ORIGINAL ARTICLE

Subfertility in Women With Rheumatoid Arthritis and the Outcome of Fertility Assessments

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Objective. Subfertility is frequently encountered among female rheumatoid arthritis (RA) patients and has been associated with disease activity and antirheumatic drugs. However, little is known about the results of the fertility assessments in these women. Our aim was to study the outcome of fertility assessments in subfertile women with RA.
Methods. A cross-sectional study was performed in a nationwide cohort of female RA patients who were pregnant or trying to conceive between 2002 and 2010 (Pregnancy-Induced Amelioration of Rheumatoid Arthritis Study). Patients who had given consent for future contact (n = 260) received a questionnaire on reproductive history, fertility examinations, and fertility treatments. Medical files were obtained from attending gynecologists.
Results. A completed questionnaire was returned by 178 women (68%), of whom 96% had ended their efforts to conceive. Eighty-two subjects (46%) had at least 1 subfertile episode, and for 61 women a diagnosis for subfertility was available. Unexplained subfertility (48%) and anovulation (28%) were the most common gynecologic diagnoses, and both occurred more often in RA patients than reported in the general population. Women with unexplained subfertility more often used nonsteroidal antiinflammatory drugs (NSAIDs) during the periconceptional period. Seventeen percent of all pregnancies were conceived after fertility treatments. Fertility treatments had equal or higher pregnancy rates in RA compared to other subfertile populations.
Conclusion. Unexplained subfertility is more often diagnosed in subfertile female RA patients than in the general population, and is related to periconceptional NSAID use. Despite the higher incidence of subfertility in women with RA, the outcome of fertility treatments in these women appears favorable.

INTRODUCTION

Fertility is compromised in women with rheumatoid arthritis (RA). They often have fewer children than they intended to have and they are more often nulliparous (1,2). In 36–42% of female RA patients diagnosed before family completion, the time to pregnancy (TTP) exceeds 12 months (1,3), whereas in the general population, this is only the case in 10–17% of couples (4–6). Since in most women with RA antirheumatic treatment has to be adjusted before they start trying to conceive, a longer TTP can result in a prolonged period with less adequately controlled disease and consequently an increased risk for permanent damage to the joints. Hence, understanding the underlying mechanisms of subfertility in RA, and treatment of these mechanisms whenever possible, would be an important step forward in the care for these patients.

Fertility in a couple might be compromised by many different factors, in the male as well as in the female partner. Male factors for subfertility include disorders in spermatogenesis or obstructions, causing oligospermia or azoospermia, and ejaculatory dysfunction. Female causes include anovulation, unilateral or bilateral tubal occlusion, and endometriosis. In 8–28% of subfertile couples, no specific cause is found during fertility assessments. They are generally referred to as couples with unexplained subfertility (5,7).

In most studies on fertility in RA, gynecologic data are missing. It has been reported that pregnant women with RA more often had a fertility treatment than pregnant

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Significance & Innovations

- Subfertility in female rheumatoid arthritis (RA) patients is most often unexplained or caused by anovulation.
- The high percentage of RA patients, diagnosed with unexplained subfertility by a gynecologist, may suggest that RA-related factors are causally involved in subfertility in women with RA.
- The diagnosis of unexplained subfertility is associated with periconceptional nonsteroidal antiinflammatory drug use.

controls (8). However, little is known on the outcome of fertility assessments, and details on subfertility diagnoses have not been reported.

To study the outcome of fertility assessments in women with RA who experience subfertility, we performed a cross-sectional study in female RA patients from the Pregnancy-Induced Amelioration of Rheumatoid Arthritis (PARA) cohort.

PATIENTS AND METHODS

Patients. Patients from the PARA study were invited to participate. The PARA study was a nationwide prospective observational cohort in the Netherlands (2002–2010) that included women with RA (1987 revised American College of Rheumatology criteria [9]) who were trying to conceive or were in their first trimester of pregnancy. PARA participants had to have a good understanding of the Dutch language and were allowed to participate more than once. Both the PARA study and this followup study were approved by the Erasmus MC Medical Ethical Review Board. Of the 297 patients in the PARA cohort, 290 women gave permission to be contacted for future research. For 30 of them no current address was known.

For comparison of the occurrence of different subfertility diagnoses in women with RA to the general population, the incidence of these diagnoses in 2 reference populations with subfertility are reported (5,7).

Data collection. Eligible patients received a printed questionnaire accompanied by a postage-paid return envelope. Questionnaires included inquiries on their reproductive history, TTP in months and mode of conception for each pregnancy, visits to a gynecologist, fertility assessments, and fertility treatments.

When patients consented, data on fertility assessments were collected from the previously attended gynecologists. The received files and letters were checked for menstrual cycle length, cycle irregularities and their classification (according to the World Health Organization classification [10]), measurements of follicle-stimulating hormone, estrogens and progesterone, presence of ovulation, history of pelvic inflammatory disease, tests for tubal

function (hysterosalpingography, laparoscopy), presence of endometriosis, abdominal adhesions, and sperm analysis. The diagnosis was recorded. Furthermore, data on performed fertility treatments and their results were collected. When not all required data could be extracted from the received information, another letter was sent to the gynecologist explicitly requesting the missing items. In cases where the fertility examination was not reported in full detail in the information received, we registered the diagnostic conclusion reported by the gynecologist, assuming the examination was performed according to the general consensus, as described in the national guideline by the Dutch Society for Obstetrics and Gynaecology (11). These guidelines describe that in all couples consulting a gynecologist for subfertility, a fertility examination includes at least the following: excluding anovulation by measuring a midluteal serum progesterone, assessing the male's fertility by performing a sperm analysis, and establishing Fallopian tube patency either by performing a *Chlamydia* antibody screening or by performing a laparoscopy or a hysterosalpingogram.

According to the national guideline (www.nvog.nl), unexplained subfertility was recorded when fertility assessments did not show any plausible explanation for the delay in the occurrence of a pregnancy (12).

RA disease characteristics were drawn from the PARA study database (13), including date of diagnosis, presence of rheumatoid factor or anti–citrullinated protein antibodies, and disease activity scores (13). Disease activity was scored using tender and swollen joint counts in 28 joints (DAS28), and serum C-reactive protein levels (14). When available, the preconceptional DAS28 of the designated PARA episode was used, otherwise the first trimester DAS28 of the same episode was used (3).

Statistical analysis. To study potential selection bias, participants and nonparticipants were compared on obstetric history and disease characteristics as recorded during the last PARA episode in which a subject had participated. Intergroup differences were calculated using the Student's *t*-test and Mann-Whitney U test for continuous outcome, and the chi-square test or Fisher's exact test for categorical outcome. Numbers of pregnancies, children, and miscarriages were compared using a Mann-Whitney U test.

The association of subfertility diagnoses with RA disease characteristics were studied using the chi-square test, Fisher's exact test, or Student's *t*-test. Disease activity scores and periconceptional use of nonsteroidal antiinflammatory drugs (NSAIDs) and prednisone from the first subfertile episode in the PARA study were used. A 2-sided *P* value less than 0.05 was considered significant. Software used was IBM SPSS statistics, version 21, and STATA/SE 14.1.

RESULTS

Participants. Of the 260 questionnaires sent, 178 (68%) were completed and returned (Figure 1). Participants and nonparticipants were compared (Table 1). Significantly
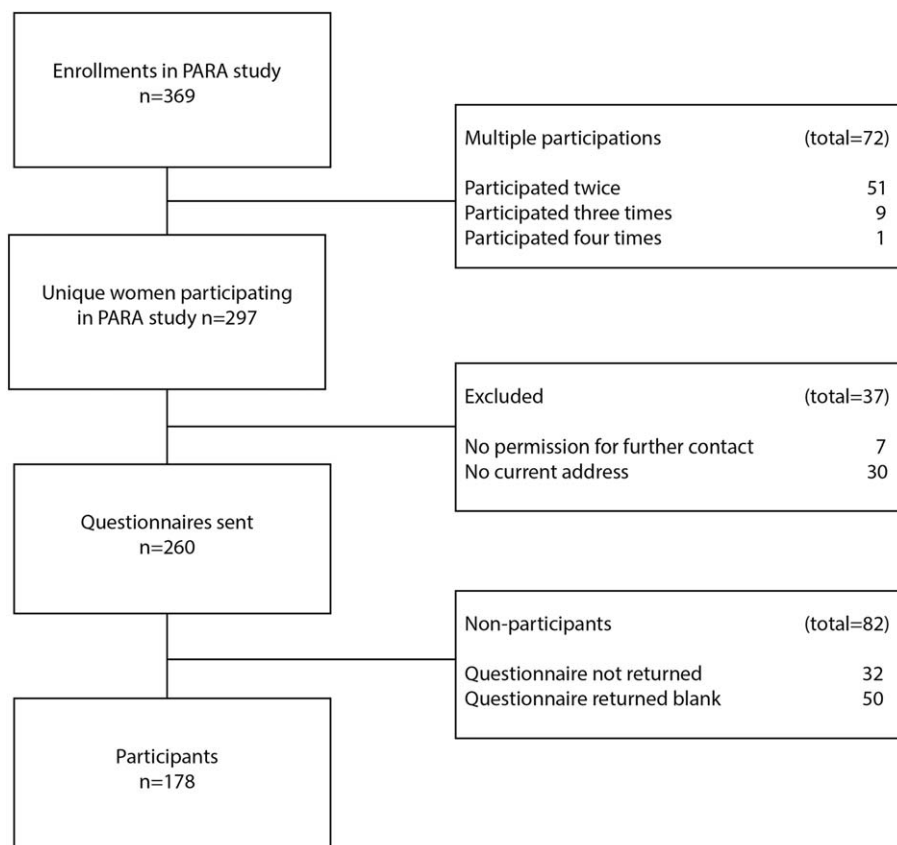
Figure 1. Flow chart of the study population and inclusion of study participants. PARA = Pregnancy-Induced Amelioration of Rheumatoid Arthritis.

more nonparticipants had not achieved a pregnancy during their most recent PARA study episode (37%) compared to participants (17%) ($P = 0.001$). More often, nonparticipants were nulliparous at the end of their participation in the PARA study (24% versus 9%; $P = 0.002$). There were more smokers among nonparticipants (22%) than in participants (6.7%) ($P = 0.001$). Participants and nonparticipants did not differ significantly regarding age, education level, number of children they had already had, disease characteristics, or percentage of miscarriages or pregnancy complications.

Reproductive history. Of the participants, 170 women (96%) had ended their efforts to establish a pregnancy. Reasons to stop trying to conceive were (multiple answers per subject possible): a complete family (72%), advanced age (20%), increase of RA symptoms or the need for antirheumatic drugs incompatible with pregnancy (together 19%), other health problems that complicated conception, or taking care of a child (3%). In 9 women (5%) there were no more fertility treatments available or their gynecologist advised against a new pregnancy. In 3% the mental burden of the wish to conceive was a reason to end their attempts at pregnancy, and in 1% relational problems played a role. In total, 28% ended their efforts before they felt their family was complete. Fifty-nine women (33%) put their efforts to conceive on hold for 1 or more intervals, and in 32% this was due to RA symptoms or

the need for antirheumatic drugs incompatible with pregnancy.

The participants had a total of 412 pregnancies, with a median of 2 pregnancies (interquartile range [IQR] 2–3, mean ± SD 2.3 ± 1.0) per woman. Of all reported pregnancies, 354 pregnancies (86%) were conceived after a diagnosis of RA. Thirty-three percent of the women had 1 or more miscarriages (median 0, IQR 0–1, mean ± SD 0.42 ± 0.69). The total number of miscarriages was 75. There were 334 live-born children in the study population (median 2, IQR 1–2, mean ± SD 1.9 ± 0.78 per woman), with a maximum of 4 children per woman. Nine women (5%) remained nulliparous, of whom 6 (3% of participants) had never been pregnant, and 3 women (2%) had only had pregnancies resulting in a miscarriage.

Fertility assessments. Eighty-two women (46%; 95% confidence interval 39%–53%) were considered subfertile because they met at least 1 of the following criteria: a TTP exceeding 12 months during at least 1 attempt to establish a pregnancy (n = 66), the use of fertility treatments to get pregnant (n = 41), or never having achieved a pregnancy (n = 6). Sixty-six women (37%) had a primary subfertility, and 16 women (9%) experienced secondary subfertility. The mean ± SD age during the first subfertile episode was 29.4 ± 3.9 years.

Subfertile women established significantly fewer pregnancies (2 [IQR 1–2, mean ± SD 2.1 ± 1.1] versus 2 [IQR

Table 1. Characteristics of participants and nonparticipants*			
	Participants (n = 178)	**Nonparticipants (n = 82)**	***P***
Current age, years	40.5 ± 4.2	40.6 ± 4.3	0.834†
Missing	1 (0.6)	–	
Education level			0.51‡
Low	11 (6.2)	5 (6.1)	
Intermediate	74 (42)	18 (22)	
High	93 (52)	28 (34)	
Missing	–	31 (38)	
At start of last PARA episode			
Age during PARA, years	32.4 ± 4.0	32.5 ± 4.0	0.905†
Missing	2 (1.1)	–	
Previous children, median (IQR)	1 (0–1)	0 (0–1)	0.55§
Mean	0.61 ± 0.63	0.59 ± 0.72	
Missing	–	1 (1.2)	
Smokers	12 (6.7)	18 (22)	< 0.001¶
Missing	2 (1.1)	2 (2.4)	
Duration of RA, years	15.0 ± 6.6	13.7 ± 5.9	0.135†
RF positivity#	129 (72)	59 (72)	0.826¶
Missing	4 (2.2)	1 (1.2)	
ACPA positivity#	114 (64)	55 (67)	0.584¶
Missing	1 (0.6)	1 (1.2)	
Periconceptional DAS28#	3.7 ± 1.2	3.5 ± 1.3	0.394†
Missing	17 (9.6)	4 (4.8)	
Obstetric outcome of last PARA participation			
Achieved pregnancy	147 (83)	52 (63)	0.001¶
Life birth**	143 (97)	50 (96)	0.653††
Miscarriages**	4 (2.7)	1 (1.9)	1.000††
Maternal complications**	39 (27)	12 (23)	0.715††
Neonatal complications**	24 (16)	7 (13)	0.824¶
Nulliparous at end of PARA study	16 (9.0)	20 (24)	0.002††
Missing	1 (0.6)	2 (2.4)	

* Values are the mean ± SD or the number (percentage) unless indicated otherwise. PARA = Pregnancy-Induced Amelioration of Rheumatoid Arthritis; IQR = interquartile range; RA = rheumatoid arthritis; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; DAS28 = Disease Activity Score in 28 joints.
† By unpaired *t*-test.
‡ By Fisher's exact test on nonmissing data.
§ By Mann-Whitney U test.
¶ By chi-square test.
# At the start of the last PARA participation.
** As a percentage of achieved pregnancies during last PARA participation.
†† By Fisher's exact test.

1–3, mean ± SD 2.5 ± 1.0]; *P* = 0.004) and had fewer children (2 [IQR 1–2, mean ± SD 1.6 ± 0.9] versus 2 [IQR 1–2, mean ± SD 2.1 ± 0.6]; *P* = 0.001) than fertile women with RA. The number of miscarriages per woman in both groups was not significantly different (*P* = 0.33).

The total number of pregnancies in the subfertile women was 168, resulting in 132 live-born children. Of these pregnancies, 52 (31%) were conceived spontaneously within 12 months, 48 spontaneously conceived pregnancies (29%) had a TTP >12 months, and 68 pregnancies (40%, i.e., 17% of all pregnancies) were conceived with the help of fertility treatments (Figure 2).

Fertility diagnoses. Eight subfertile women (10%) had never visited a gynecologist. Of the other 74 subfertile women, 65 women (88%) gave permission to collect data from their gynecologist. Data were obtained for 64 women, of whom 61 women received a diagnosis for subfertility.

The other 3 women became pregnant spontaneously before the fertility assessment was completed. The 61 women with a diagnosis were compared to the 21 subfertile women without available diagnosis, showing no significant differences regarding age, reproductive history, or disease characteristics. More women without available gynecologic files had ever used methotrexate (81% versus 54%; *P* = 0.030).

In the 61 women for whom a diagnosis for subfertility was available, subfertility was most often caused by unexplained subfertility (48% of known diagnoses), anovulation (28%), and semen abnormalities (16%) (Table 2). In 2 women (3%) anovulation was due to primary ovarian insufficiency (POI). In 5% of the couples there was both a female and a male cause for subfertility. For 8 of the 61 couples, the gynecologist did not report the result of a sperm analysis. Diagnoses in these women were unexplained (n = 2), vaginismus (n = 1), anovulation (n = 4),
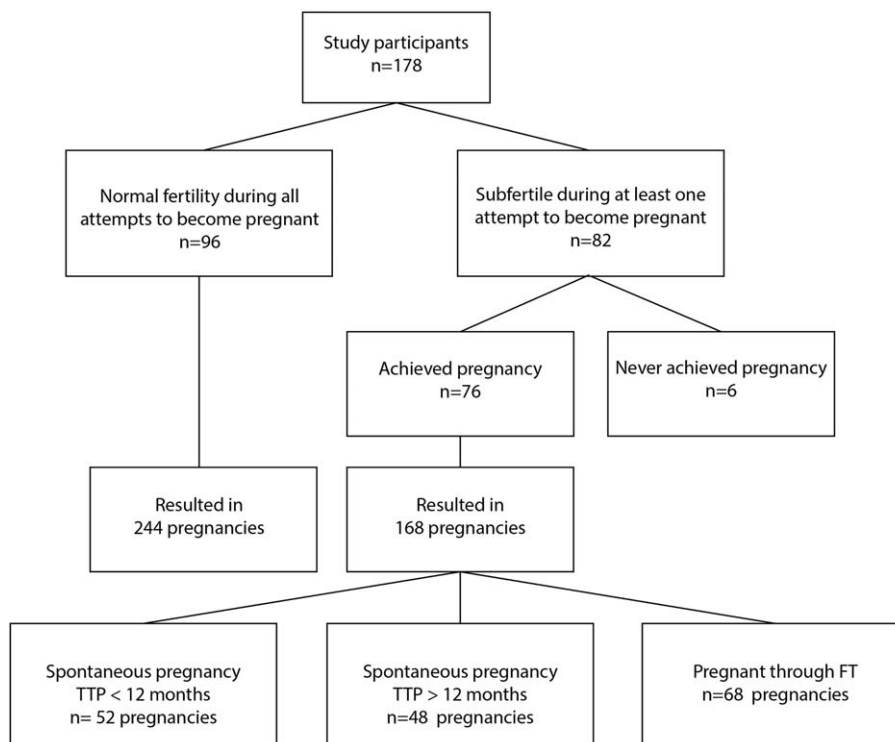
Figure 2. Overview of study participants, pregnancies, and subfertility. TTP = time to pregnancy; FT = fertility treatment.

and endometriosis (n = 1). For the 10 women for whom no gynecology file was available, the self-reported diagnoses were unexplained subfertility (n = 4), tubal factor (n = 2), anovulation (n = 3, n = 1 due to POI), and endometriosis (n = 1) (Table 2).

Of the women diagnosed by a gynecologist (n = 61), 56 (92%) had a subfertile episode in the PARA study, of whom 27 had unexplained subfertility and 14 had anovulation. When comparing women with unexplained subfertility to other subfertile RA patients, there was a significant difference in periconceptional NSAIDs use (48% versus 17%; $P = 0.013$), which was also significant when self-reported diagnoses were included (NSAIDs use 45% versus 22%; $P = 0.046$). None of the other associations, among which were disease activity and periconceptional prednisone use, were significant. Women with anovulation showed no statistically significant differences compared to ovulatory subfertile women.

Fertility treatments. The most frequently performed fertility treatments are summarized in Table 3. Treatments were performed in 59 subfertile women (72%), which is

	Diagnosis by gynecologist (n = 61)	Including self-reported diagnoses (n = 71)	Reference population	
			Hull et al, 1985 (5), %	Thonneau et al, 1991 (7), %
Diagnosis				
Unexplained subfertility†	29 (48)	33 (46)	31	12
Anovulation‡	17 (28)	20 (28)	21	32
Male factor§	10 (16)	10 (14)	26	58
Endometriosis	4 (6.6)	5 (7.0)	6	4
Tubal occlusion§	2 (3.3)	4 (5.6)	14	26
Vaginismus	2 (3.3)	2 (2.8)	NA	NA

Table 2.   Fertility diagnoses in subfertile RA patients from the PARA study*

* Values are the number (percentage) unless indicated otherwise. RA = rheumatoid arthritis; PARA = Pregnancy-Induced Amelioration of Rheumatoid Arthritis; NA = not applicable.
† Unexplained subfertility includes a diagnosis of cervical hostility.
‡ In 2 couples there was both anovulation and a male factor. In 2 women anovulation was due to premature ovarian insufficiency.
§ In 2 couples there was both anovulation and a male factor. In 1 couple there was both tubal occlusion and a male factor.

Table 3.   Fertility treatment results in female rheumatoid arthritis patients from the PARA study*

| Treatment | Subjects (n = 55)† | Treatments, no. | | Resulted in pregnancy | | Pregnancy rate | |
		Sum (range)	Missing for no. subjects	Subjects (n = 38)‡	Pregnancies (n = 64)‡	Per cycle, %	Per woman, %§
IUI¶	36	178 (1–11)	3	12	19	11	33
OI	17	77 (1–12)	3	10	15	19	59
IVF	20	42 (1–4)	1	10	17	40	50
ICSI	8	25 (1–6)	–	8	15	60	100

* PARA = Pregnancy-Induced Amelioration of Rheumatoid Arthritis; IUI = intrauterine insemination; OI = ovulation induction (with either clomiphene citrate or follicle-stimulating hormone injections); IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection.
† Eighteen women had 2 types of treatments; 4 women underwent 3 different types of treatment.
‡ One woman achieved a first pregnancy after IUI, and a second pregnancy after IVF; 1 woman conceived twice after IUI combined with OI.
§ Percentage of women with at least 1 pregnancy (of total number of women who started treatment).
¶ In 10 women, IUI was combined with mild ovarian hyperstimulation (MOH); 9 pregnancies were after IUI with MOH.

80% of the women who visited a gynecologist for subfertility. In 41 women (50% of all subfertile women), fertility treatments resulted in at least 1 pregnancy, and in 28 of these women all conceptions were with the help of fertility treatments. Thirteen of the 20 women (65%) who started an in vitro fertilization (IVF) treatment had had intrauterine inseminations (IUIs) before. Treatments not reported in the table are intravaginal insemination (1 subject), oocyte donation (1 subject), and sperm donation (2 subjects).

DISCUSSION

This study aimed to explore the outcome of fertility assessments in those RA patients with subfertility. We found that subfertility in women with RA was most often unexplained or caused by anovulation. Moreover, the majority of subfertile RA patients received fertility treatments, and a considerable number of all pregnancies were conceived after women had been treated for subfertility.

In comparison to the general population, female RA patients appear to be more often diagnosed with unexplained subfertility (5,7,15,16), whereas the percentage of subfertile women with anovulation was equal or slightly increased compared to percentages found in the general population (5,7,15,16). The incidence of POI appears to be higher than in the general population (17).

The high percentage of RA patients diagnosed by the gynecologist with unexplained subfertility may imply that fertility in female RA patients is influenced by disease-related factors. There was a significant association of periconceptional NSAIDs use with unexplained subfertility. This is in concordance with a previous study within the PARA cohort where we have shown that a longer TTP was associated with the periconceptional use of NSAIDs, also when corrected for disease activity scores (3). In this previous study, a longer TTP was also associated with an increase in periconceptional disease activity and the periconceptional use of prednisone (3). The current results showed neither significant differences in disease activity nor in periconceptional prednisone use between unexplained subfertile women and other subfertile RA women. However, since the current study was not designed to look into these associations, the numbers of patients in these comparisons were relatively small, and the timing of the study visit was not concurrent with the timing of the fertility examination, these results do not exclude disease activity or prednisone use as a cause for subfertility in RA.

Looking further into the association of NSAIDs with subfertility, NSAIDs have not been reported to compromise embryo implantation in IVF treatments (18), but there have been reports on NSAIDs interrupting the ovulatory process, possibly leading to the so-called luteinized unruptured follicle (LUF) syndrome (19–22). In LUF syndrome, ovulation is inhibited without changes in menstrual cycle length and cycle regularity and therefore patients with LUF would probably be classified as ovulatory during their fertility examination. However, among gynecologists, the existence of LUF syndrome is controversial, and criteria for the existence of LUF syndrome include a laparoscopic evaluation, with a strict timing, which is lacking in most studies on LUF syndrome (23). Another explanation of the relation of NSAIDs use with unexplained subfertility may be the effect of pain on sexual intercourse. The use of NSAIDs may indicate that these women experience more pain and therefore they might have less exposure due to a decreased frequency of intercourse. Indeed, sexual intercourse in RA patients is more often limited by pain or fatigue (24), but studies specifically addressing intercourse frequency in RA patients who try to conceive have not been performed. Furthermore, in daily practice, RA patients who are trying to achieve a pregnancy are often very motivated to have regular periovulatory intercourse. However, disease activity was higher in patients who used NSAIDs versus nonusers, suggesting that NSAIDs were taken for pain control. All patients using NSAIDs reported that this was because of RA. No patient reported the use of NSAIDs for other conditions.

The percentage of subfertile subjects who received fertility treatments was almost 50% higher than in the general population (4). Furthermore, the proportion of

pregnancies that were conceived with the help of fertility treatments conforms to earlier findings in the PARA study (25), and is also in line with a Danish National Birth Cohort study reporting that more pregnant RA patients compared to pregnant controls had received a fertility treatment (8). The pregnancy rates per treatment cycle and per woman who started treatment were comparable to other subfertile populations as far as IUI and ovulation induction were concerned (26). On the contrary, the pregnancy rates of IVF and IVF/intracytoplasmic sperm injection (ICSI) treatments were both higher in RA women (27). Therefore, embryo implantation does not seem to be compromised in RA patients. An explanation for the higher pregnancy rate after IVF or ICSI might be explained by an early start of fertility treatment relative to their previous underexposure to preovulatory sexual intercourse. On the other hand, selection bias may have occurred when women who did not get pregnant after fertility treatments were mainly in the nonparticipants group. However, since data on the results of fertility treatments in these women were scarcely available, this remains unclear.

One in 5 women had stopped trying to conceive because of active disease or antirheumatic drugs. In the PARA study, more than one-third of the women did not use any antirheumatic drugs during the periconceptional period, and less than 5% of the women used biologic agents preconceptionally, whereas the disease activity was intermediate or high in the majority of patients (3). Over the last decade, tumor necrosis factor inhibitors have been used increasingly in the periconceptional treatment of women with RA, and appear to be safe (28). Since active disease is associated with a longer TTP (3), subfertile RA patients may benefit from the preconceptional use of these biologic agents, and fewer women would need to end their efforts to build a family because of active disease.

With a higher pregnancy rate and less nulliparity than nonparticipants, the participants in this study seemed to be a more fertile selection of the PARA cohort. Therefore our current results may very well be an underestimation of the real incidence of the total subfertility and their impact on childbearing in the total female RA population. Since the incidence of subfertility in the PARA cohort was consistent with other recent studies in female RA patients of reproductive age (3), it is not likely that selection on subfertility in the recruitment for the original PARA cohort introduced bias in the current study and affected our current results.

An explanation for the lower pregnancy rate and higher nulliparity among the nonparticipants may be that they were less desirous of achieving a pregnancy than the participants. However, this was not the case. No differences were found between participants and nonparticipants in the number of children already present before the final PARA participation. Moreover, within the nonparticipants who did not achieve a pregnancy during the last PARA episode, more women underwent fertility treatments than the nonpregnant participants, although this difference was nonsignificant (data not shown). Therefore, the motivation to achieve a pregnancy appeared not to be diminished in the nonparticipants.

On the other hand, the cause of subfertility may have indirectly affected patients in their choice to participate in the current study. Fertility problems that are hard to treat, e.g., endometriosis, or a severe oligospermia or azoospermia, often have a poor treatment outcome, not leading to the desired pregnancy. Although the patients participating in the current study did not show a higher occurrence of these diagnoses than the general subfertile population, the nonparticipants were more often nulliparous. Therefore, we cannot rule out that the prevalence of these hard-to-treat cases might be more frequent in the nonparticipant group, and consequently also in the total RA population. Furthermore, there were more smokers among nonparticipants than among participants. This may point toward a less healthy lifestyle, which in turn is associated with reduced conception rates (29). Details on smoking behavior, such as package-years, are missing in the PARA study, and could not be analyzed further. However, even if all the nonparticipants with a confirmed fertility examination/fertility treatments had another diagnosis than unexplained subfertility, the percentage of subfertile RA patients with unexplained subfertility would still be higher than in the subfertile part of the general population.

In conclusion, our finding that unexplained subfertility is diagnosed more often in female RA patients than in the general population supports the idea that RA-related factors are causally involved in subfertility in women with RA. Unexplained subfertility was associated with the periconceptional use of NSAIDs. Despite the higher incidence of subfertility in women with RA, the outcome of fertility treatments in these women appears favorable. In future research on fertility in RA, attention should also be given to intercourse frequency and sexual problems, since these are scarcely studied in RA patients trying to conceive. In daily practice, when an RA patient wishes to conceive, NSAIDs should be avoided, and early consultation with an expert rheumatologist and a fertility specialist should be considered to optimize the patient's chance of a complete family.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Ms Brouwer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Brouwer, Fleurbaaij, Hazes, Dolhain.
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