Decreased chance of a live born child in women with rheumatoid arthritis after assisted reproduction treatment
a nationwide cohort study
Nørgård, Bente Mertz; Larsen, Michael Due; Friedman, Sonia; Knudsen, Torben; Fedder, Jens

Published in:
Annals of the Rheumatic Diseases

DOI:
10.1136/annrheumdis-2018-214619

Publication date:
2019

Document version
Accepted manuscript

Document license
CC BY-NC

Citation for published version (APA):

Terms of use
This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying this open access version.

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk
Decreased chance of a live born child in women with rheumatoid arthritis after assisted reproduction treatment– a nationwide cohort study

Short running title: infertility treatment in rheumatoid arthritis

Nørgård BM¹₂, Larsen MD¹, Friedman S¹₂, Torben Knudsen³, Fedder J⁴

1) Center for Clinical Epidemiology, Odense University Hospital, and Research Unit of Clinical Epidemiology, Department of Clinical Research, University of Southern Denmark, Odense, Denmark.

2) Crohn’s and Colitis Center, Brigham and Women’s Hospital, Boston, Massachusetts and Harvard Medical School, Boston.

3) Department of Medical Gastroenterology, Hospital of Southwest Jutland, Esbjerg, Denmark

4) Centre of Andrology and Fertility Clinic, Department D, Odense University Hospital, and Research Unit of Human Reproduction, Department of Clinical Research, University of Southern Denmark, Odense, Denmark.

Word count, abstract: 245

Word count, body text: 3884

Correspondence to: Bente Mertz Nørgård. Center for Clinical Epidemiology, Odense University Hospital. Sdr. Boulevard 29, entrance 216. DK-5000 Odense C. Denmark.

Mail: bente.noergaard@rsyd.dk Telephone: (+45) 2133 3258
ABSTRACT

Objectives

No studies have examined the efficacy of assisted reproductive technology (ART) treatment in women with rheumatoid arthritis. Therefore, we examined the chance of live birth after ART treatment in women with rheumatoid arthritis compared to women without rheumatoid arthritis.

Methods

Our cohort study is based on nationwide Danish health registries, comprising all women with an embryo transfer during 1 January 1994 through 30 June 2017. The cohorts comprised 1,149 embryo transfers in women with rheumatoid arthritis, and 198,941 embryo transfers in women without rheumatoid arthritis. Our outcome was live birth per embryo transfer, and we controlled for multiple covariates in the analyses. In sub-analyses we examined a chance of biochemical/clinical pregnancy after ART and a possible impact of corticosteroid use prior to embryo transfer.

Results

The adjusted odds ratio (aOR) for a live birth per embryo transfer in women with rheumatoid arthritis, relative to women without rheumatoid arthritis, was 0.78 (95% CI 0.65-0.92). The aORs for biochemical and clinical pregnancy were 0.81 (95% CI 0.68-0.95) and 0.82 (95% CI 0.59-1.15), respectively. Corticosteroid prescription prior to embryo transfer increased the OR for live birth (aOR= 1.32 (95% CI 0.85-2.05)).

Conclusions

The chance of a live birth was significantly reduced in women with rheumatoid arthritis receiving ART treatment, relative to women without rheumatoid arthritis, and our result suggested that the problem was related to an impaired chance of embryo implantation. The role of corticosteroid use prior to embryo transfer must be a subject for further research.
Keywords:

rheumatoid arthritis, assisted reproductive technology, in vitro fertilization, clinical epidemiology, reproduction
INTRODUCTION

Having a child is one of the most important life events during adulthood, but the ability to conceive naturally is often not a matter of course. Women with rheumatic disease represent one of the most common chronic disease groups diagnosed during the fertile years,[1] and therefore questions about reproductive issues become of significant importance.

The question of interest for this study is the success of infertility treatment in women with rheumatoid arthritis (RA) who cannot conceive naturally. In women with RA, former studies have focused on reproduction questions such as waiting time to pregnancy,[2] fertility rates,[3 4] probability of having a second child,[5] and the time span of reproduction.[3] Overall, these studies have indicated that it is difficult for women with RA to conceive compared with reference populations. It might be a result of the disease and/or the treatment.[2 4 6] and this theory is supported by a study showing that women with RA are more likely to have infertility treatment compared to controls.[2] So far, there have been no studies on the efficacy of assisted reproduction technology (ART) treatment in women with RA.

The relevance of examining the efficacy of ART treatment in women with RA is increasing as recent studies on other autoimmune diseases (ulcerative colitis and Crohn’s disease) have suggested a reduced chance of having a live born child after ART treatment compared to other women undergoing ART.[7-9] Those results indicated that the reduced chance might be related to difficulties with implantation of the transferred embryo.[8] Also, there is an ongoing debate whether corticosteroid drugs such as prednisolone can be used with beneficial effect in ART treatment.[10 11]

We examined the efficacy of ART treatments in women with RA, based on Danish nationwide registries with a study period of 23.5 years. In this study, ART treatments refer to in vitro
fertilization (IVF), with or without fertilization with intracytoplasmic sperm injection (ICSI), and transfer of frozen-thawed (FER) embryos. We assessed the chance of a live birth following ART treatments in women with RA compared to women without RA receiving ART treatment. In sub-analyses we examined the chance of biochemical and clinical pregnancies, and finally we examined the impact of corticosteroid treatment prior to embryo transfer.
METHODS

Setting and study population

In Denmark we have a uniform organized health care system, and there is equal and free access to the tax-supported health care services. All citizens in Denmark (population approximately 5.6 million inhabitants, > 90% Caucasians) have a unique civil registration number. This number is assigned to all residents at birth and is used across all Danish health registries for valid record linkage on an individual level. Therefore, based on Danish health registries, we were able to use a nationwide population-based design. We obtained nationwide data i) related to ART procedures and cause of infertility from the Danish ART Registry, ii) on the outcome of infertility treatment (live birth) from the Danish Medical Birth Registry (MBR), iii) from The Danish National Patient Registry (NPR) on comorbid diseases, iv) from the Prescription Registry, and v) from The Central Personal Registration system on death and immigration.[12]

The study population comprised all women registered in the ART registry with at least one embryo transfer during the study period of 1 January 1994 – 30 June 2017 (23.5 year study period), and all women had to have a valid civil registration number and be available for follow up in Denmark. In Denmark, 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 transfer, if the woman's age does not exceed 40 years. The Danish ART registry records all treatment cycles performed in both public and private clinics.[13 14] The registry was established on 1st January 1994 and registration of all treatments is compulsory for all fertility clinics.[13 14] In the ART registry, the recorded information on embryo transfer to the uterus could be a result of all preceding treatments (IVF, ICSI, FER).

Exposed cohort
From the study population, all women with a diagnosis of RA were identified in the NPR. The exposed cohort included all patients who had at least two discharge diagnoses of RA from any hospital in Denmark at any time before the date of embryo transfer (ICD-8 codes: 712.19, 712.39, 712.59; ICD-10 codes: M05 and M06 (except M06.1)).[15 16] The NPR has recorded all discharges from Danish hospitals since 1977 and all outpatient visits since 1994.[17 18] Information in the NPR includes details of hospital, department, dates of admission and discharge, procedures performed, and discharge diagnoses based on the International Classification of Diseases (ICD-8 before 1994 and ICD-10 from 1994 onward, ICD-9 was never used in Denmark). Thus, the exposed cohort comprised all embryo transfers in women diagnosed with RA before the date of embryo transfer. Because each woman with RA could have several ART treatments, the observation unit was embryo transfers.[7 19-21]

Unexposed cohort

The unexposed cohort comprised all embryo transfers in women without diagnoses of RA before the date of embryo transfer; and similarly to the exposed cohort, the observation unit was each embryo transfer.

Outcome

The outcome was a live birth within a period of 124-292 days after each embryo transfer, and a live birth was identified in the MBR. Thus, 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 20] The MBR has included information on all births in Denmark since 1 January 1973, and data are obtained by compulsory birth notification forms, completed by the midwives who attend all births.[22 23] The MBR includes data such as
date of birth, mode of delivery, parity, smoking at the start of pregnancy, gestational age at time of birth, and birth weight and length.

In sub-analyses, we examined the outcomes i) biochemical pregnancy (positive human chorionic gonadotropin, hCG at 14-16 days after embryo transfer) and ii) clinical pregnancy (pregnancy detected by ultrasound examination approximately 7-8 weeks after embryo transfer).

Data on confounders

Covariates included in the regression models were selected a priori. Data on Charlson comorbidity Index was obtained from the NPR, calculated for each treatment cycle of each woman, and was based on diagnoses recorded during all previous hospitalizations since 1977.[24] Two index levels were defined, no comorbidity (Charlson Index 0), and some comorbidity (Charlson Index ≥1). From the MBR we obtained information on parity (0, +1) and smoking at the start of pregnancy (yes/no). From the ART registry we used information on women’s age at time of embryo transfer (continuous variable), calendar year of infertility treatment (1994-1999, 2000-2005, 2006-2011, and 2012-2017), type of ART treatment (IVF, ICSI, FER), and cause of infertility (female factor, male factor, or mixture of factors/idiopathic). Since 2006, the ART registry has also included data on body mass index (categorized according to the World Health Organization classifications as underweight (<18.5 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25.0–29.9 kg/m2), and obesity (≥30 kg/m2)), partner’s age, alcohol intake (yes/no), and smoking at the time of embryo transfer (yes/no). Biologic therapy has been available in Denmark since 2004, and in a subset of our cohort we examined a possible confounding impact of biologic therapy.

In sub-analyses we used data on prescribed corticosteroid prior to embryo transfer based on prescriptions according to the anatomical therapeutical chemical (ATC) classification system in
women with RA, and we calculated the duration of RA at the time of each ART treatment (calculated from the date of the first diagnosis of RA in the NPR until the date of embryo transfer).

**Statistical analyses**

*Main analyses for the outcome of live birth in women with RA*

We constructed contingency tables 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 women with RA relative to women without RA, and the model accounted for multiple embryo transfers in the same woman. In the final regression model we adjusted 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 regression model, including data from 2006, we furthermore adjusted for BMI, partner’s age, maternal smoking at the time of embryo transfer, and alcohol, but as this did not change the estimates these factors were omitted from the final model. Using only data from 2004, we examined a possible confounding impact of biologic therapy three months prior to embryo transfer. Use of biologics had however no impact on our results and was omitted from the final model. We also examined a possible impact of use of azathioprine, but because it had no impact our results, it was omitted from the final model.

*Sub-analysis I/the chance of biochemical and clinical pregnancies in women with RA*

We estimated the chance of a biochemical pregnancy (positive hCG) in women with RA relative to women without RA receiving ART. In the multilevel logistic regression we adjusted for Charlson Index, women’s age at time of embryo transfer, calendar year of infertility treatment, type of infertility treatment, and cause of infertility. These analyses were performed to investigate whether a reduced chance of live birth in the main analyses could be due to a reduced chance of conceiving after embryo transfer. From 2006 the ART registry includes complete data on clinical pregnancies.
and we also examined the chance of clinical pregnancy in women with RA relative to women without RA receiving ART (adjusted for Charlson Index, women’s age at time of embryo transfer, calendar year of infertility treatment, type of infertility treatment, and cause of infertility).

Sub-analysis 2/impact of corticosteroid use prior to embryo transfer on the chance of live birth
A possible impact of corticosteroid use prior to embryo transfer in women with RA was studied in sub-cohorts. Information on corticosteroid use was obtained from the nationwide Prescription Registry.[25] Since 1 January 1995 data on out-patient drug prescriptions have been available from this nationwide registry, and all pharmacies in Denmark are equipped with a computerized accounting system which sends key data on out-patient drug prescriptions directly to this prescription database.[25] We thus obtained prescription history of each person with RA (oral corticosteroid use according to ATC codes H02AB02 dexamethasone, H02AB04 methylprednisolone, H02AB06 prednisolone, H02AB07 prednisone, H02AB09 hydrocortisone). According to these information, we established two sub-cohorts among ART treatments in women with RA: a) the exposed cohort were ART treatments in women with RA who had at least one prescription for corticosteroids in a period of 3 months before the date of embryo transfer, and b) the unexposed cohort were ART treatments in women with RA who had not been treated with corticosteroids in the period of 3 months before the date of embryo transfer. Live birth in the exposed cohort a) was compared to the unexposed cohort b). As the nationwide Prescription Registry is valid from 1995, the study period for the sub-analyses was restricted to data from 1995. In the multilevel logistic regression models we adjusted for duration of RA, Charlson Index, women’s age, calendar year of infertility treatment, type of infertility treatment, and cause of infertility. Corresponding to the above, we also examined an impact of prescription of corticosteroids in a period of only 1 month before the date of embryo transfer.
All analyses were conducted using Stata 15 software (StataCorp LP, College Station, TX, USA).

RESULTS

Table 1 shows the characteristics for the all ART treatments in women with RA (exposed cohort) and women without RA (unexposed cohort). A total of 1,149 ART treatments in 354 women with RA were included and 198,941 ART treatments in 66,913 women without RA. Regarding the median age of women, and details on BMI, smoking, alcohol, and parity, the descriptive characteristics were similar in the exposed and unexposed cohorts. In the RA cohort, the cause of infertility was referred to as a female factor in 17.9% of the cases and a mixture of factors in 50.6% of the cases; the corresponding figures among the unexposed cohort were 24.9% and 43.3%, respectively. Among embryo transfers in patients with RA, the median duration of RA at the time of embryo transfer was 82 months (25%-75% percentiles: 42 -134 months). Biologic therapy, available since 2004, was used 80 times within a period of three months prior to embryo transfer in the exposed cohort and 141 times in the unexposed cohort.

Live births

There were 208 live births in the exposed cohort (by 181 women), and 47,077 live births in the unexposed cohort (by 39,325 women). The ORs for an ART treatment in women with RA leading to a live birth, compared to ART treatments in women without RA, are given in Table 2. Both the crude and the adjusted chance of a live birth was significantly reduced per ART treatment in women with RA (adjusted OR (aOR)=0.78 (95% CI 0.65 - 0.92)).

Sub-analysis 1/the chance of biochemical pregnancy and clinical pregnancy

Regarding the chance of a biochemical pregnancy after embryo transfer, the results are shown in Table 3. The adjusted chance of a positive hCG in women with RA, relative to women without RA, was significantly reduced, aOR=0.81 (95% CI 0.68-0.95). Our analyses on the chance of a clinical
pregnancy after ART in women with RA, relative to women without RA, showed similar results, aOR=0.82 (95% CI 0.59-1.15).

**Sub-analysis 2/impact of corticosteroid prior to embryo transfer**

When we examined the impact of prescription of corticosteroids 3 months prior to embryo transfer, the aOR of live birth was 1.32 (95% CI 0.85-2.05) (table 4). Restricting the time period for prescription of corticosteroid to only one month prior to embryo transfer, the aOR for live birth in women with RA was 1.83 (95% CI 1.07-2.37), compared to women with RA who did not have a prescription of corticosteroid.
DISCUSSION

In this nationwide study, based a study period of 23.5 years, we found that ART treatments in women with RA had a significantly decreased chance of live birth per embryo transfer, compared to ART treatments in women without RA. Our results also suggested that the reason for a decreased chance of live birth was related to decreased chance of implantation of the embryo (significantly decreased chance of a biochemical pregnancy after embryo transfer in women with RA and a decreased chance of clinical pregnancy). Lastly, our results suggest that women with RA who had a corticosteroid prescribed before embryo transfer might have an improved chance of a live birth compared to women with RA without corticosteroid prescription before embryo transfer, but our results were not unambiguous.

This is the first study to examine the chance of a live born child in women with RA receiving ART treatment, and therefore our results cannot be compared to others. The relevance for studying the success after ART is however important for a number of reasons: i) the number of women with RA during the fertile years is increasing,[1] ii) earlier studies have suggested that a higher proportion of women with RA were childless compared to references and that the relative fertility rates were reduced after the diagnosis of RA (0.88 (95% CI, 0.84-0.93)),[4] iii) women with RA are more likely to seek help from ART compared to references (9.8% versus 7.6%),[2] and iv) the results in women with other autoimmune diseases have suggested a reduced chance of live birth after ART treatment (ORs for live birth after ART in women with ulcerative colitis and Crohn’s disease were 0.78 (95% CI, 0.67-0.91) and 0.61 (95% CI, 0.47-0.79), respectively).[7] So far, it is unknown which mechanisms might be responsible for these results,[8] and the outcome of live birth can be affected by several factors related to the stages of fertilization, implantation and maintenance of the pregnancy throughout each trimester until child birth.

In this study our findings suggest that the reason of a decreased chance of live birth in women with
RA was related to decreased chance of conceiving for each embryo transfer. Therefore, the reduced chance of live birth after ART treatment in women with RA might be related to the stage of implantation, and not the stage of pregnancy period itself. It is well-known that endometrial receptivity is a key element in a successful ART. It is also known that the immune system is central to establishing receptivity and initiating a pregnancy,[10 26 27] and effective therapies for impaired endometrial receptivity have been the focus for several former studies. In a recent review, Roberson et al. summarize which former therapies have been tried in an effort to improve endometrial receptivity to prevent failure after ART treatment.[10] One candidate drug is corticosteroid with potent and broad-spectrum anti-inflammatory and immunosuppressive properties, but other candidate therapies have also been tried (corticosteroid plus low-dose aspirin and doxycycline).[10] The review concludes that there is no consensus view on the utility of corticosteroid in ART, and the possible efficacy of peri-implantation corticosteroid therapy remains controversial in non-selected IVF and ICSI patients.[10] A Cochrane meta-analysis has indicated that there might be subset of women with immune disorders receiving IVF that benefit from immunosuppressive therapy.[11] The impact of corticosteroid prior to embryo transfer, found in our study, could be due to a suppression of ”abnormalities in the immune system” in women with RA, but we have to underline that this is speculative. Further studies must examine the underlying mechanisms for an effect of corticosteroid in women with RA. In our study, corticosteroid could be prescribed for a number of reasons, including ii) the 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/or ii) patients with RA could receive corticosteroids because it is a well-known treatment for RA,[28 29] and because they constitute an important part of supplementary treatment to control of disease activity.[30 31] In our data, the underlying reason for prescribing corticosteroids cannot be established.
Our study has several strengths, including the large size, accurate classification of exposure, high validity of outcome data, and the ability to consider the most important confounders. First, our study is based on a nationwide study population including all patients with RA who had ART treatments during a long study period, compared to all other ART-treated women as controls. 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,[13 14] and the nature of our large cohorts of ART cycles provides a high statistical power. Data from the health registries used in this study are based on obligatory registrations, and we have a high completeness and validity.[17 18 22 23 25] Second, to ensure accurate exposure assessment (i.e., the diagnosis of RA) we only included women if they had at least two diagnoses of RA before ART treatment. The validity of the diagnosis has been studied based on the Danish NPR and was 80%, and when the patients had at least two diagnoses, RA was confirmed in up to 91%.[32] Third, regarding our outcome measurements on live birth, the data from the MBR have both very high completeness and validity as all new-born children are registered in the MBR.[22 23] Fourth, 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. Finally, we were able to control for important confounders, including Charlson comorbidity index, women’s age, calendar year of ART treatment, type of ART treatment, cause of infertility, and smoking. In a restricted study period we were also able to adjust for BMI, biologic therapy, partner’s age, smoking at the time of embryo transfer, and alcohol, but inclusion of these factors in the model had no impact our results.

Our study also has limitations. Some might argue that our finding of a decreased chance of live birth per embryo transfer in women with RA may not be related to the disease itself but impacted by related factors such as disease activity and/or the medications used to treat RA. Our results do not
reveal whether the decreased chance of live birth per embryo transfer in women with RA is related to the disease itself or to factors closely related to RA. Since this is a large register-based study, we cannot perform individual charts review, and we cannot obtain information on clinical details such as disease extent, disease activity, and exact medication. In our analyses of an impact of corticosteroid prior to embryo transfer we had no opportunity to assess a possible importance of the dose of corticosteroids, or the timing of use of corticosteroid prior to embryo transfer, as information on use of corticosteroid was based solely on prescriptions. Thus, we had no information on patient compliance. We had information on several confounders, but we can never rule out an impact of unknown confounding. We had no information on socioeconomic status but we have no reason to believe that our results are confounded by such factors.

In the general population in Denmark, up to 16% of all women have problems with infertility, and when combining non-achievement of a first and/or a subsequent pregnancy the infertility proportion reaches 24.2%.[33] Seeking help from ART has therefore become common, and children born after ART often contribute up to 5% of national birth cohorts.[34] Patients starting the process of ART treatment need information about their potential for a successful live birth, and one of the ways to report this is the chance for a live birth per embryo transfer as we did in the present study. Because of an increasing prevalence of many chronic diseases in women during the reproductive period, questions about the efficacy of ART in these women become more and more important. Thus, clinicians will likely be faced with an increasing number of questions related to ART, not only from women with RA, but also from women with other chronic disease.[1]

We conclude that women with RA have a decreased chance of a live birth per embryo transfer compared to women without RA, and the problem might be related to impaired chance of embryo implantation. Our results on the role of corticosteroid prior to embryo transfer are not unambiguous, and future studies must examine the mechanisms between corticosteroid, and other medications for
RA, in relation to fertilization and implantation. These are the first results on the efficacy of ART treatment in women with RA, and future studies have to confirm our findings. Several factors might thus be related to a decreased chance of a live birth after ART treatment in women with RA: the disease itself/disease associated factors, different ART techniques, imbalance in reproductive hormones in the process of ART, impaired chance of implantation of the embryo, autoimmunity, or other factors yet to be elucidated. Hopefully, these first results will support treatment decisions in patients with RA seeking ART, and our results suggest that the patients should be told that they cannot expect the same success per embryo transfer as other women seeking ART.
Contributors

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

MDL: data collection, data analyses, interpretation of results, manuscript editing, approved the final version.

SF: interpretation of results, manuscript editing, approved the final version.

TK: interpretation of results, manuscript editing, approved the final version.

JF: assistance with data analyses, interpretation of results, manuscript editing, approved the final version.

Funding

The study was supported by the Research Foundation of the Region of Southern Denmark, and the Free Research Foundation at Odense University Hospital, Denmark.

Competing interests

None

Permissions

The study was approved by the Danish Data Protection Agency (j.nr. 2012-58-0018, 17/37434).

According to Danish law, there are no ethical approvals of register-based studies necessary.
REFERENCES


Table 1 Descriptive characteristics of study cohorts of assisted reproductive technology (ART) treatments in women with rheumatoid arthritis and without rheumatoid arthritis during the study period of January 1 1994 through 30 June 2017

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Exposed cohort (embryo transfers in women with rheumatoid arthritis) (N=1,149)</th>
<th>Unexposed cohort (embryo transfers in women without rheumatoid arthritis) (N=198,941)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at embryo transfer</td>
<td>Median (25%-75% percentiles) 35 (31-38)</td>
<td>34 (30-37)</td>
</tr>
<tr>
<td>Partner’s age at embryo transfer</td>
<td>Median (25%-75% percentiles) 36 (32-39)</td>
<td>36 (32-40)</td>
</tr>
<tr>
<td>Female/male factor infertility</td>
<td>Female factor, N (%) 197 (17.9)</td>
<td>46,444 (24.9)</td>
</tr>
<tr>
<td></td>
<td>Male factor, N (%) 345 (31.4)</td>
<td>59,507 (31.9)</td>
</tr>
<tr>
<td></td>
<td>Mixture of factors/idiopathic, N (%) 556 (50.6)</td>
<td>80,836 (43.3)</td>
</tr>
<tr>
<td>Type of preceding treatment</td>
<td>IVF, N (%) 498 (43.9)</td>
<td>89,913 (45.5)</td>
</tr>
<tr>
<td></td>
<td>CSI, N (%) 375 (33.0)</td>
<td>69,174 (35.0)</td>
</tr>
<tr>
<td></td>
<td>FER, N (%) 262 (23.1)</td>
<td>38,682 (19.6)</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;18.5 (underweight), N (%) 15 (2.1)</td>
<td>3,364 (3.4)</td>
</tr>
<tr>
<td></td>
<td>18.5-24.99 (normal), N (%) 436 (60.6)</td>
<td>64,047 (63.9)</td>
</tr>
<tr>
<td></td>
<td>25.00-29.99 (overweight), N (%) 179 (24.9)</td>
<td>23,019 (23.0)</td>
</tr>
<tr>
<td></td>
<td>≥30.00 (obese) N (%) 89 (12.4)</td>
<td>9,846 (9.8)</td>
</tr>
<tr>
<td>Smoking at the time of embryo transfer</td>
<td>Non-smoker, N (%) 648 (88.8)</td>
<td>91,144 (91.5)</td>
</tr>
<tr>
<td></td>
<td>Smoker, N (%) 82 (11.2)</td>
<td>8,437 (8.5)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>No, N (%) 419 (59.9)</td>
<td>52,857 (55.4)</td>
</tr>
<tr>
<td></td>
<td>Yes, N(%) 280 (40.1)</td>
<td>42,632 (44.6)</td>
</tr>
</tbody>
</table>
Calendar year of infertility treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>N (%).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994-1999</td>
<td>56</td>
</tr>
<tr>
<td>(4.9)</td>
<td>30,664</td>
</tr>
<tr>
<td>(15.4)</td>
<td></td>
</tr>
<tr>
<td>2000-2005</td>
<td>191</td>
</tr>
<tr>
<td>(16.6)</td>
<td>46,142</td>
</tr>
<tr>
<td>(23.2)</td>
<td></td>
</tr>
<tr>
<td>2006-2011</td>
<td>426</td>
</tr>
<tr>
<td>(37.1)</td>
<td>60,153</td>
</tr>
<tr>
<td>(30.2)</td>
<td></td>
</tr>
<tr>
<td>2012-2017</td>
<td>476</td>
</tr>
<tr>
<td>(41.4)</td>
<td>61,982</td>
</tr>
<tr>
<td>(31.2)</td>
<td></td>
</tr>
</tbody>
</table>

Parity

<table>
<thead>
<tr>
<th>Parity</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, N</td>
<td>144</td>
</tr>
<tr>
<td>(69.9)</td>
<td>31,333</td>
</tr>
<tr>
<td>(67.9)</td>
<td></td>
</tr>
<tr>
<td>1+, N</td>
<td>62</td>
</tr>
<tr>
<td>(30.1)</td>
<td>14,811</td>
</tr>
<tr>
<td>(32.1)</td>
<td></td>
</tr>
</tbody>
</table>

Comorbidity at embryo transfers

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No comorbidity</td>
<td>668</td>
</tr>
<tr>
<td>(58.1)</td>
<td>181,773</td>
</tr>
<tr>
<td>(91.4)</td>
<td></td>
</tr>
<tr>
<td>Some comorbidity</td>
<td>481</td>
</tr>
<tr>
<td>(41.9)</td>
<td>17,168</td>
</tr>
<tr>
<td>(8.6)</td>
<td></td>
</tr>
</tbody>
</table>

Duration of rheumatoid arthritis at time of embryo transfer (months)

| Median (25-75 percentiles) | 82 (42-134) |

Table 2 The chance of live birth in women with rheumatoid arthritis in the study cohorts of assisted reproductive technology (ART) treatments during the study period of 1 January 1994 through 30 June 2017.

<table>
<thead>
<tr>
<th>Live birth</th>
<th>Exposed cohort (embryo transfers in women with rheumatoid arthritis)(^a)</th>
<th>Unexposed cohort (embryo transfers in women without rheumatoid arthritis)(^b)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR(^c) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, N(%)</td>
<td>208 (18.10)</td>
<td>47,077 (23.66)</td>
<td>0.70 (0.59-0.84)</td>
<td>0.78 (0.65-0.92)</td>
</tr>
<tr>
<td>No, N(%)</td>
<td>941 (81.90)</td>
<td>15,1864 (76.34)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Number of embryo transfers in the exposed cohort: 1,149 (number of women: 354).

\(^b\) Number of embryo transfers in the unexposed cohort: 198,941 (number of women: 66,913).
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 observations=186,710, number of women=66,133

Table 3 The chance of a biochemical pregnancy and a clinical pregnancy in women with rheumatoid arthritis having assisted reproductive technology (ART) treatments.

|                                | Exposed cohort (embryo transfers in women with rheumatoid arthritis) | Unexposed cohort (embryo transfers in women without rheumatoid arthritis) | Crude OR (95% CI) | Adjusted OR (95% CI)^
|--------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------|----------------------
| Biochemical pregnancy (hCG)^b  | Yes, N (%) 795 (70.04)                                               | 70,346 (35.62)                                                           | 0.76 (0.65-0.88)  | 0.81 (0.68-0.95)     |
|                                | No, N (%) 340 (29.96)                                                | 127,155 (64.38)                                                          |                   |                      |
| Clinical Pregnancy (ultrasound)^c | Yes, N (%) 204 (77.57)                                               | 35,114 (82.23)                                                           | 0.74 (0.53-1.03)  | 0.82 (0.59-1.15)     |
|                                | No, N (%) 59 (22.43)                                                 | 7,590 (17.77)                                                            |                   |                      |

^a 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).

^b Number of embryo transfers in the exposed cohort: 1,135 (number of women: 354) missing 14. Number of embryo transfers in the unexposed cohort: 197,501 (number of women: 66,870) missing 1,440.

^c Restricted to 2006-June 2017 due to only valid data on ultrasound from 2006. Number of embryo transfers in the exposed cohort: 263 (number of women: 182) missing/no information: 640. Number of embryo transfers in the unexposed cohort: 42,704 (number of women: 29,451) missing/not taken 79,925.
Table 4 The chance of live birth in women with rheumatoid arthritis who had prescriptions for corticosteroids 3 months prior to embryo transfer, compared with women with rheumatoid arthritis who did not have prescriptions for corticosteroids 3 months prior to embryo transfer, study period of 1 January 1995 through 30 June 2017.

<table>
<thead>
<tr>
<th>Exposed cohort (embryo transfers in women with rheumatoid arthritis with prescriptions for corticosteroids prior to embryo transfer)</th>
<th>Unexposed cohort (embryo transfers in women with rheumatoid arthritis who did not have prescriptions for corticosteroids prior to embryo transfer)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR(^c) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, N(%)</td>
<td>51 (19.69)</td>
<td>156 (17.61)</td>
<td>1.20 (0.81-1.77)</td>
</tr>
<tr>
<td>No, N(%)</td>
<td>208 (80.31)</td>
<td>730 (82.39)</td>
<td>1.32 (0.85-2.05)</td>
</tr>
</tbody>
</table>

\(^a\) Number of embryo transfers in the *exposed* cohort: 259

\(^b\) Number of embryo transfers in the *unexposed* cohort: 886

\(^c\) 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), and disease duration of rheumatoid arthritis. Number of observations=825 (number of women=258)
Key messages

What is already known about this subject?

- Rheumatic disease represents one of the most common chronic diseases in women during the fertile years and former studies have indicated that women with rheumatoid arthritis have difficulty conceiving compared with reference populations. The efficacy of assisted reproduction (ART) in women with rheumatoid arthritis has never been studied.

What does this study add?

- In this nationwide study we found that ART treatments in women with rheumatoid arthritis had a significantly decreased chance of live birth per embryo transfer, compared to ART treatments in women without rheumatoid arthritis, and our data suggest that the reason is related to decreased chance of implantation of the embryo.

- Our results on the role of corticosteroid prior to embryo transfer are not unambiguous, and future studies must examine the mechanisms between corticosteroid, and other medications for rheumatoid arthritis, in relation to fertilization and implantation.

How might this impact on clinical practice or future developments?

- These first data on the efficacy of ART treatment in women with rheumatoid arthritis suggest that they cannot expect the same success per embryo transfer as other women seeking ART. Future studies have to examine the role of corticosteroids prior to embryo transfer in women with autoimmune diseases.

- Our results should be considered when planning the offered number of ART treatment cycles in women with rheumatoid arthritis, and when preparing clinical guidelines for ART treatments.