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a 20-year nationwide cohort study**

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# **Live birth and adverse birth outcomes in women with ulcerative colitis and Crohn's disease receiving assisted reproduction– a 20 year nationwide cohort study**

Short running title: infertility treatment in inflammatory bowel disease

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## **ABSTRACT**

### **Objective**

In this study, we examine the chance of live births and adverse birth outcomes in women with ulcerative colitis (UC) and Crohn's disease (CD) compared to women without inflammatory bowel disease (IBD) who have undergone assisted reproductive technology (ART) treatments.

### **Design**

This is a nationwide cohort study based on Danish health registries, comprising all women with an embryo transfer during 1 January 1994 through 2013. The cohorts comprised 1,360 ART treatments in 432 UC women, 554 ART treatments in 182 CD women, and 148,540 treatments in 52,489 women without IBD. Our primary outcome was live birth per ART treatment cycle. We controlled for multiple covariates in the analyses. Our secondary outcomes were adverse birth outcomes.

### **Results**

The chance of a live birth per embryo transfer was significantly reduced in ART treatments in UC women, OR=0.73, 95% CI: 0.58-0.92; but not significantly reduced in the full model of ART treatments in CD women, OR=0.77, 95% CI: 0.52-1.14. Surgery for CD before ART treatment significantly decreased the chance of live birth per embryo transfer, OR=0.51, 95% CI: 0.29-0.91. In children conceived through ART treatment by UC women, the OR of preterm birth was 5.29 (95% CI: 2.41-11.63) in analyses including singletons and multiple births; restricted to singletons the OR was 1.80, 95% CI: 0.49-6.62.

### **Conclusion**

Our results suggest that women with UC and CD receiving ART treatments cannot expect the same success per embryo transfer as other infertile women. Women with CD may seek to initiate ART treatment prior to needing CD surgery. Increased prenatal observation in UC pregnancies after ART should be considered.

## SUMMARY BOX:

### 1. What is already known about this subject:

- Women with UC and CD might have decreased fertility due to several factors including voluntary childlessness, prior surgery, decreased ovarian reserve, and increased disease activity.
- Assisted reproductive technology (ART) is an appropriate intervention for women with UC and CD who are unable to conceive naturally.
- There is little evidence of the efficacy of ART treatment in women with UC and CD. The cumulative live birth rate after 6 cycles of in vitro fertilization has only been described in 71 UC women and 49 CD women.
- No studies have examined the risk of adverse birth outcomes in children after ART treatments in UC and CD women.

### 2. What are the new findings:

- In UC women receiving ART, the chance of a live birth per embryo transfer is significantly decreased.
- UC surgery before ART treatment does not negatively impact the chance of live birth per embryo transfer.
- In children conceived through ART treatment by women with UC, the risk of preterm birth is increased.
- In CD women receiving ART, the chance of a live birth per embryo transfer is decreased (but not significant in the full model).
- CD surgery before ART treatment significantly decreases the chance of a live birth per embryo transfer.
- In children conceived through ART treatment by women with CD, there is no increased risk of adverse birth outcomes.

### 3. How might it impact on clinical practice in the foreseeable future?

- Infertile women with UC and CD may seek to initiate ART treatment more quickly if they are unable to conceive naturally as they cannot expect the same success per embryo transfer as other infertile women.

- Women with UC will be reassured that surgery before ART treatment does not impact the chance of a live birth per embryo transfer.
- Increased prenatal observation in UC pregnancies after ART should be considered.
- Women with CD may seek to initiate ART treatment prior to needing CD surgery.
- Women with CD will be reassured that children born after ART treatment have normal birth outcomes.

## INTRODUCTION

The incidence of ulcerative colitis (UC) and Crohn's disease (CD) continue to increase in many countries, and Denmark is one of the countries in the world with the highest reported incidence rate (23 per 100,000 per year for UC and 10 per 100,000 per year for CD).[1-5] As the majority of patients with UC and CD are diagnosed in the fertile years,[5] clinicians are increasingly faced with fertility and pregnancy related issues. Pregnancy attempts in UC and CD women are most often well planned, and when contemplating medical or surgical therapy, some of the most urgent questions patients of childbearing age have are those regarding disease impact on fertility, safety of a future pregnancy, and risk of adverse birth outcomes.

In the general population in Denmark, up to 10-15% of all women have problems with infertility, leading many to seek assisted reproduction,[6, 7] which includes in vitro fertilization (IVF), with or without fertilization with intracytoplasmic sperm injection (ICSI), and transfer of frozen-thawed (FER) embryos. The proportion of UC and CD women with infertility problems is likely to be at least the same as in the general population or even higher due to adhesions of the fallopian tubes and ovaries associated with prior abdominal surgery.[8] Former studies have found a considerable reduction in postoperative fertility in UC women requiring ileoanal pouch anastomosis (IPAA),[9-12] and after CD surgery.[13,14] Excluding voluntary childlessness, additional causes of infertility may include increased disease activity and low ovarian reserve.[13,15,16] Serum anti-Mullerian hormone, an indicator of ovarian reserve, is lower in women with CD, especially during periods of active disease, compared to healthy controls.[15,16]

Assisted reproductive technology (ART) is an appropriate fertility intervention for women with UC and CD who are unable to conceive naturally. Therefore, questions regarding the success of ART treatment in women with UC and CD are highly relevant, especially prior to surgery for these conditions. There is little evidence of the efficacy of ART treatment in patients

with UC and CD. The cumulative live birth rate after 6 IVF cycles has only recently been described in 71 UC women and 49 CD women and compared to patients without inflammatory bowel disease (IBD),[17, 18] but the analyses did not take into account a possible impact of confounding factors which may affect fertility such as prior surgery, comorbid disease, body mass index (BMI), and tobacco use.

We examined the efficacy of ART in UC and CD women, compared to non-IBD women, on a much larger scale. In this study we used the power of the Danish nationwide registries that contain all relevant information on ART treatments and births, and compiled data corresponding to a study period of 20 years on unselected patient cohorts. In Denmark, the cumulative proportion of infertility is 16-26% in women who try conceiving for  $\geq 12$  months, and more than 15,000 ART treatments are initiated each year.[19] For the purposes of this study, ART refers to traditional IVF, ICSI, and FER. The primary outcome studied was live birth, and we assessed the chance of live birth following ART treatments in UC women compared to non-IBD women, and in CD women compared to non-IBD women. In sub-analyses, we examined the impact of UC and CD surgery prior to ART treatment. As secondary outcomes, we compared the risk of adverse birth outcomes in children after ART treatments in UC and CD women with children after ART in women without IBD.

## **MATERIALS AND METHODS**

### **STUDY POPULATION AND SETTING**

All citizens in Denmark (population approximately 5.6 million inhabitants, > 90% Caucasians) have equal and free access to the tax-supported health care system, and its uniform organization allowed us to use a nationwide population-based design. We obtained nationwide Danish data from the following registries: (i) data related to ART treatments and cause of infertility from the Danish ART Registry, (ii) data on the primary outcome of infertility treatment (live birth) from the Danish Medical Birth Registry (MBR), (iii) data from The Danish National Patient Registry (NPR) on comorbid diseases, and surgical procedures performed in women with UC and CD, and (iv) data from The Central Personal Registration system on death and immigration. Data from all sources were unambiguously linked on an individual level using the unique civil registration number (assigned to all Danish residents at birth from the Central Personal Registration system) and used in all Danish healthcare registries.[20]

The study population comprised all women (with a valid civil registration number and available for follow up in Denmark) registered in the ART registry with at least one embryo transfer during the study period of 1 January 1994 – 31 December 2013 (20 year study period). The Danish health care system offers infertile couples and single women up to three fully reimbursed IVF or ICSI treatment cycles with fresh embryos and an unlimited number of frozen embryo transfer and insemination cycles (in practice, 3–6 cycles) if the woman's age does not exceeds 40 years. All initiated treatment cycles for infertility are recorded in the Danish ART registry. The registry was established on 1<sup>st</sup> January 1994 and includes data on ART treatments in both public and private clinics, and registration of all treatments is compulsory.[21,22] In the ART registry, the embryo transfer to the uterus could be a result of all kinds of preceding treatments (IVF, ICSI, FER).



## EXPOSED COHORTS

From the study population, all UC and CD women were identified in the NPR. The NPR includes records of all discharges from Danish hospitals since 1977 and all outpatient visits since 1994.[23, 24] Information in the NPR includes patients' civil registration numbers, hospital, department, dates of admission and discharge, procedures performed, and up to 20 discharge diagnoses based on the International Classification of Diseases (ICD-8 before 1994 and ICD-10 from 1994 onward). All eligible patients who had a discharge history of UC from any hospital in Denmark (ICD-8 codes: 563.19, 569.04; ICD-10 codes: DK51.x (except DK51.9 for unspecified disease)) before the date of embryo transfer were identified. If a UC woman had a former diagnosis in the NPR with codes of CD she was only included if the latest given diagnosis was UC. Similarly, all eligible patients who had a discharge history of CD (ICD-8 codes: 563.01; ICD-10 codes: DK50.x) before the date of embryo transfer were identified. If a woman with a CD diagnosis had a former diagnosis of UC she was only included if the latest given diagnosis was CD.

For the primary outcome (live birth), the exposed cohorts comprised all ART treatment cycles in women with UC or CD. Because each UC or CD woman could have several ART treatments, the observation unit was treatment cycle.[25-27]

For the secondary outcomes (adverse birth outcomes), the exposed cohorts comprised all children who were conceived through ART treatment by women with UC or CD. Because each UC or CD woman could have several births, and each birth could include several children, the observation unit was child.

## UNEXPOSED COHORTS

For the primary outcome, the unexposed cohort comprised all ART treatment cycles in women without UC or UC (non-IBD women); and the observation unit was treatment cycle.

For the secondary outcomes, the unexposed cohort comprised all children born after ART treatment by non-IBD women; and the observation unit was child.

## PRIMARY AND SECONDARY OUTCOMES

The primary outcome was live birth within a period of 124-292 days after the date of each embryo transfer, and was identified in the MBR. Thus, a live birth was considered to be the result of the particular ART treatment if the difference was 140–308 days (20–44 weeks) [25] from the last menstruation start, corresponding to 124- 292 days after embryo transfer. The MBR includes information on all births in Denmark since 1 January 1973, and data are obtained from birth forms, completed by the midwives who attend all births.[28,29] The forms include data on the mother's civil registration number, date of birth, parity, and smoking status during pregnancy, as well as gestational age, birth weight, and congenital anomalies (CAs).

Our secondary outcomes included i) low birth weight (LBW) at term (birth weight < 2500 g in children with a gestational age of  $\geq 37$  weeks), ii) preterm birth (birth before 37 completed weeks of pregnancy), and iii) CAs.

## DATA ON CONFOUNDERS

Covariates were selected a priori. From the NPR we obtained data on comorbid diseases for all women in the study population, and a comorbidity index score in terms of Charlson Index was calculated for each treatment cycle of each woman and covers 19 major disease categories weighted according to their prognostic impact.[30] We computed the index based on diagnoses recorded during all previous hospitalizations since 1977, and two index levels were defined: no comorbidity (Charlson Index 0), some comorbidity (Charlson Index  $\geq 1$ ). From the MBR we obtained data on parity (0, +1) and smoking during pregnancy (yes/no). The ART registry did not include

information on all confounders during the entire study period. For the entire study period we had data on women's age at time of embryo transfer (continuous variable), calendar year of infertility treatment (1994-1998, 1999-2003, 2004-2008, 2009-2013), type of preceding treatment (IVF, ICSI, FER), and cause of infertility (female factor, male factor, or mixture of factors/idiopathic). From 2006, the ART registry also included information on body mass index (calculated as body weight divided by height squared and categorized according to the World Health Organization classifications as underweight (<18.5 kg/m<sup>2</sup>), normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25.0–29.9 kg/m<sup>2</sup>), and obese (>=30 kg/m<sup>2</sup>)), partner's age, alcohol intake (yes/no), and smoking at the time of embryo transfer (yes/no).

For UC women we calculated the duration of UC at the time of each ART treatment (calculated from the date that the first diagnosis of UC appeared in the NPR, unless they had a later diagnosis of CD, until the date of embryo transfer in the ART registry). Likewise, the disease duration for CD women was calculated from the date that the first diagnosis of CD appeared in the NPR, unless they had a later diagnosis of UC, until the date of embryo transfer.

For UC and CD women we identified those who had undergone surgery prior to the date of embryo transfer. Identified were UC women who had relevant surgeries according to the following codes in the new and former version of the “Nordic Classification of Surgical Procedures”: codes of KJFH; i.e. all types of colectomies; and colectomy codes of 45020, 45060, 45080, 45840, or 45880. For CD women the following codes were used: KJFB00, KJFB01, KJFB20/21/30/31, KJFB33, KJFB34, KJFB40/41/43/44/46/47/50/51/60/61/63/64, KJFB96, KJFB97, KJFH00/01/10/11/20/96, KJGB00/01/10/11/30/31, KJFA60, 43440, 43460, 43520, 43540, 43680, 43700, 43740, 43760, 43780, 43800, 43820, 43840, 43860, 43880, 44060, 44120, 44150, 44160, 44790, 44900, 44920, 44940, 44960, 44980, 45020, 45060, 45080, 45100, 45120, 45200, 45240, 45320, 45480, 45690,

45840, 45860, 45880, 46290. The number of UC or CD related surgeries was recorded prior to each treatment cycle.

## STATISTICAL ANALYSES

### **Live birth (primary outcome)**

Contingency tables were constructed for the main study variables according to the exposed and unexposed cohorts. We used multilevel logistic regression analyses to compute crude and adjusted relative risk estimates (prevalence odds ratio [OR] with 95% confidence intervals [95% CI]) for live births following ART treatments in UC and CD women relative to women without IBD, and the model accounted for multiple embryo transfers in the same woman. Adjustment was made for Charlson Index, women's age at time of embryo transfer, calendar year of infertility treatment, type of infertility treatment, and cause of infertility. In an extended model, including data from 2006, we further adjusted for BMI, partner's age, smoking at the time of embryo transfer, and alcohol.

In a sensitivity analysis we included only first time ART treatment for each UC or CD woman and only if they had non-missing information on BMI, smoking at the time of embryo transfer, and alcohol.

### **Sub-analysis on the impact of UC or CD surgery on the chance of live birth**

A possible impact of UC or CD surgery before infertility treatment was examined in UC or CD women, respectively. Thus, among ART treatments in UC women two sub-cohorts were established: a) exposed cohort of ART treatments in UC women who had had at least one UC related surgery before the date of embryo transfer, and b) unexposed cohort of ART treatments in UC women who had not had surgery before the date of embryo transfer. Live birth in the exposed cohort a) was compared to the unexposed cohort b). Likewise, among ART treatments in CD women, the exposed cohort consisted of ART treatments in CD women who had had at least one

CD related surgery before the date of embryo transfer, and the unexposed cohort consisted of ART treatments in CD women who had not had surgery before the date of embryo transfer. In multilevel logistic regression models we adjusted for duration of UC or CD, Charlson Index, women's age, calendar year of infertility treatment, type of infertility treatment, and cause of infertility. Due to power considerations it was not possible to adjust for smoking at the time of embryo transfer, BMI, and alcohol.

All surgery codes given to UC women at the three latest operation dates prior to ART treatment were recorded according to the following categories: i) "Partial colon resection (no ostomy)": 45020, ii) "Total colon resection (no ostomy)": 45060, KJFH00, KJFH96, iii) "Total colon resection + ileostomy (rectum left in place)": KJFH10, KJFH11, iv) "Rectal/anus resection": 45080, 45840, 45880, KJFH20, v) "Ileal pouch anal anastomosis": KJFH33. All CD surgery codes from the three latest operation dates before the first embryo transfer were identified, and the surgery codes were categorized according to i) "Ileocecal resection": 43700, KJFB20, KJFB21, ii) "Ileocolonic resection (more than ileocecal)": 45060, 43860, 43820, 44900, 43800, 43880, 43840, KJFB33, KJFB30, KJFH00, iii) "small bowel resection or stricturoplasty": 43680, 44060, 44790, 43780, 43760, 43440, 44120, KJFB00, KJFA60, iv) "Stomas but rectum left in place": 43740, 45240, KJFH10, KJFB60, v) "Colon resection": 44980, 44940, 45120, 44960, 44920, 45320, 45020, KJFB43, KJFB40, KJFB46, vi) "Rectal/Anus resection": 45880, 45840, 45080, 45860, KJGB30, KJFH20.

### **Adverse birth outcomes (secondary outcomes)**

We used multilevel logistic regression analyses, accounting for multiple children by the same woman, to compute crude and adjusted relative risk estimates for adverse birth outcomes (LBW at term, preterm birth, and CAs) in children after ART treatment in UC women compared to children after ART in non-IBD women, and likewise in CD women compared to children after ART in non-

IBD women. The risk estimates of LBW at term, preterm birth and CAs were adjusted for mother's age, parity, calendar year of infertility treatment, type of infertility treatment, cause of infertility, and smoking during pregnancy. Estimates of LBW at term and CAs were further adjusted for singleton/multiple births.

In a sub-analysis we used multilevel logistic regression to compare the risk of adverse birth outcomes among singletons after ART treatment in UC women compared to singletons after ART in non-IBD women, and likewise in CD women compared to singletons after ART in non-IBD women.

All analyses were conducted using Stata 13 software (StataCorp LP, College Station, TX, USA).

## **RESULTS**

Table 1 shows the characteristics for the all ART treatments in exposed and unexposed cohorts. A total of 1,360 ART treatments in 432 UC women, and 554 ART treatments in 182 CD women, were included during the study period of January 1, 1994 to December 31, 2013. The unexposed cohort included 148,540 ART treatments in 52,489 women without IBD. The median age of women and the distribution of details according to BMI and smoking were similar in the exposed and unexposed cohorts while fewer CD women consumed alcohol than UC and unexposed women. In the UC cohort, the cause of infertility was referred to as a female factor in 34.5% of the cases and a mixture of factors in 44.5% of the cases; the corresponding figures among the CD cohort were 46.6% and 36.9%, and unexposed cohort were 30.1% and 38.0%, respectively. The vast majority of women in all cohorts had no comorbid diseases. Among embryo transfers in UC patients, the median duration of UC at the time of embryo transfer was 8 years (25%-75% percentiles: 4 -12), and surgery had been performed prior to the transfer in 34.5% of the cases. Among embryo

transfers in CD patients, the median duration of CD at the time of embryo transfer was 9 years (25%-75% percentiles: 4-13) and surgery had been performed prior to the transfer in 64.1% of the cases.

**Table 1.** Descriptive characteristics of study cohorts of ART treatments in women with UC, CD and without IBD during the study period of January 1, 1994 through 2013

|  | Exposed cohort<br>(embryo transfers<br>in women with<br>UC)<br>N = 1360 <sup>a,b</sup> | Exposed cohort<br>(embryo<br>transfers in<br>women with CD)<br>N=554 <sup>a,c</sup> | Unexposed<br>cohort (embryo<br>transfers in non-<br>IBD women)<br>N=148,540 <sup>a,d</sup> |
|--|--|---|--|
| Age at embryo transfer                 |  |   |  |
| Median (25%-75% percentiles)           | 33 (30-36)   | 32 (30, 35)   | 33 (30, 37)  |
| Partner's age at embryo transfer       |  |   |  |
| Median (25%-75% percentiles)           | 35.5 (32-39)   | 35 (31, 37)   | 35 (32, 39)  |
| Female/male factor                     |  |   |  |
| Female factor, N (%)                   | 442 (34.5)   | 234 (46.6)  | 41,011 (30.1)  |
| Male factor, N (%)                     | 269 (21.0)   | 83 (16.5)   | 43,610 (32.0)  |
| Mixture of factors/idiopathic N (%)    | 570 (44.5)   | 185 (36.9)  | 51,852 (38.0)  |
| Type of preceding treatment            |  |   |  |
| IVF, N (%)                             | 718 (53.0)   | 290 (52.6)  | 72,971 (49.3)  |
| ICSI, N (%)                            | 403 (29.7)   | 166 (30.1)  | 51,237 (34.6)  |
| FER, N (%)                             | 234 (17.3)   | 95 (17.2)   | 23,713 (16.0)  |
| BMI                                    |  |   |  |
| < 18.5 (underweight), N (%)            | 15 (2.3)   | 16 (7.2)  | 1765 (3.1)   |
| 18.5-24.99 (normal), N (%)             | 450 (69.7)   | 125 (56.3)  | 37,082 (64.4)  |
| 25.00- 29.99 (overweight), N (%)       | 134 (20.7)   | 69 (31.1)   | 13,157 (22.9)  |
| >= 30.00 (obese), N (%)                | 47 (7.3)   | 12 (5.4)  | 5,548 (9.6)  |
| Smoking at the time of embryo transfer |  |   |  |
| Non-smoker, N (%)                      | 617 (93.8)   | 192 (87.3)  | 51,819 (90.0)  |
| Smoker, N (%)                          | 41 (6.2)   | 28 (12.7)   | 5,773 (10.0)   |
| Alcohol                                |  |   |  |
| No, N (%)                              | 304 (52.0)   | 135 (70.3)  | 29,367 (54.5)  |

|  |              |            |                |
|--|--------------|------------|----------------|
| Yes, N (%)   | 281 (48.0)   | 57 (29.7)  | 24,548 (45.5)  |
| Calendar year of infertility treatment                       |              |            |                |
| 1994-1998, N (%)   | 110 (8.1)    | 84 (15.2)  | 24,016 (16.2)  |
| 1999-2003, N (%)   | 254 (18.7)   | 128 (23.1) | 35,899 (24.2)  |
| 2004-2008, N (%)   | 469 (34.5)   | 188 (33.9) | 44,467 (29.9)  |
| 2009-2013, N (%)   | 527 (38.8)   | 154 (27.8) | 44,158 (29.7)  |
| Parity   |              |            |                |
| 0, N (%)   | 169 (62.4)   | 65 (70.7)  | 24,102 (69.0)  |
| 1+, N (%)  | 102 (37.6)   | 27 (29.3)  | 10,845 (31.0)  |
| Comorbidity at embryo transfer                               |              |            |                |
| No comorbidity, N (%)  | 1,202 (88.4) | 476 (85.9) | 136,982 (92.2) |
| Some comorbidity, N (%)                                      | 158 (11.6)   | 78 (14.1)  | 11,558 (7.8)   |
| Duration of UC/CD at time of embryo transfer                 |              |            |                |
| Median (25%-75% percentiles)                                 | 8 (4, 12)    | 9 (4, 13)  | -              |
| UC/CD operations before time of embryo transfer <sup>#</sup> |              |            |                |
| No, N (%)  | 891 (65.5)   | 199 (35.9) | -              |
| Yes, N (%)   | 469 (34.5)   | 355 (64.1) | -              |
| Number of UC operations before embryo transfer <sup>#</sup>  |              |            |                |
| 1, N (%)   | 242 (51.6)   | -          | -              |
| 2-3, N (%)   | 227 (48.4)   | -          | -              |
| Number of CD operations before embryo transfer <sup>#</sup>  |              |            |                |
| 1, N (%)   | -            | 175 (49.3) | -              |
| 2-3, N (%)   | -            | 159 (44.8) | -              |
| >3, N (%)  | -            | 21 (5.9)   | -              |

<sup>a</sup> Number of women in exposed UC cohort = 432 , in exposed CD cohort = 182 and in unexposed cohort = 52,489

<sup>b</sup>Missing (%), UC women: partner's age (42.5), female/male factor (5.8), type of treatment (0.4), parity (80.1), BMI (52.5), smoking at the time of embryo transfer (51.6), alcohol (57.0)

<sup>c</sup>Missing (%), CD women: age of partner (49.6), fertility factor (9.4), ART treatment (0.5), parity (83.4), BMI (59.9), smoking at the time of embryo transfer (60.3), alcohol (65.3)

<sup>d</sup>Missing (%), non-IBD women: partner's age (53.4), female/male factor (8.1), type of treatment (0.4), parity (76.5), BMI (61.3), smoking at the time of embryo transfer (61.2), alcohol (63.7)

<sup>#</sup>It is possible to have more than one type of UC or CD operation at the same day



## LIVE BORN CHILDREN (PRIMARY OUTCOME)

The ORs for an ART treatment in UC and CD women leading to a live birth, compared to ART treatments in non-IBD women, are given in Table 2. The chance of a live birth was significantly reduced per ART treatment in UC women, and compared to the crude OR (0.79, 95% CI: 0.67-0.92), the ORs were virtually unchanged across two different models of adjustment (in the fully adjusted model, OR=0.73, 95% CI: 0.58-0.92). The chance of a live birth was significantly reduced per ART treatment in CD women according to the crude OR (0.62, 95% CI: 0.48- 0.80), and in the fully adjusted model the chance of live birth was still reduced but not significantly (OR=0.77, 95% CI: 0.52-1.14) In the model without lifestyle factors, the OR was significantly reduced (Table 2).

In the sensitivity analyses, we included only first time ART treatment for each UC and CD woman and only if she had non-missing information on life-style factors (BMI, smoking at the time of embryo transfer, alcohol). For UC women, the result of this analysis was similar to the overall result of live birth (OR, adjusted = 0.79, 95% CI: 0.53-1.18), and also for CD the result was similar compared to the overall result as we still found a decreased, but not significant, chance of live birth.

**Table 2.** Crude and adjusted odds ratios (OR), with 95% confidence interval (95% CI), for live birth in the study cohorts of ART treatments in women with UC compared to women without IBD; similar results for women with CD (January 1, 1994 through 2013)

| Ulcerative colitis |  |   |                      |                                      |                                      |
|--------------------|--|---|----------------------|--------------------------------------|--------------------------------------|
|                    | Exposed cohort (embryo transfers<br>in women with UC) N = 1,360 <sup>a</sup> | Unexposed cohort (embryo transfers<br>in non-IBD women) N =148,540 <sup>b</sup> | Crude OR<br>(95% CI) | Adjusted OR <sup>c</sup><br>(95% CI) | Adjusted OR <sup>d</sup><br>(95% CI) |
| Live birth         |  |   |                      |                                      |                                      |
| Yes, N (%)         | 272 (20.00)  | 35,321 (23.78)  | 0.79 (0.67-0.92)     | 0.78 (0.67-0.91)                     | 0.73 (0.58-0.92)                     |
| No, N (%)          | 1,088 (80.00)  | 113,219 (76.22)   |                      |                                      |                                      |
| Crohn's disease    |  |   |                      |                                      |                                      |
|                    | Exposed cohort (embryo transfers<br>in women with CD) N=554 <sup>a</sup>     | Unexposed cohort (embryo transfers<br>in non-IBD women) N=148,540 <sup>b</sup>  | Crude OR<br>(95% CI) | Adjusted OR <sup>c</sup><br>(95% CI) | Adjusted OR <sup>d</sup><br>(95% CI) |
| Live birth         |  |   |                      |                                      |                                      |
| Yes, N (%)         | 94 (16.97)   | 35,321 (23.78)  | 0.62 (0.48-0.80)     | 0.61 (0.47-0.79)                     | 0.77 (0.52-1.14)                     |
| No, N (%)          | 460 (83.03)  | 113,219 (76.22)   |                      |                                      |                                      |

<sup>a</sup>Number of women in exposed UC cohort = 432, and in exposed CD cohort = 182. Intraclass Correlation Coefficient (ICC)= 0.13

<sup>b</sup>Number of women in unexposed cohort = 52,489

<sup>c</sup>Adjusted for: Charlson Index, women's age, calendar year of treatment, type of treatment (IVF, ICSI, FER), cause of infertility (female factor, male factor, or mixture of factors/idiopathic). Number of obs.=137,640, number of women=52,015.

<sup>d</sup>Extended model using data from 2006, adjusted for: Charlson Index, women's age, calendar year of treatment, type of treatment (IVF, ICSI, FER), cause of infertility (female factor, male factor, or mixture of factors/idiopathic), BMI, partner's age, smoking at the time of embryo transfer, and alcohol. Number of obs.= 48,575, number of women= 20,082.

## SUB-ANALYSEIS ON THE IMPACT OF UC OR CD SURGERY ON THE CHANCE OF LIVE BIRTH

The overall results regarding a possible impact of UC or CD surgery before infertility treatment on the chance of live birth are given in Table 3. For UC, the result suggested no negative impact of former surgery on the chance of live birth. The result was very robust across the crude and adjusted OR (crude OR=0.92, 95% CI: 0.64-1.31, and adjusted model OR=0.91, 95% CI: 0.61- 1.36). When examining all types of UC-relevant surgical procedures on the three latest dates of operations for all UC patients before their first-time ART cycle we found that 195 procedures were performed and distributed as follows (the most common procedure first): a) Total colon resection (no ostomy), N=60 (30.8%), b) Total colon resection + ileostomy (rectum left in place), N=53 (27.2%), c) Rectal/anus resection, N=45 (23.1%), d) Ileal pouch anal anastomosis, N=36 (18.5%), and e) Partial colon resection (no ostomy), N=1 (0.51%).

For CD, the results suggested a negative impact of former surgery on the chance of live birth. Women with former surgery for CD were less likely to have a live birth after an embryo transfer than women who had not had surgery (crude OR=0.56; 95% CI 0.33-0.93, and adjusted OR=0.51; 95% CI 0.29-0.91). All surgeries in women with CD from the three latest operation dates before the first embryo transfer were identified as: "Ileocecal resection": N=50 (24.3 %), "Ileocolonic resection (more than ileocecal)": N=44 (21.4 %), "small bowel resection or stricturoplasty": N=42 (20.4 %) "Stomas but rectum left in place": N=26 (12.6 %), "Colon resection": N=23 (11.2 %) "Rectal/Anus resection": N=20 (10.2%).

**Table 3.** Crude and adjusted odds ratios (OR), with 95% confidence interval (95% CI), for live birth in the cohort of ART treatments in women with UC who *had* undergone surgery before infertility treatment, compared to ART treatments in UC women who *had not* undergone surgery before infertility treatment; similar results for women with CD (January 1, 1994 through 2013)

| Ulcerative colitis |  |  |                   |                                   |
|--------------------|--|--|-------------------|-----------------------------------|
|                    | Exposed cohort (embryo transfers in UC women who had prior surgery) N=469 <sup>a</sup> | Unexposed cohort (embryo transfers in UC women who had no prior surgery) N= 891 <sup>a</sup> | Crude OR (95% CI) | Adjusted OR <sup>c</sup> (95% CI) |
| Live birth         |  |  |                   |                                   |
| Yes, N (%)         | 89 (18.98)   | 183 (20.54)  | 0.92 (0.64-1.31)  | 0.91 (0.61-1.36)                  |
| No, N (%)          | 380 (81.02)  | 708 (79.46)  |                   |                                   |
| Crohn's disease    |  |  |                   |                                   |
|                    | Exposed cohort (embryo transfers in CD women who had prior surgery) N=355 <sup>b</sup> | Unexposed cohort (embryo transfers in CD women who had no prior surgery) N=199 <sup>b</sup>  | Crude OR (95% CI) | Adjusted OR <sup>c</sup> (95% CI) |
| Live birth         |  |  |                   |                                   |
| Yes, N (%)         | 50 (14.08)   | 44 (22.11)   | 0.56 (0.33-0.93)  | 0.51 (0.29-0.91)                  |
| No, N (%)          | 305 (85.92)  | 155 (77.89)  |                   |                                   |

<sup>a</sup>Number of women in exposed UC cohort = 130, and in the unexposed cohort = 303. Intraclass Correlation Coefficient (ICC) = 0.17.

<sup>b</sup>Number of women in exposed CD cohort = 99, and in the unexposed cohort = 88. Intraclass Correlation Coefficient (ICC) = 0.11.

<sup>c</sup>Adjusted: duration of disease (UC or CD), Charlson index, women's age, calendar year of treatment, type of treatment (IVF, ICSI, FER), cause of infertility (female factor, male factor, or mixture of factors/idiopathic). UC analyses: Number of obs.= 1,276, number of women= 427. CD analyses: Number of obs.= 499, number of women= 178.

## ADVERSE BIRTH OUTCOMES (SECONDARY OUTCOMES)

The results on adverse birth outcomes are given in Table 4 including both singletons and multiple births. Children by UC women had a significantly increased risk of preterm birth when compared to women without IBD (OR=5.29, 95% CI: 2.41-11.63). The relative risk of LBW at term and CAs were OR=1.48 (95% CI: 0.69-3.13) and OR=1.52 (95% CI: 0.87-2.64), respectively. Children by women with CD had no significantly increased risk of preterm birth, LBW at term, or CAs when compared to children by women without IBD (preterm birth: adjusted OR=0.44; 95% CI: 0.09-2.21; LBW at term: adjusted OR=1.41; 95% CI: 0.40-4.89; CAs: adjusted OR=0.59; 95% CI: 0.19-1.79).

In a sub-analysis we estimated the risk of adverse birth outcomes among only singletons and the results are given in Table 5. Among singletons delivered by women with UC, the relative risks for LBW at term and CAs were close to unity, and the relative risk of preterm birth was OR=1.80 (95% CI: 0.49-6.62). For children delivered by women with CD, we still did not find significantly increased risk of preterm birth, LBW at term, or CAs.

**Table 4.** Crude and adjusted odds ratios (OR), with 95% confidence interval (95% CI), for adverse birth outcomes in the study cohorts of children after ART in women with UC compared to children after ART in women without IBD; similar results in women with CD (January 1, 1994 through 2013)

| Ulcerative colitis               |   |   |                   |                                   |
|----------------------------------|---|---|-------------------|-----------------------------------|
|                                  | Exposed cohort <sup>a</sup> (embryo transfers in women with UC) | Unexposed cohort <sup>b</sup> (embryo transfers in non-IBD women) | Crude OR (95% CI) | Adjusted OR <sup>f</sup> (95% CI) |
| <b>Preterm birth<sup>d</sup></b> |   |   |                   |                                   |
| Yes, number (%)                  | 100 (30.77)   | 9,708 (23.00)   | 3.53 (1.72-7.22)  | 5.29 (2.41-11.63)                 |
| No, number (%)                   | 225 (69.23)   | 32,493 (77.00)  |                   |                                   |
| <b>LBW at term<sup>e</sup></b>   |   |   |                   |                                   |
| Yes, number (%)                  | 13 (5.75)   | 1,802 (5.55)  | 1.07 (0.49-2.30)  | 1.48 (0.69-3.13) <sup>g</sup>     |
| No, number (%)                   | 213 (94.25)   | 30,684 (94.45)  |                   |                                   |
| <b>Congenital abnormalities</b>  |   |   |                   |                                   |
| Yes, number (%)                  | 61 (18.83)  | 6,652 (15.73)   | 1.29 (0.77-2.17)  | 1.52 (0.87-2.64) <sup>g</sup>     |
| No, number (%)                   | 263 (81.17)   | 35,643 (84.27)  |                   |                                   |
| Crohn's disease                  |   |   |                   |                                   |
|                                  | Exposed cohort <sup>c</sup> (embryo transfers in women with CD) | Unexposed cohort <sup>b</sup> (embryo transfers in non-IBD women) | Crude OR (95% CI) | Adjusted OR <sup>f</sup> (95% CI) |

| Preterm birth <sup>d</sup> |            |                |                  |                               |
|----------------------------|------------|----------------|------------------|-------------------------------|
| Yes, number (%)            | 18 (16.98) | 9,708 (23.00)  | 0.42 (0.09-1.93) | 0.44 (0.09-2.21)              |
| No, number (%)             | 88 (83.02) | 32,493 (77.00) |                  |                               |
| LBW at term <sup>e</sup>   |            |                |                  |                               |
| Yes, number (%)            | 5 (5.62)   | 1,802 (5.55)   | 0.99 (0.28-3.49) | 1.41 (0.40-4.89) <sup>g</sup> |
| No, number (%)             | 84 (94.38) | 30,684 (94.45) |                  |                               |
| Congenital abnormalities   |            |                |                  |                               |
| Yes, number (%)            | 13 (12.15) | 6,652 (15.73)  | 0.70 (0.27-1.84) | 0.59 (0.19-1.79) <sup>g</sup> |
| No, number (%)             | 94 (87.85) | 35,643 (84.27) |                  |                               |

Intraclass Correlation Coefficient (ICC): Preterm ICC = 0.82, LBW ICC = 0.54, CA ICC = 0.62.

<sup>a</sup>Number of obs. (women), Preterm-UC: 325 (231), LBW-UC: 226 (177), CA-UC: 324 (230).

<sup>b</sup>Number of obs. (women), Preterm-non-IBD: 42,201 (29,898), LBW-non-IBD: 32,486 (24,918), CA-non-IBD: 42,295 (29,968)

<sup>c</sup>Number of obs. (women), Preterm-CD: 106 (78), LBW-CD: 89 (68), CA-UC: 107 (79)

<sup>d</sup>Birth before 37 completed weeks of pregnancy

<sup>e</sup>Birth weight < 2500 g in children born at gestational age ≥ 37 weeks

<sup>f</sup>Adjusted for: women's age, parity, type of treatment (IVF, ICSI, FER), calendar year of treatment, cause of infertility (female factor, male factor, or mixture of factors/idiopathic), and smoking during pregnancy.

<sup>g</sup>Also adjusted for singleton birth/multiple births

**Table 5.** Crude and adjusted Odds ratios (OR), with 95% confidence interval (95% CI), for adverse birth outcomes in singletons after ART in women with UC compared to singletons after ART in in women without IBD; similar results in women with CD (January 1, 1994 through 2013)

| Ulcerative colitis         |   |   |                   |                                   |
|----------------------------|---|---|-------------------|-----------------------------------|
|                            | Exposed cohort <sup>a</sup> (embryo transfers in women with UC) | Unexposed cohort <sup>b</sup> (embryo transfers in non-IBD women) | Crude OR (95% CI) | Adjusted OR <sup>f</sup> (95% CI) |
| Preterm birth <sup>d</sup> |   |   |                   |                                   |
| Yes, number (%)            | 33 (15.14)  | 2,593 (9.20)  | 1.61 (0.48-5.39)  | 1.80 (0.49-6.62)                  |
| No, number (%)             | 185 (84.86)   | 25,589 (90.80)  |                   |                                   |
| LBW at term <sup>e</sup>   |   |   |                   |                                   |
| Yes, number (%)            | 3 (1.61)  | 496 (1.94)  | 0.81 (0.24-2.81)  | 1.12 (0.32-3.98)                  |
| No, number (%)             | 183 (98.39)   | 25,122 (98.06)  |                   |                                   |
| Congenital abnormalities   |   |   |                   |                                   |
| Yes, number (%)            | 27 (12.44)  | 3,721 (13.16)   | 0.94 (0.61-1.43)  | 1.14 (0.74-1.76)                  |
| No, number (%)             | 190 (87.56)   | 24,547 (86.84)  |                   |                                   |
| Crohn's disease            |   |   |                   |                                   |
|                            | Exposed cohort <sup>c</sup> (embryo transfers in women with CD) | Unexposed cohort <sup>b</sup> (embryo transfers in non-IBD women) | Crude OR (95% CI) | Adjusted OR <sup>f</sup> (95% CI) |



|                            |            |                |                   |                   |
|----------------------------|------------|----------------|-------------------|-------------------|
| Preterm birth <sup>d</sup> |            |                |                   |                   |
| Yes, number (%)            | 8 (10.00)  | 2,593 (9.20)   | 1.03 (0.10-10.30) | 0.83 (0.05-13.55) |
| No, number (%)             | 72 (90.00) | 25,589 (90.80) |                   |                   |
| LBW at term <sup>e</sup>   |            |                |                   |                   |
| Yes, number (%)            | 1 (1.37)   | 496 (1.94)     | 0.69 (0.08-5.75)  | 0.91 (0.11-7.94)  |
| No, number (%)             | 72 (98.63) | 25,122 (98.06) |                   |                   |
| Congenital abnormalities   |            |                |                   |                   |
| Yes, number (%)            | 10 (12.35) | 3,721 (13.16)  | 0.92 (0.46-1.84)  | 0.72 (0.32-1.64)  |
| No, number (%)             | 71 (87.65) | 24,547 (86.84) |                   |                   |

Intraclass Correlation Coefficient (ICC): Preterm ICC = 0.99, LBW ICC = 0.41, CA ICC = 0.09.

<sup>a</sup>Number of obs. (women), Preterm-UC: 218 (187), LBW at term-UC: 186(160), CA-UC: 217 (186).

<sup>b</sup>Number of obs. (women), Preterm-non-IBD: 28,182 (24,169), LBW-non-IBD: 25,618 (22,142 ), CA-non-IBD: 28,268 (24,283)

<sup>c</sup>Number of obs. (women), Preterm-CD: 80 (70), LBW at term-CD: 73 (64), CA-CD: 81 (71)

<sup>d</sup>Birth before 37 completed weeks of pregnancy

<sup>e</sup>Birth weight < 2500 g in children born at gestational age ≥ 37 weeks

<sup>f</sup>Adjusted for: women's age, parity, type of treatment (IVF, ICSI, FER), calendar year of treatment, cause of infertility (female factor, male factor, or mixture of factors/idiopathic), and smoking during pregnancy.

## **DISCUSSION**

In this nationwide study with data from a span of 20 years, we found that ART treatments in UC and CD women had a decreased chance of leading to live birth per cycle, compared to ART treatments in women without IBD. Comparing embryo transfers in CD women who had had surgery before infertility treatment to embryo transfers in CD women without prior surgery, we found a decreased chance of live births in women who had had surgery. There was no further effect of surgery on live births in women with UC. The risk of preterm birth in children after ART by women with UC was 5-fold increased compared to children after ART by women without IBD, but the risk vanished when evaluating only singletons.

This is the first study, based on nationwide data, analysing the chance of live birth after ART treatment in women with UC and CD. Earlier, the outcome of ART treatment had been studied in 71 UC and 49 CD female patients from two tertiary care centers.[17,18] The 71 UC women and 49 CD women were compared to 470 controls from the general infertile population, and the proportion of live births after the first ART cycle was similar among controls (30.2%) and patients with UC (33.8%) and CD (30.6%). Our overall results differ from these findings. We found that among 1,360 embryo transfers in women with UC, and 554 embryo transfers in women with CD, there was a decreased chance of live birth per cycle, compared to 148,540 embryo transfers in women without IBD. It is worth noticing that this result is very robust as the crude OR and the ORs from two adjusted models in both UC and CD were close. Some might argue that our finding of a decreased chance of live birth per cycle in UC and CD women may not be related to the IBD itself but impacted by IBD related factors such as disease activity and/or IBD medications. The results in our study do not indicate whether the decreased chance of live birth per cycle in UC and CD women is related to the disease itself or to factors closely related to IBD. It is unlikely that disease activity, at least at the stages of fertilization and implantation, is the factor responsible for our results as

women with IBD in Denmark are not referred for ART treatment unless they have quiescent disease. However, since this is a large register-based study and it was not possible to review individual charts, we cannot rule out a negative effect of active IBD, especially during a pregnancy. In addition, we were unable to look at medication use in our IBD patients, and even if, theoretically, we had information on IBD medication, we could not adjust for such information in our main analyses as similar medication was not used in the unexposed cohort. Furthermore, as far as we can determine, no studies have indicated that underlying maternal medical treatment impacts the result of ART treatments. It is reassuring that in several studies adalimumab, given prior to embryo transfer, improves the success of ART in women with immune-mediated infertility.[31-33].

There are some emerging results on the rates of adverse conception and pregnancy outcomes in general, without the use of ART, in women with IBD. Mahadevan's study of the Kaiser database in Northern California [34] and another recent meta-analysis [35] indicated that women with IBD have adverse conception and pregnancy outcomes as well as an increased risk of pregnancy complications. The outcome of live birth can be affected at the stages of fertilization, implantation and maintenance of the pregnancy throughout each trimester, but there is little knowledge on the factors that decrease the chance of a live birth or the most vulnerable stage (or stages) following ART treatment in women with IBD. It is possible that women with UC and CD have subclinical inflammation or increased immune factors not yet elaborated [36] such as antiphospholipid, antinuclear, antithyroid, and antisperm antibodies or other undiscovered autoantibodies that decrease fertility, and therefore underlying maternal factors may impact the chance of a live birth after ART. In addition, initial research is now being done on microbiome changes during pregnancy in non-IBD women. One study including 91 pregnant women showed significant changes in the gut microbiota over the course of pregnancy.[37] Specifically, Koren et al. observed an overall increase in Proteobacteria and Actinobacteria from the first to third

trimester, a decrease in *Faecalibacterium* and a decrease in the diversity of the microbiota.[38] During pregnancy, a woman's immune system must adapt to avoid rejection of the fetus. At this time, the relationship between the observed changes in the microbiome and the immune system and the role of the bacteria are not known. It has been hypothesized that the changes in microbiome may promote weight gain or may stimulate the innate immune response, the latter of which may affect the disease course during pregnancy. In addition, the impairment of innate immunity that has previously been reported in IBD may improve during pregnancy with changes in the microbiome and hormones that affect this immune response. The mechanism by which disease inflammation may be increased or decreased during pregnancy is not entirely understood.[39,40] In pregnancy, the T helper 2 cell (Th2) responses are increased. CD is typically characterized by an exaggerated CD4 T helper 1 (Th1) cell response. The increased Th2 response in pregnancy may affect the Th1 response that is upregulated in CD, resulting in decreased risk of flare. Since UC is a Th2-driven disease and Th2 responses are increased during pregnancy, UC patients may have an increased risk of a flare.[41]

Regarding the impact of surgery, it was suggested in the study by Pabby et al, [16] based on the same 71 UC patients as the study from Oza et al, [17] that the cumulative live birth rate after six ART cycles was comparable in UC women with IPAA (22 patients) and without IPAA (49 patients), but the study was descriptive in nature and did not take confounders into consideration. In our study, 469 embryo transfers in UC women with prior surgery were compared to 891 embryo transfers in UC women without prior surgery, and both the crude and the adjusted OR were very close to unity indicating no negative impact of former UC surgery on the chance of live birth per cycle. The effect of CD surgery on the chance of live birth after ART treatment has never previously been studied. In our study, 355 embryo transfers in CD women with prior surgery were compared to 199 transfers in CD women without prior surgery and both the crude and adjusted OR

showed a significant decrease in live births after CD surgery. There are several possible explanations for these results. First, women with UC may have an increased risk of a flare during pregnancy due to the increased Th2 response. An ileoanal pouch anastomosis or ileostomy is a type of “cure” which removes all present inflammation that could affect a pregnancy. Therefore surgery in UC women might not have a negative impact on live birth especially since ART bypasses pelvic adhesions. Conversely, surgery for CD often does not remove all inflammation and CD commonly recurs after surgery. It is also possible that CD patients who need surgery have increased disease severity which would account for worse ART outcomes. These results are very important when counselling UC and CD women concerning surgery if they are also considering a pregnancy.

Our study is the first to examine the risk of adverse birth outcomes in children after ART treatment in UC and CD women, and therefore our results cannot be compared with others. Our results suggest a significant 5-fold increased risk of preterm birth in children after ART treatment in UC women when the OR was adjusted for important confounders such as women’s age, parity, type of ART treatment, calendar year of treatment, cause of infertility, and smoking during pregnancy. Analysing the risk of preterm birth in children among only singletons, there was no significant increase. We did not find a significantly increased risk of LBW at term or CAs. CD women did not have an increased risk of adverse birth outcomes after ART treatment.

The precision and the validity of our results depend on the size of the study, accurate classification of exposure, quality of outcome data, and the ability to take into account the influence of confounders. According to these aspects our study has several strengths. First, the study is based on a nationwide study population of all Danish UC and CD women who have received ART treatment (and all other ART treated women as controls) as we had access to the ART registry that is based on mandatory reporting of all individual treatment cycles. Second, the nature of the health registries allowed a 20 year-long study period and a large cohort of ART treatments providing us

with high statistical power. Third, the data from the used health care registries have a very high completeness and validity, i.e. according to exposure assessment (diagnoses of UC and CD), the completeness of diagnoses of UC and CD has been examined in a Danish study using the pathology system as a reference standard – showing that of all patients with a confirmed diagnosis of UC or CD, 94% were included in the NPR, in which we had access to obligatory registration of UC and CD diagnoses from both hospitals and outpatient visits.[42] Furthermore, the overall validity of diagnosis of UC in the NPR was 94% and for CD 97% in patients diagnosed at specialized departments.[42] Regarding our outcome measurements (live birth and adverse birth outcomes) the data from the MBR have both very high completeness and validity as all newborn children are registered in the MBR and the variables used as outcomes in this study are of high validity.[43] Fourth, we had information on several confounders, including Charlson comorbidity Index, women's age, calendar year of treatment, type of infertility treatment, cause of infertility, BMI, partner's age, smoking at the time of embryo transfer, smoking during pregnancy, and alcohol. Data on type of performed surgeries in UC and CD patients are of high quality, as data from the NPR on surgical procedures have positive predictive values of 94-100%. Finally, our outcome data were obtained independently of the hypotheses investigated and exposure measurement, preventing differential misclassification of the outcome measurements.

The study also has limitations. We lacked detailed information on the severity of UC and CD and details regarding the specific location of UC and CD lesions, although such information would only be relevant for the analysis comparing sub-cohorts of UC or CD women. As discussed above, we had no information on disease activity and medical therapy for underlying maternal diseases in our cohorts. A further limitation is that we were not able to assess adverse birth outcomes among stillborn or very early abortions (including those due to antenatal diagnoses of CAs). Thus we might have underestimated the 'true' relative risks, if CA is more prevalent in ART

treatments in UC and CD women ending in stillbirth or very early abortions compared to women without IBD.

We conclude that women with UC and CD have a decreased chance of a live birth per ART treatment cycle compared to women without IBD. In addition, CD women, but not UC women, with prior surgery have a decreased chance of a live birth per cycle. These findings might be related to the disease itself or to factors closely related to UC and CD and call for additional studies within this area. Our results further suggest that increased prenatal observation in UC pregnancies after infertility treatment should be recommended. Hopefully, these results will inform treatment decisions regarding the use of ART in UC and CD and particularly recommendations for CD surgery and timing of attempts at conception. Future research will hopefully elucidate the mechanism of UC, CD, and CD surgery on conception and maintenance of pregnancy. Also, from a counseling point of view, it would be interesting to examine the “take home chance” of having a baby *per patient* where the analytic unit is the woman and not the cycle.

## **Contributors**

BMN: funding, conception, design, data collection, assistance with data analysis, interpretation of results, manuscript writing and editing, approved the final version.

PVL: design, data collection, data analysis, interpretation of results, manuscript editing, approved the final version.

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## **Competing interests**

None

## **Permissions**

The study was approved by the Danish Data Protection Agency (j.nr. 2014-41-3466). According to Danish law, there are no ethical approvals of register-based studies necessary.



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