

# Corticosteroids Prior to Embryo Transfer in Assisted Reproduction in Women with Crohn's Disease and Ulcerative Colitis – A Nationwide Cohort Study

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**Purpose:** Former studies have suggested that women with Crohn's disease (CD) and ulcerative colitis (UC) have a decreased chance of a live born child after assisted reproductive technology (ART) treatment. It is debated whether corticosteroids before ART may improve outcomes, either by decreasing inflammatory bowel disease-related inflammation or increasing endometrial receptivity. We examined the efficacy of corticosteroids before embryo transfer in women with CD and UC.

**Patients and Methods:** Our cohort study is based on nationwide Danish health registries, comprising women with CD and UC receiving an embryo transfer (1 January 2006 through 2017). Exposed cohorts constituted women with CD and UC who had received corticosteroids within three months before embryo transfer, and the unexposed cohorts women with CD and UC who did not receive corticosteroids. Our primary outcome was live birth. We controlled for multiple covariates in the analyses.

**Results:** We examined 2408 embryo transfers. In patients with CD, 114 embryo transfers were preceded by a corticosteroid prescription, and 964 were not. The corresponding numbers in UC were 122 and 1208, respectively. The adjusted odds ratio (aOR) for live birth in women with CD receiving corticosteroids before embryo transfer, relative to women with CD not receiving corticosteroids, was 0.89 (95% CI 0.49–1.63). The corresponding aOR in UC was 0.98 (95% CI 0.55–1.74).

**Conclusion:** Corticosteroids prior to ART in women with CD and UC did not increase the chance of a live born child. The exact impact of corticosteroids prior to embryo transfer in patients with CD and UC still remains to be determined.

**Keywords:** corticosteroids, Crohn's disease, ulcerative colitis, inflammatory bowel disease, assisted reproductive technology, ART, assisted reproduction

## Introduction

Endometrial receptivity is the key element in assisted reproductive technology (ART) treatment, and a successful implantation of the embryo is a result of complex processes dependent upon many variables, most of which are still not adequately defined.<sup>1,2</sup> A substantial proportion of patients fail to become pregnant following ART treatment, and these failures seem to be concentrated across all age groups in specific subgroups of patients. The failures may be due to a limitation of current tools to select the most competent embryo or even more likely due to systemic

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factors, such as inflammation, that affect the maternal environment and negatively impact an embryo's ability to implant.<sup>2</sup> Several attempts have therefore been made to find effective therapies to improve embryo implantation, and a number of candidate drugs have been examined including systemic corticosteroids,<sup>3–5</sup> combined prednisolone and low molecular weight heparin,<sup>1</sup> heparin,<sup>6</sup> low dose aspirin alone and in combination with prednisolone,<sup>5</sup> and immunoglobulin and prednisone.<sup>7</sup> However, there have been no general recommendations in this area and more epidemiological evidence has been requested.<sup>2,8</sup>

In former studies we have examined the efficacy of ART treatment in women with Crohn's disease (CD), ulcerative colitis (UC), and rheumatoid arthritis.<sup>9,10</sup> These suggest a reduced chance of a live birth after ART treatment in women with these diseases, compared to other women receiving ART treatment. Our data also indicate that the problem might be related to impaired embryo implantation.<sup>9–11</sup> It is possible that increased systemic inflammation in patients with CD, UC and rheumatoid arthritis might affect ART success either via decreased endometrial receptivity or another mechanism. In women with rheumatoid arthritis, we examined the impact of corticosteroids prior to embryo transfer, and although not statistically significant, our data suggested that corticosteroids prescribed before embryo transfer improved the chance of a live birth.<sup>10</sup> The impact of corticosteroids prior to ART treatment in patients with CD and UC however, has never been studied.

We hypothesized that treatment with corticosteroids prior to embryo transfer would increase the chance of a live born child, and we examined this question in a nationwide Danish population of women with CD and UC receiving ART treatment. Specifically, we examined the association between prescriptions of corticosteroids within three months before embryo transfer in women with CD and UC, compared to women with CD and UC not receiving corticosteroids prior to embryo transfer, and i) delivery of a live born child (primary outcome), and ii) positive biochemical pregnancy and positive clinical pregnancy (secondary outcomes).

## Materials and Methods

### Design and Setting

This study is a nationwide cohort study. In Denmark we have a uniform organized health care system with free

access to the tax-supported health care services, and the population comprises approximately 5.6 million inhabitants, > 90% Caucasians. All citizens have a unique civil registration number, which is assigned to all residents at birth, and this number is used in all Danish registries for valid record linkage on an individual level.

### Data Sources

In this study we used a nationwide population-based approach, and we obtained data from the following registries: i) data on all ART procedures from the Danish ART Registry.<sup>12,13</sup> The ART registry was established on 1 January 1994, and records all treatment cycles performed in public and in private clinics, and registration of all ART treatments is mandatory for all fertility clinics in Denmark, ii) data from The Danish National Patient Registry (NPR) on patients with diagnoses of CD and UC. The registry includes records of all discharges from Danish hospitals since 1977 and all outpatient visits since 1995. The information includes the 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),<sup>14,15</sup> iii) data on prescriptions from the nationwide Danish prescription registry. Since 1 January 1995, data on outpatient drug prescriptions have been available from the prescription registry maintained by the Danish Medicine Agency and all pharmacies send key electronic data to the registry (key variables are the type of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) Classification system, and the date of filed prescription),<sup>16</sup> iv) data from the Danish Medical Birth Registry (MBR) provided information on our primary outcomes, ie information on live birth. The registry has recorded data on all births in Denmark since 1973, comprising data on the mother, the birth, and the child,<sup>17,18</sup> and v) data from The Civil Registration System on death and immigration.<sup>19</sup>

Data on our secondary outcomes, ie on biochemical and clinical pregnancy was collected from the ART registry and data on confounders from the NPR, the MBR, the prescription registry and the ART registry.

### Study Population and Study Period

We had two study populations, one comprised all women with CD registered in the ART registry with at least one embryo transfer during the study period of 1 January 2006–30 December 2017, and a corresponding

study population included women with UC. All women had a valid civil registration number and were available for follow up in Denmark.

Identification of patients with CD and UC was based on information from the NPR. All eligible patients with CD had a discharge history of CD (ICD-8 codes: 563.01; ICD-10 codes: DK50.x) before the date of embryo transfer, and if a woman with a CD diagnosis had a former diagnosis of UC she was only included in the cohort of CD women if the latest given diagnosis was CD. Similarly, all eligible patients with UC had a discharge history of UC from any hospital in Denmark (ICD-8 codes: 563.19, 569.04; ICD-10 codes: DK51.x) before the date of embryo transfer, and if a woman with UC had a former diagnosis of CD she was only included if the latest given diagnosis was UC.

We included all embryo transfers in women with CD and UC based on information on the ART procedures in this study, ie in vitro fertilization (IVF), with or without fertilization with intracytoplasmic sperm injection (ICSI), and transfer of frozen-thawed (FET) embryos. Infertile couples and single women are offered up to three reimbursed IVF/ICSI treatment cycles with fresh embryos, and an unlimited number of frozen embryo transfers, as long as the woman's age does not exceed 40 years. We used data from the ART registry from 2006 to be able to include information on confounders such as mother's body mass index, partner's age, and maternal smoking at the time of embryo transfer, and alcohol information, and because we needed complete data on the outcome of clinical pregnancies.

## The Exposed and Unexposed Cohorts

The analytic unit is embryo transfer. The exposed cohorts constituted i) embryo transfers in women who had a discharge history of CD before the date of embryo transfer and who had reimbursed a prescription for steroids within three months before the date of embryo transfer, and ii) embryo transfers in women who had a discharge history of UC before the date of embryo transfer and who had reimbursed a prescription for steroids within three months before the date of embryo transfer.

Steroids are available only by prescription in Denmark and prescriptions of oral corticosteroids were used according to ATC codes H02AB02 dexamethasone, H02AB04 methylprednisolone, H02AB06 prednisolone, H02AB07 prednisone, H02AB09 hydrocortisone. The unexposed cohorts constituted i) embryo transfers in women with

CD who had not reimbursed a prescription for corticosteroids within three months before the date of embryo transfer, and ii) embryo transfers in women with UC who had not reimbursed a prescription for corticosteroids within three months before the date of embryo transfer.

The same woman could thus contribute to both cohorts if prior to one cycle, she received a corticosteroid prescription and in another cycle, she did not.

## 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).<sup>9,20</sup> The secondary outcomes were a biochemical pregnancy (positive pregnancy test, positive human chorionic gonadotropin (hCG) at 14–16 days after embryo transfer) and a clinical pregnancy (ie positive ultrasound examination 7–8 weeks after embryo transfer).

## Data on Confounders

Covariates included in the regression models were selected a priori. Charlson Comorbidity Index was obtained from the NPR, calculated according to each embryo transfer and was based on diagnoses recorded during all previous hospitalizations since 1977.<sup>21</sup> Two index levels were defined, no comorbidity (Charlson Index 0), and some comorbidity (Charlson Index  $\geq 1$ ). From the MBR we obtained information on parity (0, +1). From the ART registry we used information on the women's age at the time of embryo transfer, calendar year of ART (2006–2009, 2010–2013, 2014–2017), type of ART treatment (IVF, ICSI, FET), cause of infertility (female factor, male factor, or mixture of factors/idiopathic), body mass index (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 obesity ( $\geq 30$  kg/m<sup>2</sup>)), partner's age, alcohol intake (yes/no), and smoking at the time of embryo transfer (yes/no). We retrieved data on medication for CD and UC from the prescription registry according to azathioprine/mercaptopurine (ATC codes: L04A X01, azathioprine, and L01B B02, mercaptopurine), and aminosalicylic acids (ATC code: A07EC), and from the NPR we retrieved data on the use of TNF- $\alpha$  inhibitors (recorded as procedure codes in the NPR).

## Statistical Analyses

We constructed contingency table for the main study variables according to the exposed and unexposed cohorts of embryo transfers in women with CD and UC separately. 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 our primary and secondary outcomes following embryo transfers in exposed women, relative to unexposed women, and the model accounted for multiple embryo transfers in the same woman. In the regression model we adjusted for Charlson Index, women's age at the time of embryo transfer, calendar period of ART treatment, type of infertility treatment, cause of infertility, body mass index, partner's age, maternal smoking at the time of embryo transfer, alcohol, and use of medications for chronic inflammatory bowel disease (IBD). The data on medications, used within six months prior to the embryo transfer, in the cohorts of women with CD and UC included azathioprine, mercaptopurine, aminosalicic acids, and TNF- $\alpha$  inhibitors.

In sub-analyses I we combined the cohorts of women with CD and UC into just one IBD cohort, which increased the statistical precision, and we calculated the adjusted OR for live birth, biochemical, and clinical pregnancy. These analyses were adjusted for the same confounders as our main analyses.

In sub-analyses II, we estimated the chance of a live born child among only those embryo transfers that ended in a positive clinical pregnancy, and again we compared women with IBD having corticosteroids within three months prior to embryo transfer to women with IBD not having corticosteroids prior to embryo transfer.

All analyses were conducted using Stata 15 software (StataCorp LP, College Station, TX, USA).

## Ethical Considerations

The study was approved by the Danish Data Protection Agency under the Region of Southern Denmark (journal number 17/37434). According to Danish law, there are no ethical approvals of register-based studies necessary.

## Results

We included 2408 embryo transfers in women with CD and UC. In patients with CD, 114 embryo transfers were preceded by the use of corticosteroid prescription (exposed), and 964 were not (unexposed). In patients

with UC, 122 embryo transfers were preceded by the use of corticosteroids (exposed), and 1208 were not (unexposed). [Table 1](#) displays the characteristics for all study cohorts. There were no major differences between exposed and unexposed according to maternal age, paternal age, maternal smoking, parity and co-morbidity, in cohorts of CD and UC, respectively. In all cohorts, most of the reasons for ART treatment were due to a mixture of maternal and paternal factors/idiopathic, most patients received IVF or ICSI, and most mothers were of normal weight (with the exception of exposed women with CD where the proportions of normal weight and overweight were the same). In women with CD receiving corticosteroids prior to embryo transfer, 7.9% used azathioprine/6-mercaptopurine, 10.5% used 5-aminosalicylates, and 21.1% received anti-TNF treatment within a six-month period prior to embryo transfer. The corresponding proportions, in women with CD not receiving corticosteroids prior to embryo transfer, were 8.9%, 5.5% and 9.6%, respectively ([Table 1](#)). In women with UC receiving corticosteroids prior to embryo transfer, 4.9% used azathioprine/6-mercaptopurine, 30.3% used 5-aminosalicylates, and 2.5% had biologic treatment within a six-month period prior to embryo transfer. The corresponding proportions, in women with UC having no corticosteroids prior to embryo transfer, were 3.9%, 24.8% and 1.2%, respectively ([Table 1](#)).

In embryo transfers in women with CD receiving corticosteroids within three months prior to embryo transfer, 20.2% delivered a live born child, versus 22.5% in embryo transfers of women with CD receiving no corticosteroids. The corresponding adjusted OR for live birth was 0.89 (95% CI 0.49–1.63), [Table 2](#). In embryo transfers in women with ulcerative colitis receiving corticosteroids within three months prior to embryo transfer, 16.4% ended in a live born child, versus 20.1% in embryo transfers of women with CD receiving no corticosteroids. The corresponding adjusted OR for live birth was 0.98 (95% CI 0.55–1.74), [Table 3](#).

The results for our secondary outcomes, biochemical and clinical pregnancy after embryo transfers, in women with CD are shown in [Table 4](#). In women with CD receiving corticosteroids within three months prior to embryo transfer 34.8% had a positive hCG, versus 31.8% in women with CD not receiving corticosteroids. The adjusted OR for a positive hCG was 1.04 (95% CI 0.61–1.77). The adjusted OR for a clinical pregnancy was 0.66 (95% CI 0.22–1.95), [Table 4](#). The results for biochemical

**Table I** Descriptive Characteristics of the Study Cohorts of Women with Crohn's Disease and Ulcerative Colitis with and Without Prescriptions of Corticosteroids Three Months Prior to Embryo Transfer

Characteristics	Crohn's Disease				Ulcerative Colitis			
	Exposed Cohort (Steroid Prior to Embryo Transfers) <sup>a</sup>		Non-Exposed Cohort (No Steroid Prior to Embryo Transfers) <sup>b</sup>		Exposed Cohort (Steroid Prior to Embryo Transfers) <sup>c</sup>		Non-Exposed Cohort (No Steroid Prior to Embryo Transfers) <sup>d</sup>	
Number of embryo transfers (women)	114	(60)	964	(354)	122	(66)	1208	(414)
Age at embryo transfer Median (25–75% percentiles)	35.5	(32–38)	33	(30–37)	36	(34–39)	35	(31–38)
Partner's age at embryo transfer Median (25–75% percentiles)	36	(32–39)	35	(31–38)	37	(34–41)	36	(32–39)
Female/male factor infertility								
Female factor, N (%)	23	(20.2)	182	(18.9)	13	(10.7)	246	(20.4)
Male factor, N (%)	22	(19.3)	198	(20.5)	17	(13.9)	249	(20.6)
Mixture of factors/idiopathic, N (%)	69	(60.5)	584	(60.6)	92	(75.4)	713	(59.0)
Type of ART treatment								
IVF, N (%)	59	(52.7)	395	(41.8)	48	(40.7)	550	(45.8)
ICSI, N (%)	33	(29.5)	315	(33.3)	47	(39.8)	361	(30.0)
FET, N (%)	20	(17.9)	235	(24.9)	23	(19.5)	291	(24.2)
BMI								
<18.5 (underweight), N (%)	3	(2.9)	22	(2.8)	5	(5.0)	34	(3.5)
18.5–24.9 (normal), N (%)	42	(41.2)	428	(55.2)	63	(62.4)	676	(70.6)
25.0–29.9 (overweight), N (%)	42	(41.2)	242	(31.2)	23	(22.8)	180	(18.8)
≥30.0 (obese), N (%)	15	(14.7)	83	(10.7)	10	(9.9)	68	(7.1)
Smoking at the time of embryo transfer								
Non-smoker, N (%)	96	(98.0)	686	(91.0)	102	(100.0)	910	(94.9)
Smoker, N (%)	2	(2.0)	68	(9.0)	0	(0.0)	49	(5.1)
Alcohol								
No, N (%)	65	(70.7)	458	(64.0)	60	(61.9)	466	(52.1)
Yes, N (%)	27	(29.3)	258	(36.0)	37	(38.1)	429	(47.9)
Calendar year of infertility treatment								
2006–2009, N (%)	21	(18.4)	254	(26.3)	16	(13.1)	391	(32.4)
2010–2013, N (%)	44	(38.6)	305	(31.6)	47	(38.5)	396	(32.8)
2014–2017, N (%)	49	(43.0)	405	(42.0)	59	(48.4)	421	(34.9)
Parity								
0, N (%)	51	(44.7)	414	(42.9)	40	(32.8)	401	(33.2)
1+, N (%)	63	(55.3)	550	(57.1)	82	(67.2)	807	(66.8)
Co-morbidity at embryo transfers								
No comorbidity, N (%)	89	(78.1)	777	(80.6)	99	(81.1)	1011	(83.7)
Some comorbidity, N (%)	25	(21.9)	187	(19.4)	23	(18.9)	197	(16.3)
Co-medication within 6 months prior to embryo transfer								
Azathioprine/mercaptopurine, N (%)	9	(7.9)	86	(8.9)	6	(4.9)	47	(3.9)
Aminosalicylic acid, N (%)	12	(10.5)	53	(5.5)	37	(30.3)	299	(24.8)
TNF- $\alpha$ inhibitors, N (%)	24	(21.1)	93	(9.6)	3	(2.5)	14	(1.2)

**Notes:** <sup>a</sup>Missing, age of partner (9.6%), fertility factor (0%), ART treatment (1.8%), parity (0%), BMI (10.5%), smoking at the time of embryo transfer (14.0%), alcohol (19.3%).

<sup>b</sup>Missing, age of partner (9.0%), fertility factor (0%), ART treatment (2.0%), parity (0%), BMI (19.6%), smoking at the time of embryo transfer (21.8%), alcohol (25.7%).

<sup>c</sup>Missing, age of partner (5.7%), fertility factor (0%), ART treatment (3.3%), parity (0%), BMI (17.2%), smoking at the time of embryo transfer (16.4%), alcohol (20.5%).

<sup>d</sup>Missing, age of partner (8.6%), fertility factor (0%), ART treatment (0.5%), parity (0%), BMI (20.7%), smoking at the time of embryo transfer (20.6%), alcohol (25.9%).



**Table 2** Live Birth in Women with Crohn's Disease Prescribed Corticosteroid Three Months Prior to Embryo Transfer, Compared to Those Without a Corticosteroid Prescription

	Exposed Cohort (Steroid Use Prior to Embryo Transfers) <sup>a</sup>		Unexposed Cohort (No Steroid Use Prior to Embryo Transfers) <sup>b</sup>		Crude OR (95% CI)	Adjusted OR (95% CI) <sup>c</sup>
<b>Live birth</b>						
Yes, N (%)	23	(20.2)	217	(22.5)	0.88 (0.54–1.46)	0.89 (0.49–1.63)
No, N (%)	91	(79.8)	747	(77.5)		

**Notes:** <sup>a</sup>Number of embryo transfers in the exposed cohort: 114 (number of women: 60). <sup>b</sup>Number of embryo transfers in the unexposed cohort: 964 (number of women: 354). <sup>c</sup>Adjusted for Charlson Index, women's age, calendar year of treatment, type of treatment (IVF, ICSI, FET), cause of infertility (female factor, male factor, or mixture of factors/idiopathic), BMI, partner's age, smoking, alcohol and use of IBD medication (azathioprine/mercaptopurine, Aminosalicic acid and TNF- $\alpha$  inhibitors) 6 months prior to embryo transfer.

**Table 3** Live Birth in Women with Ulcerative Colitis Prescribed Corticosteroid Three Months Prior to Embryo Transfer, Compared to Those Without a Corticosteroid Prescription

	Exposed Cohort (Steroid Use Prior to Embryo Transfers) <sup>a</sup>		Unexposed Cohort (No Steroid Use Prior to Embryo Transfers) <sup>b</sup>		Crude OR (95% CI)	Adjusted OR (95% CI) <sup>c</sup>
<b>Live birth</b>						
Yes, N (%)	20	(16.4)	243	(20.1)	0.85 (0.49–1.49)	0.98 (0.55–1.74)
No, N (%)	102	(83.6)	965	(79.9)		

**Notes:** <sup>a</sup>Number of embryo transfers in the exposed cohort: 122 (number of women: 66). <sup>b</sup>Number of embryo transfers in the unexposed cohort: 1208 (number of women: 414). <sup>c</sup>Adjusted for Charlson Index, women's age, calendar year of treatment, type of treatment (IVF, ICSI, FET), cause of infertility (female factor, male factor, or mixture of factors/idiopathic), BMI, partner's age, smoking, alcohol and use of IBD medication (azathioprine/mercaptopurine, Aminosalicic acid and TNF- $\alpha$  inhibitors) 6 months prior to embryo transfer.

**Table 4** Clinical and Biochemical Pregnancies in Women with Crohn's Disease Prescribed Corticosteroid Three Months Prior to Embryo Transfer, Compared to Those Without a Corticosteroid Prescription

	Exposed Cohort (Steroid Use Prior to Embryo Transfers)		Unexposed Cohort (No Steroid Use Prior to Embryo Transfers)		Crude OR (95% CI)	Adjusted OR (95% CI) <sup>c</sup>
<b>Biochemical pregnancy (positive hCG)<sup>a</sup></b>						
Yes, N (%)	39	(34.8)	305	(31.8)	1.25 (0.79–1.99)	1.04 (0.61–1.77)
No, N (%)	73	(65.2)	654	(68.2)		
<b>Clinical Pregnancy (positive ultrasound)<sup>b</sup></b>						
Yes, N (%)	29	(76.3)	255	(83.9)	0.60 (0.26–1.42)	0.66 (0.22–1.95)
No, N (%)	9	(23.7)	49	(16.1)		

**Notes:** <sup>a</sup>Number of embryo transfers in the exposed cohort: 114 (number of women: 60) and unexposed cohort: 964 (number of women: 354). <sup>b</sup>Number of embryo transfers in the exposed cohort: 39 (number of women: 31) and unexposed cohort: 305 (number of women: 215). <sup>c</sup>Adjusted for Charlson Index, women's age, calendar year of treatment, type of treatment (IVF, ICSI, FET), cause of infertility (female factor, male factor, or mixture of factors/idiopathic), BMI, partner's age, smoking, alcohol and use of IBD medication (azathioprine/mercaptopurine, Aminosalicic acid and TNF- $\alpha$  inhibitors) 6 months prior to embryo transfer.

and clinical pregnancy after embryo transfers in women with UC are shown in Table 5. In women with UC receiving corticosteroids within three months prior to embryo transfer, 29.5% had a positive hCG, versus 31.1% in women with UC not receiving corticosteroids. The adjusted OR for a positive hCG was 0.95 (95% CI

0.55–1.64). The adjusted OR for a clinical pregnancy was 1.13 (95% CI 0.37–3.42), Table 5.

In the sub-analyses I, combining the cohorts of embryo transfers in women with CD and UC into embryo transfers in women with IBD, we compared our outcomes among embryo transfers in women with IBD having corticosteroids

**Table 5** Clinical and Biochemical Pregnancies in Women with Ulcerative Colitis Prescribed Corticosteroid Three Months Prior to Embryo Transfer, Compared to Those Without a Prescription

	Exposed Cohort (Steroid Use Prior to Embryo Transfers)		Unexposed Cohort (No Steroid Use Prior to Embryo Transfers)		Crude OR (95% CI)	Adjusted OR (95% CI) <sup>c</sup>
<b>Biochemical pregnancy (positive hCG)<sup>a</sup></b>						
Yes, N (%)	36	(29.5)	372	(31.1)	0.93 (0.58–1.50)	0.95 (0.55–1.64)
No, N (%)	86	(70.5)	825	(68.9)		
<b>Clinical Pregnancy (positive ultrasound)<sup>b</sup></b>						
Yes, N (%)	26	(74.3)	280	(76.5)	0.99 (0.41–2.43)	1.13 (0.37–3.42)
No, N (%)	9	(25.7)	86	(23.5)		

**Notes:** <sup>a</sup>Number of embryo transfers in the exposed cohort: 122 (number of women: 66) and unexposed cohort: 1208 (number of women: 414). <sup>b</sup>Number of embryo transfers in the exposed cohort: 36 (number of women: 29) and unexposed cohort: 372 (number of women: 274). <sup>c</sup>Adjusted for Charlson Index, women's age, calendar year of treatment, type of treatment (IVF, ICSI, FET), cause of infertility (female factor, male factor, or mixture of factors/idiopathic), BMI, partner's age, smoking, alcohol and use of IBD medication (azathioprine/mercaptopurine, Aminosalicic acid and TNF- $\alpha$  inhibitors) 6 months prior to embryo transfer.

within three months prior to embryo transfer to women with IBD having no corticosteroids prior to embryo transfer. The adjusted OR for live birth was 0.91 (95% CI 0.60–1.37), the adjusted OR for a positive hCG was 0.99 (95% CI 0.68–1.45), and the adjusted OR for a positive clinical pregnancy was 0.82 (95% CI 0.38–1.78).

In sub-analyses II, our cohorts of IBD women who had a positive clinical pregnancy after embryo transfer constituted i) 55 embryo transfers in women with IBD (29 (UC) + 26 (CD)) who had prescription of corticosteroids three months prior to embryo transfer, and ii) 535 (255(CD) + 280 (UC)) embryo transfers in women with IBD who did not have prescription of corticosteroid three months prior to embryo transfer. The adjusted OR for a live born child was 0.90 (95% CI 0.36–2.21).

## Discussion

We examined the impact of use of corticosteroids prior to embryo transfer in 2408 embryo transfers in women with CD and UC, and our overall results suggest that corticosteroids within three months prior to embryo transfer do not increase the chance of a live born child. When we examined the association between the use of corticosteroids prior to embryo transfer and the chance of a positive biochemical pregnancy or a positive clinical pregnancy, our data also suggested that corticosteroids did not increase the chance of a live born child. Our relative risk estimates were not statistically significant and the results should be interpreted with caution. Even though our findings suggest that corticosteroids do not increase the chance

of a live born child, it does not preclude that specific subgroups of patients with CD and UC might benefit from corticosteroids prior to embryo transfer.

The possible efficacy of peri-implantation corticosteroid therapy remains controversial.<sup>4,8</sup> It is known that the immune system is central to establishing endometrial receptivity and initiating a pregnancy,<sup>4,22,23</sup> and glucocorticoids are master regulators of intracellular signalling and can directly regulate embryo implantation and endometrial remodelling.<sup>24,25</sup> Most attention has been given to glucocorticoids as it has been proposed that these may improve the intrauterine environment by acting as immunomodulators to reduce the uterine natural killer cell count and normalise the cytokine expression profile in the endometrium and by suppression of endometrial inflammation.<sup>8</sup> Glucocorticoids have thus been advocated to improve the intrauterine environment, and perhaps improve embryo implantation in ART treatment. In a recent Cochrane review, Boomsma et al found no evidence that steroids helped to improve live birth rates in patients undergoing ART.<sup>8</sup> However, there was some evidence of increased pregnancy rates, rather than live birth rates, among women undergoing ART treatment (in women undergoing ICSI), and it was suggested that a subset of women with immune disorders receiving ART may benefit from immunosuppressive therapy.<sup>8</sup>

Glucocorticoids are one aspect of the complex process of endometrial receptivity and implantation, and many other factors are involved, for instance cytokines, hormones, proteomic, metabolomics and the quality of the embryo itself.

In former studies we have examined the efficacy of ART treatment in women with UC and CD, studies that suggested a reduced chance of live birth after ART treatment (ORs for live birth after ART treatment in women with UC and CD were 0.78 (95% CI, 0.67–0.91) and 0.61 (95% CI, 0.47–0.79), respectively).<sup>9,26</sup> Also in a former study, we found that the reduced chance of live birth after ART treatment in women with UC and CD may be related to the stage of implantation as we found a decreased chance of biochemical/clinical pregnancy,<sup>11</sup> but the possible underlying causes are unknown. These former studies did not examine whether corticosteroids prior to embryo transfer may improve the chance of a live born child, and they did not take into account an effect of other medications used to treat UC and CD (as a proxy for disease activity). Based on the present study we conclude that we still do not know why patients with IBD may have a decreased chance of a live born child after ART treatment, or may have difficulties related to the stage of implantation, and we still do not know which subgroups of patients with CD and UC might, or might not, benefit from treatment with corticosteroids. In our study, corticosteroids have probably not been randomly prescribed, and might have been given primarily to the most affected patients with CD and UC. Even if it is not supported by our data, we could suggest that the prognosis according to success in fertility treatment would have been worse for those severely affected individuals, if they were not prescribed corticosteroids. Only a randomized controlled trial would fully reveal the impact of corticosteroids on ART outcomes.

We were able to control our analyses for aminosalicic acids, immunomodulators and TNF- $\alpha$  inhibitors, as a proxy for disease activity, and a major role of increased disease activity in our analyses is not very likely. Also, in Denmark it is common practice to perform ART only in women who are in remission. Determining a possible rest-confounding effect of disease activity left in our analyses would require a thorough review of all nationwide medical charts for clinical details. In our study, corticosteroids could be prescribed for a number of reasons. Danish fertility doctors are familiar with the theory of a possible positive role of corticosteroids in terms of an improved chance of implantation in relation to ART and therefore they may prescribe corticosteroids, but patients with IBD could also receive corticosteroid prescriptions because of disease activity. The underlying reason for using corticosteroids cannot be established in this study, as our data from the nationwide

Danish prescription registry do not provide information on the indications for prescribing corticosteroids.

Our study has several strengths: i) We were able to perform a nationwide study based on all patients with CD and UC receiving ART in Denmark, and we had highly valid data on diagnoses of CD and UC,<sup>27</sup> ii) Our study population was based on complete and valid data from the ART registry which is based on mandatory reporting of all treatment cycles in public and private clinics,<sup>12,13</sup> iii) Data from the health registries used in this study are based on obligatory registrations, and we have a high completeness and validity,<sup>14–18</sup> iv) Our design, based on Danish health registries, allowed complete follow up of the study cohorts and our outcomes were retrieved independently of the exposure status, thereby preventing selection bias and differential misclassification of the outcome measurement, and finally v) We were able to control for important confounders, including comorbidity index, calendar year of ART treatment, type of ART treatment, cause of infertility, body mass index, women's age and partners' age, smoking, alcohol and medication used to treat IBD. The study also has limitations. In a register-based study like this we cannot perform a review of individual medical charts, and therefore we have no further information on a possible impact of disease extent or disease severity/activity. As mentioned we have however adjusted for the use of IBD medications within a period of six months prior to embryo transfer, which can be regarded as a surrogate measurement of disease activity. Our main limitation is that we had no opportunity to assess a potential importance of the dose of corticosteroids, or the exact timing of the use of corticosteroids prior to embryo transfer, as information on the use of corticosteroids was based solely on filled prescriptions. Although we had information on several confounders, we can never rule out an impact of unknown confounding. When performing analyses on CD and UC separately, some of our risk estimates had low statistical precision, but as CD and UC are different diseases, we regard it most valuable to split the analyses according to each disease. In sub-analyses, however, we reported risk estimates on IBD in general.

Seeking help from ART has become common, and children born after ART treatment contribute to 9% of Danish national birth cohorts.<sup>28</sup> Patients with CD and UC who seek assisted reproduction need information about their potential for a successful live birth, and one way to report the outcome of ART is the chance of a live



birth per embryo transfer as reported in this study. The incidence of CD and UC is still increasing,<sup>29</sup> and the clinicians will thus be faced with an increasing number of questions related to ART from patients with CD and UC, and also whether corticosteroids may improve ART results. Our results can help in these discussions.

## Conclusion

These are the first nationwide results of the efficacy of corticosteroids prior to embryo transfer in women with CD and UC, and future studies must examine the underlying mechanisms behind a possible role of corticosteroids in relation to fertilization and implantation in women with CD and UC. The association between corticosteroids and ART treatment outcomes should be examined in larger study populations with access to more detailed information on the timing and the dose of corticosteroids, information on biomarkers for disease activity, reproductive hormone levels, and hopefully biomarkers for endometrial receptivity.

## Data Sharing Statement

According to Danish legislation, our own approvals to use these register data for the current study do not allow us to distribute or make patient data directly available to other parties. Any interested researchers may apply for access to data through an application to the Research Service at the Danish Health Data Authority (forskerservice@sundheds-data.dk). Also, access to data from the Danish Health Data Authority requires approval from the Danish Data Protection Agency. The authors of this paper do not have special access privileges to the data used in the current study.

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## Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

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