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Reduced Ovarian Function in Female Rheumatoid Arthritis Patients Trying to Conceive

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Objective. Subfertility, a time to pregnancy (TTP) longer than 12 months, is present in 40% of female patients with rheumatoid arthritis (RA) who are actively trying to conceive. Because patients with RA appear to reach menopause at a younger age, diminished ovarian function may explain the reduced fertility. Serum anti-Müllerian hormone (AMH) levels are the best proxy to measure ovarian function. Our objectives were to study AMH levels in female patients with RA and determine the association of preconception serum AMH levels with TTP.

Methods. A post hoc analysis was performed before conception in patients of the Pregnancy-Induced Amelioration of Rheumatoid Arthritis (PARA) cohort. Serum AMH levels were compared with those in an existing cohort of healthy controls using analysis of covariance. Associations between AMH and TTP were studied using the Cox proportional hazard analysis.

Results. Preconception serum was available in 209 women of the PARA cohort (aged 32.1 ± 3.9 years), of whom 45% were subfertile in the current episode. The median AMH level was 2.5 µg/l (interquartile range: 1.5-4.6). AMH levels were significantly lower compared with those in healthy controls ($P < 0.001$), with 17% of patients having levels below the age-specific 10th percentile. A multivariable analysis showed a negative association of AMH with the presence of anticitrullinated protein antibodies (ACPAs) ($P = 0.009$). AMH levels showed no significant association with TTP ($P = 0.26$).

Conclusion. Women with RA have lower AMH levels than healthy controls, and AMH levels were lower in ACPA-positive patients. However, because preconception AMH levels were not associated with TTP, the reduced AMH levels do not explain the reduced fertility in patients with RA.

INTRODUCTION

Subfertility is a common problem in women with rheumatoid arthritis (RA). Approximately 40% of female patients with RA suffer from subfertility (a time to pregnancy [TTP] longer than 12 months despite regular unprotected intercourse) compared with 10%-15% -of women from the general population (1–3). Overall, patients with RA have fewer children and are more often nulliparous compared with healthy controls (4).

A longer TTP in patients with RA has been associated with older age, no previous pregnancies, higher disease activity, and the periconception use of nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisone (2). However, little is known about ovarian function in patients with RA and its effect on fertility. Because women with RA appear to reach menopause at a slightly younger age (4,5) and because several autoimmune disorders have been

related to primary ovarian insufficiency (6,7), the ovarian follicle pool in female patients with RA may be reduced at a relative early age. Recently reported results of a small study do suggest a reduced ovarian reserve in women with established RA (8). Because in general, a woman becomes less fertile approximately 10 years before she experiences menopause, a younger menopausal age is related to an earlier decrease in fertility (9), reflected by a longer TTP or not achieving pregnancy at all.

The reduced fertility with increasing age is strongly correlated with the decline in the number of follicles present in the ovary (9). The size of the primordial follicle pool can be estimated by measuring serum levels of anti-Müllerian hormone (AMH), which is specifically produced by the granulosa cells of the small growing ovarian follicles (10,11). AMH levels are highest in early adulthood and decline with age until they are undetectable at around menopause (12).

Unlike other hormonal markers for ovarian function, such as follicle-stimulating hormone (FSH), fluctuations in serum AMH levels throughout the menstrual cycle are small (13). Altogether, at present, a woman's serum AMH level is the most reliable predictor for the age at which she will enter menopause (14). Regarding fertility, AMH levels have been reported to add to the prediction of live birth in assisted reproductive technology cycles (15–18), and low serum AMH levels have been described to be associated with a reduced chance of natural conception (19), although conflicting results have been reported (20).

To study ovarian function in women with RA, we measured serum AMH levels in women with RA who had participated in a nationwide cohort study before conception, and we studied the association of preconception AMH levels with TTP in these women.

PATIENTS AND METHODS

Patients. A post hoc analysis was performed within the Pregnancy-Induced Amelioration of Rheumatoid Arthritis (PARA) study, a nationwide prospective cohort study from 2002 to 2010 from the Netherlands. Patients were recruited in 2002-2008 by their attending rheumatologist when they had a diagnosis of RA according to the American College of Rheumatology (ACR) 1987 classification criteria (21) and were trying to conceive or were in their first trimester of pregnancy. Patients had to have a good understanding of the Dutch language (22) The PARA study was approved by the Medical Ethics Research Committee of Erasmus University Medical Center Rotterdam.

For the current study, only those patients who were assessed during the preconception period were included in the analysis. In patients who participated twice or more in the PARA study, only the first occurring preconception visit was selected.

Data collection. During the PARA study, patients were visited at their homes by a member of the research team. Assessments took place before conception (when possible), during each trimester of pregnancy, and 6, 12, and 26 weeks after delivery. Before the preconception study visit took place, all contraceptive methods had to have been stopped. At every visit, patients filled out questionnaires on obstetric history, medication use, health, and daily functioning. Disease activity was measured, and a blood sample was drawn (22).

All data were collected in the PARA database. Variables used for analysis included the following: date of start of trying to conceive, age at start of trying to conceive, age at drawing of serum sample, duration of disease, occurrence of any previous pregnancies, presence of rheumatoid factor (RF), presence of anticitrullinated protein antibodies (ACPAs), disease activity at the preconception study visit, patient-reported erosions, use of prednisone or sulfasalazine at time of study visit, use of NSAIDs at time of study visit, and whether the subject had ever used methotrexate.

Subfertility was defined as not achieving a pregnancy within 12 months of trying to conceive.

Measurements. Disease activity was measured using a tender and swollen joint count for 28 joints (disease activity score in 28 joints [DAS28]) combined with serum C-reactive protein (CRP) levels (DAS28-CRP) (23). Details on the measurement of RF and ACPAs can be found in the original report on the PARA study (22).

Serum samples were stored at –80°C. Serum AMH levels (μg/l or ng/ml) were measured using picoAMH assay developed by Ansh Labs (24). The limit of detection (LoD) was 0.0012 μg/l.

Controls. Serum AMH values were compared with those of an existing healthy control group that was recruited for a previous study aimed at creating a nomogram of serum AMH levels in women from birth until menopause (12). All 554 adult women ages 18-47 years were selected. They had regular menstrual cycles, and the majority had conceived one or more children. (12). Because serum AMH levels in the control group were reported as values measured with the GenII Beckman Coulter assay (Beckman Coulter Inc), a conversion factor was used to compare the AMH levels in the patient group with those in the controls (25): AMH (picoAMH assay in ng/ml) = (1.45 × AMH_{GenII}) + 0.32.

Statistics. Serum AMH levels were skewed to the right and were log transformed for analysis. To make log transformation possible, serum AMH levels below the LoD (0.0012 μg/l) were imputed by dividing the LoD by the square root of 2 (26). Numbers of missing values were reported. Missing values were imputed using multiple imputation with chained equations. All variables of interest (see Data collection section) that had missing values were included in the imputation as well as all other variables intended to be put into the Cox proportional hazard analysis. Because of the survival nature of the data, the event variable (_d) (occurrence of pregnancy) and the Nelson Aalen estimator (estimation of baseline hazard [$H_0(t)$]) were also included in the imputation procedure (27). Being outcome variables, missing values of _d, and the Nelson Aalen estimator were not imputed.

An analysis of covariance (ANCOVA) was performed to compare log-transformed AMH levels, corrected for age, between patients with RA and controls. Associations of various variables with AMH levels were tested separately using linear multiple regression on the log-transformed AMH values. A multivariable analysis was performed by entering all variables of interest into the multiple linear regression. Because AMH can be considered a proxy for ovarian age despite a woman's calendar age, the multivariable analysis was performed both with and without age as a covariate.

To study the TTP, a Kaplan-Meier curve was drawn. To avoid negative values of TTP for women who conceived within the first menstrual cycle, a pseudo date of the positive preg-

nancy test was calculated by adding 28 days to the first day of the final menstrual period. The Cox proportional hazard analysis was performed, with the occurrence of pregnancy as the event variable. Aside from log-transformed AMH levels and age, covariables were selected on the basis of our previous study on TTP in RA: never been pregnant before; disease duration; presence of RF and ACPAs; DAS28; use of NSAIDs, prednisone, and sulfasalazine at time of preconception study visit; and whether a subject had ever used methotrexate. Smoking was not included because the percentage of smokers in the PARA study was low and had no effect on TTP in the previous study (2). Presence of erosions was added as a measure for long-term disease severity. In a second analysis, age was excluded to study whether unadjusted AMH levels showed an association with TTP.

P values below 0.05 were considered statistically significant. The statistical software used was Stata software version 14.1.

RESULTS

Patients. A serum sample taken at the first (preconception) study visit was available in 209 patients within the PARA study (Figure 1). Baseline characteristics and missing values are reported in Table 1.

During follow-up after the preconception study visit, pregnancy was achieved in 159 women (76%). In 47 women (22%), the episode did not result in a pregnancy. Three women (1.4%) were lost to follow-up, and it was not known whether a pregnancy was achieved. In the women who got pregnant, the median TTP since patients actively tried to conceive was 6.1 months (interquartile range [IQR]: 2.6-15.4 months). In women who did not achieve pregnancy, the median follow-up period was 17.3 months (IQR: 14.4-25.8 months). A Kaplan-Meier curve for TTP is shown in Figure 2.

Ninety-four women (45%) were subfertile based on a TTP >12 months or a follow-up time >12 months without achieving a pregnancy. For six women (2.9%), it was unknown whether they fulfilled the criteria for subfertility because it was unknown whether they achieved pregnancy during the follow-up (n = 3) or because their follow-up time ended before they had been trying to conceive for 12 months (n = 3).

Serum AMH levels and RA disease characteristics. The median serum AMH level at the preconception study visit was 2.5 µg/l (IQR: 1.5-4.6), with one woman having an AMH level
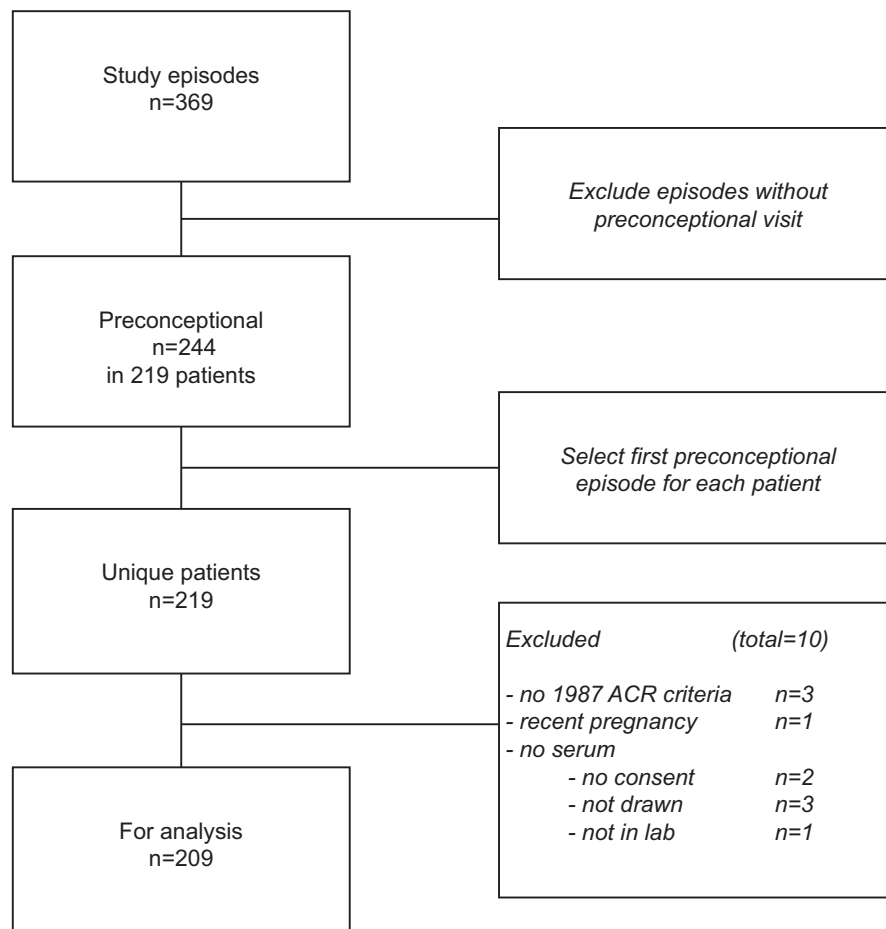

Figure 1. Flow diagram for available patients within the PARA study before conception. ACR, American College of Rheumatology.

Table 1. Baseline characteristics

Variable	Before Conception (N = 209)
Age, mean ± SD, y	
At start of trying to conceive	31.7 ± 3.9
At study visit	32.1 ± 3.9
Previous pregnancies, n (%)	
0	110 (53)
1	67 (32)
2	25 (12)
3 or more	7 (3.4)
Previous miscarriages, n (%)	
0	181 (87)
1	20 (9.6)
2 or more	8 (3.8)
Disease characteristics	
Duration of RA	
At start of trying to conceive, median (IQR), y	4.1 (1.7-9.0)
At study visit, median (IQR), y	4.5 (2.0-9.4)
Missing, n (%)	2 (1.0)
RF-positive, n (%)	153 (73)
Missing	2 (1.0)
ACPA-positive, n (%)	137 (66)
Presence of erosions (patient), n (%)	107 (51)
Missing	41 (20)
DAS28-CRP at study visit, mean ± SD	3.73 ± 1.17
Missing, n (%)	3 (1.4)
Antirheumatic drugs used at time of study visit, n (%)[a]	
None	19 (9.1)
Prednisone	89 (43)
Sulfasalazine	76 (36)
Hydroxychloroquine	16 (7.7)
NSAIDs (including COX-2 inhibitors)	94 (45)
Biologics	8 (3.8)
Ever used methotrexate	148 (71)
Missing	1 (0.5)

Abbreviation: ACPA, anticitrullinated protein antibody; COX-2, cyclooxygenase 2; DAS28-CRP, disease activity score using a joint count of 28 and C-reactive protein levels; IQR, interquartile range; RA, rheumatoid arthritis; RF, rheumatoid factor; NSAID, nonsteroidal anti-inflammatory drug.
[a]When using antirheumatic drugs, patients could be using more than one of the reported drugs.

Figure 2. Kaplan-Meier curve depicting the time to pregnancy in women with rheumatoid arthritis who are trying to conceive. Time = 0 is the moment indicated by the patients at which they had first actively tried to conceive.

the 10th and 50th percentiles; in 73 patients (34.9%), AMH levels were between the 50th and 90th percentiles; and in 6 (2.9%) patients, AMH levels were above the 90th percentile. ANCOVA with log-transformed AMH levels showed significantly lower AMH levels, corrected for age, in patients compared with controls ($P <$ 0.001).

Monovariable analyses showed a significant negative association of log-transformed AMH levels with increasing age ($\beta =$ −0.070 [95% CI: −0.11 to −0.031]; $P =$ 0.001) and the presence of ACPAs ($\beta =$ −0.38 [95% CI: −0.71 to −0.056]; $P =$ 0.022) (Table 2). Serum AMH levels were not associated with never having been pregnant before, disease duration, presence of RF, DAS28-CRP, presence of erosions, use of NSAIDs, use of prednisone, sulfasalazine use, or past use of methotrexate. A multivariable linear
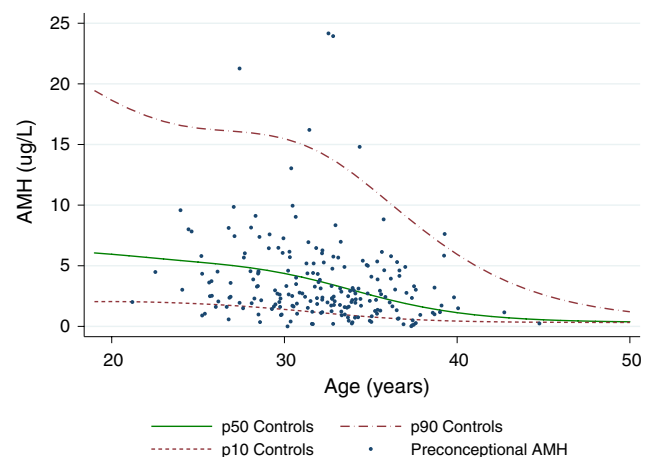
Figure 3. Preconception serum anti-Müllerian hormone (AMH) levels in 209 women with rheumatoid arthritis who are trying to conceive, plotted against the 10th percentile (p10), 50th percentile (p50), and 90th percentile (p90) of serum AMH values in healthy controls (12).

below the LoD. The individual preconception serum AMH levels were plotted in the nomogram created for healthy controls (12) (Figure 3). In 36 women (17.2%; 95% confidence interval [CI]: 12.1%-22.3%), the AMH levels were below the 10th percentile for their age; in 94 patients (45.0%), AMH levels were between
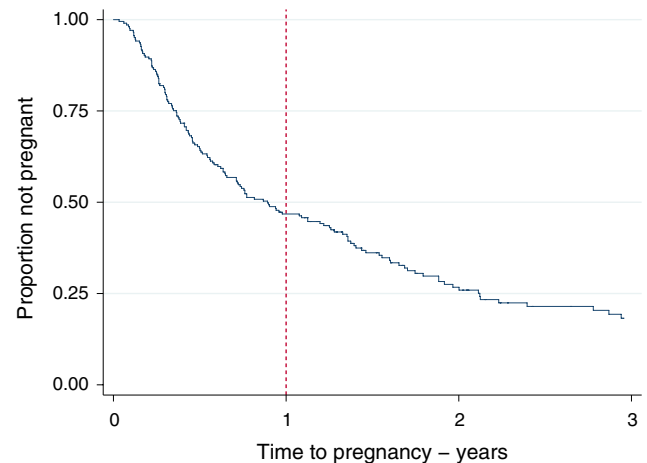
Table 2. The association of AMH levels (log transformed) with disease-related factors in women with rheumatoid arthritis (N = 209)

| | Association With Log-Transformed AMH Levels (in µg/l) | | | |
| | Uncorrected for Age | | Corrected for Age | |
Variable	β	95% Confidence Interval	β	95% Confidence Interval
Monovariable associations				
Age, per y	−0.070	−0.11 to −0.031[**]	...	...
Never been pregnant before	0.16	−0.15 to 0.47	0.33	−0.28 to 0.35
Disease duration, per y	−0.022	−0.048 to 0.004	−0.018	−0.044 to 0.0074
RF positivity	−0.040	−0.40 to 0.32	0.033	−0.32 to 0.38
ACPA positivity	−0.38	−0.71 to −0.056[*]	−0.29	−0.61 to 0.036
DAS28-CRP, per point	−0.012	−0.15 to 0.12	−0.0020	−0.13 to 0.13
Presence of erosions	−0.24	−0.61 to 0.14	−0.25	−0.61 to 0.11
NSAIDs used before conception	0.040	−0.28 to 0.36	0.021	−0.29 to 0.33
Prednisone used before conception	0.031	−0.29 to 0.35	0.014	−0.30 to 0.32
Sulfasalazine	0.14	−0.18 to 0.47	0.15	−0.17 to 0.47
Ever used methotrexate	0.053	−0.29 to 0.40	0.036	−0.30 to 0.37
Multivariable analysis				
Age	...	...	−0.061	−0.10 to −0.020[**]
Never been pregnant before	0.13	−0.19 to 0.44	0.22	−0.30 to 0.34
Disease duration, per y	−0.022	−0.053 to 0.0076	−0.18	−0.047 to 0.012
RF positivity	0.30	−0.15 to 0.76	0.30	−0.14 to 0.75
ACPA positivity	−0.57	−0.99 to −0.14[**]	−0.47	−0.89 to −0.051[*]
DAS28-CRP, per point	0.001	−0.14 to 0.14	0.0080	−0.13 to 0.15
Presence of erosions	−0.085	−0.53 to 0.36	−0.14	−0.57 to 0.29
NSAIDs used before conception	0.010	−0.33 to 0.35	−0.001	−0.33 to 0.33
Prednisone used before conception	−0.0004	−0.34 to 0.34	−0.010	−0.34 to 0.32
Sulfasalazine	0.17	−0.16 to 0.50	0.18	−0.15 to 0.50
Ever used methotrexate	0.11	−0.25 to 0.47	0.095	−0.26 to 0.45

Abbreviation: ACPA, anticitrullinated protein antibody; AMH, anti-Müllerian hormone; DAS28-CRP, disease activity score using a joint count of 28 and C-reactive protein levels; NSAID, nonsteroidal anti-inflammatory drug; RF, rheumatoid factor.
* *P* < 0.05; ** *P* < 0.01.

regression of log-transformed AMH levels that included all of the above covariates showed a significant negative association with the presence of ACPAs, both corrected for age (β = −0.47 [95% CI: −0.89 to −0.051]; *P* = 0.028) as well as uncorrected for age [β = −0.57 (95% CI: −0.99 to −0.14]; *P* = 0.009) (Table 2).

AMH and TTP. For the Cox proportional hazard analysis, the preconception study visit, at which the first serum was drawn, was considered as the start of follow-up. Of the 209 women, 205 women were included in the analysis. Four women were excluded because it was unknown whether pregnancy had occurred (n = 3) or what the exact follow-up time was (n = 1). Log-transformed AMH levels, corrected for age, were not significantly associated with TTP (hazard ratio [HR]: 1.09 [95% CI: 0.94-1.27]; *P* = 0.26). A longer TTP was associated with older age (HR: 0.96 per year [95% CI: 0.91-1.00]; *P* = 0.052),

with never having been pregnant before (HR: 0.43 [95% CI: 0.30-0.62]; *P*<0.001), with increasing disease activity (HR: 0.85 per point of DAS28 [95% CI: 0.73-0.98]; *P* = 0.026), and with use of NSAIDs at the preconception study visit (HR: 0.5 [95% CI: 0.40-0.81]; *P* = 0.002) (Table 3). An interaction term between age and AMH was not significant (*P* = 0.20) and was not included in the model. When leaving age out of the model, the uncorrected AMH levels also showed no significant association with TTP (HR: 1.14 [95% CI: 0.98-1.33]; *P* = 0.093) (data not shown).

DISCUSSION

In female patients with RA trying to conceive, we found that preconception serum AMH levels, corrected for age, were lower than those in healthy controls. Presence of ACPAs showed a significant negative association with AMH levels. However, serum

Table 3. Cox regression for time to pregnancy, counting from the moment of AMH measurement, in women with rheumatoid arthritis who are trying to conceive (N = 205)

Variable	Hazard Ratio	95% Confidence Interval	P
Log-transformed AMH level (in µg/l)	1.09	0.94-1.27	0.26
Age, per y	0.96	0.91-1.00	0.052
Never been pregnant before	0.43	0.30-0.62	<0.001
Disease duration, per y	0.99	0.96-1.02	0.50
RF positivity	0.73	0.47-1.15	0.17
ACPA positivity	1.12	0.71-1.76	0.62
DAS28-CRP, per point	0.85	0.73-0.98	0.026
Presence of erosions	1.57	0.87-2.85	0.13
NSAIDs used before conception	0.57	0.40-0.81	0.002
Prednisone used before conception	0.77	0.54-1.10	0.16
Sulfasalazine	0.89	0.64-1.26	0.52
Ever used MTX	1.12	0.77-1.62	0.55

Abbreviation: ACPA, anticitrullinated protein antibody; AMH, anti-Müllerian hormone; DAS28-CRP, disease activity score using a joint count of 28 and C-reactive protein levels; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; RF, rheumatoid factor.

AMH levels were not significantly associated with the TTP in patients with RA, not even when used as a substitute for age.

The lower AMH levels in patients with RA confirm recent findings in a small study on AMH levels in RA in which 33 patients with RA had lower AMH levels compared with age-matched controls (8). In a previous study, however, we have shown that AMH levels at the time of RA diagnosis were not significantly different from those in controls (28). Apparently, during the course of the disease, RA has a negative effect on the AMH levels. This is in line with studies on other chronic conditions that have reported reduced AMH levels in women with cystic fibrosis (29), in girls with newly diagnosed cancer (30), and in women with Crohn disease (31) or systemic lupus erythematosus (32). Also, in women with type 2 diabetes mellitus, a reduced ovarian reserve has been reported, as reflected by elevated FSH levels and reduced antral follicle counts, compared with in controls (33). Overall, these findings support the hypothesis that ovarian function is affected by a woman's overall health status. Apparently, a woman's capacity to reproduce is compromised in times when the soma is less healthy. In women with RA, this is also reflected in the younger age at which they appear to reach menopause, as has been reported in previous case-control studies (4,5). Lower AMH levels, and the subsequently higher chance for early menopause, may have implications not only for a woman's fertility but also for her overall long-term health because women who reach menopause at a younger age have an ongoing unfavorable health state, with increased lifetime risk for conditions such as osteoporosis and cardiovascular disease (6).

In agreement with the other study on AMH in established RA (8), we did not find a significant association of AMH levels with disease duration. However, we did observe a significant association of lower AMH levels with the presence of ACPAs. ACPA-positive RA is nowadays considered a different disease entity from ACPA-negative disease, which has been related to a more severe disease, responding poorer to antirheumatic therapy (34). The stronger reduction in ovarian function in ACPA-positive patients may be caused either by the difference in disease mechanism or by higher levels of circulating cytokines or immune cells affecting the ovaries during active disease. Another possible explanation would be that the long-term use of antirheumatic drugs, such as methotrexate, affects the ovaries (35). However, no significant effect of past use of methotrexate on TTP in RA has been reported (2). Therefore, it will be interesting to analyze the effect of circulating cytokines and cumulative antirheumatic drug use on AMH levels in women with RA in future studies.

The significant association of lower AMH levels with ACPA-positive disease was not found in our previous study on ovarian function in recently diagnosed RA (28). The women in the previous study were part of an early RA program in which they were identified using the 2010 European League Against Rheumatism (EULAR)/ACR criteria for RA and treated in an early phase of the disease. The explanation for the difference in the association of low AMH levels with ACPAs may be found in the cumulative disease activity, which was expected to be higher in the current study, in which the women not only had a longer disease duration but probably also had received later and less intensive antirheumatic treatment compared with the early RA group, as is illustrated by the fact that only 71% of patients in the current study ever used methotrexate.

Although we did find an association of lower serum AMH levels with ACPA-positive disease, the presence of erosions was

not associated with lower AMH levels. Because in our study, the presence of erosions was not assessed directly through x-ray examination but based on patient reports, this variable may be biased. Moreover, whereas ACPAs are often positive early in the course of RA, erosions generally arise at a later stage of the disease. Furthermore, the presence of erosions may vary depending on the effect of the antirheumatic treatment a patient has received over time. Studies with a longer follow-up or in larger patient groups are needed to explore the association of serum AMH levels with the presence of erosions.

The comparison of AMH levels with controls has to be interpreted with caution. As explained in the Methods section, the AMH levels in controls were previously measured using an assay by another manufacturer, and a conversion factor was applied (25). The use of conversion formulae for comparison of AMH levels from different assays has been debated. Especially with higher AMH levels, the precision of using regression equations decreases (25). However, the number of patients in our study with AMH levels around or above the 90th percentile of controls were low. Furthermore, the focus of our current report was on the lower AMH levels, and therefore less precision loss is to be expected. Indeed, using other conversion formulae that have been reported (25), significantly lower AMH levels in patients with RA compared with controls were still observed.

Another point of consideration is the lower LoD for the applied picoAMH assay. After replacement of very low AMH levels in our cohort with the conversed LoD of the older AMH assay used in the control group, the reported significantly lower AMH levels in patients with RA compared with controls were still observed ($P <$ 0.001; data not shown).

Although AMH levels in patients with RA were lower than those in healthy controls and although the TTP in the patients with RA was longer, the individual serum AMH levels did not show a significant association with TTP. This might be related to the fact that the range of AMH levels, especially within the younger age groups, is large. There appears to be an association of lower AMH levels with lower natural conception rates, but spontaneous conceptions do occur in women with very low AMH levels, and no meaningful AMH threshold for natural conception has been established (36). Apparently, AMH levels provide information on the number of early follicles available in the ovaries, but they do not necessarily reflect the quality of the remaining oocytes. Therefore, individual testing of AMH levels to predict the occurrence of pregnancy has not yet been broadly applied in daily practice.

Despite the absence of a clear association of serum AMH levels with a woman's TTP in the current literature (36,37), there appears to be an association of AMH levels with results in assisted reproductive techniques (ARTs). Many studies have shown that AMH levels are a reliable indicator for ovarian response after stimulation for ARTs such as in vitro fertilization (IVF) (38–40). A recent registry study on ARTs in patients with RA showed a decreased chance of pregnancy per embryo transfer but did not report on oocyte yields (41).

No other studies on IVF treatments and ovarian stimulation results in patients with RA have been available thus far. Given our current results, patients with established RA who are undergoing IVF may have a lower oocyte yield than would be expected by age alone.

Although comorbidities and body mass index (BMI) might affect both AMH levels and TTP, these were not included in the analyses. Patient-reported comorbidities with a possible effect on AMH levels were rare and therefore not included. BMI was not recorded during the PARA study. Because women with both overweight and underweight more often experience fertility problems, often through ovulation disorders, this may affect our results. In a previous study of a representative Dutch RA cohort of women aged 18-42 years, the median BMI was 24.2 (IQR: 21.9-28.3) (28) Therefore, we do not expect significant differences if BMI were added to the analyses.

Concerning disease characteristics, our study cohort appears to be representative of patients with established RA. However, we have to consider the changes in management of RA since the end of the PARA study follow-up in 2010. Nowadays, antirheumatic treatment is based on treat-to-target guidelines. Moreover, biological disease-modifying antirheumatic drugs (DMARDs) are prescribed more often and also earlier in the disease course. Because several biologicals appear to be safe during pregnancy (42), they are also prescribed more often in women trying to conceive. The number of women in our study using biological DMARDs was too small for further analysis. A recent small study has reported stable AMH levels after 1 year of treatment with tumor necrosis factor α inhibitor, with a drop in disease activity (43). Further studies in larger groups are needed to investigate the effect of early treatment strategies and biological treatment on ovarian function and AMH levels, fertility, and offspring in patients with RA.

Serum AMH levels were decreased in women with RA, and lower AMH levels were associated with ACPA-positive disease, which is often related to a more severe disease state. Although AMH levels were not related to the TTP in women with RA, the lower AMH levels over all age groups in our study should raise awareness among both patients and rheumatologists that women with RA, especially when ACPAs are positive, have a less favorable profile regarding fertility. Women with RA should consider starting a family at a younger age. Rheumatologists should focus on effective treatment within a reasonable time span, and referral to a fertility specialist should be considered early in the process to counsel patients on their individual prospects. Because decreased AMH levels may result in an early occurrence of menopause, further studies in patients with RA should clarify the long-term effect of RA and antirheumatic drugs on the age at which menopause occurs.

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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 published and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Brouwer, Dolhain, Hazes, Visser, Laven.
Acquisition of data. Brouwer, Dolhain, Hazes, Visser, Laven.
Analysis and interpretation of data. Brouwer, Dolhain, Hazes, Visser, Laven.

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