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The impact of medical therapies and factors related to treatment procedures in women with rheumatoid arthritis and inflammatory bowel disease receiving assisted reproduction: a nationwide cohort study

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Objective: To examine whether medications used to treat rheumatoid arthritis (RA)/chronic inflammatory bowel disease (IBD), or factors related to the assisted reproductive technology (ART) procedures, impact the success of ART. In women with RA/IBD, initial studies have shown a reduced chance of a live-born child after ART.
Design: Cohort study.
Setting: Nationwide Danish health registries.
Patients: All Danish women with a fresh embryo transfer from January 1, 2006, through 2018. The cohorts comprised 1,824 embryo transfers in women with RA/IBD and 97,191 embryo transfers in women without RA/IBD.
Interventions: Observational, noninterventional study.
Main Outcome Measure: Live birth per fresh embryo transfer.
Results: The chance of a live birth in women with RA/IBD receiving ART, compared with other women receiving ART, had an adjusted odds ratio (OR) of 0.79 (95% confidence interval [CI], 0.68–0.91). Prescribed corticosteroids before embryo transfer were positively associated with a live-born child (adjusted OR, 1.21; 95% CI, 1.12–1.31), while the use of antiinflammatory/immunosuppressive agents did not have significant importance. Intracytoplasmic sperm injection was associated with a reduced chance (adjusted OR, 0.94; 95% CI, 0.90–0.97). Type of hormone treatment protocol did not have significant importance, and transfer at the blastocyst stage was positively associated with a live-born child (adjusted OR, 1.54; 95% CI, 1.46–1.62).
Conclusions: In women with RA and/or IBD, prescribed corticosteroid before embryo transfer and embryo transfer at the blastocyst stage were associated with successful ART. Intracytoplasmic sperm injection was associated with a slightly reduced chance. Antiinflammatory/immunosuppressive agents and type of hormone protocols did not have significant importance. (Fertil Steril® 2021;116: 1492-500. ©2021 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: ART, inflammatory bowel disease, live birth, rheumatoid arthritis

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Having a child is one of the most significant life events, but the ability to conceive naturally is often not a matter of course. In the general population in Denmark, up to 16% of all women have problems with infertility, and when combining nonachievement of a first and/or a subsequent pregnancy, the infertility proportion reaches 24.2% (1). For those who cannot conceive naturally, the efficacy of assisted reproductive technology (ART) becomes crucial.

Women with rheumatoid arthritis (RA) and chronic inflammatory bowel disease (IBD) represent some of the most common chronic diseases diagnosed during the fertile years (2). As several studies have indicated that it is more difficult for women with RA and IBD to conceive compared with reference populations (3–6), questions related to ART treatment become of significant importance. To date, evidence on the success of ART treatment in women with RA and IBD is sparse. The only study published on women with RA suggested that the chance of a live birth after ART was significantly reduced, relative to women without RA (7). In addition, the largest studies in the area of IBD have suggested that the chance of live birth after ART in women with ulcerative colitis or Crohn disease was reduced, compared with other women receiving ART (8, 9). However, several significant questions related to the success of ART treatment in women with RA and IBD remain to be studied. Some of the most obvious questions are related to an impact of medications for the underling conditions of RA and IBD and whether factors related to the ART procedure itself may have an impact on the success of ART. In women with RA and IBD, an impact of corticosteroid before embryo transfer has been studied in a few studies (7, 10), but no studies have examined an impact of the type of medications used to treat RA or IBD, and no studies have examined the importance of factors related to the ART procedures (including cell stage at embryo transfer and type of hormone treatment protocols).

RA and IBD share immune-mediated etiologic mechanisms (11), including both common genetics and environmental susceptibility factors (12–14). Because these diseases are both part of the autoimmune spectrum with similar features and treatments, we expected a similar response to ART in patients with infertility. Therefore, this study includes all women in Denmark with RA and IBD receiving ART, and we studied which factors, related to medications (corticosteroids, antiinflammatory/immunosuppressive agents) and selected ART procedures (type of ART, cell stage at embryo transfer, and hormone treatment protocols), predicted a live-born child.

MATERIALS AND METHODS

Setting and Study Population

This is a nationwide population-based cohort study based on Danish health registries. The data used derived from the following: the Danish ART Registry (data on ART procedures and cause of infertility) (15); the Danish Medical Birth Registry with data on children born in Denmark, including data on the outcome of infertility treatment (live birth); the Danish National Patient Registry including data on maternal diseases; the Prescription Registry including data on all filled prescriptions; and the Central Personal Registration system including information on death and immigration (16). The unique civil registration number, assigned to all Danish residents, is used across all Danish health registries and is used for valid record linkage on an individual level.

Based on the aforementioned registries, the study population included all fresh embryo transfers in Denmark from January 1, 2006, to December 31, 2018, that is, all frozen-thawed embryo transfers were excluded. The study population included only fresh embryo transfers as we assessed the impact of gonadotropin-releasing hormone (GnRH) treatment protocols.

Exposed and Unexposed Cohorts

The exposed cohort comprised fresh embryo transfers in women who had diagnoses of RA and/or IBD before the time of embryo transfer. To ensure a valid assessment of RA and IBD before the time of embryo transfer, we required at least two hospital diagnoses for RA (International Classification of Diseases [ICD]-8, 71219, 71239, and 71259; ICD-10, M05 and M06 [excluding M061]) or IBD (Crohn ICD-8, 56301, and ICD-10, K50; ulcerative colitis, ICD-8, 56319 and 56904, and ICD-10, K51).

The unexposed cohort comprised embryo transfers from the study population where the women did not have diagnoses of RA or IBD before embryo transfer.

Outcome

Our outcome was a live birth per embryo transfer. A live birth was identified in the Danish Medical Birth Registry where a live birth was considered to be the result of the particular ART procedure if the difference was 140–308 days (20–44 weeks) from the last menstruation start, corresponding to 124–292 days after embryo transfer (7, 8, 17). The Danish Medical Birth Registry has included details on all births in Denmark since January 1, 1973, and the registration is mandatory for all births in Denmark (18–20). The registry includes data such as date of birth, gestational age, birth weight, mode of delivery, and parity.

Data on Covariates

Possible covariates were defined a priori and obtained from the registries. The following covariates were retrieved from the ART registry: information on women's age at time of embryo transfer (continuous variable), calendar year of ART treatment in three categories (2006–2009, 2010–2013, and 2014–2018), cause of infertility (female only, male only, both/idiopathic), type of ART procedure (in vitro fertilization [IVF], intracytoplasmic sperm injection (ICSI)), body mass index of women (underweight [<18.5 kg/m^2], normal weight [18.5–24.9 kg/m^2], preobesity [25.0–29.9 kg/m^2]), and obesity [>30 kg/m^2]), smoking (yes/no), alcohol (yes/no), cell stage at transfer (cleavage-stage embryo or blastocyst), and GnRH

treatment protocol (long and short treatment protocols with GnRH agonists and antagonists, respectively). In both protocols, patients were treated with follicle-stimulating hormone from cycle days 2–3 until triggering with human chorionic gonadotropin (hCG) or GnRH agonist, respectively. In the long GnRH hormone treatment protocol, patients were treated with GnRH agonist from day 21 in the cycle, immediately before the treatment cycle and until triggering with hCG approximately 34 hours before oocyte aspiration. In the short protocol, patients were treated with GnRH antagonist from a follicle size of 14 mm until triggering with GnRH agonist or hCG approximately 34 hours before oocyte aspiration.

Data on the Charlson comorbidity index were obtained from the Danish National Patient Registry, calculated for each treatment cycle for each woman, and were based on diagnoses recorded during all previous hospitalizations since 1977 as the onset of the Danish National Patient Registry (21, 22). Two index levels were defined: no comorbidity or some comorbidity. Furthermore, if the women had diagnoses of RA, RA was excluded from the Charlson comorbidity index as RA constituted the one of the exposures. IBD is not part of the index. The Danish National Patient Registry was established in January 1977 and includes records of all discharges from Danish hospitals since the beginning and on all outpatient visits since 1995. Information includes hospital, department, dates of admission and discharge, procedures performed during hospitalization (including treatment with biologic therapies), and discharge diagnoses based on the ICD (in the 8th version before 1994 and the 10th version hereafter) (21, 23). From the nationwide Danish prescription registry, established in 1995, we used data on filled prescriptions of systemic corticosteroids, aminosalicylic acids, and thiopurines (24). The nationwide prescription registry, maintained by the Danish Medicines Agency, holds information on all outpatient drug prescriptions, and all pharmacies send electronic key information to the registry including information on the type of drug prescribed according to Anatomical Therapeutic Chemical (ATC) classification and dates on filled prescriptions.

Statistical Methods

Descriptive characteristics are given for the exposed and unexposed cohorts.

First, to give an overall estimate of the chance of a live-born child in women with RA and IBD, we analyzed data across three adjusted models. We, thus, applied multilevel logistic regression analyses to compute crude and adjusted relative risk estimates (prevalence odds ratio [OR] with 95% confidence intervals [95% CIs]) for live births after ART treatments in women with RA and IBD, relative to women without RA and IBD. The models accounted for multiple embryo transfers in the same woman.

Thereafter, we displayed, in a prediction model, the selective impact of type of medications used to treat RA and IBD and the impact of specific ART treatment procedures. Thus, in the model, we included filled prescriptions of oral corticosteroids up to 3 months before embryo transfer (ATC codes: H02AB02 dexamethasone, H02AB04 methylprednisolone, H02AB06 prednisolone, H02AB07 prednisone, and H02AB09 hydrocortisone), azathioprine/mercaptopurine up to 6 months before embryo transfer (ATC codes: L04A X01 and L01B B02), aminosalicylic acids up to 6 months before embryo transfer (ATC code: A07EC), tumor necrosis factor α inhibitors up to 6 months before embryo transfer (recorded as procedure codes in the National Patient Registry), type of treatment (IVF, ICSI), cell stage at transfer (embryo [days 2–3], blastocyst [days 5–7]), and long versus short treatment protocols with GnRH agonists and antagonists, respectively. Simultaneously, the analyses were adjusted for other confounders such as maternal age at embryo transfer, body mass index, calendar year of transfer, Charlson comorbidity index, cause of infertility, smoking, and alcohol.

We also performed stratified analyses according to only RA and only IBD.

Approvals

In Denmark, registry studies do not require ethical approvals by law but need approval from the Danish Data Protection Agency. This study was approved by the Danish Data Protection Agency (journal number 17/37434).

RESULTS

We included 1,824 embryo transfers in women with RA or/and IBD (exposed cohort). Of these, 22.8% had Crohn disease, 40.1% had ulcerative colitis, and 38.4% had RA (Table 1). A total of 97,191 embryo transfers in women without RA and IBD constituted the unexposed cohort. There were no major differences between the exposed and unexposed cohorts as regards age of the woman, age of her partner, smoking, alcohol, and cause of infertility (Table 1). Women in the exposed cohort had more comorbidities (26.9%) compared with those in the unexposed cohort (10.8%). A total of 15.2% of the women with RA or/and IBD received corticosteroids within 3 months before embryo transfer compared with 5.4% in the unexposed cohort. In women with RA or/and IBD, the proportions of women who filled prescriptions for aminosalicylic acids, thiopurines, and biologics were 12.2%, 1.5%, and 6.1%, respectively (Table 1). Methotrexate is contraindicated during pregnancy, and as expected, we found no prescriptions of methotrexate before the time of embryo transfer in the exposed and unexposed cohorts.

The Overall Chance of Live Birth in Women with RA and/or IBD

In embryo transfers in women with RA or/and IBD, 19.4% had a live birth per transfer compared with 24.5% in the unexposed cohort (Table 1). The adjusted ORs of the overall chance of a live birth are presented in Table 2. Across three different adjusted models, the ORs were virtually the same: 0.76 (95% CI, 0.67–0.87) (model a); 0.80 (95% CI, 0.70–0.91) (model b); and 0.79 (95% CI, 0.68–0.91) (model c).

TABLE 1

Descriptive characteristics among embryo transfers in women with rheumatoid arthritis (RA) or/and inflammatory bowel diseases (IBD) and references (no RA/IBD).

	Embryo transfers in women with RA or/and IBD n = 1,824	Embryo transfers in references n = 97,191
Crohn disease, n (%)[a]	416 (22.8)	-
Ulcerative colitis, n (%)[a]	731 (40.1)	-
Rheumatoid arthritis, n (%)[a]	700 (38.4)	-
Maternal age (median (IQR))	35(31–38)	34(31–38)
Partners age (median (IQR))	36 (32–40)	36 (32–40)
Body mass index, n (%)		
Underweight	34 (1.9)	2,669 (2.8)
Normal	940 (51.5)	52,787 (54.3)
Preobesity	384 (21.1)	19,138 (19.9)
Obese	205 (11.2)	8,267 (8.5)
Missing	261 (14.3)	14,150 (14.7)
Charlson comorbidity index, n (%)		
No comorbidity	1,334 (73.1)	86,685 (89.2)
Some comorbidity	490 (26.9)	10,506 (10.8)
Smoking, n (%)		
Nonsmoker	1,436 (78.7)	75,786 (78.0)
Smoker	130 (7.1)	6,987 (7.2)
Alcohol, n(%)		
No	889 (48.7)	44,331 (45.6)
Yes	637 (34.9)	35,814 (36.9)
Year of embryo transfer, n (%)		
2006–2009	447 (24.5)	30,509 (31.4)
2010–2013	579 (31.7)	31,710 (32.6)
2014–2018	798 (43.8)	34,972 (36.0)
Cause of infertility, n (%)		
Female only	282 (15.5)	14,934 (15.4)
Male only	477 (26.2)	30,691 (31.6)
Mixture of factors/idiopathy, n (%)	1,065 (58.4)	51,526 (53.0)
Hormone treatment protocol, n (%)		
Short GnRH	652 (35.8)	31,323 (32.2)
Long GnRH	688 (37.7)	40.986 (42.8)
Not classified	484 (26.5)	24,882 (25.6)
Treatment, n (%)		
IVF	968 (53.1)	48,241 (49.6)
ICSI	852 (46.7)	48,677 (50.1)
Cell stage at transfer, n (%)		
Embryo	1,565 (85.8)	84,701 (87.2)
Blastocyst	259 (14.2)	12,490 (12.9)
Steroid treatment 3 months before embryo transfer, n (%)	277 (15.2)	5,268 (5.4)
Aminosalicylic acids 6 months before embryo transfer, n (%)	223 (12.2)	337 (0.4)
Azathioprine/mercaptopurine 6 months before embryo transfer, n (%)	27 (1.5)	112 (0.1)
Biologics 6 months before embryo transfer, n (%)	112 (6.1)	97 (0.1)
Live-born child, n (%)	354 (19.4)	23,821 (24.5)

Note: GnRH = gonadotropin-releasing hormone; IBD = inflammatory bowel disease; IQR = interquartile range; RA = rheumatoid arthritis.
[a] Add up to more than 1,824 as some women have both diagnoses of inflammatory bowel disease and rheumatoid arthritis.

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The Impact on the Type of ART Procedures and Medications in Women with RA and/or IBD

The specific impact of the type of ART procedures and medications is displayed according to crude and adjusted ORs in Table 3. Embryo transfer at the blastocyst stage and of prescribed corticosteroids before embryo transfer were associated with an increased chance of a live-born child (adjusted ORs, 1.54 [95% CI, 1.46–1.62] and 1.21 [95% CI, 1.12–1.31], respectively). Intracytoplasmic sperm injection was associated with a small reduced chance of a live birth (adjusted OR, 0.94; 95% CI, 0.90–0.97). The type of GnRH treatment protocols or antiinflammatory/immunosuppressive agents did not have significant importance on the chance of live birth.

Stratified Results According to RA and IBD

We stratified the analyses according to RA and IBD (Supplemental Table 1, available online). The adjusted ORs of the overall chance of a live birth are presented across three different adjusted models. There were no major differences between RA and IBD (adjusted ORs, 0.85 [95% CI, 0.66–1.09] and 0.76 [95% CI, 0.64–0.91], respectively).

In stratified analyses, for only RA and IBD, we displayed the impact of specific factors related to the type of ART procedures and medications (Supplemental Table 2, available online). The results were similar to the main analyses. In patients with RA, embryo transfer at the blastocyst stage and prescribed corticosteroids before embryo transfer were associated with an increased chance of a live-born child (adjusted

TABLE 2

The overall chance of a live-born child per transfer in women with RA or/and IBD after assisted reproductive technology. Results from multilevel mixed effects regression models.

	Crude OR	Adjusted OR model [a]	Adjusted OR model [b]	Adjusted OR model [c]
No RA or IBD	Reference	Reference	Reference	Reference
IBD RA	0.73 (0.63–0.83)	0.76 (0.67–0.87)	0.80 (0.70–0.91)	0.79 (0.68–0.91)

Note: IBD = inflammatory bowel disease; OR = odds ratio; RA = rheumatoid arthritis.
[a] Adjusted for age and calendar period.
[b] Adjusted for age, Charlson comorbidity index, hormone treatment, cell stage, steroid treatment up to 3 months after transfer, aminosalicylic acids, azathioprine, biological therapy and female–male factor, calendar period, and IVF/ICSI.
[c] Adjusted for age, Charlson comorbidity index, hormone treatment, cell stage, steroid treatment up to 3 months after transfer, aminosalicylic acids, azathioprine, biological therapy and female–male factor infertility, calendar period, IVF/ICSI, smoking, alcohol, and body mass index.

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ORs, 1.54 [95% CI, 1.46–1.62] and 1.21 [95% CI, 1.12–1.30], respectively). Intracytoplasmic sperm injection was associated with a reduced chance of a live birth (adjusted OR, 0.93; 95% CI, 0.90–0.97), and so was the use of biologics within 6 months before embryo transfer (adjusted OR, 0.62; 95% CI, 0.38–0.98). In patients with IBD, embryo transfer at the blastocyst stage and prescribed corticosteroids before embryo transfer were associated with an increased chance of a live-born child (adjusted ORs, 1.54 [95% CI, 1.46–1.62] and 1.20 [95% CI, 1.12–1.30], respectively). Intracytoplasmic sperm injection was associated with a reduced chance of a live birth (adjusted OR, 0.94; 95% CI, 0.90–0.97), and so was the use of biologics within 6 months before embryo transfer (adjusted OR, 0.61; 95% CI, 0.39–0.96).

DISCUSSION

The overall chance of a live birth in women with RA/IBD undergoing ART, compared with other women undergoing ART, was statistically significantly reduced. We found a statistically significant advantage of a transfer at the blastocyst stage and of prescribed corticosteroids before embryo transfer. Intracytoplasmic sperm injection, compared with IVF, was associated with a small, but significant, reduced chance of a live birth. The type of treatment protocols, and antiinflammatory/immunosuppressive agents within 6 months before embryo transfer, did not have significant importance on the chance of live birth. Stratified analyses on only RA and only IBD showed similar results.

Few studies have been published on the chance of a successful ART in women with RA and IBD, and the most methodologically solid studies have found a decreased chance of a live-born child (7–9, 25, 26). The underlying reasons for unsuccessful outcome of ART in these women have not been studied. Several studies have suggested that the decreased chance of a live-born child is not because of a problem carrying the child throughout pregnancy. On the

TABLE 3

The chance of a live-born child per transfer in women with RA and/or IBD after ART. The specific impact of type ART procedures and medications is displayed according to crude and adjusted odds ratio (and 95% CI). In the multivariate model, all factors are mutually adjusted.

RA or/and IBD	Crude ORs for live-born child (95% CI)	Multivariate model[a]: ORs for live-born child (95% CI)
Treatment		
IVF	1(ref.)	1(ref.)
ICSI	1.12 (1.08–1.16)	0.94 (0.90–0.97)
GnRH treatment		
None	1(ref.)	1(ref.)
Short	1.00 (0.96–1.04)	1.02 (0.97–1.07)
Long	1.04 (0.99–1.08)	1.05 (1.00–1.10)
Cell stage at transfer		
Embryo	1 (ref.)	1 (ref.)
Blastocyst	1.54 (1.47–1.61)	1.54 (1.46–1.62)
Steroid treatment		
No	1 (ref.)	1 (ref.)
Yes	1.18 (1.10–1.27)	1.21 (1.12–1.31)
Aminosalicylic acids		
No	1 (ref.)	1 (ref.)
Yes	0.83 (0.65–1.07)	0.87 (0.67–1.14)
Azathioprine		
No	1 (ref.)	1 (ref.)
Yes	0.88 (0.55–1.41)	0.82 (0.51–1.34)
Biological therapy		
No	1 (ref.)	1 (ref.)
Yes	0.71 (0.46–1.10)	0.66 (0.42–1.03)

Note: GnRH = gonadotropin-releasing hormone; IBD = inflammatory bowel disease; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OR = odds ratio; RA = rheumatoid arthritis.
[a] The model is also adjusted for age at time of embryo transfer, calendar period, body mass index, comorbidity index, smoking, alcohol, cause of infertility, and female–male factor.

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contrary, the results indicate a decreased chance of embryo implantation after ART (7, 25). We, therefore, explored whether medications used to treat RA and IBD, or specific ART procedures, negatively impacted the chance of a successful outcome, and to our knowledge, we are the first to study these factors in women with RA/IBD.

Regarding medications, it is reassuring that RA and IBD immunosuppressive therapies did not significantly reduce the chance of a live-born child. There are no general recommendations in Denmark to treat women with RA/IBD with corticosteroids before ART, and an impact of corticosteroid therapy before implantation remains controversial (27–29). It is known that the immune system is central to establishing endometrial receptivity (30, 31), and glucocorticoids are significant for intracellular signaling and can directly regulate embryo implantation (32, 33). Glucocorticoids have, thus, been suggested to improve endometrial receptivity and implantation and perhaps improve embryo implantation in ART, but glucocorticoids are part of a complex process involving several other factors such as cytokines, hormones, proteomic, and the quality of the embryo itself. Two former cohort studies have examined an impact of corticosteroids in women with RA and IBD and showed divergent results (7, 10). A Cochrane review from 2012 concluded that there is no evidence that steroids helped to improve live birth rates in ART, but the use of glucocorticoids in a subgroup of women undergoing IVF was associated with an improvement in the pregnancy rates of borderline statistical significance (29). Robertson et al. (28) argued that unless overt immune pathology is evident, the use of corticosteroid is not warranted and may be harmful, and they encouraged investigators to perform studies on subgroups of women with specific types of underlying diseases. Our results should be seen in this perspective.

Regarding ART procedures, we found that ICSI, compared with IVF, was associated with a small reduced chance of a live birth. In general, it is not surprising that IVF may be superior to ICSI in cases of non-male factor infertility (34, 35), but to our knowledge, it has not previously been examined in women with RA/IBD. Our analyses are adjusted for underlying reason for infertility, and still, IVF seems to be superior to ICSI. In case of male factor infertility or missing fertilization in IVF, ICSI is an advantage, but for other couples receiving ART, ICSI is more controversial (36, 37). Several studies have supported that there is no advantage of ICSI over conventional IVF in several women when used for non-male factor fertility (34, 35, 37). In some cases where the oocytes are immature, the success rates may be higher with conventional IVF because fertilization may happen later (where the oocytes are more mature) compared with the time chosen for ICSI. We also found an increased chance of live birth per transfer at the blastocyst stage, compared with cleavage-stage embryos, which is not new or surprising (38, 39). The success rates when using blastocysts are generally much higher because embryos undergoing arrest between days 2 and 5 are excluded from blastocyst transfer. Culture media have significantly improved that moving embryo culturing to day 5 or 6 is the usual strategy today. In addition, moving the embryo culturing to day 5 or 6 and transfer at the blastocyst stage rather than day 2 or 3 at the cleavage stage is also because the prevalence of aneuploidy in blastocysts is lower than in cleavage-stage embryos (40).

Regarding the impact type of GnRH treatment protocol, we found that the type of stimulation protocol did not have significant importance. The impact of the type of stimulation has been widely studied, and numerous clinical trials and meta-analyses, based on studies comparing GnRH agonist and antagonist protocols, have shown a consistent conclusion that GnRH antagonist protocol results in similar live birth rate (41, 42). However, choosing the type of stimulation protocol is not simple, and no single ovarian stimulation protocol is necessarily suitable for all patient populations. This is documented in a recent study by Zhang et al. (43), showing that the benefit of GnRH antagonist protocol highly depends on factors such as ovarian reserve and women's age.

Our study has several strengths. First, we performed a nationwide study based on all Danish patients receiving ART, and the study was based on health registries widely used for valid clinical epidemiological research (19, 21, 23, 24, 44). Second, information on the study population derived from the ART registry, which is based on mandatory reporting of all treatment cycles in public and private clinics (15, 45). Third, we had complete follow-up on all patients in the study cohorts, and our outcome was retrieved independently of the exposure status, and thereby, we prevented selection bias and differential misclassification of the outcome. Fourth, we were able to assess the impact of several factors, which is significant for the efficacy of ART, including comorbidity, age, body mass index, medications used to treat underlying diseases of IBD/RA, and factors related to ART procedures. The study also has limitations. Our information on medications is based on filled prescriptions. We did not have access to information on the exact dose of medications, and in a study like this, based on health registries, it is not possible to review all medical records. Therefore, we did not have additional information on the dose of medications or severity of underlying diseases. However, in Denmark, ART treatments are performed on patients with quiescent disease and not on women with increased disease activity. We included a large number of covariates in our models, but in an observational study like this, we can never rule out an impact of unknown confounders. In the most optimal situation, it would be desirable to have data on, for instance, the type of embryo culture media, embryo culture, embryo quality, selection of embryo with the highest implantation potential, and biomarkers of endometrial receptivity. Unfortunately, the ART registry does not include such information. Our data do not include canceled cycles. Our study population is based on women who reach the state of an embryo transfer, and our results, therefore, specifically apply to those women. Future studies examining which factors lead to a scenario where embryo transfer cannot be performed are highly relevant, for example, studies examining whether patients with IBD/RA have poor stimulation or poor embryo development.

In conclusion, it is reassuring that IBD and RA medications did not decrease the chance of a live-born child, and this speaks in favor of a continuation of pharmacologic

therapies for RA and IBD in relation to ART. Our results suggest a positive impact of corticosteroids before embryo transfer, but details related to dose and timing have to be examined in future studies, and the picture of the relationship between corticosteroids and the efficacy of ART is far from complete. Intracytoplasmic sperm injection was not superior to IVF in women with RA/IBD. Blastocyst transfer was superior to embryo transfer at days 2–3, and the type of hormone stimulation protocol did not impact the chance of a live-born child. Future studies, based on other settings, should be performed in this area as our results need to be confirmed and expanded with even more detailed datasets. Important parameters for future studies could include information on reproductive hormone levels, biomarkers for disease activity, and endometrial receptivity.

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Data availability: According to Danish legislation, our 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. Thus, the authors of this paper do not have special access privileges to the data used in the current study. Any interested researchers may apply for access to data through an application to the Research Service at the Danish Health Data Authority (forskerservice@sundhedsdata.dk). In addition, access to data from the Danish Health Data Authority requires approval form the Danish Data Protection Agency.

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El impacto de las terapias médicas y los factores relacionados con los procedimientos de tratamiento en mujeres con artritis reumatoide y enfermedad inflamatoria intestinal que reciben reproducción asistida: un estudio de cohorte a nivel nacional.

Objetivo: Examinar si los medicamentos utilizados para tratar la artritis reumatoide (AR) / enfermedad inflamatoria intestinal crónica (EII), o los factores relacionados con los procedimientos de técnicas de reproducción asistida (ART), influyen en el éxito del ART. En mujeres con AR / EII, los estudios iniciales han demostrado una menor probabilidad de tener un hijo nacido vivo después del TAR.

Diseño: Estudio de cohorte.

Entorno: Registros sanitarios daneses a nivel nacional.

Pacientes: Todas las mujeres danesas con una transferencia de embriones frescos desde el 1 de enero de 2006 hasta 2018. Las cohortes comprendieron 1.824 transferencias de embriones en mujeres con AR / IBD y 97.191 transferencias de embriones en mujeres sin AR / IBD.

Intervenciones: Estudio observacional, no intervencionista.

Medidas principales de resultados: Nacidos vivos por transferencia de embriones frescos.

Resultados: La probabilidad de un nacimiento vivo en mujeres con RA/IBDI que recibieron TRA, en comparación con otras mujeres que recibieron TRA, tuvo una razón de probabilidades ajustada (OR) de 0,79 (intervalo de confianza [IC] del 95%, 0,68-0,91). Los corticosteroides recetados antes de la transferencia de embriones fueron positivamente asociados con niño nacido vivo (OR ajustado, 1,21; IC del 95%, 1,12–1,31), mientras que el uso de agentes antiinflamatorios / inmunosupresores no tuvo una importancia significativa. La inyección intracitoplasmática de espermatozoides se asoció con una probabilidad reducida (OR ajustado, 0,94; IC del 95%, 0,90-0,97). El tipo de protocolo de tratamiento hormonal no tuvo una importancia significativa y la transferencia en la etapa de blastocisto se asoció positivamente con niño nacido vivo (OR ajustado, 1,54; IC del 95%, 1,46-1,62).

Conclusiones: En mujeres con RA y/o IBD, la prescripción de corticosteroides antes de la transferencia de embriones y la transferencia de embriones en la etapa de blastocisto fue asociada con el éxito en las TRA. La inyección intracitoplasmática de espermatozoides se asoció con una probabilidad ligeramente reducida. Los agentes antiinflamatorios / inmunosupresores y el tipo de protocolos hormonales no tuvieron una importancia significativa.