaints and IBD disease activity is crucial for treatment. In non-pregnant IBD patients endoscopic investigations such as colonoscopy and sigmoidoscopy are the gold standard for assessment of inflammation of the gastrointestinal tract. Inevitably, pregnant IBD patients with suspected disease relapse will require endoscopic investigations to determine the location and severity of the disease activity and consequently treat the relapse adequately. However, the safety of endoscopic procedures during pregnancy is less well investigated.

IBD MEDICATION DURING PREGNANCY

Most drugs to treat IBD are of low risk and, with the exception of methotrexate (MTX) and thalidomide, can be continued in females and males with a wish to conceive. MTX and thalidomide are teratogenic [20, 21], and barrier methods are recommended during therapy. If conception occurs during MTX therapy, the drug needs to be stopped and high-dose folate replacement should be started. Furthermore therapeutic abortion should be discussed with an obstetrician. To avoid fetal MTX exposure it is recommended to stop at least for 3–6 months before trying to conceive.

In contrast to the abovementioned drugs, sulfasalazine and aminosalicylates are considered safe [22, 23]. Sulfasalazine treatment interferes with folate absorption, so a higher dose of folic acid supplementation around conception is recommended (2 mg/day of folic acid). Physicians should be cautious about mesalazine formulations containing dibutyl phthalate coating. Dibutyl phthalate coating has been down-graded from FDA Category B to C because of an increased risk of malformations in the male urogenital tract in animal studies [24]. In addition, a high level of phthalates exposure is possibly associated with precocious puberty [25]. In males, the use of sulfasalazine is related to infertility, but this infertility is reversible after stopping sulfasalazine [26, 27].

In case of IBD relapse during pregnancy, the use of corticosteroids might be necessary. Although the use of corticosteroids in the first trimester has been reported to be associated with an increased risk of orofacial malformations [28], a recent large population-based study showed no increased risk of orofacial clefts in children exposed to corticosteroids in utero [29]. Neonatal adrenal suppression due to the use of corticosteroids in late pregnancy of woman with IBD has been reported, and infants should therefore be checked by a pediatrician

after birth. Furthermore corticosteroids are known to increase the risk of hypertension and diabetes mellitus in patients, and pregnant females should be followed-up stringently [30]. There is just one case series of eight Crohn's disease (CD) patients treated with budesonide during pregnancy, which did not show an increased risk of adverse pregnancy outcome [31].

Whether to use immunosuppressive drugs during pregnancy is a subject of frequent debate amongst health care professionals, parents to be and the treating gastroenterologist. Thiopurines cross the placenta: in cord blood, the metabolite 6-TG was detected at levels that were on average half of the maternal levels [32]. Most studies have shown the thiopurines to be safe in females and males, with no increased risk of malformations in the newborn [33-37], although a recent meta-analysis showed an increased risk of preterm birth [38]. The included studies in this meta-analysis however, have limited quality by their retrospective design and lack of adjustment for confounding factors. It has been reported that 6-thioguanine (6-TG) passes the placenta [39], but further safety data are not available.

A meta-analysis assessing the use of cyclosporine during pregnancy (not in IBD) showed no adverse fetal outcomes [40]. Evidence on the use of cyclosporine in IBD is limited to small series of women that had severe relapses during pregnancy, in which no increased risk of adverse fetal outcome was found [41].

Infliximab (IFX) and adalimumab (ADA) are IgG1 antibodies, and cross the placenta [42, 43]. Several studies suggest that IFX is of low risk in pregnancy, at least in terms of short-term outcomes, and does not seem to be teratogenic [44, 45] In addition, the preliminary data from the Pregnancy IBD and Neonatal Outcome (PIANO) study also suggest that the use of IFX is safe during pregnancy [46]. For ADA, the data available are limited, but also show no increase in the rate of adverse pregnancy outcomes for pregnancies exposed to ADA [42, 43, 46]. This is confirmed by a recent systematic review that showed no adverse outcome in the children exposed to anti-TNF in utero [47]. The long-term effect on the developing immune system and the risk of infectious disease in the newborn remains unknown. Therefore, discontinuation of the treatment around gestational week 22-24 might be considered to limit the intra-uterine exposure to these agents; this strategy showed no increased incidence of relapse in a small prospective cohort, but should only be applied when the female is in sustained remission and when there are no other indications to continue anti-TNF [42]. Certolizumab pegol crosses the placenta by passive diffusion. A study including 10 pregnancies exposed to certolizumab showed very low (less than 2 µg/mL) to undetectable levels of certolizumab in cord blood [42].

Metronidazole is used for the treatment of active pouchitis as well as in perianal disease. Recently, in a large cohort study, metronidazole used at different stages of pregnancy was

not associated with adverse pregnancy outcomes [48]. Human studies with ciprofloxacin have not shown an increase in spontaneous abortion or congenital abnormality incidence [49]. However, animal studies demonstrated musculoskeletal abnormalities [50]. It is recommended that these antibiotics be avoided in the first trimester.

AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis was to investigate several clinical aspects of pregnancy in IBD patients drawn from frequently asked questions (FAQs) and concerns from IBD patients with a reproductive wish. These patient FAQs are shown below. All studies included in this thesis can be translated into practical advice to pregnant IBD patients.

FAQ 1: 'Does IBD affect my fertility?'

Conclusive data on fertility and fecundity in IBD women is limited. It has been generally accepted that restorative proctocolectomy with ileal pouch anal anastomosis (IPAA), especially when operated with an open approach [51], can significantly reduce fecundity in women with ulcerative colitis (UC) through formation of adhesions and subsequent mechanical blockage of the fallopian tubes [52-57]. Data on non-surgically treated IBD patients however, remain conflicting and difficult to interpret. Several previous studies have shown IBD women to have fewer children than the general population [58-61]. The reason for this observed difference remains elusive, as the retrospective nature of these studies makes it hard to differentiate between voluntary childlessness due to incorrect beliefs or education and involuntary infertility.We compared subfertility rates, time to pregnancy and the use of fertility treatment such as in vitro fertilization (IVF) between the two groups. To answer the question whether IBD influences fertility, we compared fertility in women with IBD to fertility in women without IBD in **Chapter 2**.

FAQ 2: 'What is my risk of disease relapse during pregnancy and how will disease activity influence birth outcomes?'

In **Chapter 3**, we explore risk factors for disease relapse during pregnancy and furthermore we assess the effect of disease relapse during pregnancy on birth outcomes. The effects of disease activity on birth outcomes have been reported earlier, although these outcomes do not seem representative in the era of biologicals. We comment on this phenomenon in **Chapter 4**. Also, the retrospective and registry based nature of these studies makes it difficult to determine how these pregnant patients were treated for their disease flare. In this prospective cohort study in which patients are treated with contemporary IBD medication, we

aimed to identify risk factors for disease activity during pregnancy in order to create a profile of the 'high risk' patients and determine the effect of disease relapse on birth outcomes.

FAQ 3: 'Can I influence the course and outcomes of pregnancy by adhering to a certain lifestyle/guidelines?'

Previously it has been shown that women with pregestational diabetes mellitus benefit from preconception care. This is reflected in better glycaemic control throughout pregnancy and better birth outcomes than diabetic women who did not receive preconception care [62, 63]. The effects of preconception care on disease course during pregnancy and pregnancy outcomes are discussed in **Chapter 5**. The aim of this study was to investigate the effect of preconception care in IBD women on IBD disease course as well as birth outcomes.

FAQ 4: 'Is it safe to undergo colonoscopy during pregnancy if necessary?'

In the case of a suspected disease relapse during pregnancy, it is necessary to investigate the severity and extent of IBD by endoscopy, because these parameters will influence the choice of therapy. **Chapter 6** and **Chapter 7** discuss the safety of lower gastrointestinal endoscopies during pregnancy. These diagnostic methods remain the gold standard for assessing disease activity, location and severity of inflammation in the gastrointestinal tract. The safety of these procedures during pregnancy has only been studied in three retrospective cohorts [64-66]. Additional derivative data can be found in case series and case reports in obscure journals. Our aim was to give a comprehensive overview of available data and furthermore assess the safety of lower gastrointestinal endoscopy in a prospective cohort.

FAQ 5: 'Is anti-TNF safe to use during pregnancy, and if so; must I continue anti-TNF the entire pregnancy? What are the long term effects on my child?'

Chapter 8 discusses the effects of a tailored approach of anti-TNF treatment during pregnancy. Based on previous literature [43, 67-70], we assumed anti-TNF is not teratogenic and safe to continue during pregnancy. Nonetheless, previous data also showed neonates exposed to anti-TNF during pregnancy will be born with clinically significant anti-TNF levels in the serum [71]. The long term effects of fetal exposure to a strong immunomodulator in a developing immune system is unknown. We therefore hypothesized that there is a balance between limiting fetal exposure to anti-TNF and preventing the mother from acquiring disease relapse during pregnancy. We assessed the effects of stopping anti-TNF around gestational week 22 in IBD women in sustained remission. Furthermore, we compared one year child outcomes such as number of infections, allergies and growth between children

exposed to anti-TNF in utero to children born to healthy mothers.

Chapter 9 provides a summary and a general discussion of the main findings in this thesis. Also, suggestions for future studies are discussed in this chapter.

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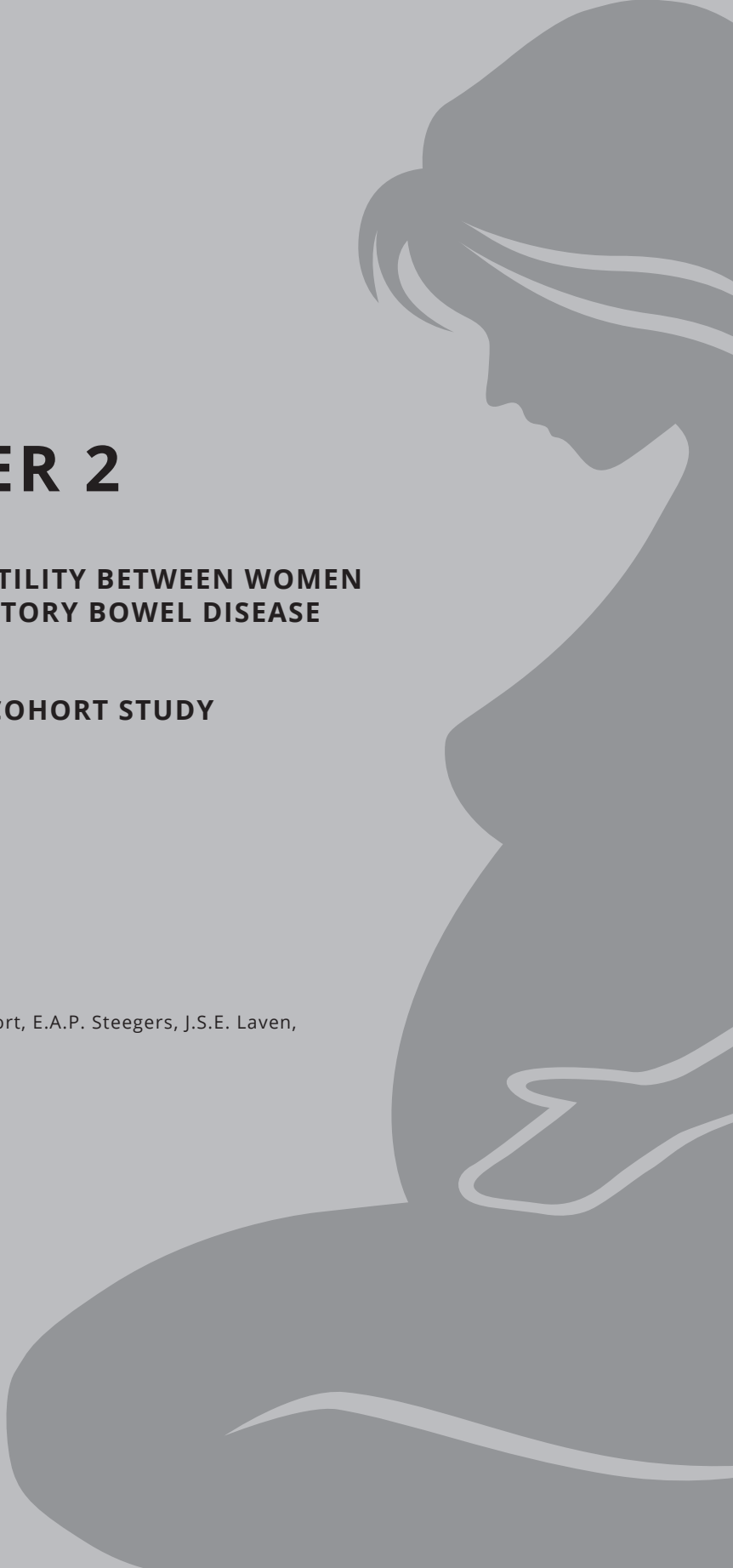
CHAPTER 2

COMPARING FERTILITY BETWEEN WOMEN WITH INFLAMMATORY BOWEL DISEASE AND CONTROLS;

A PROSPECTIVE COHORT STUDY

A. de Lima, M. van Amelsfort, E.A.P. Steegers, J.S.E. Laven, C.J. van der Woude

Submitted



ABSTRACT

Introduction

Inflammatory bowel disease (IBD) often arises in young people and questions about fertility are common. The aim of this study was to compare fertility between IBD women and non-IBD controls.

Methods

All consecutive IBD women with a pregnancy wish that visited the preconception outpatient IBD clinic of the Erasmus MC from 2008-2014 were prospectively followed. Non-IBD controls were drawn from the large birth cohort 'Generation R'. Subfertility was defined as: inability to conceive within 12 months of unprotected intercourse and/or the use of fertility treatment. Subfertility rates between IBD women and non-IBD controls were compared. Secondary aim was to identify risk factors for subfertility in IBD women.

Results

In the total IBD cohort 333 women were trying to establish a pregnancy. From this cohort 227 patients were included (236 CD (70.9%), 87 UC (26.1%), 10 IBDU (3.0%)) along with 804 non-IBD controls. Median time to pregnancy (TTP) was 2.2 (0.9-6.1) months in the IBD group versus 3.0 (2.0-7.0) months in the non-IBD group (p=0.0001). IBD was not significantly associated with subfertility (aOR=0.96, 95%CI: 0.62-1.49). However, IBD women more often underwent fertility treatment than non-IBD controls (21 (11.3%) vs 30 (3.7%), p=0.001). Type of IBD, bowel surgery, peri-anal disease, any form of IBD medication and disease activity in the year during which conception was attempted were not associated with subfertility in IBD women.

Discussion

This study shows that IBD is associated with a normal time to pregnancy and subfertility is not more frequently encountered in IBD patients.

INTRODUCTION

Inflammatory Bowel Disease commonly affects people during their reproductive life span [1, 2]. Strikingly, voluntary childlessness is still common in women with IBD, because of incorrect beliefs, fear of adverse pregnancy outcomes or concerns about fertility [3, 4]. Correct counselling in these patients is therefore essential, however, conclusive data on fertility and fecundity in IBD women is scarce. It has been generally accepted that restorative proctocolectomy with ileal pouch anal anastomosis (IPAA), especially when operated with an open approach [5], can significantly reduce fecundity in women with ulcerative colitis (UC) through formation of adhesions and subsequent mechanical interference with the ovum pick-up mechanism [6-11]. Data on non-surgically treated IBD patients however, remain conflicting and difficult to interpret. Several previous studies have shown IBD women to have fewer children than the general population [3, 4, 12, 13]. The reason for this observed difference remains elusive, as the retrospective nature of these studies makes it hard to differentiate between voluntary childlessness due to incorrect beliefs or lack of proper education and infertility. Other reasons for reduced fertility include active inflammation of the colon [13] or terminal ileum [14] and sexual dysfunction in CD patients with peri-anal disease because of dyspareunia [15]. The primary aim of this study is to compare subfertility in IBD women with a pregnancy wish to a non-IBD control group. As a secondary aim we will investigate risk factors for subfertility within the IBD group.

METHODS

Study design and population

A prospective clinical cohort study was established at the Erasmus MC IBD preconception outpatient clinic [16]. From December 2008 until June 2014 all women with a confirmed diagnosis of IBD trying to establish a pregnancy were followed up until that pregnancy occurred and subsequently until they delivered. At this specialized outpatient clinic, an experienced gastroenterologist counselled and treated IBD patients before pregnancy and bi-monthly during their pregnancy. All consultations were performed in a standardized manner adhering to ECCO guidelines [1, 17]. At every visit, data on disease activity, medication use and pregnancy complications was recorded. In case of disease activity patients were seen every 2 weeks at our outpatient clinic with additional follow up at the department of obstetrics and gynaecology.Time to pregnancy (TTP), the use of and type of fertility

treatment, IBD medication use and disease history and subsequent pregnancy outcomes were prospectively recorded. In addition, paternal data was retrospectively collected through chart review and questionnaires done by telephone. The non-IBD control group was recruited from the Generation R cohort.[18] Generation R is a large prospective birth cohort (n=9778) from the same geographical region as the IBD patients in our cohort originate from. In the Generation R cohort, women are prospectively followed up during pregnancy and their children will be prospectively followed up until the age of 18. Children in this cohort were born between 2002 and 2006. A random sample of approximately 800 children from live, singleton births participating after birth was drawn. This sample was age, - and ethnicity matched with our IBD group and the selection was made blinded for the time to conception, fertility treatment and pregnancy outcome.

Out of the Generation R database, TTP and the use of fertility treatment were obtained to compare subfertility rates in IBD women with non-IBD controls. Furthermore, we also collected several confounding variables, such as maternal ethnicity, maternal BMI [19], parity, maternal smoking status [20] and alcohol use, and paternal age, paternal BMI [19], paternal smoking status and alcohol use [21].

Outcome measurements and definitions

The primary aim of this study was to compare subfertility in IBD women to subfertility in non-IBD controls. Subfertility was defined as the inability to conceive within 12 months of unprotected intercourse and/or use of any fertility treatment. In addition, time to pregnancy (TTP) was measured as the duration of time in months from cessation of contraception onwards until conception as calculated by the obstetrician based on repetitive first trimester ultrasound scans. Women not pregnant at time of analysis, and who had not conceived within the first 12 months of unprotected intercourse or were being treated for infertility were classified as subfertile. A fertility treatment was defined as aid of any reproductive assisting technique (ovulation induction, intra-uterine insemination (IUI), in-vitro fertilization (IVF) and IVF/intra-cytoplasmatic sperm injection (ICSI)) to conceive.

Bias

The non-IBD control group consists exclusively of women who were already pregnant at time of enrolment. Therefore, we limited our comparative analysis between the IBD women and the non-IBD controls to pregnancies resulting in live births. We described the TTP, percentage of subfertility and fertility treatment for the total IBD group separately.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics (version 23.0 Chicago III, USA). Descriptive statistics were reported as means with standard deviation (SD) for parametric data and as medians with interquartile range (IQR) for non-parametric data. Categorical variables are depicted as absolute numbers with percentages. Proportions were compared using the Chi-square and Fisher exact test. The Student's t-test was used to compare continuous parametric variables and the Mann Whitney-U test was used to compare non-parametric continuous variables. Missing data was imputed by means of multiple imputation, under the condition that the data was missing at random and no more than 30% of data was missing per variable. Multiple logistic regression was used to examine the effects of several IBD specific factors on subfertility. All odds ratios (ORs) are displayed as crude ORs and adjusted ORs. The Bonferroni method was used to adjust for multiple comparisons. All tests were performed two-tailed and tested at a significance level of 0.05, except for the multiple logistic regression models where the Bonferroni correction was used to adjust for multiple testing ($p>0.01$).

Ethical consideration

The local ethics committee approved publication of the data from the IBD group. The use of data from the Generation R cohort was also approved by the local ethics committee and informed consent in writing has been obtained.

RESULTS

Baseline characteristics

The IBD preconception outpatient clinic was consulted 333 times for a new pregnancy wish. The IBD group consisted of 227 women in whom 289 pregnancies occurred. Pregnancy outcomes are shown in Figure 1.

The majority of IBD women were diagnosed with CD (n=236, 70.9%), and the remaining part was diagnosed with UC (n=87, 26.1%) or IBDU (n=10, 3%). Baseline characteristics are shown in Table 1. The IBD women were slightly older than the non-IBD controls (30,5 (4,4) vs 29,9 (5,0) yrs, p=0.04). Furthermore, the overall education level in non-IBD women was higher in comparison to the IBD group (p=0.001). Median BMI was comparable between the groups,

Table 1 Baseline Characteristics

Maternal characteristics		IBD Group (n=333)	Non-IBD controls (n=804)	*P*
Mean age (yrs)		30.5 (4.4)	30.5 (4.7)	0.85
Ethnicity (%)	Caucasian	279 (83.8)	643 (80.0)	0.14
	Non Caucasian	54 (16.2)	161 (20.0)	
Education (%)	Low	7 (2.1)	54 (6.7)	0.002
	Middle	159 (47.7)	292 (36.3)	0.001
	High	132 (39.6)	432 (53.7)	0.001
Median BMI (IQR)		22.9 (21.0-25.6)	22.7 (20.8-25.7)	0.55
Parity (%)	Nulliparous	217 (65.6)	442 (56.2)	0.0001
	Multiparous	74 (34.4)	344 (42.8)	
Smoking (%)		60 (18.0)	173 (21.5)	0.14
Alcohol use around conception (%)		10 (3.0)	304 (37.8)	0.0001
Medication (%)	5-ASA	90 (27.0)	-	-
	Steroids	27 (8.1)	-	-
	Thiopurines	128 (38.4)	-	-
	Anti-TNF	123 (36.9)	-	-
Gynaecologic history (%)	PCOS	10 (3.0)	n/a	-
	Endometriosis	8 (2.4)	n/a	-
	PCOS and endometriosis	1 (0.3)	n/a	-
	Uterus bicornis	1 (0.3)	n/a	-
	Status after ovariectomy	2 (0.6)	n/a	-
	Premature ovarian failure	2 (0.6)	n/a	-
	Tubal pathology	1 (0.3)	n/a	-
Paternal characteristics		**IBD Group (n=333)**	**Non-IBD controls (n=804)**	***P***
Mean age (yrs)		32.8 (5.6)	33.0 (5.3)	0.67
Median BMI (IQR)		25.1 (22.0-28.2)	25.3 (21.8-28.8)	0.53
Smoking (%)		80 (24.0)	211 (26.2)	0.06
Alcohol use (%)		168 (50.5)	417 (51.9)	0.05
Andrologic history (%)	None	312 (93.7)	n/a	-
	Oligospermia	10 (3.0)	n/a	-
	Asthenozoospermia	9 (2.7)	n/a	-
	Azoospermia	2 (0.6)	n/a	-

however the non-IBD group had a higher proportion of morbidly obese (BMI>35) women (17 (5.1%) vs 70 (8.7%), p=0.04). Women in the IBD group were more often without any children (65.6%) than the non-IBD controls (56.2%) (p=0.0001). There were no statistically significant differences in paternal baseline data between the IBD and the non-IBD group. In the IBD group, 25 women (11.0%) were diagnosed with a gynaecologic condition of possible influence on fertility. Data on gynaecologic comorbidity in the non-IBD women was not available.

Time to pregnancy

IBD women had a shorter median time to pregnancy (TTP) compared to the non-IBD controls (2.2 (IQR 0.9-6.1) months vs 3.0 (IQR 2.0-7.0) months, p=0.0001)

Subfertility

Thirty-four (18.3%) IBD women fulfilled the subfertility criteria, compared to 96 (18.6%) non-IBD women (p=0.0008) (Table 2). IBD was not independently associated with subfertility, after adjusting for parity, education level and parental smoking (aOR=0.96, 95% CI: 0.62-1.49). IBD women more often underwent fertility treatment compared to the non-IBD controls. Twenty-one IBD women (10.1%) underwent any type of fertility treatment compared to 36 women (3.8%) in the non-IBD group (p=0.001). IBD women undergoing fertility treatment were on average older than the IBD women not undergoing fertility treatment (32.3 yrs vs 30.4 yrs, p=0.008). Particularly in-vitro fertilization (IVF) and intrauterine insemination (IUI) were more common in IBD women compared to the non-IBD controls. IBD was significantly associated with fertility treatment after adjustment for maternal smoking and BMI (aOR=2.79, 95% CI: 1.56-5.00). Ten IBD women with a total of 14 pregnancies who underwent fertility treatment, had fertility treatment before they had reached the threshold of 12 months unprotected intercourse without successful conception and had been referred to a fertility clinic within a year. Reasons for early referral to a fertility clinic included: PCOS (n=3), partner subfertility (n=2), hormonal disorder/menstrual cycle disorder (n=3) and gynaecological condition of unknown origin (n=2).

Subfertility in the total IBD cohort

Out of the total IBD cohort (n=333), 66 (19.8%) women fulfilled the subfertility criteria. The median TTP was 2.4 months (0.9-7.2).

Table 2 Time to conception and subfertility in the IBD-group and non-IBD controls

	IBD group (n=186)	Non-IBD controls (n=804)	*P*	Crude OR (95%CI)	Adjusted OR (95% CI)
Median time to pregnancy (TTP) (months)	2.2 (0.9-6.1)	3.0 (2.0-7.0)	0.0001	-	-
Subfertility (%)	34 (18.3)	96 (18.6)	1.00	0.98 (0.64-1.51)	0.96 (0.62-1.49) [a]
Fertility treatment (%)	21 (11.3)	30 (3.7)	0.001	2.91 (1.63-5.20)	2.79 (1.56-5.00) [b]
IUI	5 (2.7)	3 (0.4)	0.01	-	-
ICSI	1 (0.5)	0 (0.0)	0.21	-	-
IVF	10 (5.4)	12 (1.5)	0.007	-	-
Ovulation induction	5 (2.7)	15 (1.9)	0.58	-	-

[a] Adjusted for: parity, maternal education level and maternal and paternal smoking
[b] Adjusted for: parity and maternal smoking

Table 3 IBD-associated risk factors for subfertility

	Crude OR	95%CI	Adjusted OR*	95%CI	*P***
Type of IBD (CD vs UC)	0.86	0.47-1.59	0.81	0.42-1.56	0.52
Previous IBD related surgery	1.31	0.68-2.52	0.96	0.46-2.01	0.92
Peri-anal disease	1.36	0.69-2.69	1.42	0.68-2.97	0.36
Medication use	0.63	0.31-1.28	0.65	0.30-1.40	0.27
5-ASA	1.38	0.75-2.55	1.40	0.72-2.74	0.33
Steroids	0.44	0.10-1.98	0.43	0.09-2.06	0.29
Thiopurine	0.44	0.24-0.84	0.45	0.23-0.89	0.02
Anti-TNF	0.59	0.31-1.09	0.53	0.26-1.07	0.08
Number of flares***	0.65	0.38-1.09	0.63	0.37-1.09	0.10
≥ 1	0.90	0.50-1.62	0.85	0.44-1.63	0.62
≥ 2	1.14	0.45-2.87	0.75	0.22-2.53	0.63
≥ 3	6.27	1.52-25.82	3.70	0.59-23.25	0.16

* Adjusted for: maternal age, maternal BMI and male related fertility disorders
** Significance level of p>0.01
*** Number of disease flares in the time period when trying to conceive

The effect of IBD-associated factors on subfertility

Several IBD-specific factors of possible influence on subfertility were analysed within the IBD group. Results are shown in Table 3. No statistically significant association was found between subfertility and type of IBD, previous bowel surgery, peri-anal fistulizing disease, IBD medication use and disease activity in the year attempting to become pregnant. Nonetheless, thiopurine use was associated with subfertility after adjusting for male related fertility disorders, maternal age and maternal BMI (aOR=0.45, 95%CI: 0.23-0.89). However, this model was non-significant after adjustment for multiple comparisons.

IPAA

In this IBD cohort, 5 women with previous restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) surgery were included. Three women had undergone open surgery, one woman laparoscopic surgery and in one woman the surgical technique was unknown. In these 5 women, 7 pregnancies occurred. The median TTP in IBD women with IPAA was 6.0 (4.4-24.0) months, which is higher than IBD women in general with a median TTP of 2.4 (0.9-7.2) months, but not statistically significant (p=0.09). Two out of 7 cases with IPAA (28.6%) met the subfertility criteria, due to paternal infertility (n=1) and tubal damage because of IPAA surgery (n=1), compared to 64 out of 250 cases (25.6%) in the general IBD group (p=1.00).

DISCUSSION

The present study shows subfertility in IBD women is comparable to subfertility in controls. Although the average time to pregnancy was significantly shorter in IBD women, fertility treatment was more common amongst IBD women compared to non-IBD controls. Within the IBD group, we were unable to identify specific risk factors for subfertility. Finally, because some women seemed to have embarked on fertility treatment within the first year after they stopped using contraception it seems that fertility treatment is started earlier in women with IBD.

Previous studies on infertility and subfertility in IBD women showed that the rate of involuntary infertility in both CD and UC women is comparable to a control population [3, 22-24], but in particular voluntary childlessness in IBD women is increased compared to controls. In this cohort, none of the IBD women remained voluntarily childless, as all included women were trying to conceive. Although the IBD women and the non-IBD controls in this study were of

comparable age, at baseline parity differed significantly between the groups, suggesting the IBD women start their families at a later point in life than non-IBD controls.

A survey based case-control study from the 1980's however showed a significant difference in infertility between women with CD and controls, as 42% of women with CD failed to become pregnant compared to 28% controls (p=0.0025) [25]. However, that study did not differentiate between involuntary infertility and voluntary childlessness. Moreover, that study reflected a time period where IBD women were generally advised not to become pregnant.

Within the IBD group in this study, no specific risk factors for subfertility could be identified. Interestingly, in contrast to previous literature reports, previous bowel surgery was not associated with subfertility. This finding can be explained by a lack of power and the low percentage of UC patients who underwent IPAA surgery (n=7, 8.9%). The majority of patients had IBD related surgery such as ileocecal resection (n=47, 59.5%) and (partial) colectomy (n=21, 26.6%), and these types of surgery are not expected to largely influence fertility.

The observed increased use of fertility treatment in IBD women in this study can be attributed to several factors. Firstly, all women in the Generation R cohort were included when they were already pregnant. This leads to a bias in the control group which could result in an overestimation of subfertility or fertility treatment in the IBD group. This is reflected in the fact that the percentage of IBD women undergoing fertility treatment does not differ from the percentage of women undergoing fertility treatment in the general population. Second, the IBD women were already in the medical circuit and seen regularly by a physician which could have facilitated earlier referral to a fertility doctor. Interestingly, the median time to pregnancy was significantly shorter in the IBD group. However, this comprises an average difference of approximately 24 days, and therefore may be clinically irrelevant.

This study has several strengths. This study is the first to prospectively investigate subfertility in IBD women in a relatively large cohort. Furthermore, none of the women were discouraged by their physician to conceive and every included woman had an active pregnancy wish, eliminating bias from voluntary childlessness.

The largest drawback of this study is that we were unable to compare subfertility between IBD women who were not yet pregnant to non-IBD controls who were not yet pregnant. Our control group consisted exclusively of women already pregnant. Therefore, we possibly excluded control women with more severe subfertility problems. Another limitation of this study was the absence of data on female and male related fertility disorders in the non-IBD controls.

Conclusion

In this prospective study, we show IBD is not associated with overall subfertility compared to non-IBD, fertile controls. We found no association between type of IBD, previous IBD related surgery, peri-anal disease, and medication and disease activity on subfertility.

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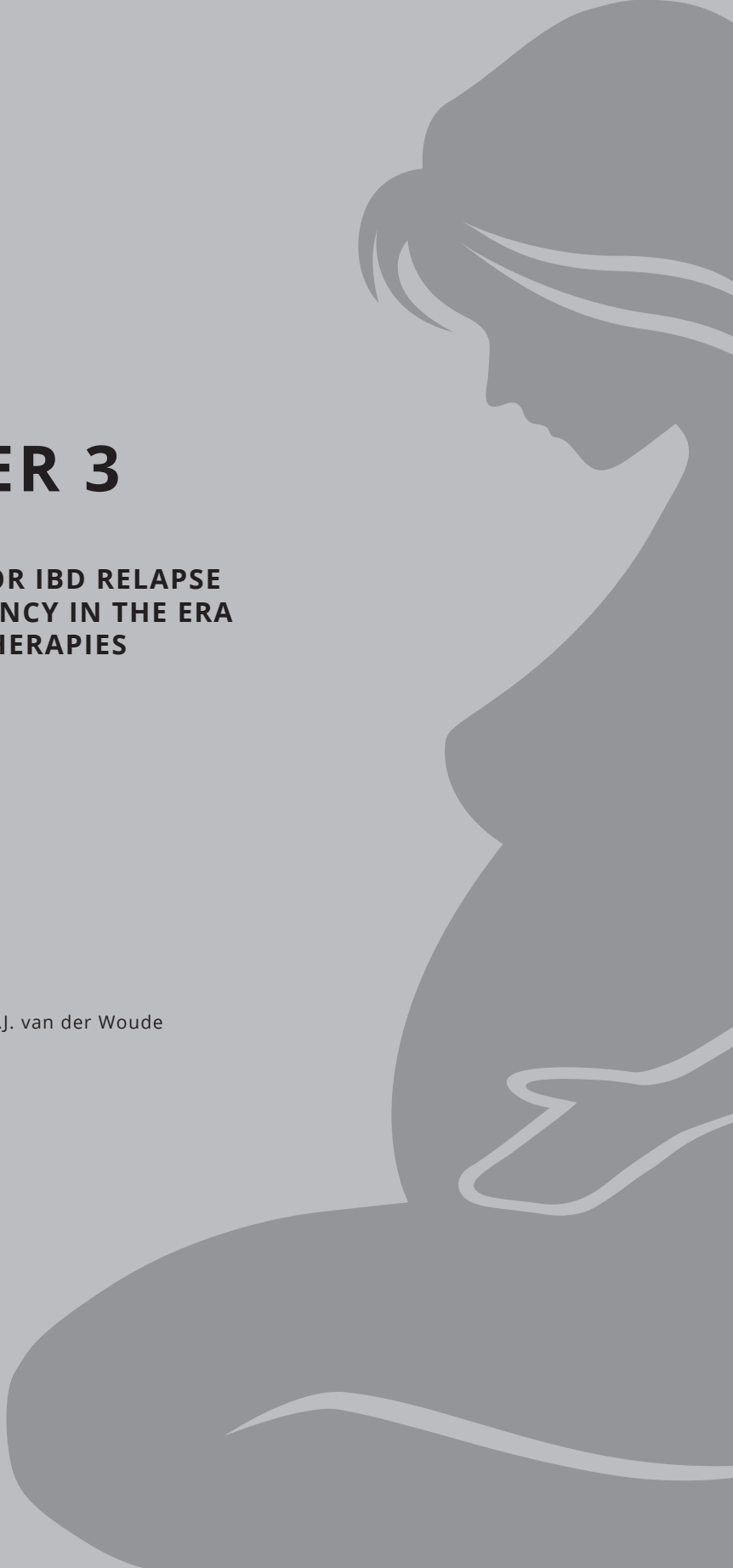
CHAPTER 3

RISK FACTORS FOR IBD RELAPSE DURING PREGNANCY IN THE ERA OF NOVEL IBD THERAPIES

A. de Lima, Z. Zelinkova, C.J. van der Woude

Submitted



ABSTRACT

Introduction

Disease relapse data during pregnancy in a cohort with representation of contemporary IBD medication has not been thoroughly investigated. The aim of this study was therefore (1) to evaluate the risk factors for disease relapse and (2) to study the effects of disease activity on birth outcomes in a cohort with adequate representation of current treatments.

Methods

From 2008-2014, IBD women were recruited from an ongoing prospective clinical cohort. All pts with confirmed IBD diagnosis with a pregnancy wish or pregnancy were prospectively followed up until pregnancy and delivery. Disease activity was monitored throughout pregnancy.

Results

A total of 298 pregnancies were observed in 229 IBD pts (157 CD, 66 UC, 6 IBDU), resulting in 226 live births. A risk factor for periconceptional disease activity was the presence of disease activity in the year preceding conception (aOR=9.24, 95% CI: 4.06-20.93). Periconceptional disease activity was associated disease activity during pregnancy (aOR=7.29, 95% CI: 3.41-15.57). UC was associated with relapse during pregnancy, independent of maternal age, smoking, periconceptional disease activity, previous IBD surgery and the use of immunosuppressives or anti-TNF (aOR=3.71, 95% CI:1.86-7.40). Disease activity was not associated with adverse birth outcomes.

Discussion

This study shows periconceptional disease activity and ulcerative colitis are risk factors for disease activity during pregnancy. In addition, the presence of disease activity one year preceding conception is associated with periconceptional disease activity. Disease activity only minimally affected birth outcomes, reflecting the stringent follow-up and treatment of this group of patients.

INTRODUCTION

Women with Inflammatory Bowel Disease (IBD) are often of childbearing age, as 50% of IBD patients are diagnosed before the age of 35 [1]. Active IBD appears to increase the risk of adverse pregnancy outcomes like spontaneous abortion and preterm birth [2-5], therefore in general the benefits of continuing IBD maintenance medication during pregnancy outweigh the possible risks for the child. To decrease the risk for flares during pregnancy it seems most important to limit disease activity during the conceptional phase. Conception occurring in a time of remission does not increase the risk of disease relapse or persistent disease activity during pregnancy, whereas active disease at time of conception increases the risk of persisting disease activity or another flare during pregnancy [2, 4, 6-11]. The effects of disease activity on birth outcomes have been reported earlier, although these outcomes do not seem representative in the era of biologicals. Also, the retrospective nature of these studies makes it difficult to determine how these pregnant patients were treated for their disease flare. The aim of this study was (1) to assess risk factors for disease activity during pregnancy and (2) to investigate the effect of disease activity on birth outcomes in a prospective clinical cohort where pregnant patients with active disease are treated as non-pregnant patients and with representation of the entire spectrum of contemporary IBD medication.

METHODS

Study Design and Population

We performed a prospective, clinical cohort study of all consecutive pregnant IBD patients seen at the IBD preconception clinic between the years 2008 and 2014. The underlying study population consisted of IBD women treated at a tertiary referral center for their IBD as well as IBD women from general hospitals in the Netherlands referred to our specialized IBD preconception clinic because of a pregnancy wish or early pregnancy. Only IBD patients with histologically confirmed diagnosis were included, also patients with a first presentation of IBD during pregnancy were included. All consecutive IBD patients with a pregnancy wish who were not yet pregnant had regular follow up visits every three months and follow up visits bi-monthly during pregnancy with an experienced gastroenterologist. At first visit, we obtained detailed medical and obstetrical history, current and past (IBD) medication use, life style details like smoking and folate intake, pre-pregnancy Body Mass Index (BMI), and disease activity assessment. During follow up visits, disease activity was monitored through physician

assessment and laboratory work (see Disease activity measurements below). Weight gain, medication changes and life style changes were documented. If the patient experienced complaints in between visits, the patient contacted our outpatient clinic or IBD nurse by telephone or email, and these patients were invited at the outpatient clinic for emergency visit. In case of confirmed relapse, the patient was followed up every two weeks in the outpatient setting until remission. After delivery, birth outcomes were obtained either from the medical files from the gynecologist or by telephonic interview with the patient. Three to four months after delivery, the patient returned for regular visits at the IBD outpatient clinic.

Disease activity and outcome measurements

Disease activity was measured at every visit through physician assessment. In case of diarrhea, fecal cultures were obtained to rule out common causes of infection/gastroenteritis. In addition, we acquired fecal samples for fecal calprotectin levels. Clinically, Crohn's disease (CD) activity was monitored with the Harvey Bradshaw Index (HBI) and ulcerative colitis (UC) activity with the Simplified Clinical Colitis Activity Index (SCCAI). HBI for CD > 5 and SCCAI for UC > 2, and/or fecal calprotectin >200 µg/g (n=< 200 µg/g) was considered active disease. Based on these criteria, the patient was treated medically for a relapse according to current ECCO guidelines [12], and if after a week complaints did not subside, the patient underwent (incomplete) colonoscopy to assess the extent and severity of the inflammation. For CD, we discriminated between luminal, fistulizing or stricturing disease activity. Patients with a first presentation of IBD during pregnancy were excluded from the analyses for risk factors for disease activity around conception and during pregnancy, however we included these patients in the analysis to assess the effect of disease activity on birth outcomes.
As birth outcomes we documented birth weight, gestational term at birth and presence and type of congenital abnormalities at birth or at 3 months follow up.

Definitions

Periconceptional disease activity was defined as active disease (as described above) at any time from 8 weeks before conception until the first 2 weeks of pregnancy. Disease relapse in the year preceding conception was defined as active disease (as described above) at any time in the year preceding the periconceptional period. Ongoing activity until the periconceptional time frame was classified as periconceptional activity and did not count as relapse in the year preceding the periconceptional period. Severity of relapse during pregnancy was pragmatically defined using therapeutic response. Mild to moderate relapse was defined as relapse treated with intensification of current drugs or start of 5-ASA or budesonide and/or isolated peri-anal fistulizing activity. Moderate to severe relapse was

defined as relapse which required prednisone or anti-TNF for remission induction and/or which required hospital admission. Low birth weight was defined as birth weight lower than 2500 grams and preterm birth as delivery prior to gestational week 37. Small for gestational age (SGA) referred to a weight below the 10th percentile for gestational age [13].

Statistical analysis

All analyses were performed using IBM SPSS statistics (version 20.0 Chicago III, USA). Descriptive statistics of continuous variables are depicted as means with standard error of the mean (SEM) or medians with interquartile range (IQR). Comparisons across groups of continuous data was done using student T-tests and Mann Whitney U tests, respectively. Categorical variables are depicted in absolute numbers and percentages and compared across groups using Chi-square or Fisher's exact tests. Univariate and multivariate analyses were executed with logistic regression. All tests were performed using 2-tailed tests and tested at a significance level of 0.05.

Ethical considerations

The Institutional Review Board of the Erasmus MC University Medical Center approved publication of this data.

RESULTS

The total cohort consisted of 336 cases, resulting in 298 pregnancies in 229 women. The remaining 38 women were included in the cohort because of a pregnancy wish, but who were not yet pregnant at the time of the analysis or who had no more reproductive wish. Baseline characteristics for the entire cohort and for CD and UC/IBDU patients separately are shown in Table 1. On average, CD patients had a longer disease duration (7.3 yrs vs 4.8 yrs, p=0.005), were more often treated with immunosuppressive drugs (IS) (52 (21.8%) vs 11 (11.3%), p=0.03) or anti-TNF monotherapy (65 (27.2%)vs 11 (11.3%), p=0.001) and had more often undergone IBD related surgery (108 (45.2%) vs 12 (12.4%), p=0.0001) than patients with UC or IBDU. Patients with UC or IBDU were more often treated with 5-ASA monotherapy (23 (9.6%) vs 32 (33.0%), p=0.0001), slightly more often treated with anti-TNF and 5-ASA/steroids combination therapy (2 (0.8%) vs 8 (8.2%), p=0.001) and were more often referred to our preconception outpatient clinic by general hospitals (103 (43.1%) vs 54 (55.7%), p=0.04) than patients with CD. Six (1.8%) patients had a first presentation of IBD during pregnancy.

Table 1 Baseline Characteristics

		Total cohort (n=336)	CD (n=239)	UC/IBDU (n=97)	*P*
Median age (yrs)		30.4 (27.9-33.1)	30.3 (27.6-33.0)	31.1 (27.9-33.7)	0.18
Median disease duration (yrs)		6.7 (3.5-10.1)	7.3 (4.2-10.3)	4.8 (2.5-8.7)	0.005
Parity (%)	Nulliparous	217 (64.6%)	159 (66.5%)	58 (59.8%)	0.26
	Multiparous	119 (35.4%)	80 (33.5%)	39 (40.2%)	
First presentation of IBD during pregnancy (%)		6 (1.8%)	2 (0.8%)	4 (4.1%)	0.26
CD location (%)	Ileal	66 (19.6%)	66 (27.6%)	-	-
	Colonic	52 (15.5%)	52 (21.8%)	-	-
	Ileocolonic	121 (36.0%)	121 (50.6%)	-	-
	Upper GI involvement	9 (2.7%)	9 (3.8%)	-	-
	Perianal fistulizing disease	62 (18.5%)	62 (25.9%)	-	-
CD behaviour (%)	Non-stricturing, non-penetrating	138 (41.1%)	138 (57.7%)	-	-
	Stricturing	6 (1.8%)	6 (2.5%)	-	-
	Penetrating	53 (15.8%)	53 (22.2%)	-	-
	Stricturing and penetrating	42 (12.5%)	42 (17.6%)	-	-
UC location (%)	Proctitis	10 (3.0%)	-	10 (10.3%)	-
	Left-sided	44 (13.1%)	-	44 (45.4%)	-
	Extensive	43 (12.8%)	-	43 (44.3%)	-
IBD maintenance medication (monotherapy)	None	51 (15.2%)	39 (16.3%)	12 (12.4%)	0.41
	5-ASA	55 (16.4%)	23 (9.6%)	32 (33.0%)	0.0001
	Steroids	9 (2.7%)	7 (2.9%)	2 (2.1%)	1.00
	Thiopurine	63 (18.8%)	52 (21.8%)	11 (11.3%)	0.03
	Anti-TNF	76 (22.6%)	65 (27.2%)	11 (11.3%)	0.001
IBD maintenance medication (combination)	5-ASA + Steroids	4 (1.2%)	2 (0.8%)	2 (2.1%)	0.33
	Thiopurine + 5-ASA/steroids	24 (7.1%)	15 (6.3%)	9 (9.3%)	0.35
	Anti-TNF + 5-ASA/steroids	10 (3.0%)	2 (0.8%)	8 (8.2%)	0.001
	Anti-TNF + Thiopurine	40 (11.9%)	31 (13.0%)	9 (9.3%)	0.46
Extra intestinal manifestations (n)	Yes	68 (20.9%)	53 (22.2%)	15 (15.5%)	0.18
	No	257 (79.1%)	186 (77.8%)	82 (84.5%)	-
IBD surgery (%)	Bowel resection	80 (24.0%)	74 (31.0%)	12 (12.4%)	0.0002
	Perianal surgery	34 (14.2%)	34 (14.2%)	0 (0.0%)	0.001
Median number of relapses in year preceding conception		0 (0-1)	0 (0-1)	0 (0-1)	0.17
Reffered by general hospital (n)		157 (46.7%)	103 (43.1%)	54 (55.7%)	0.04

Table continues on next page

Table 1 Baseline Characteristics **Continued**

	Total cohort (n=336)	CD (n=239)	UC/IBDU (n=97)	*P*
Median pre-pregnancy BMI	22.9 (21.0-25.6)	23.5 (21.3-26.0)	22.5 (20.4-25.2)	0.06
Smoking 3 months before pregnancy (n)	60 (19.2%)	47 (19.7%)	13 (13.4%)	0.21
Folic acid intake (n)	212 (73.6%)	156 (65.3%)	58 (59.8%)	0.46

Risk of relapse during pregnancy and in the puerperal period

Overall, forty-eight (16.4%) conceptions occurred in times of active disease, while disease activity during pregnancy occurred in 83 (29.7%) of pregnancies. In the three months after delivery, 38 (12.8%) women had a new disease relapse. In 19 pregnancies, the disease activity during pregnancy was persistent disease activity from the periconceptional period into the first trimester and in some cases into the second and third trimester. Consequently, the absolute risk of disease relapse during pregnancy, not including persistent activity from the periconceptional period, was 21.5%. During pregnancy, 47 (56.6%) had a mild-moderate relapse, and 36 (43.4%) had a moderate-severe relapse. Eleven (9.8%) patients were admitted to the hospital to be treated for their disease flare, while the remaining patients could be treated in an outpatient setting. Median fecal calprotectin were significantly higher in women who experienced disease relapse during pregnancy (46.5 vs 1141.1, p=0.0001). The fecal calprotectin cut-off of >200 µg/g significantly corresponded with disease relapse during pregnancy (X2; p=0.005).ERRRRRssss

Disease activity in CD and UC patients

Forty-seven (24.4%) CD patients had active disease during pregnancy, compared to 36 (46.2%) UC patients (p=0.001). In each trimester, UC patients had a higher absolute risk of disease activity (see Figure 1), however this difference was only statistically significant in the second trimester (p=0.02). The majority of CD patients had active luminal disease (n=32, 68.0%), and the remaining CD patients had isolated peri-anal fistulizing disease activity (n=11, 23.4%) or active extra-intestinal manifestations (n=4, 8.6%). There was no difference in disease activity severity between the CD and UC patients (19 (40.4%) vs 17 (19.4%) patients with moderate-severe disease activity, p=0.66).

Risk factors for disease activity around conception

Risk factors for disease activity around conception and during pregnancy are provided in Table 2. Presence of disease activity in the year preceding conception increased the risk of disease activity around conception (RR=4.8, 95%CI: 2.6-8.8). The presence of disease activity in the year preceding conception was independently associated with periconceptional disease activity, after adjustment for disease duration, smoking, previous IBD surgery and the use of IS or biologicals (aOR=9.24, 95% CI:4.06-20.93). Disease activity around conception was not associated with disease duration, ulcerative colitis or smoking.

Table 2 Risk factors for disease activity around conception and during pregnancy

	Periconceptional disease activity			Disease activity during pregnancy		
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	***P***	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**	***P***
Disease duration (yrs)	0.97 (0.90-1.04)	0.96 (0.89-1.03) [a]	0.26	0.95 (0.90-1.01)	0.97 (0.91-1.03) [a]	0.35
Ulcerative colitis	0.61 (0.29-1.28)	0.63 (0.28-1.41) [b]	0.26	2.66 (1.53-4.63)	3.71 (1.86-7.40) [e]	0.0001
Disease activity in year preceding conception	6.76 (3.32-13.76)	9.24 (4.06-20.93) [c]	0.0001	2.13 (1.26-3.62)	0.81 (0.40-1.64) [f]	0.55
Smoking	0.90 (0.38-2.17)	0.98 (0.39-2.44) [d]	0.96	1.12 (0.46-2.73)	1.01 (0.37-2.74) [d]	0.98
Periconceptional disease activity	-	-	-	7.80 (3.87-15.72)	7.29 (3.41-15.57) [g]	0.0001

[a] Adjusted for education level, smoking, previous surgery for IBD, and the use of IS or biologicals
[b] Adjusted for age, smoking, previous IBD surgery and the use of IS or biologicals
[c] Adjusted for disease duration, smoking, previous IBD surgery and the use of IS or biologicals
[d] Adjusted for age and education level
[e] Adjusted for age, smoking, previous IBD surgery, the use of IS or biologicals and periconceptional disease activity
[f] Adjusted for disease duration, smoking, previous IBD surgery, the use of IS or biologicals and periconceptional disease activity
[g] Adjusted for age, smoking and disease activity in the year preceding conception

Risk factors for disease relapse during pregnancy

Ulcerative colitis was significantly associated with disease activity during pregnancy (RR=1.9, 95%CI: 1.3-2.7) (aOR=3.71, 95%% CI: 1.86-7.40), after adjustment for maternal age, smoking during pregnancy, periconceptional disease activity, previous IBD surgery and the use of immunosuppressive medication or biologicals. Disease activity around conception was also significantly associated with disease activity (both persistent activity and newly acquired

disease flares) during pregnancy (RR=3.8, 95% CI: 2.8-5.2) (aOR=7.29, 95% CI: 3.41-15.57), after adjustment for maternal age, smoking, and presence of disease activity in the year preceding conception. Disease activity during pregnancy was not associated with disease duration, presence of disease activity in the year preceding conception or smoking.

Treatment of disease activity

Out of the 47 pregnancies with disease activity in CD women, 25 (53.2%) women (luminal activity (n=16), peri-anal fistulizing activity (n=9)) did not successfully reach remission before the end of pregnancy. Within three months after delivery however, 8 (50% of) CD women with luminal activity at delivery achieved remission, but only one (11.1%) woman with peri-anal fistulizing disease activity achieved remission. For UC, out of the 36 pregnancies with disease activity, 11 (30.6%) women did not successfully reach remission before the end of pregnancy (p=0.27). Four (36.4%) UC women with disease activity at delivery achieved remission in the three months postpartum. Furthermore, to be expected, newly acquired disease activity in the third trimester was inversely associated with achieving successful remission before the end of pregnancy, independent of smoking and the type of disease activity (aOR=0.29, 95%CI: 0.11-0.78).

Birth outcomes

The 298 pregnancies resulted in 226 (75.8%) live births, 57 (19.1%) spontaneous abortions, 1 (0.3%) stillbirth, 2 (0.7%) elective abortions, 9 (3.0%) women who were still pregnant at the time of analysis and 3 (1.0%) pregnancies that were lost to follow up. Overall, 9 infants were born with congenital abnormalities, including polydactyly (n=3), cleft lip and/or palate (n=3), nevus pigmentosus (n=1), ventricular septal defect (n=1) and an atrial septal defect (n=1).

Effects of disease activity on birth outcomes

Disease activity around conception and in the first trimester was not associated with the risk of spontaneous abortion (aOR=1.63, 95%CI: 0.81-3.27). Overall, neonates born to mothers with disease activity during pregnancy had median lower birth weights than neonates from pregnancies without any disease activity (3200 g vs 3395 g, p=0.04) (see Table 3). Pregnancies with disease activity also resulted more often in low birth weight (LBW) infants (15 (15.5%) vs 9 (7.0%), p=0.03). After adjustment for gestational age at birth, disease activity during pregnancy was no longer independently associated with low birth weight (aOR=2.75, 95% CI: 0.95-7.98). Gestational term did not differ between pregnancies with and without disease activity. Furthermore, disease activity was not associated with preterm birth or SGA infants.

Table 3 The effect of disease activity on birth outcomes

	Total IBD live births (n=226)	No disease activity during conception/ pregnancy (n=134)	Any disease activity during conception/ pregnancy (n=92)	*P*	Crude OR (95% CI)	Adjusted OR (95% CI)
Spontaneous abortion (%)	57 (19.1%) *	43 (23.1%) *	14 (12.5%) *	0.03	1.56 (0.79-3.10)	1.63 (0.81-3.27) [a]
Birth weight (g)	3360 (2883-3635)	3395 (3000-3694)	3200 (2800-3510)	0.04	-	-
Low birth weight (%)	24 (10.9%)	9 (6.7%)	15 (16.3%)	0.03	2.65 (1.11-6.36)	2.75 (0.95-7.98) [b]
Gestational age at birth (wks)	39.0 (38.0-40.0)	39.0 (38.0-40.1)	39.0 (37.3-39.6)	0.10	-	-
Preterm birth (%)	25 (11.3%)	12 (9.0%)	13 (14.1%)	0.28	1.64 (0.71-3.78)	1.78 (0.76-4.19) [c]
Small for gestational age (%)	14 (6.3%)	7 (5.2%)	7 (7.6%)	0.58	1.46 (0.50-4.33)	1.62 (0.52-5.03) [c]
Congenital abnormalities (%)	9 (4.0%)	5 (3.7%)	4 (4.3%)	1.00	-	-

* Percentages for spontaneous abortion calculated over all pregnancies (n=298, n=186 without any disease activity, n=112 with disease activity)

[a] Adjusted for maternal age and smoking

[b] Adjusted for gestational age at birth

[c] Adjusted for smoking

Stratification for disease severity showed lower median birth weight in the moderate-severe disease activity group compared to the mild-moderate disease activity group (3375 g vs 3080 g, p=0.01) (See Table 4). The proportion of LBW babies was also higher in the moderate-severe disease activity group, however, after adjustment for gestational age at birth, moderate-severe disease activity was not associated with LBW (aOR=3.39, 95% CI: 0.80-14.37).

Table 4 The effect of the severity of disease relapse on birth outcomes

	Total IBD live births (n=226)	Mild-moderate relapse during conception/ pregnancy (n=52)	Moderate-severe relapse during conception/ pregnancy (n=40)	*P*	Crude OR (95% CI)	Adjusted OR (95% CI)
Spontaneous abortion (%)	57 (19.1%)*	12 (16.6%)	2 (5.0%)	0.02	0.22 (0.05-1.04)	0.20 (0.04-1.01) [a]
Birth weight (g)	3360 (2883-3635)	3375 (2900-3660)	3080 (2427-3400)	0.01	-	-
Low birth weight (%)	24 (10.9%)	4 (7.7%)	11 (27.5%)	0.02	4.46 (1.30-15.32)	3.39 (0.80-14.37) [b]
Gestational age at birth (wks)	39.0 (38.0-40.0)	39.0 (38.0-40.0)	38.1 (36.7-39.6)	0.05	-	-
Preterm birth (%)	25 (11.3%)	4 (7.7%)	9 (22.5%)	0.07	1.04 (0.43-2.54)	1.16 (0.47-2.87) [c]
Small for gestational age (%)	14 (6.3%)	3 (5.8%)	4 (10.0%)	0.46	1.78 (0.37-8.44)	1.58 (0.32-7.74) [c]
Congenital abnormalities (%)	9 (4.0%)	3 (5.8%)	1 (2.5%)	0.63	-	-

* Percentages for spontaneous abortion calculated over all pregnancies (n=298)

[a] Adjusted for maternal age and smoking

[b] Adjusted for gestational age at birth

[c] Adjusted for smoking

Birth outcomes compared between CD and UC patients

CD patients had statistically significant more spontaneous abortions than UC patients (47 (22.4%) vs 10 (11.8%), p=0.04). Six spontaneous abortions in the CD group however occurred in the same woman while she was in remission. The cause of these repeated spontaneous abortions is unknown. If this patient is excluded from the analysis, there is no difference in spontaneous abortions between CD and UC patients (41 (20.0%) vs 10 (12.3%), p=0.17). Other birth outcomes did not differ between CD and UC patients (See Table 5, Supplementary data).

Table 5 The effect of type of IBD on birth outcomes

	Total IBD live births (n=226)	CD (n=155)	UC/IBDU (n=71)	*P*	Crude OR (95% CI)	Adjusted OR (95% CI)
Spontaneous abortion (%)	57 (19.1%) *	47 (22.9%) *	10 (12.3%) *	0.04	0.46 (0.22-0.95)	0.42 (0.19-0.91) [a]
Birth weight (g)	3360 (2883-3635)	3365 (3000-3641)	3260 (2800-3620)	0.23	-	-
Low birth weight (%)	24 (10.9%)	15 (9.7%)	9 (12.7%)	0.64	1.31 (0.54-3.15)	1.06 (0.36-3.12) [b]
Gestational age at birth (wks)	39.0 (38.0-40.0)	39.0 (37.6-40.0)	39.4 (38.0-40.2)	0.14	-	-
Preterm birth (%)	25 (11.3%)	15 (9.7%)	10 (14.1%)	0.37	0.76 (0.43-1.36)	0.73 (0.34-1.17) [c]
Small for gestational age (%)	14 (6.3%)	8 (5.2%)	6 (8.5%)	0.39	1.64 (0.55-4.92)	2.26 (0.70-7.31) [c]
Congenital abnormalities (%)	9 (4.0%)	7 (4.5%)	2 (2.8%)	0.72	-	-

* Percentages for spontaneous abortion calculated over all pregnancies (n=298)

[a] Adjusted for maternal age and smoking

[b] Adjusted for gestational age at birth

[c] Adjusted for smoking

DISCUSSION

In the present study, we assessed risk factors for disease activity around conception and during pregnancy and found periconceptional disease activity and the presence of ulcerative colitis to be independent risk factors for disease relapse during pregnancy. In turn, the occurrence of disease activity one year prior to conception is independently associated with periconceptional disease activity. The effects of disease activity on birth outcomes were minimal compared to previous studies.

This study confirms previous reports of periconceptional disease activity increasing the risk of disease activity during pregnancy [7, 8]. A recent met-analysis showed disease activity around conception to increase the risk of disease activity during pregnancy for both UC and

CD (RR=2.0, 95% CI: 1.5-3.0) and (RR=2.0, 95% CI: 1.2-3.4), respectively [6]. This meta-analysis however, was limited by a high risk of bias and large heterogeneity of the included studies. Also, the proportion of IBD patients treated with IS or anti-TNF was very low, rendering this study difficult to place in a contemporary perspective [14]. The overall relative risk ratio (RR) for disease activity around conception on the risk of disease activity during pregnancy found in this study, is higher than the pooled RR found in the above mentioned meta-analysis (RR=3.8, 95% CI: 2.8-5.2). This could be an effect of patient selection, as the patients in the present study are drawn from a tertiary referral center and are more often treated with IS and anti-TNF. This could lead to a selection of IBD patients with a more severe disease course and a higher risk of relapse overall. Nonetheless, this study confirms that counseling of IBD patients with a pregnancy wish should mainly focus on the importance of disease remission around conception.

The presence of disease activity in the year preceding conception was found to be an independent risk factor for developing disease activity around conception. Our findings are in line with data from non-pregnant IBD patients, however our cohort is the first to investigate this risk in an IBD population with an active pregnancy wish. In non-pregnant UC women, it has been established that frequent flares predict even more flares in the following years [15].

In the present study, UC patients experienced more disease relapses during pregnancy than patients with CD. The demonstrated relapse risk in UC women appears to be elevated compared to the non-pregnant UC population over the course of 9 months [10], however, this study lacks a non-pregnant control group to infer pregnancy has a negative effect on the course of UC. A recent multi-center study has shown pregnant UC patients to relapse more often than non-pregnant UC patients [10]. However, the treatment for the non-pregnant patients was not reported, rendering the data difficult to interpret. This difference was not detected for CD patients [10, 16], suggesting that pregnancy may alter the course of UC but not CD. The risk of relapse during pregnancy in CD patients in this study (24,4%) is comparable to the risk of relapse in non-pregnant CD patients over the course of 9 months [17-19].

In contrast to previous studies [2, 4, 5, 20-28], disease activity in this cohort did not increase the risk of adverse pregnancy outcomes like spontaneous abortion, low birth weight (LBW) babies, preterm birth or small for gestational age (SGA) babies. Median birth weight was slightly lower in the patients with any disease activity during pregnancy, but the proportion of LBW was not increased in patients with disease activity. The difference in median birth weight was mainly driven by the patients with moderate-severe relapse rather than the patients with mild-moderate relapse. The relatively favorable pregnancy outcomes in this study could be the result of stringent follow up of all patients in this cohort. All patients were seen regularly and

in case of symptoms of disease activity, patients immediately underwent diagnostic work up and subsequent treatment. Furthermore, this is the first study to assess the effect of disease activity on pregnancy outcome with an adequate representation of novel IBD therapeutics. Better disease control might have contributed to these favorable birth outcomes.

The risk of spontaneous abortion in this study was associated with the presence of CD. This finding is in line with a previous retrospective study, investigating the effect of CD on pregnancy outcomes [8]. A more recent study found an increased risk of spontaneous abortion in post-IBD diagnosis pregnancies than pre-IBD diagnosis pregnancies [18]. This risk was not specific for CD patients. Nonetheless, the high proportion of spontaneous abortion in the CD patients in this study is driven greatly by one woman with 6 repeated spontaneous abortions. If this outlier is take out of the equation, the number of spontaneous abortions in CD is still numerically higher than in UC, but this difference is no longer statistically significant.

This study has several important strengths. In contrast to the majority of retrospective and registry based studies on this subject, this is a large, prospective cohort from a single center. We underline these patients all had stringent follow up during pregnancy by means of routine visits at our preconception clinic. Furthermore, this cohort represents a pregnant IBD population treated with current IBD medication. In previous cohorts, patients on 5-ASA, steroids or no medication at all were included. This inevitably leads to selection of either patients with a mild disease course or sub-optimally treated patients. Importantly, this type of bias has been avoided in the present study.

The lack of a non-pregnant IBD control group makes it hard to demonstrate a deleterious effect of pregnancy on the course of UC. We can only show a significant difference between CD and UC patients. Another limitation of this study is the absence of a healthy control group to compare birth outcomes. Furthermore, we were not able to discriminate between mild to moderate and moderate to severe disease activity in a standardized manner (e.g. by CDAI or UCAI). A pragmatic definition for disease relapse severity has been used in this study, however, we do not feel this importantly influenced our results.

The findings in this study may facilitate identification of high-risk IBD patients for disease relapse during pregnancy. All IBD women should be monitored closely during pregnancy, but physicians may be extra cautious in UC women. Furthermore, it has been previously established that periconceptional disease activity increases the risk of disease activity during pregnancy. This study however, shows that patients with disease activity in the year before conception have an increased risk of periconceptional disease activity. These patients with frequent flares of disease activity can, age permitting, be advised to conceive when the

disease has been in remission for a year. Finally, birth outcomes in this cohort were more reassuring than in previous studies, and underline that stringent follow-up of IBD women during pregnancy will benefit mother and child.

Conclusion

This study shows periconceptional disease activity and the presence of UC are important risk factors for disease activity during pregnancy. In turn, any disease activity in the year preceding conception is associated with periconceptional disease activity. Although IBD women with disease activity during pregnancy had median lower birth weights compared to women without disease activity, the effect of disease activity on birth outcomes appears less deleterious than previously reported. Diligent counseling and follow-up remains important in this delicate group of IBD patients.

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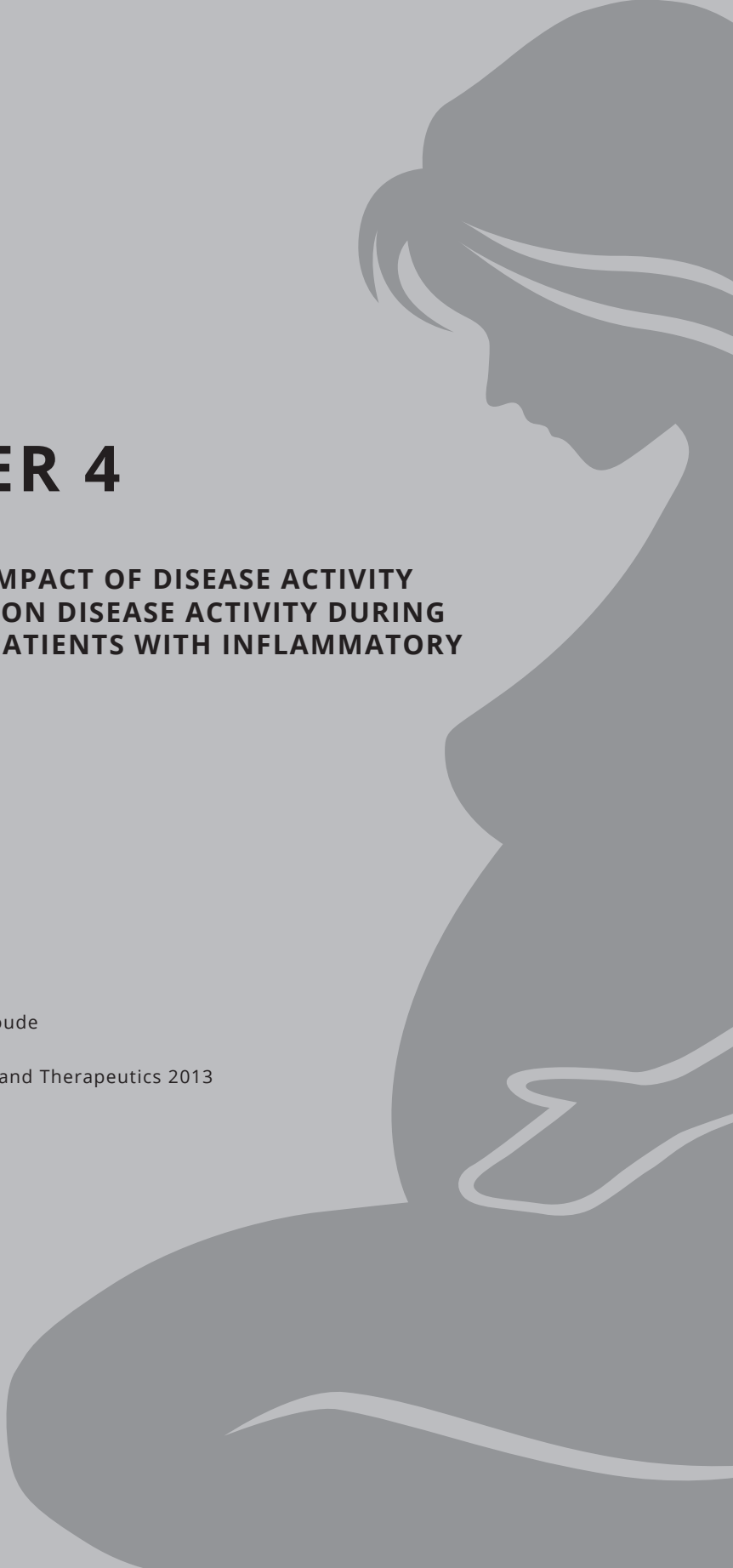
CHAPTER 4

COMMENTARY: IMPACT OF DISEASE ACTIVITY AT CONCEPTION ON DISEASE ACTIVITY DURING PREGNANCY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

A. de Lima, C.J. van der Woude

Alimentary Pharmacology and Therapeutics 2013



COMMENTARY

Disease remission at conception seems favourable for maintaining remission during pregnancy and child outcome; it is therefore part of preconception advice in females with inflammatory bowel disease [1]. In this meta-analysis [2], the authors investigate the robustness of data justifying this advice and conclude that disease activity around conception increases the risk of disease activity during pregnancy. We agree with the authors that most of the included studies are retrospective, thus have a high risk of bias, and heterogeneity between the studies is large and should therefore be interpreted with caution. However, we do not share their surprise in detecting no significant difference in effect estimate from the early 1950s until 2006. Despite the currently expanding number of patients on immunosuppressives (IS) and anti-TNF, all selected studies in this meta-analysis, including the most recent one [3], included females that were mostly treated with 5-ASA and/or steroids [Crohn's disease (CD) 66% and ulcerative colitis (UC) 83%], with only a minority treated with immunosuppressives (CD 22% and UC 10%) and almost none was treated with anti-TNF (0.5% CD and 0% UC). This might partly explain the similarity in effect estimate over the decades. Furthermore, disease activity seemed to be limited, as the number of patients on IS/anti-TNF was small and severe disease activity will negatively affect patients' sexual function and fertility, especially in those patients who underwent surgery [4-6]. This will inevitably lead to a universal selection of patients with relatively mild disease activity around conception. In conclusion, this meta-analysis is an excellent first step in quantifying how disease activity around conception affects course during pregnancy, but shows the limitation of retrospective research that has been done in most of the pregnancy cohorts, and invites further prospective studies including more recent IBD treatments to bring the effect estimates into the 21st century.

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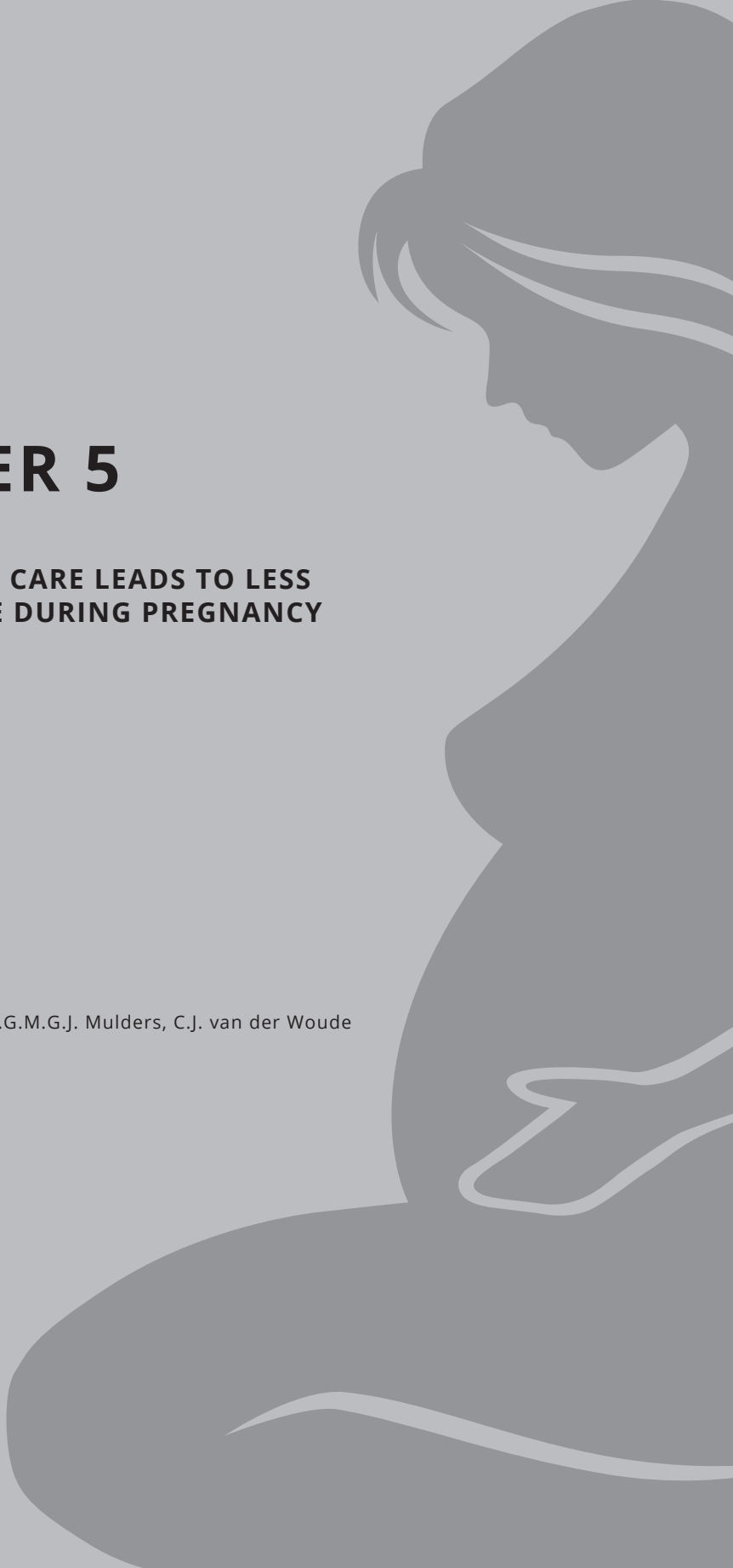
CHAPTER 5

PRECONCEPTION CARE LEADS TO LESS DISEASE RELAPSE DURING PREGNANCY IN IBD WOMEN

A. de Lima, Z. Zelinkova, A.G.M.G.J. Mulders, C.J. van der Woude

Submitted



ABSTRACT

Introduction

Women with Inflammatory Bowel Disease (IBD) may have incorrect beliefs about their disease and its medication in relation to pregnancy. The aim of this study was to assess the effect of preconception care (PCC) on (1) patients behavior during pregnancy, (2) on disease relapse during pregnancy and (3) on birth outcomes.

Methods

From 2008 till 2014, all IBD women visiting the IBD preconception outpatient clinic (POC) were prospectively followed. We compared patients who received PCC prior to pregnancy (PCC group) to patients visiting the POC when already pregnant (no-PCC group). We collected data on life style, medication adherence, planning of conception, disease activity and birth outcomes. We compared adherence to medical advice, disease relapse rates during pregnancy and birth outcomes.

Results

The PCC group (n=155) was on average younger (29.7 yrs vs 31.4 yrs, p=0.001) and more often nulliparous (76.1% vs 51.2%, p=0.0001) compared to the no-PCC group (n=162). PCC was associated with adherence to IBD medication during pregnancy (aOR=5.69, 95% CI: 1.88-17-27), adequate folic acid intake (aOR=5.26, 95% CI: 2.70-10.26) and smoking cessation (aOR= 4.63, 95% CI: 1.22-17.55). PCC reduced disease relapse during pregnancy independent of parity, disease duration and preconceptional disease activity (aOR=0.51, 95%CI: 0.28-0.95). Finally, the PCC group less often delivered babies with low birth weight (aOR= 0.08, 95% CI: 0.01-0.48).

Discussion

This is the first prospective study showing that preconception care reduces disease relapse rate during pregnancy by promoting IBD medication adherence and smoking cessation. Preconception care is a protective factor for low birth weight babies.

INTRODUCTION

Women with Inflammatory Bowel Disease (IBD) tend to have incorrect beliefs, unfounded fears and insufficient knowledge when it comes to their disease and its medication in relation to pregnancy [1-4]. Lack of correct knowledge could lead to decreased IBD medication adherence during pregnancy [5], which increases the risk of disease relapse and consequently the risk of pregnancy complications [6-8]. Therefore, to rectify misperceptions amongst patients and eventually achieve substantial health gain for both mother and child, patient education by means of IBD-specific preconception care (PCC) seems warranted. Previous studies have shown patient education and a single consultation with a physician on IBD and pregnancy to be effective in increasing knowledge [9] and promoting correct IBD medication adherence during pregnancy [5]. In general, the goal of PCC in IBD patients is to identify and modify medical and behavioral risk factors for adverse maternal and pregnancy outcomes. The importance of timely PCC (i.e before pregnancy occurs) is founded in the idea that early embryonic development and the placentation phase is crucial for pregnancy outcomes. This critical phase is often already passed when a woman first finds out about the pregnancy, and therefore advice when already pregnant can come too late. In IBD women, PCC has the added value of educating the patient in the importance of conceiving in times of quiescent disease as this is an important risk factor for disease relapse during pregnancy [10-16]. In addition, the IBD medication regimen can be adjusted to one compatible with pregnancy. To date, it is unknown if IBD-specific PCC has the ability to prevent disease relapse during pregnancy. However, the efficacy of PCC in women with a chronic disease such as pregestational diabetes mellitus has been previously shown [17 18]. The aim of this study was therefore (1) to investigate the effect of PCC in IBD women before pregnancy on IBD medication adherence and general factors such as smoking behavior , (2) to assess the effect of PCC on disease relapse during pregnancy and consequently (3) to assess birth outcomes.

METHODS

Study design and setting

From January 2008 until July 2014, we conducted an ongoing prospective clinical cohort study at the IBD preconception outpatient clinic (POC) Erasmus MC, a tertiary referral hospital. All IBD women in the fertile age range (18-42) visiting the regular IBD outpatient clinic were routinely asked for a pregnancy wish. In case of an active pregnancy wish within 2 years, the

patient was referred to the POC (see Figure 1). At the POC, 30-45 minutes are scheduled for each new patient to discuss reproduction aspects in relation to IBD adhering to recent ECCO guidelines [15 19]. In addition, general health promoting advice was given (folic acid intake, smoking cessation, no alcohol during pregnancy) at the POC. The emphasis of this specialized consultation lies on the importance of conceiving in times of quiescent disease. If necessary, IBD medication alterations are made. In case of quiescent disease and non-teratogenic medication, 'green light' for pregnancy was given. All patients received a written letter after the consultation with the given advice summarized. Patients were followed up every three months until conception and every two months during pregnancy and in case of disease activity during pregnancy every 2 weeks.

Participants

All IBD women with an active pregnancy wish or who were already pregnant treated at the regular IBD outpatient clinic at our institution were included in the cohort. Additionally, IBD women referred to the POC because an active pregnancy wish or an ongoing pregnancy from other hospitals were included in the cohort, only when no preconception care was available in the referring hospital. For the purpose of this study, we compared IBD women who received the preconception advice when they were not yet pregnant (preconception group) to IBD women who first presented themselves at the POC when they were already pregnant (no-preconception group). All IBD women received the same advice, follow up and treatment during pregnancy.

Variables and data measurement

At baseline visit (either before or during pregnancy), we obtained the patient demographics, disease history, obstetric history, data on smoking and alcohol use and clinical assessment of the disease activity through Harvey Bradshaw Index (HBI) for CD patients and Simple Clinical Colitis Activity Index (SCCAI) for UC patients. From 2010, fecal calprotectin was measured to assess disease activity (fecal calprotectin >200µg/g). At every follow up visit, disease activity was clinically monitored, medication and folic acid adherence was assessed, as well as smoking habits and alcohol intake. In a large proportion of anti-TNF treated patients and patients treated with thiopurines, patient reported medication adherence was validated with maternal serum drug levels during pregnancy or at delivery. At the end of pregnancy birth outcomes (birth weight, gestational age, congenital abnormalities, APGAR score) were recorded.

Bias

The primary aim of this study was to investigate the effect of preconception counseling prior to pregnancy on IBD patients` behavior and consequently on disease activity during pregnancy. Inherently, the observational, non-randomized study design creates a bias in the selection of patients. This was countered by consecutively and structurally asking for a pregnancy wish in all IBD women who were treated at our regular outpatient clinic. Therefore, the patients recruited from our own hospital probably suffer less from selection bias than patients who were referred to our POC from other hospitals.

Study size

Based on previous studies [15], we expected a risk of disease activity during pregnancy of approximately 30%. In the case of a reduction in disease activity during pregnancy of 50% in the study group, at a significance level of 0.05 and desired power of 80%, 121 patients per arm were necessary. In the study period we included a total 336 cases eligible for inclusion, with an equal distribution of patients between study arms.

Statistical methods

Analyses were performed using IBM SPSS statistics (version 20.0 Chicago III, USA). All descriptive statistics are shown as medians with interquartile ranges (IQR) for continuous variables and as absolute numbers with percentages for categorical variables. Comparisons for continuous variables are performed using Mann Whitney U tests and Chi-square or Fisher's exact tests for categorical variables. These tests were performed two tailed and at a significance level of 0.05. The effect of preconception advice on patient behavior, disease activity and birth outcomes was calculated using both univariate and multivariate logistic regression. Crude and adjusted odds ratio's (ORs) are displayed with 95% confidence intervals (CI). The significance level was adjusted for multiple comparisons using the Bonferroni method.

RESULTS

Participants

In total, 144 IBD women conveyed 167 pregnancy wishes to us at our IBD preconception outpatient clinic. Twelve women (7.7%) were lost to follow up after the first consultation, because they were unable to attend follow up visits for financial or logistic reasons. This resulted in a study group of 132 women with 155 pregnancies with preconception advice prior to these pregnancies (PCC group). Another 115 IBD women visited the preconception outpatient clinic when they were already pregnant (no-PCC group). These 115 women accounted for 169 pregnancies. Six women (3.6%) were first diagnosed with IBD during pregnancy, and these women were excluded from further analysis. Another woman in this group was lost to follow up because of logistic reasons. The control group consisted of 108 IBD women with 162 pregnancies, without preconception advice prior to these pregnancies.

Descriptive data

Patient demographics are shown in Table 1. IBD women in the PCC group were on average younger, had a shorter disease duration and were more often nulliparous compared to IBD women in the no-PCC group. IBD women in the PCC group also underwent more fertility treatments such as in vitro fertilization (IVF) (p=0.0001). In the no-PCC group the majority of pregnancies (80.9%) were planned. Merely 10% of women referred to the POC by another hospital were referred because of active disease or difficult to control disease.

The effect of preconception care on behavior during pregnancy

At first consultation, in 13 IBD women (8.4%) medication adjustments were necessary to avoid teratogenicity during pregnancy (n=7), or because of inefficacy or side effects to medication (n=6). One woman who first presented at the POC when already pregnant had used methotrexate periconceptionally. This was immediately discontinued and replaced by anti-TNF. In the group receiving PCC prior to pregnancy, conception occurred in the majority of cases (61.3%) after the green light for pregnancy date. Importantly, PCC was associated with correct IBD medication adherence during pregnancy independent of parity (aOR=5.69, 95% CI: 1.88-17-27). In addition, PCC was significantly associated with adequate folic acid intake (aOR= 5.26, 95% CI: 2.70-10.26) and smoking cessation (aOR=4.63, 95% CI: 1.22-17.55) independent of education level. All crude and adjusted ORs are shown in Table 2. Within the PCC group, we were unable to identify risk factors for non-adherence to the advice (see Supplemental table 1).

Table 1 Baseline characteristics

Variable		PCC (n=155)	No PCC (n=162)	*P*
Maternal age (yrs)		29.7 (26.5-32.4)	31.4 (28.7-34.1)	0.001
Type of IBD (%)	Crohn's Disease	113 (72.9)	112 (69.1)	0.54
	Ulcerative Colitis	35 (22.6)	48 (29.6)	
	IBD Unclassified	7 (4.5)	2 (1.2)	
Disease duration (yrs)		5.1 (2.4-9.3)	8.0 (5.2-11.9)	0.0001
Parity (%)	Nulliparous	118 (76.1)	83 (51.2)	0.0001
	Multiparous	37 (23.9)	79 (28.8)	
Marital status (%)	Not married	72 (46.5)	73 (45.1)	0.91
	Married	83 (53.5)	88 (54.3)	
Planned pregnancy (%)	No	0 (0.0)	18 (11.1)	0.0001
	Yes	133 (85.8)	131 (80.9)	
Education level (%)	Low	2 (1.3)	4 (2.5)	0.69
	Medium	69 (44.5)	89 (54.9)	0.07
	High	66 (42.6)	60 (37.0)	0.36
Smoking before pregnancy (%)	No	111 (71.6)	134 (82.7)	0.14
	Yes	32 (20.6)	25 (15.4)	
BMI before pregnancy (IQR)		23.3 (21.2-26.0)	22.7 (20.8-25.3)	0.25
Fertility treatment (%)	No	113 (72.9)	145 (89.5)	0.0001
	Yes	33 (22.6)	15 (9.4)	
Relapse in the year preceding pregnancy (%)	None	89 (57.4)	92 (56.8)	1.00
	One or more	66 (42.6)	70 (43.2)	
Never preconception advice (%)		-	129 (79.6)	-

The effect of preconception advice on IBD disease activity

Preconception advice was significantly associated with less disease activity during pregnancy (aOR=0.51, 95% CI: 0.28-0.95), independent of parity, disease duration and periconceptional disease activity. This association could not be found between preconception advice and periconceptional disease activity (aOR=1.02, 95% CI: 0.50-2.09) (See Table 3).

Table 2 The effect of preconception advice on behavioural parameters

Variable		PCC (n=155)	No PCC (n=162)	*P*	Crude OR (95% CI)	Adjusted OR (95% CI)
Medication change necessary before pregnancy (%)	No	142 (91.6)	161 (99.4)	0.0006	7.54 (1.67-33.98)	7.12 (1.56-32.51) [a]
	Yes	13 (8.4)	1* (0.6)	-	-	-
Adequate planning of conception (%)	No	16 (10.3)	-	-	-	-
	Yes	95 (61.3)	-	-	-	-
Correct adherence to IBD medication during pregnancy (%)	No	4 (2.6)	22 (13.6)	0.002	5.78 (1.94-17.18)	5.69 (1.88-17-27) [b]
	Yes	151 (97.4)	140 (86.4)	-	-	-
Adequate folic acid intake (%)	No	14 (9.0)	61 (37.7)	0.0001	5.71 (3.01-10.86)	5.26 (2.70-10.26) [a]
	Yes	118 (76.1)	90 (55.6)	-	-	-
Quit smoking during pregnancy (%)	No	7 (29.2)	17 (70.8)	0.009	5.90 (1.70-20.48)	4.63 (1.22-17.55) [a]
	Yes	17 (70.8)	7 (29.2)	-	-	-
Alcohol intake during pregnancy (%)	No	125 (80.6)	151 (93.2)	1.00	0.81 (0.22-2.92)	0.74 (0.20-2.71) [a]
	Yes	4 (2.6)	6 (3.7)	-	-	-

* Periconceptional methotrexate use

[a] Adjusted for education level

[b] Adjusted for parity

Table 3 Effects of preconception care on disease activity

		PCC (n=155)	No PCC (n=162)	*P*	Crude OR (95% CI)	Adjusted OR (95% CI)
Periconceptional disease activity (%)	No	107 (69.0)	131 (84.5)	0.53	0.80 (0.43-1.51)	1.02 (0.50-2.09) [a]
	Yes	19 (12.3)	29 (17.9)	-	-	-
Disease activity during pregnancy (%)	No	90 (58.1)	102 (63.0)	0.05	0.58 (0.34-0.99)	0.51 (0.28-0.95) [b]
	Yes	28 (18.1)	55 (34.0)	-	-	-

[a] Adjusted for parity, disease duration and number of relapses in year preceding pregnancy

[b] Adjusted for parity, disease duration and periconceptional disease activity

The effect of preconception advice on birth outcomes

Table 5 shows the effect of preconception advice on birth outcomes. Preconception advice was protective for low birth weight in the newborn (aOR=0.08, 95% CI: 0.01-0.48) independent of gestational age at birth. However, no significant association was found between preconception advice and small for gestational age (SGA) babies (aOR=0.22, 95% CI: 0.05-1.00).

Table 5 Effects of preconception care on birth outcomes

	PCC (n=129) **	No PCC (n=162)	*P* ***	Crude OR (95% CI)	Adjusted OR (95% CI)	*P* ***
Live births (%)	97 (75.2)	127 (78.4)	0.58	0.84 (0.48-1.44)	0.79 (0.45-1.38) [a]	0.40
Spontaneous abortions (%)	26 (20.2)	31 (19.1)	0.88	1.07 (0.60-1.91)	1.10 (0.61-2.00) [a]	0.75
Birth weight (g)	3373 (2955-3679)	3363 (2829-3630)	0.52	-	-	-
Low birth weight (<2500 g) (%)	7 (7.2)	16 (12.6)	0.19	0.53 (0.21-1.35)	0.08 (0.01-0.48) [b]	0.006
Gestational age at birth (wks)	38.4 (34.0-40.0)	38.0 (36.1-39.5)	0.50	-	-	-
Preterm birth (< 37 wks) (%)	13 (13.4)	10 (7.9)	0.19	1.80 (0.75-4.31)	1.74 (0.73-4.16) [c]	0.22
Small for gestational age (SGA) * (%)	3 (3.1)	12 (9.4)	0.06	0.30 (0.08-1.09)	0.22 (0.05-1.00) [d]	0.05
Congenital abnormalities (%)	3 (3.1)	6 (4.7)	0.74	0.63 (0.16-2.60)	0.92 (0.20-4.14) [e]	0.91

* Small for gestational age: birth weight below 10th percentile for gestational age
** Patients not yet pregnant excluded from analysis
*** Significance level ≤ 0.006
a Adjusted for maternal age at conception
b Adjusted for gestational age
c Adjusted for mode of delivery
d Adjusted for smoking during pregnancy
e Adjusted for correct folic acid intake

DISCUSSION

In the present study, we show preconception care leads to less disease relapse during pregnancy and preconception care positively influences birth outcomes by protecting against low birth weight. These effects can be attributed to the beneficial of preconception care on planning pregnancy in times of quiescent disease, correct IBD medication adherence, and smoking cessation during pregnancy (see Supplemental table 2).

Previously, a questionnaire based study reported medication adherence during pregnancy in women with ulcerative colitis of approximately 60% [5]. Counseling was also found to have beneficial effects on medication adherence, however counseling was non-standardized and given by a variety of different physicians. Also in non-pregnant IBD women high adherence was reported in approximately 60% of cases [17 20]. In this study, medication adherence rates are higher than 60% in both the IBD women receiving PCC (97.4%) and in IBD women who did not receive PCC (86.4%). The difference in adherence rates between this study and previous studies may be explained by the high level of motivation for a healthy pregnancy in our cohort of pregnant IBD women. In addition, patients could have falsely reported about their adherence because they knew this would be socially desirable. In the majority of anti-TNF treated patients and in part of the thiopurine treated patients we measured maternal drug levels at birth or during pregnancy. These levels greatly corresponded with the patient reported adherence. However, these data were not measured or unavailable for all patients. In this study, we did not check adherence through checking the prescription data with the pharmacy.

To our surprise, this study did not detect an effect of PCC on periconceptional disease activity, although the focus of the PCC was on the importance of quiescent disease at conception. We can only speculate about the explanation for this finding, but we believe this could be a result of a discrepancy between physician declared disease remission and the patient's own feeling of wellbeing combined with a strong reproductive desire.

PCC in all women with a pregnancy wish has many advantages, and can be seen as the purest disease prevention available. One of the biggest drawbacks of PCC however, is that the pregnancy has to be planned. In IBD women, it must also be clear that besides the gynecologist, the gastroenterologist has a major part to play in this respect. We tried to counter these two issues by actively inquiring after a pregnancy wish in all IBD women in the reproductive age at our regular outpatient clinic. With this approach, all patients were aware of the existence of the IBD preconception outpatient clinic and we were able to offer PCC

to IBD women with a pregnancy wish but who were undecided about when they wanted to start trying.

Although this study is a prospective study, it is limited by its non-randomized design and may therefore be unable to truly unravel the effects of PCC because the study and control group suffer from different types of bias. One could argue the group receiving PCC was an inherently more health-motivated or higher educated group than the non-PCC group. In our baseline data, we cannot detect a difference in education level or smoking status before pregnancy. Although 'health-motivation' is not measured, these data indicate a minimal difference between the two groups, probably achieved by the previously mentioned consecutive inclusion of all IBD women with a pregnancy wish at our own hospital.

In conclusion, preconception care seems effective in achieving desirable behavioral modifications in IBD women in terms of folic acid intake, smoking cessation and correct IBD medication adherence, eventually leading to less disease relapse during pregnancy. And most importantly preconception care positively influences birth outcomes.

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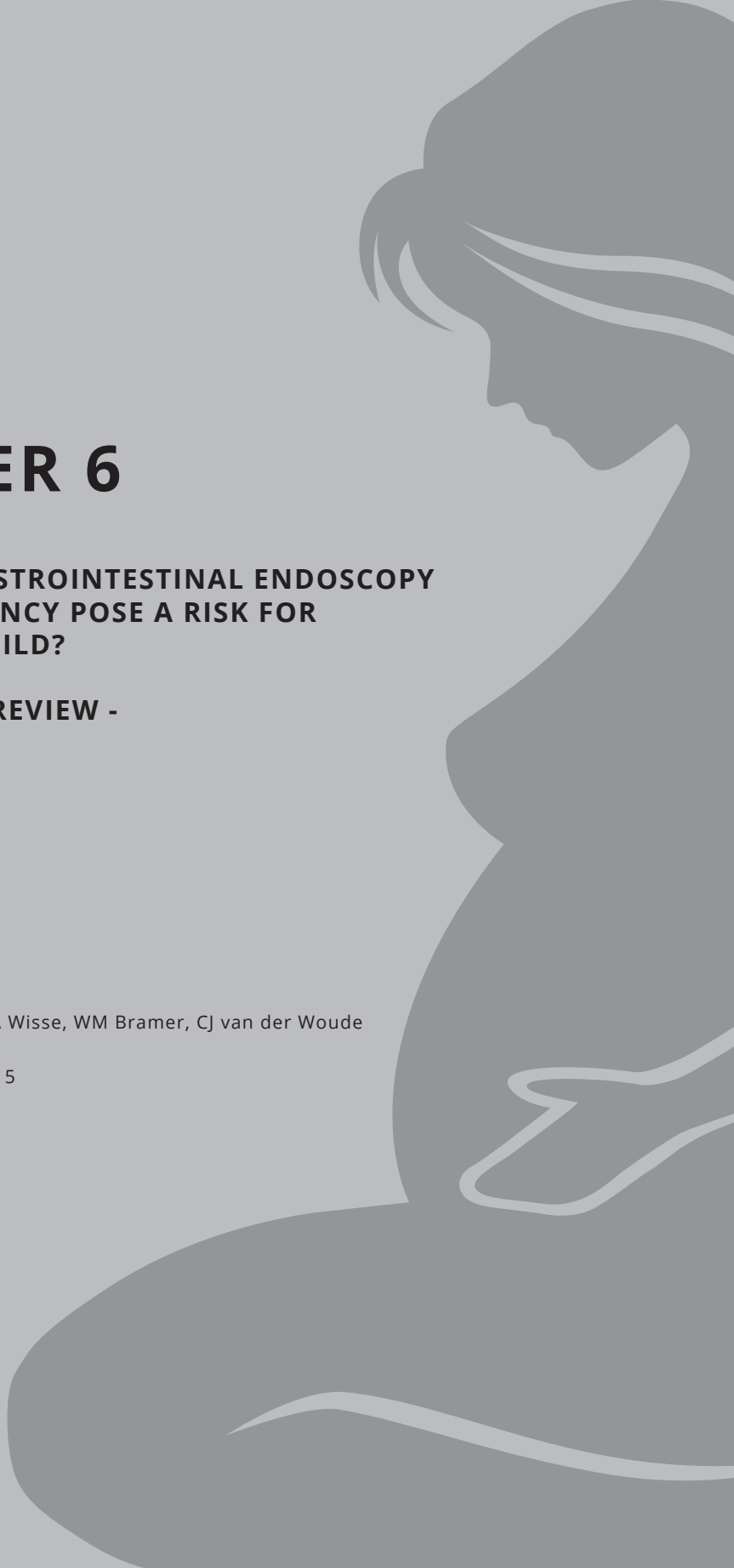
CHAPTER 6

DOES LOWER GASTROINTESTINAL ENDOSCOPY DURING PREGNANCY POSE A RISK FOR MOTHER AND CHILD?

- A SYSTEMATIC REVIEW -

A. De Lima, B. Galjart, PHA Wisse, WM Bramer, CJ van der Woude

BMC Gastroenterology 2015



ABSTRACT

Introduction

Gastrointestinal endoscopy plays a crucial role in the diagnosis and management of gastrointestinal disorders. When endoscopy is indicated during pregnancy, concerns about the effects on pregnancy outcome often arise. The aim of this study was to assess whether lower gastrointestinal endoscopies (LGEs) across all three trimesters of pregnancy affects pregnancy outcomes.

Methods

A systematic literature search was performed using Embase (including MEDLINE), Medline OvidSP, Cochrane Central Register of Controlled Trials, Web-of-Science, Google scholar and Pubmed. All original research articles from 1990 until May 2014 involving pregnant women who underwent LGE for any indication were included. Adverse pregnancy events like spontaneous abortion, preterm birth and fetal demise were assessed for a temporal and etiological relation with the LGE.

Results

In total, 5514 references were screened by two independent reviewers. Eighty-two references met the inclusion criteria and were selected. Two retrospective, controlled studies, one uncontrolled study and 79 case reports were identified. In the three studies, birth outcomes did not differ between women undergoing LGE during pregnancy, compared to women that had an indication for LGE but in whom LGE was not performed because of pregnancy. In 79 case reports, 92 patients are described who underwent 100 LGE's during pregnancy. LGEs performed in all trimesters (n=32, 39 and 29) were both temporally and etiologically related to 1, 3 and 2 adverse events, respectively.

Discussion

Based on the available literature, this review concludes that lower gastrointestinal endoscopy during pregnancy is of low risk for mother and child in all three trimesters of pregnancy.

INTRODUCTION

Gastrointestinal endoscopy plays a crucial role in the diagnosis and management of acute and chronic gastrointestinal disorders. In general, sigmoidoscopy and colonoscopy are regarded of low risk, because of the very low rate of serious complications following lower gastrointestinal endoscopy (LGE). [1, 2] Endoscopic procedures during pregnancy are less common, and although an estimated 6000 pregnant women in the United States annually have an indication for endoscopy, the safety of endoscopy during pregnancy remains unknown. [3] LGE during pregnancy raises important safety questions, including whether medication or bowel preparation is associated with placental abruption or fetal trauma during endoscopic intubation [4] and fetal demise due to maternal hypoxia [4], hypotension or cardiac arrhythmias. [5] Despite the paucity of data, oesophagoduodenoscopy [6, 7] and sigmoidoscopy [8] are considered relatively safe during pregnancy. The safety of colonoscopy during pregnancy remains more elusive and under debate. In recent ASGE guidelines LGE is regarded of low risk during pregnancy, and it is concluded that if possible this should be deferred to the second trimester. [9] Recently, we had to perform several endoscopies in other trimesters and therefore we decided to perform a systematic literature search to assess the effect of the timing of LGE during pregnancy on adverse pregnancy outcomes like spontaneous abortion, stillbirth and premature labor.

METHODS

Search strategy

A systematic database search for citations about LGE during pregnancy was performed by the first author (ADL) and an information specialist (WMB) on May 26th 2014. This search was performed in the following databases: Embase (including MEDLINE), Medline OvidSP, Cochrane Central Register of Controlled Trials, Web-of-Science, Google scholar and Pubmed. The detailed digital search strategy is provided in the Appendix.

Review and study selection process

Titles and abstracts identified through the search strategy were assessed by two independent reviewers for potential eligibility. All original research articles, including case reports, were included. References were excluded on title and abstract based on the following exclusion

criteria: all references published before 1990, all references not in English, all references regarding different subjects, conference proceedings and animal studies. Disagreements were settled in consensus and, if necessary, after discussion with a third independent reviewer. The manuscripts deemed potentially eligible for inclusion were obtained for full text review. The full texts were assessed by the two independent reviewers ((1) ADL and (2) BG and PHAW), using pre-defined eligibility criteria. Articles were included when the study population consisted of at least one pregnant female and LGE was performed during pregnancy. Articles on ectopic pregnancy were excluded, as well as articles without outcome information on the mother and the child. Discussions with the third independent (CJW) reviewer were used to resolve disagreements.

Data extraction

Data from the eligible reports was extracted using a standardized form by the primary reviewers. Differences in the extracted data were resolved through consensus or, if necessary, discussion with the third independent reviewer. For each study, the following data was extracted considering the following:

1. Procedure (type of endoscopy, gestational week of endoscopy)
2. Participants (including age, indication for endoscopy)
3. Interventions (additional surgery, medical treatment, gestational week of other interventions)
4. Outcomes (including birth outcomes, fetal adverse events, maternal adverse events, gestational week of adverse events)

Definitions

Sigmoidoscopy was defined as endoscopic intubation no further than the splenic flexure, and colonoscopy was defined as endoscopic intubation beyond the splenic flexure.

Miscarriages or spontaneous abortion were defined as fetal loss prior to 20th gestational week. Stillbirth or fetal demise was defined as fetal loss beyond the 20th gestational week. Premature delivery was defined as delivery before gestational week 37.

A temporal relation between an adverse event and LGE was found as plausible if the adverse event occurred within 1 week of the LGE and defined as unlikely when the adverse event occurred more than 1 week after endoscopy.

An etiological relation was found plausible if a temporal relation existed and, in addition, based on sound, medical reasoning the adverse event could be linked to the LGE. Etiological relations were classified on an ordinal scale as: unlikely, possible, probable and likely. These relations were determined in consensus, based on the following definitions.

Unlikely relation: LGE or its preparation or sedation cannot explain maternal/fetal adverse event, based on sound, medical reasoning. Elective abortions and induced labor or elective caesarean sections were all classified as unlikely related to LGE.

Possible relation: LGE or its preparation or sedation could explain maternal/fetal adverse event, however in between LGE and the occurrence of the adverse event another intervention was also performed (e.g. laparotomy).

Probable relation: LGE or its preparation or sedation could explain maternal/fetal adverse event, no other interventions between LGE and adverse event were performed, however, the underlying maternal disease could still also explain the adverse event.

Likely relation: LGE or its preparation or sedation could explain maternal/fetal adverse event, no other interventions between adverse event were performed, maternal disease does not seem etiologically related to the adverse event.

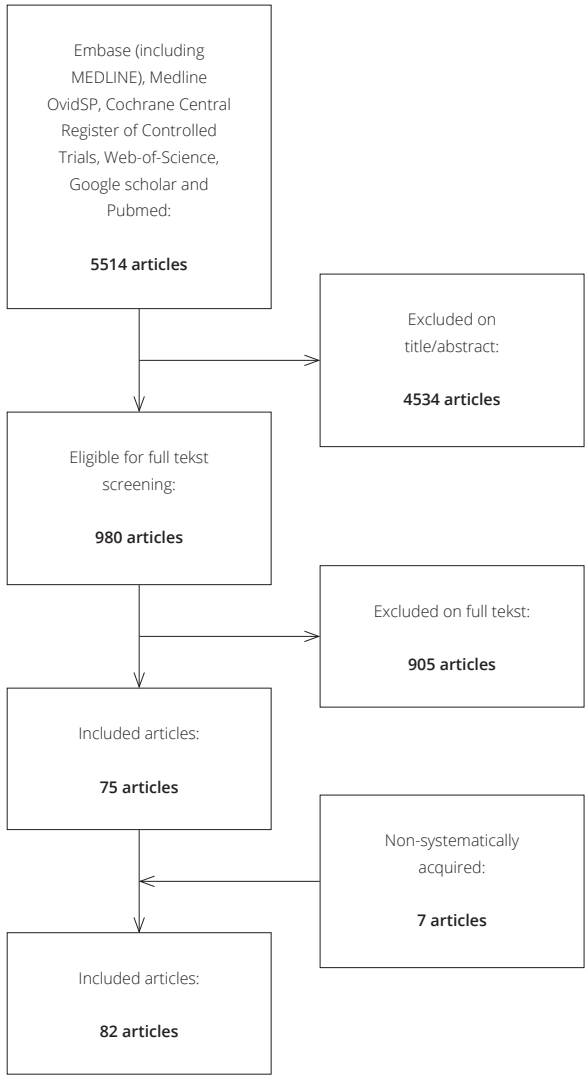
RESULTS

The search yielded a total of 5514 citations. After reviewing title and abstracts, 980 manuscripts were selected for further review. After review of the full text, 75 articles were included, including one retrospective uncontrolled study, two retrospective, controlled studies and 72 case reports or series. An additional non-systematic search yielded another 7 case reports, resulting in a total of 82 articles (See flowchart in Figure 1).

Description of the studies

An uncontrolled, retrospective, multicenter study in 1995, [10] which was published again one year later as an expanded cohort with added controls, [8] reported 46 pregnant patients undergoing 48 sigmoidoscopies and 8 pregnant patients undergoing 8 colonoscopies. There were no differences in birth outcomes between the pregnant patients undergoing endoscopy during pregnancy compared to the pregnant patients not undergoing endoscopy during

Figure 1 Flowchart of study selection process



pregnancy. Both groups had similar indications for endoscopy. In addition, there were no differences in birth outcomes compared to the national American rates at that time. No adverse maternal events were reported following endoscopy. Following sigmoidoscopy, 4 voluntary abortions and 3 fetal demises occurred. All fetal demises were temporally and etiologically unrelated with the endoscopies. Following colonoscopy, there was one voluntary abortion and one fetal demise, both also temporally and etiologically unrelated with the colonoscopy.

In 2010, a study focusing exclusively on colonoscopies during pregnancy was published. [3] This retrospective, controlled cohort study reported on the safety and efficacy of colonoscopy in 20 pregnant patients. These pregnant patients were matched 1:1 with 20 pregnant controls with the same indication for colonoscopy but who did not undergo colonoscopy due to pregnancy. The study group was also compared to the pregnancy outcomes of the American national average. The majority of colonoscopies were performed in the second trimester of pregnancy (n=16), with only 2 colonoscopies performed in respectively the first and third trimester. The study group trended towards worse pregnancy outcomes like stillbirth, premature delivery, low birth weight, low APGAR score, congenital defects and infant death after live birth, compared to the American national average. These non-significant differences can be attributed to the underlying illness in the study group according to the authors. When compared to the control group as described above, the study group tended to have slightly better fetal outcomes compared to the control group in terms of premature delivery, low birth weight, APGAR scores, congenital defects, neonatal ICU stay, infant postpartum hospitalization and infant death after live birth.

Description of the case reports

The 79 case reports describing 92 patients are summarized and categorized per trimester in Tables 1, 2 and 3.

Indications for LGE

Roughly, five major indications for endoscopy could be distinguished: (1) IBD and other colitis, (2) malignancy, (3) volvulus or incarcerated uterus, (4) non-malignant colonic obstruction and (5) gastrointestinal bleeding.

Adverse events related to LGE

All temporally and etiologically related adverse events identified from the case reports are summarized in Table 4.

First trimester

In the first trimester, 32 LGEs were performed in 30 patients. All complications following LGE in the first trimester are listed in Table 1. Three adverse events occurred within 1 week of the LGE. In one case report, [11] the patient underwent sigmoidoscopy at gestational week 10 and the patient had an incomplete spontaneous abortion at 10.4 weeks. The patient

Table 4 Summary of adverse events (AEs) etiologically related to LGE

	Week of LGE	Week of AE	Type of AE	Other intervention between LGE and AE	Likeliness relation
Sigmoidoscopy					
	10	10.4	Incomplete spontaneous abortion	Laparotomy	Possible
	20	20	Fetal death	Laparotomy	Possible
	28	28	Suspected perforation leading to emergency caesarean section	Laparotomy and caesarean section at same time	Likely
Colonoscopy					
	25	26	Fetal death	None	Probable
	15.2	15.3	Pregnancy termination by physicians	None	Probable
	34.0	34.1	Premature spontaneous labour	Nifedipine cessation	Possible

suffered from severe rectal bleeding due to a heterotopic, abdominal pregnancy protruding the terminal ileum. This adverse event could possibly be attributed to the LGE, because this patient also underwent laparotomy after the LGE and suffered from severe gastrointestinal bleeding. The other two temporally related adverse events in the first trimester were both elective abortions, and were therefore classified as etiologically unrelated to the LGE. [12, 13]

Second trimester

In the second trimester, 39 endoscopies were performed in 35 patients. All complications following LGE in the second trimester are listed in Table 2. Six adverse events occurred within one week of LGE. Three cases reported three fetal deaths within one week of endoscopy. In the first case, [14] the patient suffered from massive hematochezia due to multiple bleeding foci in the cecum and terminal ileum and underwent laparotomy shortly after colonoscopy. Fetal demise was evident several hours after surgery. This adverse event is possibly related to the LGE. The second patient was diagnosed with an advanced stage of colorectal carcinoma with liver metastases and ascites during pregnancy. After colonoscopy, the patient deteriorated rapidly and seven days after endoscopy fetal death was observed by ultraso nography. The mother died within 2 weeks after delivery. [15] This adverse event can probably be related to the LGE. The third case demonstrated a patient with progressive colonic

Table 1 First trimester fetal and maternal adverse events (wk 1-12)

Indication	N	Maternal adverse events	Pregnancy outcome	Spontaneous abortion	Other fetal adverse events	Temporal relation with endoscopy?	Etiological relation with endoscopy?
Sigmoidoscopy							
IBD & colitis other [20, 34-38]	6	None	Live birth (n=6)	No (n=6)	3 premature births (34, 28 and 25.5 wks)	No	No
Malignancy [12, 13]	3 (in 2 pts)	None	Elective abortion (n=2)	No (n=2)	Elective abortion (unwanted pregnancies)	Yes (n=2)	No
Volvulus and incarcerated uterus [39]	1	None	No pregnancy losses	No (n=1)	Not reported	No	No
Non-malignant colonic obstruction	0	-	-	-	-	-	-
Gastrointestinal bleeding [11]	1	None	Incomplete abortion (n=1)	Yes, incomplete abortion at 10.4 wks (n=1)	-	Yes	Possible, abdominal pregnancy, laparotomy after sigmoidoscopy
Colonoscopy							
IBD & colitis other [40-46]	12	None	Live births (n=11), stillbirth (n=1)	No (n=12)	2 premature births (32 and 33 wks), 1 stillbirth (22 wks)	Unclear, paper fails to show which outcome belongs to which patient	No, authors do not link adverse events to endoscopy
Malignancy [47-51]	5	Maternal death (n=1), none (n=4)	Live birth (n=5)	No (n=5)	3 premature births (33, 33.6 and 34 wks)	No	No
Volvulus and incarcerated uterus	0	-	-	-	-	-	-
Non-malignant colonic obstruction [52]	1	None	Live birth (n=1)	No (n=1)	None	No	No
Gastrointestinal bleeding [53, 54]	3 (in 2 pts)	None	Live birth (n=2)	No (n=2)	None	No	No
Total	**32**						

IBD = Inflammatory Bowel Disease

Table 2 Second trimester fetal and maternal adverse events (wk 13-26)

Indication	N	Maternal adverse events	Pregnancy outcome	Spontaneous abortion	Other fetal adverse events	Temporal relation with endoscopy?	Etiological relation with endoscopy?
Sigmoidoscopy							
IBD & colitis other [55-60]	8 (in 6 pts)	None (n=6)	Live birth (n=5), not reported (n=1)	Yes (n=1), no (n=4), not reported (n=1)	Low birth weight (n=2), not reported (n=1)	No	No
Malignancy [17-19, 26, 61, 62]	6	Maternal death (n=2), unreported (n=1), none (n=3)	Live birth (n=3), elective abortion (n=2), fetal death (n=1)	Yes (n=3) all prostaglandin induced or elective caesarean section	Low birth weight (n=3)	Yes (n=3), no (n=3)	Unlikely (n=3)
Volvulus and incarcerated uterus [39, 63, 64]	7 (in 5 pts)	None	Live birth (n=5)	None	Low birth weight (n=1)	No	No
Non-malignant colonic obstruction [65]	1	None	Live birth (n=1)	Yes (n=1)	Vaginal delivery at 35 wks	No	No
Gastrointestinal bleeding [14]	1	None	Stillbirth (n=1)	Yes (n=1)	Fetal demise at 20 wks within several hours of surgery	Yes	Possible, however the patient also underwent emergency surgery and suffered from a massive hemorrhage
Colonoscopy							
IBD & colitis other [43, 66-68]	6	None	Live birth (n=5), stillbirth (n=1)	Yes (n=2), no (n=4)	Unreported (n=2), none (n=4)	Unclear, paper fails to show which outcome belongs to which patient	Unclear, authors do not link adverse event (stillbirth) to endoscopy
Malignancy [15, 69-73]	6	None (n=3), maternal death postpartum (n=2), disease progression postpartum (n=1)	Live birth (n=4), unreported (n=1), fetal death at 26 wks(n=1)	Yes (n=3) at 30, 34 and 36 wks	Low birth weight (n=3), neonatal care unit admittance postpartum (n=2)	Yes, fetal death was within 1 week of colonoscopy, premature births no temporal relation with endoscopy	Probable, but fetal death most likely due to maternal deterioration because of cancer progression and sepsis
Volvulus and incarcerated uterus [74]	1	Not reported	Live birth (n=1)	No	None	No	No

Table continues on next page

Table 2 Second trimester fetal and maternal adverse events (wk 13-26) **Continued**

Indication	N	Maternal adverse events	Pregnancy outcome	Spontaneous abortion	Other fetal adverse events	Temporal relation with endoscopy?	Etiological relation with endoscopy?
Non-malignant colonic obstruction [16]	1	Mother remained hospitalized for 50 days after delivery	Stillbirth (n=1)	Yes (n=1)	Evidence of spontaneous labour, physicians terminated the pregnancy at 15 wks	Yes	Probable, however colonic perforation was feared due to worsening distention of the bowel, not per se due to the LGE
Gastrointestinal bleeding [53, 75]	2	None (n=2)	Live birth (n=1), not reported (n=1)	No (n=1), not reported (n=1)	Not reported (n=1), None (n=1)	No	No
Total	**39**						

distension caused by colonic pseudo-obstruction (Ogilvie's syndrome). After colonoscopy, radiologic studies showed no evidence of colonic perforation, but the day after colonoscopy the abdominal distension progressed further, the patient went into spontaneous labor and the physicians decided to terminate the pregnancy. [16] This adverse event could also probably be related to the LGE. Two patients diagnosed with colorectal adenocarcinoma during pregnancy underwent elective abortion within one week of LGE in gestational week 16 and 20 [17, 18] and in one patient labor was induced with prostaglandin in gestational week 26. [19] These three adverse events were therefore classified as unlikely related to the LGE.

Third trimester

In the third trimester, 27 patients underwent 29 endoscopies. All complications following LGE in the third trimester are listed in Table 3. Four case reports demonstrated adverse events within one week of endoscopy. These four cases were likely related in one, possibly related in one and unlikely related in two of the cases. The first case describes a patient who was diagnosed with ulcerative colitis upon sigmoidoscopy in the sixth week of pregnancy. In the 28th week of pregnancy she exhibited signs of exacerbation and she underwent another sigmoidoscopy with biopsies. Following the second sigmoidoscopy, colonic perforation was suspected and an emergency caesarean section and exploratory laparotomy was performed. No colonic perforation was seen intraoperatively. [20] A live, healthy baby of 1054 g was delivered. This adverse event was classified as likely to be related to the LGE. The second patient was 33 weeks pregnant with twins, when she underwent two subsequent

Table 3 Third trimester fetal and maternal complications (27-42 wks)

Indication	N	Maternal adverse events	Pregnancy outcome	Spontaneous abortion	Other fetal adverse events	Temporal relation with endoscopy?	Etiological relation with endoscopy?
Sigmoidoscopy							
IBD & colitis other [20, 33, 76]	3	None (n=2), subtotal colectomy with ileostomy after delivery (n=1)	Live birth (n=3)	No (n=1), Yes (n=2)	Premature births (28 and 34 wks), low birth weight (1850 and 1054 g)	No (n=2), yes (n=1)	Likely, after sigmoidoscopy colonic perforation was suspected, this led to an emergency caesarean section.
Malignancy [32, 77-80]	5	Not reported (n=3), death 12 months after hemicolectomy (n=1), 1,5 years after delivery discovery of pulmonary metastases (n=1)	Live birth (n=5)	Yes (n=4), No (n=1)	Premature births at 34, 34, 31 and 33 wks, all deliveries were elective, low birth weight reported (n=2)	No	Unlikely
Volvulus and incarcerated uterus [64, 81-83]	5 (in 4 pts)	None	Live birth (n=4)	None	None	Yes (n=1)	Unlikely
Non-malignant colonic obstruction [22, 84]	2	None	Live birth (n=1), not reported (n=1)	Yes (n=1)	Elective caesarean section (n=1), Not reported (n=1)	Yes (n=1)	Unlikely
Gastrointestinal bleeding	0	-	-	-	-	-	-
Colonoscopy							
IBD & colitis other [27, 66]	2	Intensive care unit admittance postpartum (n=1), none (n=1)	Live birth (n=1), not reported (n=1)	Yes (n=1), not reported (n=1)	Premature birth (32 wks) with low birth weight 2175 grams	No	Unlikely

Table continues on next page

Table 3 Third trimester fetal and maternal complications (27-42 wks) **Continued**

Indication	N	Maternal adverse events	Pregnancy outcome	Spontaneous abortion	Other fetal adverse events	Temporal relation with endoscopy?	Etiological relation with endoscopy?
Malignancy [23, 28-30, 85-88]	8	None (n=4), maternal death after delivery due to disease progression (n=4)	Live birth (n=8)	Yes (n=8)	Premature births by elective caesarean section (n=4), spontaneous premature birth (n=4)	Yes (n=1), no (n=7)	Unlikely
Volvulus and incarcerated uterus	0	-	-	-	-	-	-
Non-malignant colonic obstruction [21, 89]	3 (in 2 pts)	None	Live birth (n=1), live twin birth (n=1)	Yes (n=1)	Spontaneous premature birth of twins at wk 34	Yes	Possible, however nifedipine was also stopped around time of LGE
Gastrointestinal bleeding [31]	1	None	Elective termination at 34 wks	Yes	Not reported	No	Unlikely
Total	**29**						

colonoscopies for the treatment and decompression of acute colonic pseudo-obstruction. She was already being treated with nifedipine upon presentation for inhibition of premature contractions, and nifedipine was stopped upon hospital admission. One day after the last colonoscopy at gestational week 34, she went into spontaneous labor and delivered healthy twins. [21] This adverse event is possibly related to the LGE. The third patient underwent sigmoidoscopy because of abdominal pain and distention in the 34th gestational week. Upon endoscopy, the splenic flexure appeared necrotic and the patient immediately underwent laparotomy with an emergency caesarean section. [22] This adverse event is unlikely related to the LGE. The fourth patient was diagnosed with a malignancy of unknown origin, and in the metastatic workup a colonoscopy was performed in gestational week 32. A poorly differentiated signet cell adenocarcinoma of the transverse colon was found, and after 4 days of dexamethasone administration for fetal lung maturation an elective caesarean section was performed. [23] This adverse event was unlikely related to the LGE.

One case report and one case series did not report at what gestational week the LGE was performed and were therefore not categorized. These case reports describe three pregnant

women with IBD who underwent sigmoidoscopy for IBD disease assessment. One woman delivered a live baby of 1008 gram prematurely at 28.1 weeks. [24] A temporal relation was not found, and the authors do not link this adverse event to the sigmoidoscopy. In the case series, 2 out of 5 women underwent sigmoidoscopy, and one woman delivered a live baby prematurely. It is not reported if this woman underwent LGE. [25]

Sensitivity analysis

A sensitivity analysis was performed by elongating the time span for the temporal relation between adverse events and the LGE. Initially, all adverse events were temporally related to the LGE if they occurred within one week after the LGE, however this analysis will classify all adverse events within three weeks of the LGE as temporally related. In the first trimester, this approach yielded no extra temporally related adverse events. In the second trimester, one additional temporally related adverse event was detected. In this case, the mother was diagnosed with advanced colorectal carcinoma during pregnancy and died together with the fetus two weeks after hospital admission around gestational week 23. [26] This adverse event was unlikely to be related to the LGE. Finally, in the third trimester another seven temporally related adverse events were detected. Six premature deliveries were unlikely related to the LGE, as they were all elective caesarean sections [27-31] or induced labor. [32] The seventh patient suffered from ulcerative colitis and underwent LGE for assessment of disease activity in gestational week 32. Endoscopy showed the colon to be severely inflamed and two weeks later the patient delivered a premature baby of 1850 grams. [33] This adverse event is classified as probably related to the LGE.

DISCUSSION

The objective of this systematic review was to assess the risk of LGE in all trimesters of pregnancy.

Three retrospective cohort studies investigated the safety of LGE during pregnancy. Of these, two studies describe the same study population, and report no difference in birth outcomes and adverse events between the study and the control group. None of the reported fetal and maternal adverse events showed a temporal or an etiological relation with the LGE. [8, 10] Although these studies report no adverse events related to LGE, it remains unclear in which trimester the LGE was performed.

The third study, [3] on which the recent endoscopy guidelines [9] seem to be based, focuses exclusively on colonoscopies during pregnancy. The authors conclude that colonoscopies during pregnancy are probably safe to perform, but limit their conclusion to the second trimester because of insufficient data in the first and third trimester. Prior to this study in 2010, the authors identified 17 case reports on colonoscopy during pregnancy and add these data to their own conclusion that there is still insufficient evidence to claim safety of colonoscopy in each trimester. [3]

Overall, this systematic review identified 79 case reports, describing 100 LGE's in 92 patients. In total six (6.0%) temporally and etiologically related adverse events were found.

Out of these 79 case reports 42 case reports described 51 colonoscopies in 49 patients during pregnancy, distributed equally across the trimesters (21, 16 and 14 colonoscopies in trimester 1, 2 and 3, respectively). Three temporally and etiologically related adverse events occurred in these 49 patients (6.1%), of which 1 occurred in the third trimester [21] and was possibly related and 2 occurred in the second trimester [15, 16] and were probably related to the colonoscopy (see Table 2 and 3). Although the evidence level of these case reports is low, these data suggest colonoscopy during pregnancy is probably safe to perform. This finding is in agreement with the primary conclusion of the included studies. However, the data from our included case reports in fact suggests colonoscopy to be of similar low risk in each trimester. In addition, we identified 37 case reports, describing 49 sigmoidoscopies in 43 patients. In this subset of patients, also three temporally and etiologically related adverse events occurred in these 43 patients (7.0%), of which one occurred in the first [11] and one in the second trimester [14] and were both possibly related, and one in the third trimester [20] and was likely related to the sigmoidoscopy.
Furthermore, in our view, postponing LGE during pregnancy or even until after pregnancy might hamper the patient and the pregnancy more than the LGE itself. A diagnostic delay will inevitably induce an unwanted therapeutic delay, and therefore the risks of LGE during pregnancy must be weighed against the expected benefits. Consequently, elective endoscopies (e.g for screening purposes) should be deferred until after pregnancy.

Safety research during pregnancy is always a challenging field, as prospective studies are rarely, and experimental studies are almost never performed. Therefore, we rely on retrospective studies and case series to support our conclusions and guidelines. Although the evidence in this systematic review is anecdotal and more controlled studies are needed, this review appears to be the most extensive overview of available studies on this subject.

The major limitation of this exhaustive systematic review is the lacking of a solid control group for the summarized case reports. Furthermore, the majority of case reports describe severely ill patients in whom the true effect of LGE during pregnancy is hard to untangle. In addition, none of the case reports primarily aimed to describe the effect of LGE during pregnancy, rendering these effects subject to our interpretation. Type of bowel preparation and sedation are not mentioned in the majority of included case reports, and their effects cannot be taken into consideration. Also, mild and more subtle adverse events due to LGE could have been easily missed. We therefore focused on serious adverse events like spontaneous abortion, stillbirth and premature delivery.

Conclusion

In conclusion, we underline that LGE should only be performed during pregnancy when strongly indicated and is probably of low risk. Postponing LGE during pregnancy to the second trimester or puerperium however, is unnecessary and in most cases unwanted because of the therapeutic delay which might hamper the pregnancy outcomes more than the LGE itself.

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CHAPTER 7

A PROSPECTIVE STUDY OF THE SAFETY OF LOWER GASTROINTESTINAL ENDOSCOPY DURING PREGNANCY IN IBD PATIENTS

A. de Lima, Z. Zelinkova, C.J. van der Woude

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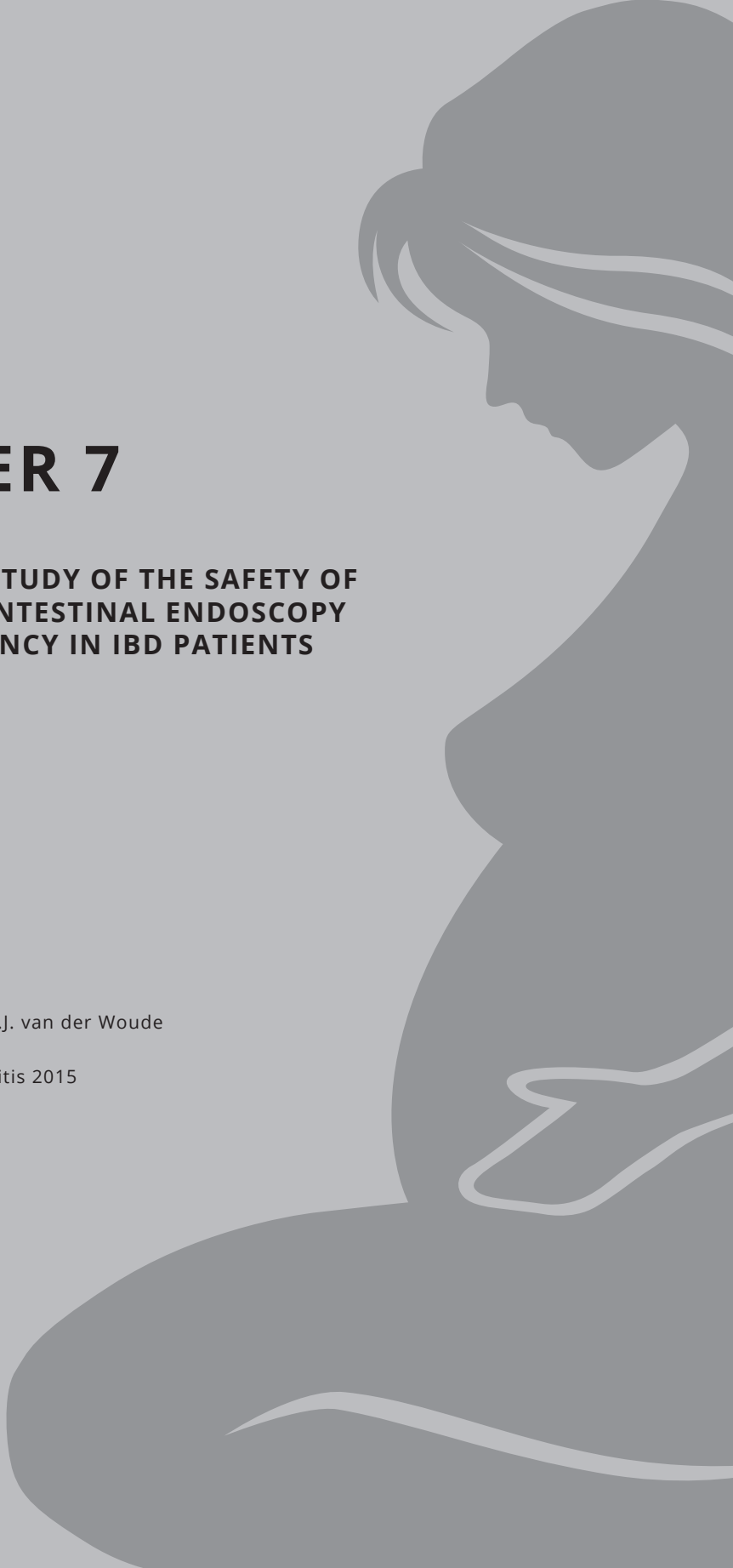

ABSTRACT

Introduction

Inflammatory bowel disease (IBD) women have a higher risk of undergoing gastro intestinal (GI) endoscopy during pregnancy than healthy women. Data on endoscopic procedures during pregnancy in IBD women is limited. The aim of this study was to investigate the safety of lower GI endoscopy during pregnancy in IBD women.

Methods

All consecutive IBD women who underwent endoscopy during pregnancy (cases) from 2008-2014 were prospectively included. Cases were matched 1:1 on age, IBD medication and disease activity with pregnant IBD pts without endoscopy during pregnancy (controls). Maternal and neonatal outcomes were compared between the cases and controls. Adverse events (AEs) were assessed for a temporal relation and for an etiological relation with the endoscopy.

Results

In total, 42 pregnant IBD pts (19 CD, 23 UC) underwent 47 lower GI endoscopies (12 colonoscopies/35 sigmoidoscopies. Median maternal age was 30 years (IQR: 28-32). Two spontaneous abortions were temporally and probably related to endoscopy, however spontaneous abortion did not occur more often in cases than controls (2 (4.8%) vs 10 (23.8%, p=0.01). Median birth weight was significantly lower in the cases compared to controls (3017 g vs 3495 g, p=0.01). There were no significant differences in terms of gestational age at birth, congenital abnormalities and APGAR scores.

Discussion

Although lower GI endoscopy in pregnant IBD women should only be performed when strongly indicated, we report no increased adverse outcomes for the mother or the newborn related to endoscopy in all three trimesters of pregnancy compared to controls.

INTRODUCTION

The onset of inflammatory bowel diseases (IBD) often coincides with the reproductive years. About half of patients are diagnosed before the age of 35 [1]. Because of the relapsing character of IBD, pregnant IBD women have an increased risk of undergoing lower gastrointestinal endoscopy compared to healthy individuals. Although theoretical dangers of lower gastrointestinal endoscopy during pregnancy have been postulated, gastrointestinal endoscopy in pregnant women, is considered generally safe [2-4]. Current ASGE guideline state lower gastrointestinal endoscopy should preferably be deferred to the second trimester [5]. However, inappropriate diagnostic work-up of suspected IBD flare of a pregnant woman, especially delay of lower gastrointestinal endoscopy, could result in suboptimal treatment. IBD activity during pregnancy has proven to be harmful for the pregnancy and the child [6-12] and therefore requires adequate diagnosis and control in any trimester of pregnancy. Therefore, we set up a prospective study to investigate the safety of lower gastrointestinal endoscopy during pregnancy in IBD women.

METHODS

Patients and design

A prospective clinical cohort study was conducted at the Erasmus University Medical Center Rotterdam between July 2008 and September 2014. During this time, all consecutive pregnant IBD women who underwent lower gastrointestinal endoscopy (cases) were selected and followed up bi-monthly during pregnancy until delivery. The control group consisted of age-, IBD maintenance medication-, and disease activity matched pregnant IBD women, recruited from our preconception outpatient clinic. Cases and controls were matched in a 1:1 ratio and the author performing the matching (AL) was blinded for the outcome of the pregnancy.

Indication for endoscopy and procedures

Patients with clinical and biochemical disease activity, as described further on, who were clinically non-responsive to one week of medical treatment (5-ASA or budesonide) for the disease flare or in whom the complaints did not spontaneously resolve within one week, were subjected to lower gastrointestinal endoscopy (cases). Patients successfully responding to medical treatment or with spontaneous resolution of complaints within one week upon

clinical and biochemical signs of clinical disease activity did not undergo lower GI endoscopy (controls). All endoscopies were performed by an experienced gastroenterologist. As bowel preparation for complete colonoscopy all patients used a form of polyethylene glycol solution (PEG) (Moviprep®, Norgine bv). Patients preparing for sigmoidoscopy used PEG solution (Prunacolon®, Takeda Nederland bv) the day before and if necessary an additional enema (Klyx®, Pharmachemie bv) on the day of endoscopy. Use of sodium phosphate bowel preparation was avoided, because of the potentially harmful effects [13]. Midazolam for sedation was not used as sedation in the first trimester [14]. In the second and third trimester of pregnancy, the supine position was avoided to reduce the risk of compression of the inferior vena cava by the gravid uterus. Fetal heart rate was not monitored in all patients during the procedure. There was no external compression used in any trimester.

Definitions

Disease activity during pregnancy in patients who did not undergo endoscopy was defined as: a Harvey Bradshaw Index (HBI) for CD > 5 and Simplified Clinical Colitis Activity Index (SCCAI) for UC > 2, and either C-reactive protein (CRP) > 9.0 mg/l (n=< 9.0 mg/l) or fecal calprotectin >200 µg/g (n=< 200 µg/g). Low birth weight was defined as birth weight lower than 2500 grams and preterm birth as delivery prior to gestational week 37. Small for gestational age (SGA) referred to a weight below the 10th percentile for gestational age [15].

Data collection and outcome measures

We recorded disease history and course, pregnancy course, life style factors like smoking and alcohol use, all medication use including sedation and bowel preparation, and pregnancy outcomes. We compared adverse pregnancy outcomes and adverse birth outcomes between the cases and controls. Furthermore, all adverse events (AE) in the endoscopy group were assessed for a temporal relation and a putative causal relation with the performed endoscopy. A temporal relation was defined as an AE occurring within one week of endoscopy. A causal relation was found plausible if (1) a temporal relation existed and (2) was based on sound, medical reasoning the adverse event could be linked to the endoscopy. Causal relations were determined in consensus between AL and CJW, based on the following definitions:

Unlikely relation: lower gastrointestinal endoscopy or its preparation or sedation cannot explain maternal/fetal AE, based on sound, medical reasoning. Elective abortions and induced labor or elective caesarean sections were all classified as unlikely related to lower gastrointestinal endoscopy.

Possible relation: lower gastrointestinal endoscopy or its preparation or sedation could explain maternal/fetal AE, however in between lower gastrointestinal endoscopy and the occurrence of the AE another intervention was also performed (e.g. laparotomy).

Probable relation: lower gastrointestinal endoscopy or its preparation or sedation could explain maternal/fetal AE, no other interventions between lower gastrointestinal endoscopy and AE were performed, however the underlying maternal disease could still also explain the AE

Likely relation: lower gastrointestinal endoscopy or its preparation or sedation could explain maternal/fetal AE, no other interventions between AE were performed, maternal disease does not seem etiologically related to the AE.

Statistical analysis

All analyses and matching of the cases and controls were performed using IBD SPSS Statistics (version 21.0 Chicago III, USA). Descriptive statistics of continuous data are displayed as means or medians with standard deviations (SD) or interquartile ranges (IQR), respectively. Categorical data are displayed as absolute numbers and percentages. Comparisons of continuous data were made using student t-tests for parametric data and Mann-Whitney U tests for non-parametric data. Comparisons of categorical data were calculated using Fisher's exact test or Chi square tests. Matching of the cases on controls was performed manually by the first author (AL) using three variables age (± 5 years), IBD maintenance medication type and disease activity in the same trimester.

Ethical statement

Publication of this data was approved by the Local Ethics Committee of the Erasmus MC University Medical Center Rotterdam.

RESULTS

In total, 42 women underwent 47 lower gastrointestinal endoscopies (diagnostic n=45, therapeutic n=2) during pregnancy. These 42 cases were matched 1:1 with 42 controls based on age, medication and disease activity during the same trimester of pregnancy. Median maternal age was 30 years (IQR: 28-32). All patients in this cohort experienced

abdominal complaints and/or diarrhea during pregnancy, requiring diagnostic work-up. Thirty-two (76.2%) patients had disease activity during pregnancy in both the cases and controls. In the cases, disease activity was confirmed by endoscopy and in the controls by a combination of clinical signs of disease relapse, elevated calprotectin, abdominal ultrasound in case of terminal ileal disease or MRI. No medication was used by 6 (14%), 5-ASA by 14 (33%), thiopurines by 14 (33%) and anti-TNF by 14 (33%) of cases and controls. Thirty-seven women underwent a single endoscopy, and five women underwent endoscopy twice. In all five patients the second endoscopy was a sigmoidoscopy. Baseline characteristics are shown in Table 1.

Table 1 Baseline charachteristics

Variable		Cases (n=42)	Controls (n=42)	*P*
Type of endoscopy (%)	Colonoscopy	12 (25.5)	-	-
	Sigmoidoscopy	35 (74.5)	-	-
Diagnosis (%)	CD	19 (45.2)	27 (64.3)	0.12
	UC	23 (54.8)	15 (35.7)	-
Mean disease duration (yrs.)		5.4 (4.8)	7.3 (4.1)	0.03
Disease location CD (%)	Ileal	3 (15.8)	9 (33.3)	0.12
	Colonic	6 (31.6)	6 (22.2)	1.00
	Ileocolonic	10 (52.6)	12 (44.4)	0.80
Disease behavior (%)	Non-stricturing, non-penetrating	10 (52.6)	14 (51.9)	1.00
	Stricturing	0 (0.0)	0 (0.0)	1.00
	Penetrating	9 (47.4)	13 (48.1)	1.00
Disease location UC (%)	Proctitis	3 (13.0)	2 (13.3)	1.00
	Left-sided	9 (39.1)	9 (60.0)	1.00
	Extensive	11 (47.8)	4 (26.7)	0.09
Median gestational week of disease activity		13 (1-23)	14.5 (1-28)	0.52
Bowel resection prior to pregnancy (%)		6 (14.3)	5 (11.9)	1.00
Smoking during pregnancy (%)		6 (14.3)	2 (4.8)	0.27
Folic acid use (%)		29 (69.0)	31 (73.8)	0.80
Median total weight gain during pregnancy (kg)		9.0 (6.0-15.0)	12.0 (9.5-18.0)	0.04

Twelve endoscopies (4 colon/8 sigmoid) were performed in the first, 19 (6 colon/13 sigmoid) in the second and 16 (2 colon/14 sigmoid) in the third trimester. The 2 therapeutic endoscopies were performed in the 30th and 32nd gestational week. The therapeutic incomplete colonoscopy at gestational week 30 was performed to dilate a stricture in the transverse colon, whereas the therapeutic endoscopy at week 32 was performed via the pre-existing ileostomy to restore continuity by endoscopically placing a 18 Ch gastric tube. No sedation was used in 23 (48.9%), midazolam only in 3 (6.4%), fentanyl only in 9 (19.1%), midazolam and fentanyl combined in 7 (14.9%) and in 5 patients (10.6%) the sedation type was undocumented. Out of the 12 colonoscopies, in 10 (83.3%) the terminal ileum was intubated, and in 2 (16.7%) patients the colonoscopy was terminated at the transverse colon because further intubation was deemed unnecessary by the physician.

Treatment of relapse

In the case group, all 42 women had clinical and biochemical disease activity during pregnancy, however in 10 out of 42 women no mucosal inflammation was observed upon endoscopy. These 10 women did not receive any medication for disease activity. In the control group, 32 women (76.2%) had clinical and biochemical disease activity during pregnancy, whereas the other 10 controls had no biochemical signs of disease activity. Median fecal calprotectin levels were 1125 µg/g (IQR: 553-1800) in the cases and 1175 µg/g (IQR: 302-1800) in the controls (p=0.79) and median CRP levels were 10.0 mg/l (3.0-23.5) in the cases and 10 mg/l (3.5-21.5) in the controls (p=0.72). Sixteen cases with clinical and biochemical disease activity were pre-treated with 5-ASA agents (n=10), oral budesonide (n=5) or steroid enema (n=1) before endoscopy. Eight out of these 16 (50.0%) pre-treated cases, required additional prednisone therapy after endoscopy. One of the cases was not treated medically after endoscopy, but the caesarean section was performed earlier than scheduled in order to start treatment directly postpartum. The remaining 15 cases who were not pre-treated before endoscopy were all treated with oral or intravenous prednisone after endoscopy.

Seventeen women (53.1%) in the control group did not use any medication for the disease flare, because 3 women recovered spontaneously, in 8 women medical treatment was deferred until after labor, 1 woman received enteral nutrition and 5 women had active fistulizing disease which was not treated medically. Fifteen women in the control group however, were treated medically (oral/local steroids (n=7), budesonide (n=3), adalimumab (n=1), 5-ASA (n=3) and metronidazole (n=1)). Cases were treated with oral or intravenous steroids more often than controls (25 (78.1%) vs 8 (25%), p=0.0001). Remission before delivery was reached in 23 cases (71.9%) and in 17 controls (53.1%) (p=0.20).

Clinical implications of endoscopy

In 10 out of 42 (23.8%) patients with clinically suspected disease activity and elevated CRP and/or calprotectin, endoscopy did not reveal any abnormalities. Endoscopy led to treatment initiation or alteration (addition of prednisone to 5-ASA or budesonide) in 24 out of 32 (75%) women with suspected clinical disease activity.

Maternal outcomes

There were no direct maternal adverse events of lower gastrointestinal endoscopy in all 42 cases (See Table 2, 3 and 4). We observed no cases of bowel perforation or bleeding. Maternal AEs were more common in the cases than in controls (22 versus 10, p=0.01). However, none of these AEs had a causal relation with the endoscopy.

Table 2 First trimester fetal and maternal AEs (cases)

Maternal complications					
Type	**Gestational week of AE**	**Gestational week of endoscopy**	**Type of endoscopy**	**Temporal relation?**	**Causal relation?**
Hyperemesis gravidarum	11	11	Sigmoidoscopy	Yes	Unlikely
Upper respiratory tract infection	11	32	Sigmoidoscopy	No	Unlikely
Hospital admittance for examination of abdominal pain (no cause found)	12	12	Sigmoidoscopy	Yes	Unlikely
Fetal complications					
Spontaneous abortion	7	6.3	Colonoscopy	Yes	Probable
Spontaneous abortion	9	8	Colonoscopy	Yes	Probable

Fetal outcomes

Fetal complications per trimester are shown in Table 2, 3 and 4. Spontaneous abortion more often occurred in the controls than in cases (10 (23.8%) vs 2 (4.8%), p=0.03). Eleven out of 12 women (91.7%) with a spontaneous abortion had active disease in the first trimester. Overall, the proportion of fetal AEs was similar in the cases and in the controls (15 versus

17, p=0.82). Median birth weight was significantly lower in the cases than controls (3017 g vs 3495 g, p=0.01) (See Table 5), but the proportion of neonates with low birth weight did not differ between the cases and controls (6 (15.0%) vs 4 (12.5%), p=1.00). We observed no differences in average gestational age at birth (38.3 wks. vs 38.8 wks., p=0.37), the proportion of preterm births (8 (20.0%) vs 4 (12.5%), p=0.53), APGAR scores after 1 minute and after 5 minutes (9 vs 9 and 10 vs 10, p=0.93 and p=0.96 respectively) and congenital abnormalities (0 (0%) vs 3 (7.1%), p=0.24). These congenital abnormalities included polydactyly (n=2) and palatoschisis (n=1). One term neonate in the case group (endoscopy in week 31, delivery in week 40.3) required resuscitation directly postpartum. Resuscitation was successful and the child is doing well. In the control group, one premature born child was admitted to the NICU for respiratory problems.

Table 3 Second trimester fetal and maternal complications (cases)

Maternal complications					
Type	**Gestational week of AE**	**Gestational week of endoscopy**	**Type of endoscopy**	**Temporal relation?**	**Causal relation?**
Hospital admittance for examination of abdominal pain (urinary tract infection and constipation)	15	15	Colonoscopy	Yes	Unlikely
Surgical treatment of abcess	20	5	Colonoscopy	No	Unlikely
Parastomal hernia	20	20	Colonoscopy	Yes	Unlikely
Acute appendicitis and appendectomy	22	26	Colonoscopy	No	Unlikely
Gestational diabetes	26	14	Sigmoidoscopy	No	Unlikely
Pancreatitis	24	27	Sigmoidoscopy	No	Unlikely
Fetal complications					
None	-	-	-	-	-

Adverse events related to endoscopy

A temporal relation between endoscopy and spontaneous abortion was found in 2 cases. The spontaneous abortions occurred at gestational week 7 and 9, and these women had

undergone complete colonoscopy at week 6.3 and 8, respectively. Upon colonoscopy, both women had severe mucosal inflammation. Etiologically, these adverse events were both classified as: probably related to the endoscopy or its preparation (see definition above). No temporal relation was found between endoscopy and the induction of spontaneous labor or preterm birth.

Table 4 Third trimester fetal and maternal complications (cases)

Maternal complications					
Type	**Gestational week of AE**	**Gestational week of endoscopy**	**Type of endoscopy**	**Temporal relation?**	**Causal relation?**
Gestational cholestasis	30	6	Colonoscopy	No	Unlikely
	36	24	Colonoscopy	No	Unlikely
	37	32	Sigmoidoscopy	No	Unlikely
Gestational diabetes	Specific week unknown	22	Sigmoidoscopy	No	Unlikely
	31	27	Sigmoidoscopy	No	Unlikely
	32	29	Sigmoidoscopy	No	Unlikely
External hemorrhoids	36	36	Sigmoidoscopy	Yes	Unlikely
Gestational hypertension	37	17	Sigmoidoscopy	No	Unlikely
Pyelonephritis/Urinary tract infection	27	12	Sigmoidoscopy	No	Unlikely
	30	32	Sigmoidoscopy	No	Unlikely
	32	2	Sigmoidoscopy	No	Unlikely
Mechanical ileus	27	21	Sigmoidoscopy	No	Unlikely
Hospital admittance for signs of preterm labour	34	15	Colonoscopy	No	Unlikely
Fetal complications					
Oligohydramnios	30	20	Sigmoidoscopy	No	Unlikely
Premature rupture of membranes	35	20	Sigmoidoscopy	No	Unlikely
Intrauterine growth retardation	32	20	Colonoscopy	No	Unlikely
	34	32	Sigmoidoscopy	No	Unlikely
	35	12	Sigmoidoscopy	No	Unlikely

Table 5 Birth outcomes

Variable		Cases (n=42)	Controls (n=42)	*P*
Live births (%)		40 (95.2)	32 (76.2)	0.03
Spontaneous abortion (%)		2 (4.8)	10 (23.8)	0.03
Median birth weight (g)		3017 (2710-3335)	3495 (2900-3735)	0.01
Median gestational age at birth (wks.)		38.3 (37.0-39.6)	38.8 (37.6-39.9)	0.37
APGAR score	After 1 minute	9 (8-9)	9 (8-9)	0.93
	After 5 minutes	10 (9-10)	10 (9-10)	0.96
Low birth weight (%)		6 (15.0)	4 (12.5)	1.00
Preterm birth (%)		8 (20.0)	4 (12.5)	0.53
Small for gestational age (%)		6 (15.0)	3 (9.4)	0.72
Congenital abnormalities		0 (0.0)	3* (7.1)	0.24
Mode of delivery (%)	Vaginal	25 (62.5)	20 (62.5)	1.00
	Caesarean section	15 (37.5)	12 (37.5)	-

*polydactyly (n=2) and palatoschisis (n=1)

DISCUSSION

Although we underline that lower GI endoscopy during pregnancy should only be performed when strongly indicated, in this study lower GI endoscopy was of low risk in all trimesters of pregnancy for the mother and the child.

Overall, our findings are in line with previous, retrospective studies on the safety of lower gastrointestinal endoscopy [2-4]. These studies did not focus on IBD women in particular, but on a combination of several diseases or complaints requiring endoscopy. As a control group, the authors in these studies selected women with the same indication for endoscopy but who did not undergo endoscopy because of their pregnancy. The authors state this type of control group is more adequate than a group of healthy, uncomplicated pregnancies, although the lack of randomization and the retrospective character of these studies may still introduce bias. In the present study we were not able to match cases and controls on the indication for endoscopy, because only IBD women with a strong indication (i.e. clinical and biochemical signs of disease activity unremitting within one week) underwent endoscopy. We

therefore chose to match cases and controls on the presence, but not the severity of disease activity during pregnancy. However, this is a major limitation within this study.

In the cases, average birth weight, but not the proportion of low birth weight babies, was significantly lower than in controls. Although this finding may not be clinically relevant, it could be explained by a difference in disease severity. As mentioned above, we did not match cases and controls on the severity of disease activity, merely on the presence of clinical disease activity during pregnancy. Treatment for relapse as well as total maternal weight gain differed significantly between the groups, also suggests a more severe disease course in the cases.
Interestingly, we found IBD women undergoing endoscopy during pregnancy had significantly less spontaneous abortions compared to controls. This finding is in line with a previous controlled study which also reports slightly, but not statistically significant, better pregnancy and fetal outcomes in cases than in controls [2]. These findings are difficult to interpret, and this study did not exclusively consist of IBD women. The authors of this study hypothesized these differences could be explained by suboptimal treatment for the underlying disease in the patients not undergoing endoscopy.

This study is limited by its sample size, and cannot draw robust conclusions on the safety of lower gastrointestinal endoscopy during pregnancy. However, a recent systematic review about this topic showed that the available literature is very scarce, and in this light a cohort of additional 42 women with endoscopy during pregnancy is a substantial expansion of the current available data (de Lima et al. 2015 accepted for publication in BMC Gastroenterology). In conclusion, this study adds to the evidence that lower gastrointestinal endoscopy in IBD women during all trimesters of pregnancy is of low risk for mother and child. When indicated, this procedure should not be deferred.

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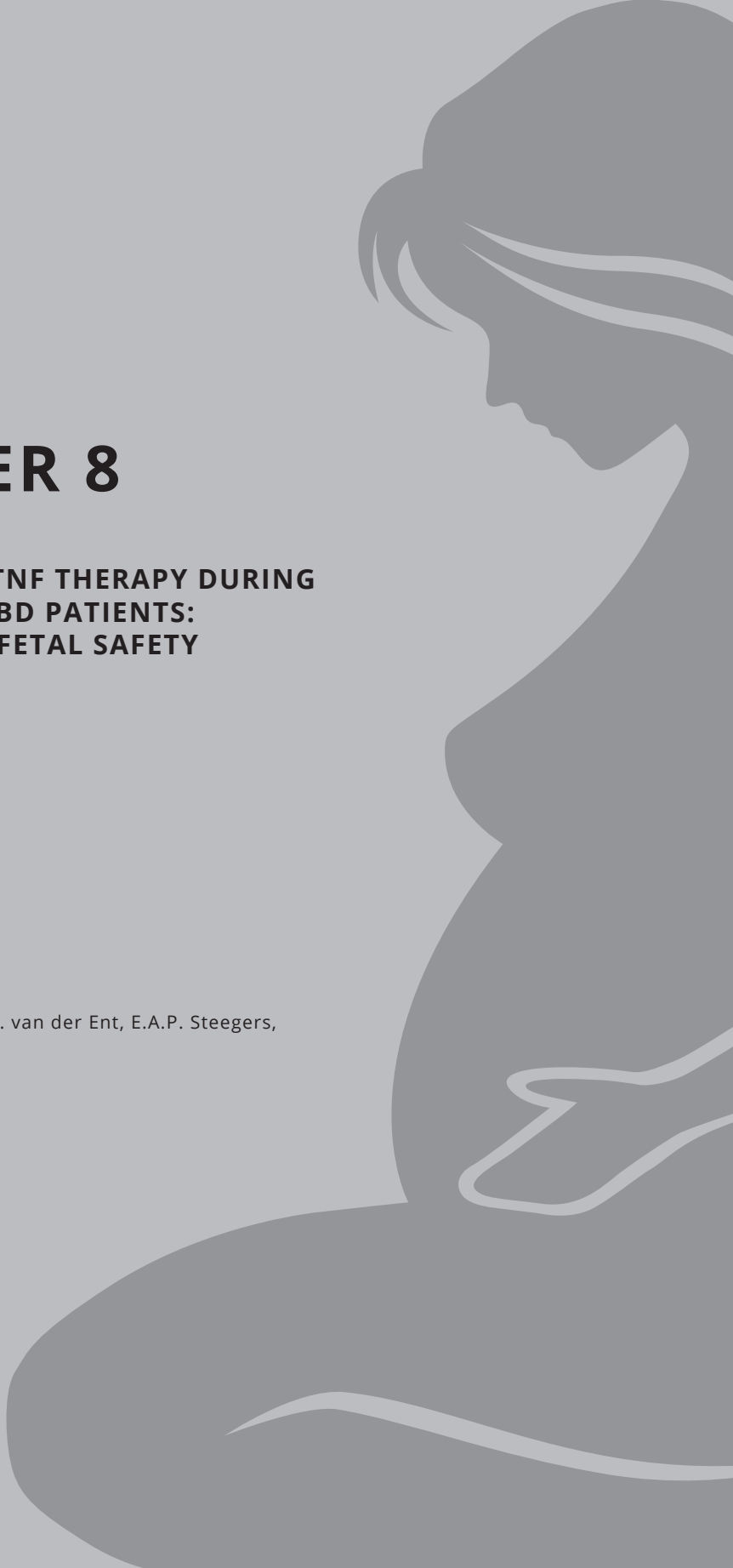
CHAPTER 8

TAILORED ANTI-TNF THERAPY DURING PREGNANCY IN IBD PATIENTS: MATERNAL AND FETAL SAFETY

A. De Lima, Z. Zelinkova, C. van der Ent, E.A.P. Steegers, C.J. van der Woude

Gut 2015



ABSTRACT

Introduction

Anti-TNF during pregnancy in inflammatory bowel disease (IBD) patients is related to high fetal anti-TNF levels. We evaluated the maternal and child safety of discontinuing anti-TNF in the 2nd trimester of pregnancy.

Methods

Two groups of IBD women were prospectively followed-up during pregnancy: women in sustained remission stopped anti-TNF before week 25 (stop group), and the remaining group continued anti-TNF beyond week 30 (continue group). Maternal, birth and one year child outcomes were compared with children of non-IBD women.

Results

Overall, 106 pts with 83 completed pregnancies were included. Relapse rate after week 22 did not differ between the stop (n=51) and continue (n=32) group (5 (9.8%) vs 5 (15.6%), p=0.14). There was no difference in allergic reactions (p=1.00) or loss of response (p=1.00) postpartum between both groups. Birth outcomes were comparable. Infants from both groups had lower birth weight (p=0.001), shorter gestational term (p=0.0001), were more often delivered via caesarean section (p=0.0001) and were less often breastfed (p=0.0001) compared to infants from non-IBD controls. Growth, infection rate, allergies, eczema and adverse reactions to vaccines were comparable across the stop and the continue group as well as the anti-TNF exposed and the children of non-IBD women at one year.

Discussion

To limit anti-TNF exposure in utero, anti-TNF can be stopped safely in the 2nd trimester in IBD women in sustained remission. In patients not in sustained remission, anti-TNF may be continued without clear additional risks to the fetus. We observed excellent one year child outcomes compared to children from non-IBD controls.

INTRODUCTION

Inflammatory Bowel Disease (IBD) typically affects young people with reproductive potential. [1] In most patients, the chronic and relapsing character of the disease calls for intensive, lifelong medical treatment to maintain disease remission. Inevitably, a proportion of female IBD patients will require medical treatment for IBD during pregnancy. Although most IBD medications are considered of low risk, a full safety profile of especially the more recent IBD medications during pregnancy has not yet been established. Until now, IBD activity during pregnancy has proven more harmful to the pregnancy than most IBD medications. [2, 3, 4] IBD women with a pregnancy wish therefore face the dual challenge of maintaining disease remission during pregnancy and at the same time avoiding possible harmful effects of medication on the fetus. One of the most recent medical treatments for IBD are anti-tumor necrosis factor alpha (anti-TNF) agents like infliximab (IFX) and adalimumab (ADA). Over the past decade, an increasing amount of evidence suggests a low risk of anti-TNF use during pregnancy. [2, 3, 4, 5, 6, 7] Both ADA and IFX however, are capable of crossing the placenta in the second and third trimester of pregnancy. Anti-TNF levels in the newborn are dependent on the timing of anti-TNF cessation during pregnancy, and these levels tend to exceed maternal anti-TNF levels. [6, 8] The long term effects of these clinically significant anti-TNF levels in children are relatively unexplored. Although a few small follow up studies [4, 9] suggest no serious adverse events in these children, one case report described a fatal case of disseminated BCG infection in an infant exposed to IFX in utero which showed that live attenuated vaccinations in children exposed to anti-TNF in utero may be associated with adverse outcome. In addition, a recent case series reported four infants exposed to infliximab in utero with severe neutropenia at birth. [10] Adverse outcomes in the newborn may be avoided by lowering peri-natal anti-TNF serum levels in the infants by stopping anti-TNF treatment in the second trimester of pregnancy in IBD women in remission. [6] At our institution, it has been standard clinical care to stop anti-TNF in IBD women in sustained remission in the 22nd gestational week. The aim of this study, was to assess the effect of anti-TNF cessation in the second trimester on the mother in terms of (1) risk of disease relapse after anti-TNF cessation, (2) loss of response and (3) allergic reactions after re-initiation of anti-TNF postpartum. As a secondary aim, the neonatal outcomes of and health status at one year of life of children exposed to anti-TNF in utero were compared to a control group of children born to non-IBD mothers matched by maternal age and ethnicity. In addition, cord blood and maternal peripheral blood anti-TNF levels at delivery were measured and compared between the stop and continue group.

METHODS

Study design and setting

A single center ongoing prospective clinical cohort study was conducted at the Erasmus University Medical Center Rotterdam. From December 2008 until June 2014, all women with a confirmed diagnosis of IBD treated with any anti-TNF agent who visited the IBD preconception outpatient clinic were enrolled in the study. In part this cohort consists of patients from a previously published cohort [6], however this study has collected additional follow-up data on these patients. At this specialized outpatient clinic, an experienced gastroenterologist counsels and treats IBD patients before pregnancy and bi-monthly during pregnancy. All consultations were performed in a standardized manner adhering to ECCO guidelines. [11, 12] At every visit, data on disease activity, medication use and pregnancy complications was recorded. In case of disease activity, patients were seen every 2 weeks at our outpatient clinic. Further these patients were followed up at the department of obstetrics.

Participants

Anti-TNF treatment in IBD women in sustained remission around gestational week 20 were discontinued before week 25 (stop group). IBD women not in sustained remission continued anti-TNF during the entire pregnancy and their last dose was administered at gestational week 30 or later (continue group), according to their regular treatment schedule. Sustained remission was defined as remission from three months prior to pregnancy and throughout pregnancy until gestational week 20. Women not in sustained remission had disease activity with or without achieved remission at any time three months prior to pregnancy and/or within the first 20 weeks of pregnancy or a history of a very difficult to achieve remission in the year preceding pregnancy. Pregnant women in whom the anti-TNF was stopped in the first trimester or at the decision of another physician were not eligible for enrollment in this study.

Control group

Birth and child outcomes of anti-TNF exposed children were compared to children born to non-IBD mothers not treated with anti-TNF as recruited from the Generation R cohort. [13] Generation R is a large prospective birth cohort (n=9778) from the same geographical region as the IBD patients in our cohort originate from. In the Generation R cohort mothers are prospectively followed up during pregnancy and their children will be prospectively followed

up until the age of 18. Children born in this cohort were born between 2002 and 2006. A random sample of approximately 800 children from live, singleton births participating after birth was drawn. This sample was age,- and ethnicity matched and the selection was made blinded for the follow-up outcomes.

Study size

The aim was to include at least 100 pregnant IBD women on anti-TNF. This study enrolled 106 pregnant IBD women on anti-TNF with 83 live births. For each participating pregnant IBD woman with a live, singleton birth, approximately ten non-IBD mother-child pairs were selected.

Variables and data measurement

The primary aim of this study was to assess maternal safety of stopping anti-TNF treatment in the second trimester of pregnancy. Disease relapse after treatment cessation and allergic reactions and secondary loss of response to anti-TNF after delivery after re-initiation of anti-TNF were measured. Only newly acquired disease activity after the median time of treatment cessation in the stop group was compared. Persistent disease activity in the continue group was excluded from the analysis. Disease activity was assessed at every 2 months during pregnancy and relapse was defined as: a Harvey Bradshaw Index (HBI) for CD > 5 and Simplified Clinical Colitis Activity Index (SCCAI) for UC > 2, and/or either C-reactive protein (CRP) > 9.0 mg/l (n=< 9.0 mg/l) or fecal calprotectin >200 µg/g (n=< 200 µg/g). If necessary, endoscopy was performed to assess mucosal inflammation. Allergic reaction upon anti-TNF re-initiation was defined as anaphylactic/ allergic reaction at the first three infusions or injections post-partum requiring treatment. Secondary loss of response to anti-TNF after delivery was defined as disease activity while on anti-TNF treatment six months after delivery requiring dose escalation or switch to another treatment strategy.

Secondary outcomes included anti-TNF levels, birth outcomes and one year child outcomes. Pregnancy and birth outcomes were noted. At delivery, umbilical cord and maternal peripheral blood samples were obtained. Cord blood anti-TNF levels were reported to the parents and precautionary advice was given based on the results. Cord blood anti-TNF levels below the cut-off of 3µg/ml were not repeated at 3 months. We used this arbitrary cut-off because in adults it is associated with response to anti-TNF treatment. [14, 15] Infants with anti-TNF levels in their cord blood exceeding the 3µg/ml, were again measured at 3 months. Patients were advised to reinitiate their anti-TNF treatment 2 weeks postpartum. Further we advised parents to refrain from daycare admittance of their child, to be extra cautious of

infectious sources and delay any possible live attenuated vaccine until anti-TNF levels in the infant were below 3 µg/ml. One year follow up of the child was obtained through telephonic questionnai res with the mothers and by obtaining the medical information of the children from the general practitioner. Anti–TNF levels in cord blood, maternal peripheral blood and if necessary in the infant at 3 months were assessed by ELISA according to a previous described protocol. [8] Birth outcomes included birth weight, gestational age at birth, APGAR (Appearance, Pulse, Grimace, Activity, Respiration) scores and congenital abnormalities.

Definitions

Low birth weight was defined as birth weight lower than 2500 grams and preterm birth as delivery prior to gestational week 37. Small for gestational age (SGA) referred to a weight below the 10th percentile for gestational age. [16] One year child outcomes included growth of the child, number of infections requiring antibiotics or hospitalization, allergies, eczema and adverse reactions to vaccinations. Abnormal growth was defined as weight or height for age and sex deviating more than ±2SD from the mean Dutch growth chart at any measurement point in the first year.

Bias

Inherently, the continue group will have an increased risk of relapse after gestational week 22 compared to the stop group. We therefore only compared newly acquired disease activity after week 22 for our primary outcome, and did not count persistent disease activity. Other confounding variables for both the primary outcome and the secondary outcomes such as smoking, alcohol use and folic acid intake were also collected.

Statistical methods

All analyses were performed using IBM SPSS statistics (version 20.0 Chicago III, USA). Descriptive statistics of continuous variables are depicted as means with standard error of the mean (SEM) and medians with interquartile range (IQR). These were compared across the study and the control group using student T-tests and Mann Whitney U tests, respectively. Categorical variables are depicted in absolute numbers and percentages and compared across groups using Chi-square or Fisher's exact tests. All tests were performed using 2-tailed tests and tested at a significance level of 0.05.

Ethical considerations

The local ethics committee approved data collection and analyses. Informed consent of the legal guardians of the children were obtained to collect 1 year follow up data of the child participants. The use of data from the 'Generation R' cohort was also approved by the local ethics committee.

RESULTS

IBD group

We followed up 106 pregnancies in 106 women treated with anti-TNF. These 106 pregnancies resulted in 87 live singleton births (82%), 18 spontaneous abortions (17%), and 1 termination of pregnancy (1%). In four women the anti TNF was stopped in the first trimester. This was indicated by a physician other than the IBD consultant. These pregnancies were excluded from further analysis. Baseline characteristics are shown in Table 1.

Non-IBD control group

The random age-, and ethnicity matched sample drawn from the Generation R cohort resulted in a control group of 804 non-exposed, non-IBD women with 804 live, singleton births.

Maternal outcomes

Maternal outcomes are shown in Table 2. The stop group had a median time off anti-TNF drugs of 21 weeks (IFX) and 20.5 weeks (ADA), whereas the continue group had a median time off anti-TNF drugs of 11.5 weeks (IFX) and 2.3 weeks (ADA) (p=0.0001 and p=0.0001). The median gestational week of anti-TNF cessation in the stop group was 22 weeks (21-23). Overall, we observed no differences in relapse rate after gestational week 22. Five women relapsed after gestational week 22 in the stop group, whereas 5 women relapsed after gestational week 22 in the continue group (p=0.14). There was no difference in concomitant treatment in both groups. Furthermore, only 2 patients developed allergic reactions to anti-TNF post-partum and only one woman experienced loss of response to anti-TNF after resumption post-partum. There were no statistically significant differences in allergic reactions and loss of response post-partum (p=1.00 and p=1.00, respectively).

Table 1 Baseline characteristics

Variable		Anti-TNF stop group (n=51)	Anti-TNF continue group (n=32)	*P*	Anti-TNF exposed group (n=83)	Non-IBD Controls (n=804)	*P*
Median maternal age in yrs. (IQR)		31.1 (28.1-33.0)	28.5 (26.4-31.1)	0.01	29.9 (27.0-32.5)	31.5 (28.2-34.1)	0.08
Ethnicity (%)	Caucasian	44 (86.3)	28 (87.5)	1.00	62 (74.7)	643 (79.9)	0.36
	Non-Caucasian	7 (13.7)	4 (12.5)	-	11 (13.3)	161 (21.1)	-
Education level (%)	Low	0 (0.0)	1 (3.1)	0.40	1 (1.2)	22 (2.7)	0.34
	Middle	25 (49.0)	15 (46.9)	0.65	40 (48.2)	244 (30.3)	0.001
	High	19 (37.3)	10 (31.3)	0.48	29 (34.9)	461 (57.3)	0.0001
Marital status (%)	Unmarried	21 (41.2)	16 (50.0)	0.65	35 (46.7)	416 (51.7)	0.33
	Married	26 (51.0)	15 (46.9)	-	39 (52.0)	360 (44.8)	-
Parity (%)	Nulliparous	35 (68.6)	21 (65.6)	0.81	56 (67.5)	442 (55.0)	0.04
	Multiparous	16 (31.4)	11 (34.4)	-	27 (32.5)	362 (45.0)	-
Planned pregnancy (%)		44 (86.3)	25 (86.2)	0.20	64 (85.3)	n/a	-
Folic acid use before pregnancy (%)		38 (74.5)	21 (65.6)	0.79	59 (71.1)	n/a	-
Smoking 3 months prior to pregnancy (%)		7 (13.7)	7 (21.9)	0.37	14 (16.9)	n/a	-
Mean BMI before pregnancy		24.7 (0.63)	23.7 (0.87)	0.32	24.3 (0.50)	23.5 (0.16)	0.13
Diagnosis (%)	Crohn's disease	45 (88.2)	18 (56.3)	0.001	63 (75.9)	-	-
	Ulcerative colitis/IBDU	5 (9.8)	14 (43.7)	-	19 (22.9)	-	-
Mean disease duration in yrs. (SEM)		7.9 (0.69)	5.4 (0.73)	0.02	6.9 (0.52)	-	-
UC Location of disease (%)	Proctitis	0 (0.0)	0 (0.0)	-	0 (0.0)	-	-
	Left sided	0 (0.0)	5 (35.7)	0.007	5 (26.3)	-	-
	Extensive	5 (100)	9 (64.3)	0.04	14 (73.7)	-	-
CD Location of disease (%)	Ileal	12 (26.7)	8 (44.4)	1.00	20 (31.7)	-	-
	Colonic	10 (22.2)	4 (22.2)	0.55	14 (22.2)	-	-
	Ileocolonic	23 (51.1)	6 (33.3)	0.02	29 (46.0)	-	-
	Perianal involvement	15 (30.0)	8 (44.4)	0.80	23 (36.5)	-	-
CD disease behavior (%)	Non-penetrating/ stricturing	30 (60.0)	6 (33.3)	0.82	36 (57.1)	-	-
	Stricturing	1 (2.0)	0 (0.0)	1.00	1 (1.6)	-	-
	Penetrating	10 (20.0)	6 (33.3)	1.00	16 (25.4)	-	-
	Stricturing and penetrating	9 (18.0)	6 (33.3)	1.00	15 (23.8)	-	-

Table continues on next page

Table 1 Baseline characteristics **Continued**

Variable		Anti-TNF stop group (n=51)	Anti-TNF continue group (n=32)	*P*	Anti-TNF exposed group (n=83)	Non-IBD Controls (n=804)	*P*
Extra intestinal manifestations (%)		17 (34.0)	7 (22.6)	0.32	24 (28.9)	-	-
IBD surgery (%)	Abdominal surgery	15 (29.4)	3 (9.4)	0.03	18 (21.7)	-	-
	Perianal surgery	11 (21.6)	3 (9.4)	0.15	14 (16.9)	-	-
Concomitant medication (%)	5-ASA	2 (3.9)	4 (12.5)	0.19	6 (8.0)	-	-
	Steroids (maintenance)	1 (2.0)	2 (6.3)	0.56	3 (3.6)	-	-
	Thiopurines	11 (21.6)	11 (34.4)	0.21	22 (26.5)	-	-
Median number of relapses in year preceding pregnancy (IQR)		0 (0-1)	0 (0-1)	0.66	0 (0-1)	-	-
Type of anti-TNF agent (%)	IFX	27 (52.9)	21 (65.6)	0.36	48 (57.8)	-	-
	ADA	24 (47.1)	11 (34.4)		35 (42.2)	-	-
Median duration of anti-TNF treatment prior to pregnancy in months (IQR)		30.0 (12.0-60.0)	24.0 (14.0-37.0)	0.26	30.0 (12.0-49.0)	-	-

Birth outcomes

Stop versus continue group

Birth outcomes are shown in Table 3. No differences in birth weight, gestational age at birth, congenital abnormalities and mode of delivery were observed between the stop and the continue group. Gestational age at birth was significantly lower in children born to IBD women with disease activity during pregnancy compared to women without disease activity (38.0 wks. vs 39.3 wks., p=0.005). There was no significant difference in birth weight between IBD mothers with disease activity during pregnancy and IBD mothers without disease activity during pregnancy (3252 g vs 3363 g, p=0.44). Women who stopped anti-TNF in the second trimester more often breastfed their child compared to the anti-TNF continuation group (20 vs 5, p=0.04).

Anti-TNF exposed versus non-IBD controls

Birth outcomes of anti-TNF exposed pregnant women (n=83) were compared to birth

Table 2 Maternal outcomes

		Anti-TNF stop group (n=51)	Anti-TNF continue group (n=32)	*P*
Median anti-TNF dose (IQR)	IFX (mg/kg)	5.0	5.0	0.09
	ADA (mg)	40.0	40.0	1.00
Median anti-TNF interval (wks.)	IFX	8.0	8.0	0.95
	ADA	2.0	2.0 12	0.86
Anti-TNF use throughout entire pregnancy (%)	IFX	-	(37.5)	-
	ADA	-	8 (25.0)	-
Smoking during pregnancy (%)		4 (7.8)	4 (12.5)	0.47
Alcohol use during pregnancy (%)		1 (2.0)	2 (6.3)	0.56
Median total weight gain during pregnancy in kg (IQR)		12.0 (10.0-15.0)	14.0 (8.0-19.0)	0.43
Median week of anti-TNF cessation (IQR)		22.0 (21.0-23.0)	33.5 (30.0-39.3)	0.0001
Median time off anti-TNF in wks. (IQR)	IFX	21 (18.7-23.8)	3.5 (0.0-9.4)	0.0001
	ADA	20.5 (18.3-21.9)	0.3 (0.0-13.3)	0.0001
Median number of infusions/ injections skipped (IQR)	IFX	3.0 (2.4-3.5)	0.7 (0.0-1.2)	0.0001
	ADA	10.4 (9.5-13.9)	0.2 (0.0-6.6)	0.0001
Periconceptional disease activity (%)		3 (5.9)	8 (25.0)	0.02
Disease relapse before 22 wks. (%)	Overall	1 (2.0)	4 (12.5)	0.07
	Anti-TNF monotherapy	1 (2.0)	3 (9.4)	0.29
	Anti-TNF + concomitant treatment	0 (0.0)	1 (3.1)	1.00
Disease relapse after 22 wks. (%)	Overall	5 (9.8)	5 (15.6)	0.14
	Anti-TNF monotherapy	2 (3.9)	4 (12.5)	0.19
	Anti-TNF + concomitant treatment	3 (5.9)	1 (3.1)	1.00
Median week postpartum of anti-TNF restart (IQR)		3.0 (2.0-6.0)	1.0 (0.0-3.0)	0.0001
Allergic reaction upon anti-TNF restart (%)		1* (1.9)	1** (3.1)	1.00
Loss of response after anti-TNF restart (%)		1 (1.9)	0 (0.0)	1.00
Relapse 3 months postpartum (%)		8 (15.7)	4 (12.5)	0.75
Median maternal anti-TNF level at delivery (µg/mL)	IFX	0.55 (0.30-1.10)	6.19 (4.75-10.0)	0.0001
	ADA	0.44 (0.30-0.60)	3.60 (0.30-4.97)	0.11

* itch after injection of ADA, treated with antihistamines

** IFX infusion reaction, treated with hydrocortisone and clemastine

Table 3 Birth outcomes

Variable		Anti-TNF stop group (n=51)	Anti-TNF continue group (n=32)	*P*	Anti-TNF exposed children (n=83)	Non-IBD controls (n=804)	*P*
Gender	Male Female	24 (47.1) 27 (52.9)	14 (43.8) 18 (56.3)	0.82 -	37 (45.1) 45 (54.9)	425 (52.9) 379 (47.1)	0.20 -
Median birth weight in grams (IQR)		3385 (3040-3620)	3177 (2853-3553)	0.22	3320 (2932-3551)	3525 (3200-3877)	0.0001
Median gestational term at birth (IQR)		39.0 (38.0-40.3)	39.0 (38.0-40.0)	0.58	39.0 (38.0-40.1)	40.1 (39.3-41.0)	0.0001
Median APGAR score (IQR)	1 min 5 min	9 (8-9) 10 (10-10)	9 (8-9) 10 (9-10)	0.43 0.21	9 (8-9) 10 (9-10)	9 (8-9) 10 (9-10)	0.28 0.81
Low birth weight (%)		5 (9.8)	3 (9.4)	1.00	8 (9.8)	29 (3.6)	0.02
Preterm birth (%)		4 (7.8)	3 (9.4)	1.00	7 (8.5)	30 (3.7)	0.08
Small for gestational age (SGA) (%)		4 (7.8)	0 (0.0)	0.16	4 (4.9)	78 (9.7)	0.17
Congenital abnormalities (%)		2* (3.9)	1** (3.3)	1.00	3 (3.7)	28 (3.5)	0.79
Mode of delivery	Vaginal Caesarean section	26 (51.0) 25 (49.0)	19 (59.4) 12 (37.5)	0.49 -	45 (54.9) 37 (43.9)	713 (88.7) 91 (11.3)	0.0001 0.0001
Breastfeeding (%)		20 (39.1)	5 (15.6)	0.04	25 (30.5)	697 (86.3)	0.0001
Cord blood sample obtained (%)	IFX ADA	16 (31.4) 18 (35.3)	15 (46.9) 7 (21.9)	0.17 0.23	31 (37.3) 22 (30.1)	n/a n/a	- -
Median anti-TNF cord blood levels (µg/mL)	IFX ADA	1.94 (0.77-2.60) 0.98 (0.54-1.46)	13.14 (8.80-16.80) 3.3 (0.34-8.19)	0.0001 0.27	7.2 (2.1-14.0) 1.1 (0.6-2.1)	n/a n/a	- -
Blood sample obtained at 3 months	IFX ADA	2 (3.9) 0 (0.0)	6 (18.8) 1 (3.1)	0.05 0.39	8 (9.6) 1 (1.2)	n/a n/a	- -
Median anti-TNF levels at 3 months (µg/mL)	IFX ADA	1.51 (0.52-n/a) -	1.78 (0.86-2.40) 0.94 (0.94-0.94)	1.00 -	1.3 (0.5-2.5) -	n/a n/a	- -

* Cleft palate and ventricular septum defect

** Polydactyly

outcomes of non-IBD maternal controls (n=804). Children born to IBD mothers treated with anti-TNF during pregnancy had statistically significant lower birth weights (3320g vs 3512g, p=0.0001) and a shorter gestational age at birth (39.0 wks. vs 40.1 wks., p=0.0001). Birth weight and gestational age at birth were significantly correlated (r=0.52, p=0.0001). There were no differences in the prevalence of SGA babies between the exposed and the non-IBD controls (4.9% vs 9.7%, p=0.17). Gestational age at birth was significantly lower in children delivered by caesarean section (38.6 wks. vs 40.0 wks., p=0.0001). The anti-TNF exposed group also had a higher proportion of low birth weight (<2500 g) babies compared to the non-IBD maternal controls (9.8% vs 3.6%, p=0.02). There were no significant differences in the proportion of preterm (<37 wks.) babies across the groups (8.5% vs 3.7%, p=0.08). No difference in congenital abnormalities was observed between the anti-TNF exposed and the non-IBD controls (3.7% vs 3.5%, p=0.79). IBD mothers more often delivered by caesarean section compared to the non-IBD controls (43.9% vs 11.3%, p=0.0001). Secondary caesarean sections were performed in 10 (27.1%) IBD women compared to 47 (51.6%) non-IBD controls (p=0.01). Labour was induced in 5 (11.1%) IBD women versus 87 (12.2%) non-IBD women (p=1.00). Breastfeeding was more common amongst the non-IBD controls than the IBD women (86.3% vs 30.5%, p=0.0001).

Anti-TNF levels

Median IFX cord blood levels were significantly lower in the stop group compared to the continue group (1.9 µg/ml vs 13.1 µg/ml, p=0.0001) and median IFX cord blood levels were significantly higher than the median IFX levels in the maternal peripheral blood (p=0.001 and p=0.003, respectively). All repeated IFX measurements in the children at 3 months were below 3 µg/ml. Similar results were seen in the ADA treated patients, but groups were too small to achieve statistical significance (n=18 vs. n=7, 0.9 µg/ml vs, 3.3 µg/ml, p=0.16).

One year follow-up data

Complete 1 year follow-up data of the children was available in 53 IBD women (70.6%) and in 459 non-IBD maternal controls (57.1%). Another 345 non-IBD control women (42.9%) had partially complete 1 year follow up data of the child. The 1 year follow up data of the children are shown in Table 4.

Between the stop group and the continue group, no differences in growth, number of infections, allergies and eczema were observed. The most common infections requiring antibiotic treatment in the children were: acute otitis media (n=19, 46.2%) and upper respiratory tract infection (n=13, 26.9%). Other less common infections included conjunctivitis (n= 3, 12%),

Table 4 Child outcomes in the first year of life

Variable		Anti-TNF stop group (n=31)	Anti-TNF continue group (n=24)	*P*	Anti-TNF exposed children (n=55)	Non-IBD controls (n=459)*	*P*
Growth	Normal (%)	30 (96.7)	24 (100.0)	1.00	54 (98.2)	789 (98.2)	0.77
	Abnormal (%)	1 (3.3)	0 (0.0)	-	1 (1.8)	15 (1.8)	-
Median no of infections (IQR)	Requiring antibiotics	0 (0-1)	0 (0-1)	0.58	0 (0-1)	(0-1)	0.22
	Requiring hospitalization	0 (0-0)	0 (0-0)	0.74	0 (0-0)	0 (0-0)	0.49
Absolute no of infections requiring antibiotics (%)	0	19 (61.3)	17 (73.9)	0.57	36 (66.7)	252 (54.9)	0.15
	1-2	10 (30.3)	3 (13.3)	0.12	13 (24.1)	183 (39.9)	0.02
	3-4	2 (6.5)	3 (13.3)	0.64	5 (9.3)	20 (4.4)	0.17
	5-6	0 (0.0)	0 (0.0)	1.00	0 (0.0)	4 (0.9)	1.00
Allergies (%)		1 (3.0)	1 (4.2)	1.00	2 (6.3)	33 (6.6)	1.00
Eczema (%)		3 (9.1)	4 (16.7)	0.67	7 (21.9)	71 (14.6)	0.30
Adverse reactions to vaccines (%)		0 (0.0)	0 (0.0)	1.00	0 (0.0)	n/a	n/a

* Follow-up varies, proportions are calculated accordingly

tonsillitis (n=1, 4%), paronychia (n=2, 8%) and rotavirus (n=1, 4%). Three infants in the stop, as well as 3 infants in the continue group were admitted to the hospital for serious infections. These infections included serious respiratory tract infections (n=4), multiple skin abscesses requiring intravenous antibiotics (n=1) and respiratory syncytial virus infection (n=1). All infections resolved without sequelae. There were no adverse reactions to vaccinations in the anti-TNF exposed group.

No statistically significant difference in growth, infections requiring hospitalization, allergies and eczema was observed between the anti-TNF exposed children and the children of non-IBD controls. Overall, there was no difference in median number of infections requiring antibiotics between the anti-TNF exposed and the controls. However, children from the non-IBD controls more often had infections requiring antibiotics (24.5% vs 39.9%, p=0.02). There was no difference in infection rate requiring antibiotics or hospitalization between the children from mothers on anti-TNF monotherapy and in mothers that were treated concomitantly with immunomodulators (IS) group (n=16 (38.1%) vs 2 (20%), p=0.29). Data on adverse reactions to vaccinations was not available in the children born to non-IBD mothers.

DISCUSSION

In this study, we assessed the safety of discontinuing anti-TNF for IBD women in the second trimester of pregnancy.

We show that in pregnant females in sustained remission anti-TNF can be stopped in the second trimester without increased risk of relapse during the time off drugs, compared to pregnant women who continue anti-TNF. The continue group as a control group may be biased in terms of relapse risk, however, we exclusively compared newly developed disease relapse after gestational week 22, and with this approach excluded persistent disease activity from the analysis. In addition, stopping was not associated with a higher risk of allergic reactions or secondary loss of response after anti-TNF re-initiation postpartum. Studies in non-pregnant IBD patients demonstrated that episodic treatment and increasing the interval between anti-TNF administration leads to an increased risk of relapse and side-effects. [17, 18] We did not measure antibodies which might be related to our contrasting results in pregnant IBD patients. [19]

Reasons for stopping anti-TNF in the second trimester are primarily the unknown effects of anti-TNF on the developing child. Preliminary results from a large prospective registry in the United States (PIANO registry), showed that combination therapy of anti-TNF and IS in IBD women during pregnancy increases the risk of infection in their offspring. [20] This was compared to IBD women using other or no medication, instead of non-IBD controls. In our study we did not observe an increased infection risk in children born to mothers treated with anti-TNF monotherapy or combination therapy. Approximately 50% of the children were treated for an infection with antibiotics and this is in line with data form an uncontrolled study with follow-up data on anti-TNF exposed children from 25 IBD mothers where 32% of children were treated with antibiotics in the first year of life. [9] We show that the infection risk in the children exposed to anti-TNF in utero is comparable to the infection risk in children born to non-IBD controls and therefore anti-TNF during pregnancy seems not associated with a higher risk for infections in the offspring. However, we have to underline that parents of anti-TNF exposed children, especially the ones with high anti-TNF cord blood levels, were advised to be extra careful of infectious sources like daycare center admittance. This advice likely confounds the infection data in this study.

IFX and ADA are both complete IgG1 antibodies, and are transported across the placenta, [21, 22] depending on the neonatal FcR expression. We have previously reported that cord blood IFX and ADA levels significantly relate to timing of anti-TNF stop during pregnancy and we

confirmed this with this larger study. [6, 8] Unfortunately, we were not able to obtain cord blood samples from all newborns (67.5%). The missing cord blood samples were missing at random because of logistic difficulties. Of interest, in the stop group; ADA cord blood levels, but not the IFX cord blood levels, never exceeded the threshold of 3 µg/ml. IFX levels at three months were still detectable, but none of the measurements in both the stop and continue group were above 3 µg/mL. However, although the cut-off value of 3 µg/ml may be an indicator for therapy response, it is unclear whether anti-TNF levels above 3 µg/ml might be related to immune-mediated complications in the child.

This study did not demonstrate a difference in the rate of congenital abnormalities at birth. However, we cannot exclude differences in the number of pregnancy terminations earlier in pregnancy because of foetal malformations related to disease or medication. We have no information on this. Furthermore, pregnancies in women with IBD are characterized by a lower birth weight of the children as well as lower gestational age at birth. Further there was an increased risk of caesarean sections in our IBD patients, mainly in CD women. These findings are in line with several previous studies. [23, 24, 25, 26, 27, 28] In this study, earlier gestational age at birth, but not lower birth weight, was associated with active disease. The observed lower birth weight in the anti-TNF exposed babies compared to non-IBD controls cannot be fully explained by shorter gestational term. It is likely that the observed lower birth weight in this study is a result of the presence of maternal IBD alone (see Supplemental Table 1), and less likely an effect of the anti-TNF exposure in utero. The latter is also in contrast to several studies which report higher TNF-alpha cord blood and placental levels are associated with fetal growth restriction, [29, 30, 31] We demonstrate in our study a catch-up growth comparable to the children born to non-IBD controls for the LBW and preterm infants born to IBD mothers at one year of age.

Although we found no deleterious effects of continuing anti-TNF during pregnancy we still feel that we have to be cautious with continuing anti-TNF in IBD women in sustained remission. First of all, this study could be underpowered to detect a significant difference in child outcome data across the anti-TNF stop-, and continue group. Second, our patients were part of a carefully monitored and counseled group. As a precaution, mothers and children with anti-TNF blood levels above 3 µg/mL were strongly advised to refrain from daycare center admittance, to be extra cautious of infections and to keep the children away from infectious sources. The cord blood anti-TNF levels reported in this study show that this advice has predominantly been given to the mothers who continued anti-TNF throughout pregnancy. These precautions are likely to have influenced the number of infections in the children born in this group. In an unregulated setting however, a difference in infection rate could have been detected. Further, the long term immunomodulatory effects of exposure

to high levels of anti-TNF in utero are still uncertain. Finally, responses to vaccinations and the development of the immune system of these children still need to be elucidated. We did not observe any adverse reactions to vaccinations, however in the Netherlands the first live attenuated vaccine is given at 14 months. Because other countries administer live attenuated vaccines at an earlier age, we feel that limiting anti-TNF exposure in utero remains important.

Based on the results of this study, stopping anti-TNF in the second trimester of pregnancy in IBD women in sustained remission appears to be feasible and safe for the mother. When indicated, the continuation of medication seems safe for the child at least in the first year.

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CHAPTER 9

SUMMARY AND GENERAL DISCUSSION

SUMMARY

In this thesis, several important aspects of fertility and pregnancy in Inflammatory Bowel Disease (IBD) patients are investigated in a prospective setting. Treating pregnant women with IBD remains challenging, because the optimal balance between optimal maternal care and fetal safety can be difficult to find. This thesis set out to answer several important frequently asked questions (FAQs) from IBD patients with a pregnancy wish.

FAQ 1: 'Does IBD affect my fertility?'

Our answer to FAQ 1 is described in **Chapter 2**. This chapter describes the effect of IBD on (sub) fertility. This study compared a cohort of IBD women with an active reproductive wish with a cohort of healthy (non-IBD) women. Subfertility was defined as the inability to conceive after 12 months of unprotected intercourse. We compared subfertility, the time to pregnancy in month and use of fertility treatments between the two groups. Furthermore, the effect of several IBD-specific factors such as IBD-phenotype, type of IBD medication, previous bowel surgery, peri-anal disease or disease activity, on subfertility were investigated. Multivariate analysis showed IBD is not associated with subfertility. IBD women however, did undergo fertility treatment more often than controls. Nonetheless, the percentage of fertility treatments in the IBD group were not elevated when compared to the national average. This is good news for patients with IBD as these data suggest fertility in IBD women is comparable to healthy controls.

FAQ 2: 'What is my risk of disease relapse during pregnancy and how will disease activity influence birth outcomes?'

Risk factors for acquiring disease relapse during pregnancy are investigated in **Chapter 3**. As a secondary aim, we analyzed the effects of disease relapse on birth outcomes. Previous studies showed that disease activity around conception is an important risk factor for maintaining active disease throughout pregnancy or acquiring new disease relapse during pregnancy. Other past studies showed disease relapse during pregnancy to negatively influence birth outcomes by inducing spontaneous abortion, preterm birth and low birth weight. These past studies however, were mostly retrospective in design and lacked sufficient patients treated with contemporary IBD medication, such as anti-TNF. The study in this chapter, assessed the risk of disease relapse in a prospective cohort of IBD women with an active reproductive wish. There was an adequate representation of contemporary IBD medication in this cohort. This study confirms disease activity around conception increases the risk of disease relapse

during pregnancy. In turn, disease relapse at any time in the year when attempting to conceive increases the risk of disease activity around conception. Therefore, IBD women can be advised to, age permitting, cease contraceptive methods after a year of disease remission. Furthermore, the effects of disease relapse during pregnancy on birth outcomes were milder than reported previously. Overall, disease relapse during pregnancy was not associated with spontaneous abortion, preterm birth, small for gestational age (SGA) babies or congenital abnormalities. However, disease relapse was associated with an average lower birth weight. Sub-analyses showed this to be mainly driven by the moderate-to-severe relapse group.

Chapter 4 briefly comments on a meta-analysis investigating the effect of disease activity around conception on disease activity during pregnancy. This meta-analysis showed that this risk remained stable over a timespan of approximately 50 years, despite improvement in therapeutic options for IBD. However, when critically reviewing the included studies, not even the most recent one has included sufficient patients treated with thiopurines and anti-TNF. This could be one of the reasons why the authors found this stable effect over time.

FAQ 3: 'Can I influence the course and outcomes of pregnancy by adhering to a certain lifestyle/guidelines?'

IBD patients are very willing to optimize their chances for a healthy pregnancy. It is therefore of the utmost importance that IBD women with a pregnancy wish receive preconception care to help them achieve this goal. The effect of preconception care in women with IBD is explored in **Chapter 5** and we found a very positive effect of preconception care on pregnancy outcomes. This study compared IBD women receiving preconception care prior to pregnancy (PCC group) with IBD women who did not receive preconception care prior to pregnancy (no-PCC group). Significantly more often, the PCC group used folic acid, quit smoking and was adherent to their IBD medication. Importantly, the PCC group less often experienced disease relapse during pregnancy and had more favorable birth outcomes. In conclusion, preconception care is effective in promoting healthy life style during pregnancy and consequently, preconception care leads to less disease relapse and better birth outcomes.

FAQ 4: 'Is it safe to undergo colonoscopy during pregnancy if necessary?'

IBD women are at increased risk of undergoing gastrointestinal endoscopy during pregnancy. The safety of this procedure during pregnancy is investigated in **Chapter 6** by means of a systematic review of the available literature. This study was not limited to women with IBD, but included pregnant women undergoing endoscopy for various indications. Three retrospective

studies showed lower gastrointestinal endoscopy is of low risk during pregnancy, although these authors strongly recommend additional studies to verify these findings. In addition, we included 79 case reports/series on lower gastrointestinal endoscopy during pregnancy. These 79 case reports described 100 lower gastrointestinal endoscopies performed during pregnancy. Out of these 100 endoscopies, 6 adverse events were temporally and etiologically related to the endoscopy of which 1 adverse event was likely to be attributed to the endoscopy. This systematic review shows lower gastrointestinal endoscopy seems of low risk during pregnancy.

In addition to the above mentioned study, we prospectively investigated the safety of lower gastrointestinal endoscopy during pregnancy exclusively in IBD women in **Chapter 7**. IBD women who underwent lower gastrointestinal endoscopy during pregnancy were matched on age, IBD medication and disease activity during pregnancy with IBD women who did not undergo endoscopy during pregnancy. Lower gastrointestinal endoscopy was not associated with maternal adverse events, spontaneous abortion or preterm birth. This study adds to the evidence that lower gastrointestinal endoscopy is probably safe during pregnancy.

FAQ 5: 'Is anti-TNF safe to use during pregnancy and if so; must I continue anti-TNF the entire pregnancy? What are the long term effects on my child?'

A growing body of evidence suggests anti-TNF is safe during pregnancy, as it not teratogenic. However, newborns exposed to anti-TNF during pregnancy are born with clinically relevant anti-TNF serum levels which can still be detectable after 6 months. The effect of this strong immunomodulator on the developing immune system has not been well explored. It has been established that the levels of anti-TNF in the serum of the newborn are directly relate to the duration of treatment of the mother during pregnancy. Therefore, we investigated the safety of early anti-TNF cessation during pregnancy in IBD women in sustained remission in **Chapter 8**. IBD women in sustained remission could safely stop anti-TNF around gestational week 22 without increased risk of disease relapse, allergic reaction or loss of response upon re-initiation of therapy post-partum. This approach expectedly led to lower anti-TNF serum levels in newborns compared to the newborns of IBD women who continued anti-TNF throughout the entire pregnancy. Furthermore, we compared one year child outcomes of anti-TNF exposed children compared to children born to healthy mothers. There were no differences in growth, infection rate, allergies, eczema and adverse reactions to vaccinations. These findings suggest anti-TNF is safe to stop in the second trimester of pregnancy if the mother's disease state allows it. If necessary however, anti-TNF can be continued throughout pregnancy without clear additional risks for the child.

GENERAL DISCUSSION AND FUTURE DIRECTIONS

In conclusion, conception and pregnancy are feasible for women with IBD. Although there may be increased risk of a complicated pregnancy course in terms of chronic medication use, endoscopy and disease relapse, this thesis shows that these risks can be limited and that birth outcomes in women with IBD are generally favorable. All our studies pointed out that there are several advices for physicians treating and researchers investigating pregnant IBD patients in the future. The most important two are discussed below.

Firstly, we show that early counseling and patient education promotes health improving behavior and pregnancy outcomes and therefore physicians should be attentive to IBD women with a pregnancy wish and intensify routine follow up visits in this group of patients. Frequent follow up visits during pregnancy allow for early disease relapse detection and control. With the exception of proven teratogenic IBD medication, most IBD medications are of low risk during pregnancy. Nonetheless, frequent follow up of pregnant IBD patients on anti-TNF also allows for tailoring the anti-TNF treatment to find the optimal balance between maternal disease control and fetal safety. And finally, frequent follow up of pregnant IBD women enables physicians to enroll these patients in study cohorts to continue research in this delicate group of patients. In the future a care path for IBD women with a pregnancy wish is needed in all hospitals treating IBD patients.

Second, medical therapy for IBD is constantly developing and innovating, therefore the safety of each new IBD treatment available will have to be investigated. Future studies should focus on the safety of new IBD treatments during pregnancy such as vedolizumab, ustekinumab and golimumab. Furthermore, children born to IBD mothers who used immunosuppressive therapy and/or biologicals should be followed preferably in prospective cohorts. The effects of in utero exposure to biologicals on the developing immune system of the child should be investigated. In rarer future cases, it would be interesting to investigate the response to anti-TNF in (adult) IBD patients who have been exposed to anti-TNF in utero, as this can be considered extreme episodic treatment. A national database including all individuals exposed to anti-TNF in utero would be useful in this respect.

Naturally, additional studies on the safety of current IBD medications during pregnancy are needed, as IBD remains a rare disease and large sample sizes are needed to truly establish safety profiles of different IBD medications during pregnancy.

CHAPTER 10

DUTCH SUMMARY

NEDERLANDSE SAMENVATTING

Inflammatoire darmziekten (IBD) zoals de ziekte van Crohn en colitis ulcerosa zijn chronische ontstekingsziekten van het maag,-darmkanaal. De ziekte is ongeneeslijk en patienten hebben vaak levenslang medicijnen nodig om de ziekte onder controle te houden. Die ziekte treedt vaak op jonge leeftijd op en vrouwelijke patienten hebben vaak een kinderwens. Dit leidt onvermijdelijk tot veel vragen over de chronische darmziekte en de medicatie om deze te behandelen in relatie tot een eventuele zwangerschap. In dit proefschrift belichten we verschillende aspecten en dilemma's rondom zwangerschap bij vrouwen met IBD. Schuingedrukt staan veelgestelde vragen door patienten met IBD met een kinderwens.

Hoofdstuk 1 geeft een inleiding en de doelen van dit proefschrift weer.

'Beinvloedt IBD de vruchbaarheid?'

Hoofdstuk 2 belicht het effect van IBD op de vruchtbaarheid. In deze studie vergeleken we een cohort van vrouwen met IBD en een zwangerschapswens met een cohort aan gezonde (niet-IBD) vrouwen. Verminderde vruchtbaarheid, ook wel subfertiliteit genoemd, werd gedefinieerd als het onvermogen om zwanger te raken na 12 maanden onbeschermde geslachtsgemeenschap. We vergeleken de tijd in maanden vanaf het stoppen van alle contraceptieve middelen tot aan het optreden van een zwangerschap en het aantal vruchtbaarheidsbehandelingen zoals in vitro fertilisatie (IVF) tussen de twee verschillende groepen. Daarnaast is er gekeken of het type IBD, medicatie, darmchirurgie in het verleden, de aanwezgheid van peri-anale fisteling of ziekte-opvlammingen in het jaar van proberen zwanger te worden invloed heeft op de vruchtbaarheid. Een multivariabel model toonde dat vrouwen met IBD niet vaker subfertiel zijn dan vrouwen zonder IBD. Vrouwen met IBD ondergingen wel vaker een vruchtbaarheidsbehandeling zoals IVF vergeleken met de gezonde controlegroep, echter het percentage vruchtbaarheidsbehandelingen bij de vrouwen met IBD is niet hoger dan het percentage in de algemene bevolking. Dit onderzoek suggereert dat de vruchtbaarheid van vrouwen met IBD vergelijkbaar is met de vruchtbaarheid van gezonde vrouwen.

'Wat is het risico op een ziekte opvlamming tijdens de zwangerschap en wat zijn de eventuele gevolgen hiervan voor het pasgeboren kind?'

Hoofdstuk 3 brengt de risico's in kaart voor het krijgen van een opvlamming van de darmziekte tijdens de zwangerschap. Daarnaast worden de effecten van een opvlamming tijdens de

zwangerschap op het pasgeboren kind belicht. Voorgaande studies toonden aan dat actieve ziekte ten tijde van de bevruchting een sterk voorspellende factor is voor aanhoudende ziekteactiviteit tijdens de zwangerschap dan wel op het krijgen van een nieuwe opvlamming tijdens de zwangerschap. Verder toonden studies in het verleden aan dat ziekteactiviteit tijdens de zwangerschap negatieve effecten kan hebben op het pasgeboren kind, zoals miskramen, vroeggeboorte en laag geboortegewicht. Deze studies waren echter vaak retrospectief van aard en includeerden vaak geen of zeer weinig patiënten met de nieuwste medicijnen om IBD te behandelen. In het onderzoek beschreven in dit hoofdstuk, is er onderzoek gedaan naar de risicofactoren en effecten van opvlamming tijdens de zwangerschap in een prospectief cohort van vrouwen met IBD met een zwangerschapswens. In dit cohort werden vrouwen behandeld met hedendaagse IBD medicijnen, zoals thiopurines en anti-TNF. Deze studie bevestigde dat ziekteactiviteit rondom de bevruchting het risico vergroot op aanhoudende ziekteactiviteit tijdens de zwangerschap of op het krijgen van een nieuwe opvlamming tijdens de zwangerschap. Er werd tevens geconstateerd dat aanwezigheid van ziekteactiviteit in het jaar waarin de patiënte zwanger probeerde te worden nog eens een verhoogd risico kan geven op het krijgen van ziekteactiviteit rondom de bevruchting. Hieruit vloeit het advies voort dat wanneer de leeftijd van de patiënt het toelaat, er het beste kan worden gestaakt met contraceptieve middelen nadat de darmziekte van de patiënt minimaal een jaar lang in remissie is. In vergelijking met de voorgaande studies, vielen de effecten van ziekteactiviteit tijdens de zwangerschap op de pasgeborene mee. Ziekte opvlamming tijdens de zwangerschap was niet geassocieerd met miskramen, vroeggeboorte, dysmaturiteit of aangeboren afwijkingen. Een ernstige ziekte opvlamming was geasscocieerd met laag geboortegewicht, maar niet met vroeggeboorte.

In **Hoofdstuk 4** wordt er kort commentaar gegeven op een meta-analyse naar de impact en het risico van ziekteactiviteit rondom de bevruchting op het krijgen van ziekteactiviteit tijdens de zwangerschap. Deze meta-analyse toonde dat dit risico stabiel bleef over een tijdspan van ongeveer 50 jaar, ondanks verbeterende therapie voor IBD in die tijd. Echter, wanneer men kritisch kijkt naar de studies in deze meta-analyse zijn er geen studies geincludeerd met voldoende patiënten die werden behandeld met thiopurines of anti-TNF. Dit kan mogelijk een van de redenen zijn waarom de auteurs een stabiel effect vonden.

'Wat kan ik doen om mijn zwangerschap en zwangerschapsuitkomsten zo positief mogelijk te beinvloeden?'

Hoofdstuk 5 beschrijft het effect van toegewijde, systematische preconceptiezorg bij vrouwen met IBD op ziekteactiviteit tijdens de zwangerschap en zwangerschapsuitkomsten. We vergeleken het zwangerschapsbeloop en de zwangerschapsuitkomsten tussen (1)

vrouwen met IBD met een zwangerschapswens die voorafgaand aan de zwangerschap werden geïnformeerd en geadviseerd door een gespecialiseerde arts over de darmziekte in combinatie met een zwangerschap met (2) vrouwen met IBD die dit niet hadden gehad. De twee groepen waren vergelijkbaar in opleidingsniveau en rookstatus voor de zwangerschap. De groep vrouwen die preconceptioneel was geadviseerd bleek minder vaak te roken en vaker medicatie-trouw tijdens de zwangerschap en slikte reeds foliumzuur voordat zij zwanger raakten. Waarschijnlijk als gevolg van het voorgaande bleek uit dit onderzoek dat de groep vrouwen met preconceptiezorg minder vaak een opvlamming van de darmziekte doormaakte tijdens de zwangerschap. De pasgeboren kinderen van de vrouwen die preconceptiezorg hadden gehad hadden minder vaak laag geboortegewicht dan de kinderen van de vrouwen zonder preconceptiezorg.

'Kan ik veilig een colonoscopie ondergaan tijdens de zwangerscap als dat nodig is?'

Hoofdstuk 6 is een systematische review van de literatuur over het effect van kijkonderzoeken van de dikke darm (colonoscopie en sigmoidoscopie) tijdens de zwangerschap op moeder en kind. In dit hoofdstuk waren er diverse indicaties voor het verrichten van de colonoscopie tijdens de zwangerschap. Deze indicaties werden grofweg ingedeeld in (1) IBD, (2) maligniteit, (3) endoscopische behandeling volvulus of geincarcereerde uterus (4) niet-maligne darmobstructie en (5) niet-maligne gastro-intestinaal bloedverlies. Er werden 82 artikelen geselecteerd, waarvan 3 retrospectieve cohort studies en de overige 79 artikelen beschreven individuele casus. De 3 cohort studies toonden geen negatieve effecten van colonoscopie tijdens de zwangerschap op de zwangerschapsuitkomsten, maar deze studies beschreven slechts kleine aantallen. De overige 79 artikelen beschreven 100 colonoscopieen bij 92 patiënten. Van deze 100 colonoscopieen tijdens de zwangerschap, identificeerden wij 6 complicaties die mogelijk gerelateerd konden zijn aan de colonoscopie. De resultaten van deze uitgebreide review suggereren dat colonoscopie en sigmoidoscopie veilig zijn in ieder trimester van de zwangerschap.

In **Hoofdstuk 7** wordt er dieper ingegaan op de veiligheid van endoscopische onderzoeken (colonoscopie en sigmoidoscopie) tijdens de zwangerschap. In dit hoofdstuk beschrijven we de effecten van colonoscopie tijdens de zwangerschap op moeder en het pasgeboren kind in een prospectief cohort van uitsluitend vrouwen met IBD. Een groep van 42 IBD vrouwen die een endoscopisch onderzoek tijdens de zwangerschap onderging werd gematcht met 42 IBD vrouwen die geen endoscopisch onderzoek ondergingen tijdens de zwangerschap. De twee groepen werden gematcht op leeftijd, IBD medicatie en ziekte activiteit tijdens de zwangerschap. Endoscopisch onderzoek was niet geassocieerd met het krijgen van een miskraam, premature weeen, vroeggeboorte, lage APGAR scores of congenitale

afwijkingen. De pasgeboren kindjes van vrouwen die wel een endoscopisch onderzoek tijdens de zwangerschap ondergingen hadden gemiddeld een lager geboortegewicht dan de pasgeboren kindjes van de controlegroep. Ook dit onderzoek suggereert dat endoscopische onderzoeken van de lage tractus digestivus tijdens de zwangerschap veilig zijn.

'Is anti-TNF veilig tijdens de zwangerschap? Moet ik anti-TNF de gehele zwangerschap doorgebruiken? Wat zijn de lange termijn effecten voor mijn kind?'

Hoofdstuk 8 beschrijft de effecten van een geindividualiseerde anti-TNF behandeling tijdens de zwangerschap. Uit eerdere onderzoeken is gebleken dat kinderen die tijdens de zwangerschap zijn blootgesteld aan anti-TNF met klinisch significante anti-TNF spiegels in het bloed geboren worden. De hoogte van de anti-TNF spiegels bij het kind hangen sterk af van de duur van de behandeling van de moeder tijdens de zwangerschap. Het is onbekend wat de invloed van dit sterke immuunbeinvloedende medicijn is op het ontwikkelende afweersysteem van het kind. Om de blootstelling aan anti-TNF tijdens de zwangerschap te beperken, werden er twee groepen gemaakt: een groep IBD vrouwen in langdurige ziekteremissie waarbij de anti-TNF gestaakt werd rond zwangerschapsweek 22 (stop groep) en een groep IBD vrouwen in niet-langurige remissie waarbij de anti-TNF tenminste tot zwangerschapsweek 30 gecontinueerd werd (continue groep). Het primaire doel van dit onderzoek was of stoppen met anti-TNF rond zwangerschapsweek 22 het risico op ziekte opvlamming bij de zwangere IBD vrouw zou vergroten. We vonden geen verschil in het aantal ziekte opvlammingen na zwangerschapsweek 22 tussen beide groepen. Dit suggereert dat, indien de vrouw in langdurige remissie is, er veilig kan worden gestaakt met anti-TNF aan het einde van het tweede trimester van de zwangerschap. Als secundaire uitkomstmaat vergeleken we alle kinderen van IBD vrouwen die blootgesteld waren aan anti-TNF met een groep kinderen van gezonde moeders die niet aan medicatie zijn blootgesteld tijdens de zwangerschap. We vergeleken groei, aantal infecties, allergieen en eczeem in het eerste levensjaar. Er werden geen verschillen gevonden tussen de kinderen blootgesteld aan anti-TNF en de kinderen die niet waren blootgesteld. Wanneer geindiceerd, kunnen IBD vrouwen doorbehandeld worden met anti-TNF tot in het derde trimester of gedurende de hele zwangerschap, zonder ernstige gezondheidsschade voor het kind.

Hoofdstuk 9 geeft een samenvatting van dit proefschrift en suggesties voor verder onderzoek. De conclusie van dit proefschrift is dat conceptie en zwangerschap haalbare doelen zijn voor vrouwen met IBD. Vrouwen met IBD hebben een verhoogde kans op een gecompliceerd zwangerschap beloop door chronisch medicatie gebruik, ziekte opvlamming en eventuele colonoscopieen, maar dit proefschrift toont aan dat de risico's hiervan beperkt zijn en dat geboorte uitkomsten van vrouwen met IBD over het algemeen gunstig zijn.

Dit proefschrift toont aan dat investeren in het adviseren en onderwijzen van IBD patienten met een zwangerschapswens leidt tot een gezondere leefstijl tijdens de zwangerschap en betere zwangerschapsuitkomsten. Artsen die vrouwen met IBD behandelen moeten aandacht hebben voor een eventuele zwangerschapswens en deze patienten frequent opvolgen. Frequente behandelcontacten maken het mogelijk om ziekte opvlamming vroeg op te sporen en te behandelen. Intensieve follow up van deze patientengroep tijdens de zwangerschap maakt het tevens mogelijk om de patient met een eventueel aangepast anti-TNF schema te behandelen met als doel een balans te vinden tussen goede behandeling van de moeder en minimale blootstelling aan anti-TNF van het kind. Verder zal intensieve follow up het prospectief opvolgen van deze patienten in studie verband faciliteren. Wij adviseren dan ook een zorgpad voor vrouwen met IBD met een zwangerschapswens in ieder ziekenhuis.

De behandelmogelijkheden voor IBD zijn constant in ontwikkeling en er komen steeds nieuwere en betere medicijnen op de markt om deze chronische ziekte te behandelen. Recente nieuwe IBD medicatie zijn bijvoorbeeld vedolizumab, ustekinumab en golimumab. Van ieder nieuw medicijn zal de veiligheid tijdens de zwangerschap moeten worden onderzocht, daarom zullen veel van de vragen gesteld in dit proefschrift actueel blijven. Echter, nader onderzoek naar kinderen blootgesteld aan immunosuppressiva en anti-TNF tijdens de zwangerschap is ook nog steeds nodig. De effecten van anti-TNF op het ontwikkelende immuunsysteem van deze kinderen moeten verder onderzocht worden. Wanneer personen die tijdens de zwangerschap zijn blootgesteld aan anti-TNF in hun latere leven voor welke diagnose dan ook anti-TNF behandeling nodig zullen hebben, is het interessant om hun respons op anti-TNF te onderzoeken. Om deze personen te kunnen identificeren zou bijvoorbeeld een landelijke database nuttig zijn.

IBD blijft een relatief zeldzame ziekte en er zullen grote aantallen patienten onderzocht moeten worden om een werkelijk veiligheidsprofiel van de verschillende medicijnen tijdens de zwangerschap vast te stellen. Uiteraard zijn er om deze reden meer studies nodig om de veiligheid van de huidige IBD medicaite tijdens de zwangerschap te onderzoeken.

CHAPTER 10

LIST OF CO-AUTHORS

LIST OF CO-AUTHORS

In alphabetical order

M. van Amelsfort
Medical Student – Department of Gastroenterology and Hepatology
Erasmus MC - University Medical Center, Rotterdam the Netherlands

W.M. Bramer
Information specialist – Medical Library
Erasmus MC - University Medical Center, Rotterdam the Netherlands

C. van der Ent
IBD Nurse - Department of Gastroenterology and Hepatology
Erasmus MC - University Medical Center, Rotterdam the Netherlands

B. Galjart
Medical Student – Department of Gastroenterology and Hepatology
Erasmus MC - University Medical Center, Rotterdam the Netherlands

S.L. Kanis
Research Physician – Department of Gastroenterology and Hepatology
Erasmus MC - University Medical Center, Rotterdam the Netherlands

Prof. Dr. J.S.E. Laven
Professor in Reproductive Health - Department of Obstetrics and Gynaecology
Erasmus MC - University Medical Center, Rotterdam the Netherlands

Dr. A.G.M.G.J. Mulders
Gynaecologist - Department of Obstetrics and Gynaecology
Erasmus MC - University Medical Center, Rotterdam the Netherlands

Prof. Dr. E.A.P. Steegers
Professor in Obstetrics and Gynaecology and Principal Investigator 'Generation R'- Department of Obstetrics and Gynaecology
Erasmus MC - University Medical Center, Rotterdam the Netherlands

P.H.A. Wisse
Medical Student – Department of Gastroenterology and Hepatology
Erasmus MC - University Medical Center, Rotterdam the Netherlands

Prof. Dr. C.J. van der Woude
Professor in Adult Inflammatory Bowel Disease – Department of Gastroenterology and Hepatology
Erasmus MC - University Medical Center, Rotterdam the Netherlands

Dr. Z. Zelinkova – Detkova
Gastroenterologist – IBD Center Thalion Bratislava, Slovakia

CHAPTER 10

PhD PORTFOLIO

PhD PORTFOLIO

PhD period: September 2012- April 2015

Oral presentations

2013 Disease relapse rates during pregnancy are higher in ulcerative colitis patients than in Crohn's disease patients
Nederlande Vereniging voor Gastroenterologie (NvGE), Veldhoven, the Netherlands

2014 Preconception care in IBD women leads to less disease relapse during pregnancy
European Crohn's and Colitis Organisation (ECCO), Copenhagen, Denmark

2014 Anti-TNF is safe to stop in in the second trimester in pregnant IBD women in sustained remission
Digestive Disease Week (DDW) Chicago (IL) United States

2015 Fertility in IBD women is comparable to fertility in non-IBD controls
Nederlandse Vereniging voor Gastroenterologie (NvGE), Veldhoven, the Netherlands

Poster presentations

2013 P635 Disease relapse rates during pregnancy – results from the Erasmus MC Rotterdam prospective cohort
European Crohn's and Colitis Organisation, Vienna, Austria

2013 Mo1368 Disease relapse rates during pregnancy – results from the Erasmus MC Rotterdam prospective cohort
Digestive Disease Week, Orlando (FL), United States

2014 Anti-TNF is safe to stop in the second trimester of pregnancy in IBD women in remission
European Crohn's and Colitis Organization (ECCO), Kopenhagen, Denmark

2014 Endoscopy in IBD women is safe in each trimester of pregnancy
European Crohn's and Colitis Organisation (ECCO), Kopenhagen, Denmark

2014 Endoscopy in IBD women is safe in each trimester of pregnancy
Digestive Disease Week (DDW), Chicago (IL), United States

2014 Preconception care leads to less disease relapse during pregnancy
Digestive Disease Week (DDW), Chicago (IL), United States

2014 Preconception care leads to less disease relapse during pregnancy
3d International Symposium on Pediatric Inflammatory Bowel Disease (PIBD), Rotterdam, The Netherlands

2014 Anti-TNF is safe to stop in the second trimester of pregnancy in IBD women in remission
3d International Symposium on Pediatric Inflammatory Bowel Disease (PIBD), Rotterdam, The Netherlands

2015 Fertility in IBD women is comparable to fertility in non-IBD controls
European Crohn's and Colitis Organisation (ECCO), Barcelona, Spain

2015 Hormonal contraceptive use is not associated with increased disease activity in IBD women – Results from an online survey
European Crohn's and Colitis Organisation (ECCO), Barcelona, Spain

Awards

2014 Diversity Award for Gender Studies – Best Abstract Endoscopy in IBD women is safe in each trimester of pregnancy
ASGE Crystal Awards, Chicago (IL), United States

Epidemiological and statistical training

2011 Study Design
NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands

2012 Erasmus Summer Programme
- ESP01 Principles of Research in Medicine
- ESP04 Clinical Decision Analysis
- ESP10 Methods of Clinical Research
- ESP 62 Markers and Prognostic Research

NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands

2012 Biostatistical methods I
NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands

2012 Clinical Epidemiology
NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands

2012 Scientific Writing in English for Publication
NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands

2013 Erasmus Winter Programme
- EWP 10 Advanced Topics in Clinical Trials
- EWP 13 Advanced Analysis of Prognosis Studies
- EWP 25 Principles of Epidemiologic Data Analysis

NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands

2013 Advanced Short Courses
- EP 19 Women's Health
- HS09 Maternal and Child Health
- HS 11 Quality of Life Measurement
- HS 18 From Problem to Solution in Public Health
- EP05 Epidemiology of infectious Diseases

NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands

2013 Erasmus Summer Programme
- ESP61 Social Epidemiology
- ESP65 The Practice of Epidemiologic Analysis

NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands

Scientific Integrity

2014 Successful completion of the BROK course

Teaching

'12-'15 Supervision of several students in obtaining and processing data, conductance of a systematic review and supervision of two Master's thesis

2014 Co-author and presenter of the E-learning 'IBD and pregnancy' for both physicians and nurses

2014 Regionaal onderwijs Dordrecht – lecture 'IBD and pregnancy' for nurses

2015 Hogeschool van Arnhem en Nijmegen – masterclass 'IBD and pregnancy' for nurses

Membership

Nederlandse Vereniging voor Gastroenterologie (NvGE)

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LIST OF PUBLICATIONS

LIST OF PUBLICATIONS

Lima de A, Woude van der CJ. Contraceptive choice in women with Inflammatory Bowel Disease. *Gyn Forum 2012-12; 23-25*

Lima de A, Woude van der CJ. Commentary: impact of disease activity at conception on disease activity during pregnancy in patients with inflammatory bowel disease.
Aliment Pharmacol Ther 2013 Oct; 38(7): 842

Lima de A, Galjart B, Wisse PH, Bramer WM, Woude van der CJ. Does lower gastrointestinal endoscopy during pregnancy pose a risk for mother and child? – a systematic review.
BMC Gastroenterol 2015 Feb 12; 15:15

Lima de A, Zelinkova Z, Ent van der C, Steegers EAP, Woude van der CJ. Tailored anti-TNF therapy during pregnacy in patients with IBD: maternal and fetal safety.
Gut 2015 May 12 - Epub ahead of print

Lima de A, Zelinkova Z, Woude van der CJ. A prospective study of the safety of lower gastrointestinal endoscopy during pregnancy in patients with Inflammatory Bowel Disease.
J Crohn Colitis 2015 - in press

Lima de A, Zelinkova Z, Woude van der CJ. Risk factors for IBD relapse during pregnancy in the era of novel IBD therapies. *Submitted*

Lima de A, Zelinkova Z, Woude van der CJ. Preconception care leads to less disease relapse during pregnancy in IBD women. *Submitted*

Lima de A, Amelsfort van M, Steegers EAP, Laven JSE, Woude van der CJ. Comparing fertility between women with Inflammatory Bowel Disease and controls; a prospective cohort study. *Submitted*

Lima de A, Kanis SL, Woude van der CJ et al. High-risk pregnancy: Management options; Gastrointestinal and Liver Diseases during Pregnancy. 5th Edition Online.
Cambridge University Press, 2016. In Press

CHAPTER 10

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CHAPTER 10

CURRICULUM VITAE

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De auteur van dit proefschrift werd geboren op 4 juli 1986 te Gorinchem. Zij behaalde haar Gymnasium diploma in 2004 aan de Christelijke Scholengemeenschap Oude Hoven te Gorinchem. Hierna ging zij Geneeskunde studeren aan de Erasmus Universiteit Rotterdam. Tijdens haar collegejaren was zij reeds gefascineerd door Inflammatoire Darmziekten en besloot haar afstudeeronderzoek te doen op de afdeling Maag,- Darm en Leverziekten in het Erasmus MC Rotterdam. Hier kwam zij via Dr. Zuzana Zelinkova en Prof. Dr. Janneke van der Woude in aanraking met het onderzoek naar zwangerschap bij vrouwen met deze chronische aandoening. Na het succesvol afronden van het afstudeeronderzoek startte zij met haar co-schappen in de omgeving van Rotterdam. Tijdens haar co-schappen begon zij tevens aan een Research Master via het Netherlands Institute for Health Sciences (NIHES) toegespitst op Maag,- Darm,- en Leverziekten. In 2012 behaalde zij cum laude haar artsendiploma waarna zij direct van start ging als arts-onderzoeker op de afdeling Maag,- Darm,- en Leverziekten in het Erasmus MC. Hier zette zij het onderzoek naar zwangerschap bij vrouwen met IBD voort onder leiding van Prof. Dr. Van der Woude. In 2014 behaalde zij haar Research Master. Op 1 mei 2015 begon zij met veel plezier aan haar opleiding tot Maag,- Darm,- en Leverarts (opleider: Dr. R.A. de Man). De vooropleiding Interne Geneeskunde volgt zij gedurende 2 jaar in het Ikazia Ziekenhuis te Rotterdam (opleider: Dr. A.A.M. Zandbergen). Zij woont samen met haar vriend Ilias Karagiannis in Gorinchem.