Fertility and Ovarian Reserve among Women with Rheumatoid Arthritis

Amanda M. Eudy, Gary McDaniel, William W. Hurd, and Megan E.B. Clowse

ABSTRACT. ***Objective.*** We sought to identify causes for infertility in women with and without rheumatoid arthritis (RA).

Methods. Women with RA were matched to healthy controls. Differences in anti-Müllerian hormone (AMH) and anovulation were analyzed.

Results. Women with RA had lower AMH (β –1.05, 95% CI –2.09 to –0.005), but no difference was observed when AMH was log-transformed. No difference in anovulation was observed. Infertility prevalence was similar between groups, primarily attributable to polycystic ovary syndrome in healthy controls but largely unexplained in women with RA.

Conclusion. AMH was lower in women with RA, but reasons for infertility among women with RA remain unknown. (First Release November 15 2018; J Rheumatol 2019;46:455–9; doi:10.3899/jrheum.180176)

Key Indexing Terms:
RHEUMATOID ARTHRITIS FERTILITY ANTI–MÜLLERIAN HORMONE PROGESTERONE

Despite decades of data suggesting infertility in women with rheumatoid arthritis (RA), we have limited understanding of why it is so common. In the Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study, a longer time to conception was associated with older age, high RA activity, and current nonsteroidal antiinflammatory drug (NSAID) and prednisone use[1]. Studies of anti–Müllerian hormone (AMH; a marker of ovarian reserve) among women with RA have yielded inconsistent results and questionable association with fertility, with some suggesting a decrease that could be associated with infertility[2,3].

We aimed to identify possible causes for infertility in women with RA by comparing ovarian reserve, anovulation, and other factors between women with and without RA.

From the Division of Rheumatology and Immunology, Department of Medicine, Duke University Medical Center; Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina, USA.

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A.M. Eudy, PhD, Postdoctoral Associate, Division of Rheumatology and Immunology, Duke University Medical Center; G. McDaniel, PA-C, Clinical Research Coordinator, Division of Rheumatology and Immunology, Duke University Medical Center; W.W. Hurd, MD, MSc, MPH, Professor and Director, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Duke University Medical Center; M.E. Clowse, MD, MPH, Associate Professor of Medicine, Division of Rheumatology and Immunology, Duke University Medical Center.

Address correspondence to A.M. Eudy, Duke University Medical Center, Division of Rheumatology and Immunology, DUMC 3490, Durham, North Carolina 27710, USA. E-mail: amanda.eudy@duke.edu

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MATERIALS AND METHODS

This study was approved by Duke Health IRB (Pro00057614).

Cross-sectional study participants. Patients with RA included women aged 20–40 years diagnosed with RA by a Duke University rheumatologist and enrolled following informed consent. Healthy controls included women without autoimmune disease recruited from the Duke Clinical Research Unit Research Volunteer Registry, matched by age and current use of hormonal contraceptives.

Exclusion criteria included (1) unilateral or bilateral ovarian surgery, (2) prior exposure to known or possible ovary-toxic medications, and (3) methotrexate (MTX) treatment for ectopic pregnancy.

Ovarian reserve. AMH was analyzed using a quantitative ELISA. AMH, a serum marker of ovarian reserve, declines slowly with age as ovarian follicles diminish. Levels remain steady across the day and the menstrual cycle, with no differences in levels between the follicular and luteal phases[4,5]. Low AMH was defined by our laboratory as < 1.23 ng/dl (ages 20–25 yrs), < 1.03 ng/dl (ages 26–30 yrs), < 0.66 ng/dl (ages 31–35 yrs), and < 0.42 ng/dl (ages 36–40). For 90% power to detect a 0.5 ng/dl in AMH between patients with RA and controls[6], we required 69 patients in each group.

Anovulation. For participants not using hormonal contraception, progesterone ≤ 3 ng/ml on days 21–23 of a menstrual cycle indicated anovulation[7]. Participants recorded medication use during the menstrual cycle of study. Thyroid-stimulating hormone (TSH), prolactin, and testosterone were measured in women with anovulation. Polycystic ovary syndrome (PCOS) was patient-reported along with associated symptoms, including hirsutism defined as Ferriman-Gallwey score ≥ 8[8,9]. Obesity was defined as body mass index ≥ 30 kg/m^2.

Infertility. All participants completed a reproductive health questionnaire. Women with a prior pregnancy reported time to conception. Infertility was defined as (1) inability to conceive after 12 months of trying, or (2) physician-reported diagnosis of infertility. Subfertility was defined as time to conception ≥ 12 months.

Analysis. Ovarian reserve and anovulation were compared between groups. Among women with RA, these measures were compared based on current and prior RA medication use, duration of MTX use, and current disease activity (Routine Assessment of Patient Index Data 3 and physician's global assessment[10]). Differences in proportions were analyzed by Fisher's exact test, and differences in continuous variables were analyzed by Wilcoxon

rank-sum test and ANOVA. AMH was log-transformed and analyzed by multivariable linear models adjusted for age, hormonal contraceptive use, and race. Anovulation was analyzed by logistic regression models adjusted for age and race.

Logistic regression models analyzed differences in infertility, and generalized linear models estimated differences in the average number of pregnancies and live births. Models were adjusted for education, marital status, and race. SAS 9.4 (SAS Institute Inc.) was used for all analyses.

RESULTS

The study included 75 women with RA and 75 healthy controls (Table 1). While matched for age (mean 32 ± SD 5.1) and contraceptive use, women in the control group were more likely to be African American, unmarried, educated beyond college, and working full time, compared to women with RA. The average duration of RA was 9 years.

Table 1. Study participant characteristics.

Characteristics	Healthy Controls, n = 75	Women with RA, n = 75
Hispanic or Latino	4 (5)	3 (4)
Race*		
Black or African American	21 (28)	8 (11)
White	48 (64)	62 (83)
Other	6 (8)	5 (7)
Missing	0	0
Education*		
High school graduate/GED	3 (4)	2 (3)
Some college but no degree	6 (8)	15 (20)
College graduate	25 (33)	34 (45)
Some graduate education	16 (21)	6 (8)
Graduate degree	25 (33)	17 (23)
Unknown	0 (0)	1 (1)
Marital status*		
Single, never married	36 (48)	21 (28)
Living with partner	8 (11)	4 (5)
Married	23 (31)	44 (59)
Divorced or separated	8 (11)	5 (7)
Unknown	0 (0)	1 (1)
Insurance		
Private/employer-based	65 (87)	62 (83)
Medicare/Medicaid	5 (7)	11 (15)
Military/veteran	0 (0)	2 (3)
None	7 (9)	1 (1)
Job status*		
Full time	58 (77)	44 (59)
Part time	10 (13)	8 (11)
On disability	0 (0)	8 (11)
Does not work for pay	7 (9)	15 (20)
Hormonal contraceptive use	35 (47)	31 (41)
RA medication history		
NSAID	–	69 (92)
Corticosteroids	–	65 (87)
Hydroxychloroquine	–	49 (65)
TNF inhibitors	–	48 (64)
Biologics	–	15 (20)
Other DMARD	–	36 (48)
Methotrexate	–	62 (83)
Mean age at first dose, yrs	–	24.4 ± 8.9
Mean average weekly dose, mg	–	17.6 ± 5.8
Mean total duration of use, mos	–	51.5 ± 64.6
Age, yrs	31.9 ± 5.1	32.0 ± 5.2
Disease duration, yrs	–	9.1 ± 8.4
RAPID-3 (scale 0–10)	–	2.5 ± 2.2
PGA (scale 0–100)	–	30.0 ± 18.1

Values are expressed as n (%) or mean ± SD. * $p < 0.05$ compared to healthy controls (race, education, marital status, and job status). DMARD: disease-modifying antirheumatic drugs; GED: General Educational Development; NSAID: nonsteroidal antiinflammatory drugs; PGA: physician's global assessment; RA: rheumatoid arthritis; RAPID-3: Routine Assessment of Patient Index Data 3; TNF: tumor necrosis factor.

Ovarian reserve. The mean AMH in women with RA was 3.0 (SD 2.6) ng/ml and 3.9 (SD 3.9) ng/ml in controls (p = 0.1; Table 2). In adjusted models, AMH in women with RA was estimated to be lower than controls (β –1.05, 95% CI –2.09 to –0.005). Clinically low AMH was found in 12% of women with RA and 9% of controls (p = 0.4). Similar results were observed when 8 patients with PCOS were excluded.

Women with RA who had ever taken MTX had lower AMH levels than women who had not (β –1.25, 95% CI –2.63 to 0.14; p = 0.08), adjusted for age, hormonal contraceptive use, and race. However, no dose response was observed between cumulative MTX dose and AMH level; current MTX use did not affect AMH. MTX was not associated with low AMH, although precision of the estimate was limited.

Anovulation. Among women not taking hormonal contraceptives, 19% of women with RA and 21% of controls had anovulation (Appendix 1). TSH, prolactin, and testosterone levels were normal in all women with low progesterone. In women with RA, there was no association between prior or current MTX, corticosteroid, or NSAID treatment and anovulation. Frequency of anovulation did not differ by disease activity.

Infertility. Among women who had ever been pregnant or tried to become pregnant, 19% of women with RA and 15% of controls reported infertility (Table 3). When adjusted for education, marriage, and race, no difference in infertility was found between women with RA and controls (OR 0.66, 95% CI 0.17–2.49). However, women with RA who were ever pregnant or ever tried to become pregnant had fewer pregnancies (β –0.83, 95% CI –1.60 to –0.07) and fewer live births (β –0.38, 95% CI –0.84 to 0.08) compared to controls. There was no difference in subfertility or the average number of months to conceive between the groups. The cause of infertility was known in all 5 healthy controls, but only 3 of 9 women with RA. AMH and anovulation did not vary in women with and without infertility.

Other causes of infertility. The frequency of PCOS was similar between women with RA and controls (Table 3). There were no observed differences in menstrual cycle frequency or the age when women first tried to become pregnant. Among planned pregnancies, both groups reported having intercourse, on average, 11–12 times per month when trying to conceive.

DISCUSSION

We observed no differences in self-reported infertility in women with RA compared to healthy controls and few differences in anovulation, maternal age at conception, and intercourse frequency. We did, however, find that AMH in women with RA was on average 1.05 ng/ml lower compared to controls, particularly in women with prior MTX use. There was no association between cumulative MTX dose and AMH, however, casting some doubt on the clinical significance of this finding. There have been mixed results reported in the literature concerning the effect of MTX on AMH, with 2 studies suggesting decreased ovarian reserve with increased duration of MTX use, but another study showing no change after 6 months of dosing[2,11,12].

Previous data suggest an association of chronic NSAID use with anovulation and subfertility[13,14,15]. A previous study found that the rate of ovulatory dysfunction increased from 5% to 25–30% when celecoxib was administered around the time of ovulation[16]. In our study, however, RA medications,

Table 2. Mean AMH in women with RA compared to healthy controls and by RA medication use.

Variables	n	Mean AMH (SD)	p	Median AMH (IQR)	p	AMH, β (95% CI)†	p	Log–transformed AMH, β (95% CI)†	p
Women with RA	75	3.0 (2.6)	0.1	2.08 (1.17–3.79)	0.06	–1.05 (–2.09, –0.005)	0.05	–0.26 (–0.61, 0.08)	0.1
Healthy controls	75	3.9 (3.9)		3.37 (1.69–4.92)		0 (ref)		0 (ref)	
RA medication use*									
MTX use ever									
Yes	62	2.8 (2.4)	0.1	2.05 (1.17–3.69)	0.2	–1.25 (–2.63, 0.14)	0.08	–0.49 (–1.04, 0.06)	0.08
No	13	4.0 (3.2)		3.63 (1.28–4.81)		0 (ref)		0 (ref)	
Current MTX use									
Yes	34	2.8 (2.5)	0.5	2.01 (1.33–3.71)	0.6	–0.29 (–1.41, 0.83)	0.6	0.02 (–0.42, 0.46)	0.9
No	40	3.2 (2.7)		2.27 (1.09–4.21)		0 (ref)		0 (ref)	
Missing	1								
TNF inhibitor use ever									
Yes	48	2.9 (2.2)	0.4	2.06 (1.10–4.07)	0.5	–0.59 (–1.70, 0.52)	0.3	–0.30 (–0.73, 0.14)	0.2
No	27	3.4 (3.1)		2.24 (1.48–3.78)		0 (ref)		0 (ref)	
Current TNF inhibitor use									
Yes	32	3.1 (2.5)	0.9	2.58 (0.89–4.82)	0.9	–0.05 (–1.16, 1.05)	0.9	–0.30 (–0.73, 0.13)	0.2
No	43	3.0 (2.6)		2.06 (1.48–3.61)		0 (ref)		0 (ref)	

† Adjusted for age, hormonal contraceptives (yes vs no), and race (nonwhite vs white). * Among women with RA. AMH: Anti-Müllerian hormone; IQR: interquartile range; RA: rheumatoid arthritis; MTX: methotrexate; TNF: tumor necrosis factor.

Table 3. Infertility in women with RA compared to healthy controls.

Variables	Healthy Controls, n = 75	Women with RA, n = 75
PCOS and associated comorbidities		
PCOS	5 (7)	3 (4)
Diabetes	1 (1)	2/74 (3)
Pre-diabetes/insulin resistance	3 (4)	3 (4)
Irregular menstrual cycles	15/73 (21)	20/73 (27)
Patient-reported hirsutism	19 (25)	19 (25)
Adult acne	40 (53)	42/74 (57)
Problem with hair loss on head	2 (3)	12 (16)*
Obese (BMI ≥ 30 kg/m^2)	21 (28)	24 (32)
BMI, kg/m^2	27.1 ± 7.8	28.6 ± 9.0
Pregnancy and conception history		
Ever tried to get pregnant	24 (32)	39 (52)*
Age when first tried to get pregnant, yrs	26.7 ± 4.4	27.3 ± 5.1
Ever pregnant	33 (44)	40 (53)
Number of planned pregnancies	n = 32	n = 47
Months to conceive	4.7 ± 5.2	3.7 ± 3.5
After diagnosis	–	3.5 (3.7)
> 12 months to conception	3 (9)	2 (4)
After diagnosis	–	2 (6)
Frequency of intercourse when trying to conceive	11.9 ± 7.5	11.9 ± 9.3
Infertility†	5/34 (15)	9/47 (19)
Reasons for infertility or inability to get pregnant‡	n = 5	n = 9
PCOS #	3 (60)	0 (0)*
Male factor	0 (0)	2 (22)
Ovulatory dysfunction	2 (40)	1 (11)
Unexplained or unknown	0 (0)	5 (56)
No answer provided	0 (0)	2 (22)

*p < 0.05 compared to healthy controls. † Among women who have ever been pregnant or tried to become pregnant. ‡ Women may have more than 1 reason for infertility; therefore, percentages do not total to 100%. # 3 healthy controls with PCOS and 0 women with RA + PCOS reported PCOS as the cause of their infertility or inability to get pregnant. BMI: body mass index; PCOS: polycystic ovary syndrome; RA: rheumatoid arthritis.

including NSAID, did not appear to be associated with anovulation, although sample sizes were limited and few women took chronic NSAID.

While the rate of infertility was similar between groups, reasons differed. PCOS or ovulatory dysfunction was the primary reported cause of infertility among controls. In contrast, the reasons for infertility were largely unknown in women with RA. Brouwer, *et al*[13] similarly reported that infertility was largely unexplained in women with RA. Interestingly, in our study, no differences in AMH or anovulation were found in women reporting infertility.

Our study benefited from a large number of participants. However, more women were taking hormonal contraceptives than expected, leaving only 65 with measured progesterone. This limited the power to detect differences in anovulation between RA and controls, and more importantly, by RA medication use. Data were self-reported, and we were unable to confirm reports of infertility. Although matched for age, controls were more likely to be African American, unmarried, working full time, and educated beyond a college degree, compared to women with RA. While these demographics do not affect ovarian reserve and ovulation, they likely affect family planning. For this reason, we adjusted comparisons of the number of pregnancies and children for these factors.

Previous data suggest sub- and infertility in women with RA[1,17]. We observed different results. We hypothesize that the relatively mild level of RA activity, and limited chronic use of NSAID and prednisone may have contributed to the normal fertility experienced within this population. Additionally, some conceptions preceded RA diagnosis, perhaps avoiding disease-related infertility. We had hypothesized that infrequently assessed causes for infertility might be behind the high rate of unexplained infertility, but we found no difference in the age at attempted conception or frequency of intercourse. Our findings suggest AMH is lower in women with RA compared to controls. A history of MTX use may affect AMH, although further research is needed to confirm this association and its possible implications.

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APPENDIX 1. Prevalence of anovulation in women with RA compared to healthy controls and by RA medication use.

Variables	N	Anovulationn, n (%)	p *	OR (95% CI)†	p
Women with RA	32	6 (19)	1.0	0.85 (0.25–2.93)	0.8
Healthy controls	33	7 (21)		1.0 (ref)	
RA medication use ◊					
Methotrexate use ever					
Yes	26	4 (15)	0.3	0.40 (0.05–3.37)	0.4
No	6	2 (33)		1.0 (ref)	
Current Corticosteroid Use					
Yes	5	1 (20)	1.0	0.63 (0.05–8.49)	0.7
No	26	5 (19)		1.0 (ref)	
Missing	1				
Current NSAID Use					
Yes	12	1 (8)	0.4	0.36 (0.03–3.83)	0.4
No/seldom	19	5 (26)		1.0 (ref)	
Missing	1				
Current RAPID-3					
Anovulation	6	3.4 ± 2.1	0.4	1.17 (0.77–1.77)	0.5
Ovulation	26	2.6 ± 2.3		1.0 (ref)	
PGA					
Anovulation	6	32.3 ± 20.8	0.6	1.01 (0.96–1.07)	0.7
Ovulation	26	28.7 ± 13.7		1.0 (ref)	

Values are n (%) or mean ± SD unless otherwise specified. * Fisher's exact test. † Adjusted for age and race (nonwhite vs white). ◊ Among women with RA. NSAID: nonsteroidal antiinflammatory drugs; RA: rheumatoid arthritis; RAPID-3: Routine Assessment of Patient Index Data 3; PGA: physician's global assessment.