

Fertility in men diagnosed with ankylosing spondylitis – a population-based study

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ABSTRACT

Introduction. Disease activity, drug exposure, infectious factors, smoking, excessive alcohol intake and stress were identified to have a negative impact on spermatogenesis and gonadal function. Population-based studies on fertility in ankylosing spondylitis (AS) men are lacking. It is not known, if men with AS have a reduced number of children. Our objective was to determine fertility in a masculine AS group by determining the family size.

Patients and methods. Men diagnosed with AS responded to a questionnaire comprising of several domains, focused on the preconception/conception period. Demographic parameters, disease related information, sexual relationship status, infertility treatment use in the couple, time to pregnancy achievement (TTP), comorbidities, exposure to gonadotoxic medication or radiation in the past, smoking, number of pregnancies and children born in the couple and couples' decision to limit family size were registered.

Results. Out of 122 AS patients, 76 accepted to participate to the interview. Hundred-eleven pregnancies were registered in the couples and 99 children were born. Forty-two men (55.26%) with AS onset fathered 58 children and 34 (44.73%) men fathered 41 children before AS onset. No statistic difference was found between the 2 sub-groups when average number of children/ family was compared (1.38 vs 1.20). A statistic significant number of men, with AS onset at conception (14/42; 33.33%), decided to limit the family size ($p=0.02$).

Twenty-seven patients (35.52%) recalled a decrease in sexual desire. In 19 (25%) of them, this phenomenon was linked to the disease burden. Decrease of sexual desire in the 2 groups showed a borderline statistic significant difference, $p=0.051$.

No statistic significant difference was obtained when TTP in the two groups were compared.

Conclusion. A lower fertility in AS patients was described in our group in comparison to general population and this phenomenon could be linked mostly to psychological factors impacting family size decision. No correlation between the low fertility and disease presence at conception was found.

Keywords: men, fertility, average number of children, ankylosing spondylitis

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease affecting the axial skeleton, entheses and occasionally the peripheral joints and extra-articular organs. It has a higher prevalence in men in comparison to women (1,2). As it develops mainly during peak reproductive years, quality of life, including sexual function and fertility status, may be negatively influenced (2,3).

Impairment of reproduction function in patients with chronic rheumatic inflammatory diseases is mainly linked to factors depending on the AS pro-

cess itself, drug management and on the patients' ability to cope with the disease (4).

Male fertility refers to a male ability to cause pregnancy in a fertile female and is related mainly to the number of born children (5). Male fecundity (his biological capacity to reproduce) is a component of the fertility rate.

There is no way of measuring the male fertility component directly, but several markers have been used in clinical practice and studies. Among biological indicators, sperm quality and quantity isolate the male component of fertility. Sperm analysis has

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proved to be superior to other markers, like serum levels of the gonadotropins follicle stimulating hormone (FSH), luteinizing hormone (LH) and inhibin B, in predicting a conception (6-9).

Indeed, studies using time-to-pregnancy (TTP) measurements may identify couple sub-fertility when pregnancy achievement takes longer than 12 months, and TTP has been shown to correlate with sperm quality and quantity as well as with sexual activity (10-12).

Fertility studies in men diagnosed with different rheumatic diseases have focused on the evaluation of sperm parameters, gonadal hormonal function, testicular alterations and anti-sperm antibodies. Disease activity, drug exposure, infectious factors, smoking, excessive alcohol intake and stress were identified to have a negative impact on spermatogenesis and gonadal function (4,13,14).

In theory, a normal spermiogram represents a surrogate measure for normal fertility which needs further confirmation due to pregnancy achievement in the couple (15). Infertility affects up to 12% of all men, but abnormal semen production is only responsible for approximately 50% of male factor infertility (16-18). In the absence of sperm analysis it is more difficult to estimate men fertility. An indirect parameter would be the calculation of the average number of children in the family.

By now, no population-based study on fertility in AS men was performed in Romania and no population-based study has ever investigated, if men with rheumatic diseases have a reduced number of children.

Our objective was to determine fertility in a masculine AS group by determining the family size.

TABLE 1. Presents the demographic data of the group.

Group parameters	
Nr. patients	76
AS axial involvement – Nr[%]	53[69.73]
AS axial and peripheral – Nr[%]	23[30.26]
mean age (y±SD)	30±5.017
marital status – Nr[%]	
married	72[94.73]
not married	4 [5.26]
AS dg at conception	58[58.58]
disease duration (y±SD)	4±2.83
Smokers – Nr[%]	23[23.23]
therapy	
NSAIDs – Nr[%]	58[58]
SSZ – Nr[%]	5[5.26]

Legend: SD – standard deviation, AS – ankylosing spondylitis, Nr – number, NSAIDs – nonsteroidal anti-inflammatory drugs, SSZ – sulphasalazine.

TABLE 2. Presents the reproduction data in the groups

Reproduction data	all over	fathers' with AS	fathers' without AS
Pregnancies Nr[%]	111[100]	66[59.45]	45[40.54]
Children Nr[%]	99[89.18]	58[58.58]	41[41.41]
Nr. children/father	1.32.	1.38.	1.2.
Elective abortion Nr[%]	7[6.3]	4[3.6]	3[2.70]
Spontaneous abortion Nr[%]	4[3.6]	3[2.70]	1[0.9]
Therapeutic abortion Nr[%]	1[0.9]	1[0.90]	0[0.0]
TTP >12 months	6[6.06]	3[5.17]	3[7.31]
Fertility treatments Nr[%]	1[0.9]	1[0.9]	0[0.0]
Erectile dysfunctions Nr[%]	0[0]	0[0.0]	0[0.0]
Sexual desire decrease Nr[%]	27[35.52]	19[32.75]	8[34.78]

Legend: Nr – number, AS – ankylosing spondylitis, TTP – time to pregnancy achievement.

PATIENTS AND METHODS

Men diagnosed with AS according to New York diagnostic criteria were selected to respond to a questionnaire comprising of several domains, focused on the preconception/conception period. Following information was recorded: demographic parameters (subjects age, marital status, diagnose of the disease in relation to the conception period), disease related information (disease onset- years, subtype of AS - axial or axial and peripheral involvement, disease activity – Bath Ankylosing Spondylitis Disease Activity Index – BASDAI, any AS specific therapy intake – including preconception period), sexual relationship status (presence of erectile dysfunction, sexual desire decrease), infertility treatment use in the couple and TTP, comorbidities (varicocele, urlian virus infection in adulthood), smoker status, any exposure to gonadotoxic medication or radiation in the past, number of pregnancies and children in the couple and couples' decision to limit family size.

The questionnaire was taken home and data was completed by the couple. Fertility was calculated as being reflected by the number of children/patients' family.

The study was approved by the ethics committee (Rehabilitation Clinical Hospital Cluj-Napoca, N 2394/3.04.2017) and informed written consent was obtained from patients.

STATISTICAL ANALYSIS

The assessment of the normality of data was performed using Shapiro-Wilk test. Descriptive statis-

tics was performed for the continuous and categorical variables in the two groups, and results were expressed as mean \pm standard deviation (SD) or number of cases and percent. Chi-square test with a significance of 0.05 was used to compare groups. The statistical analysis was performed using SPSS software version 22 and Microsoft Office Excel 2010.

RESULTS

Out of 122 AS patients, 76 accepted to participate to the interview (53 diagnosed with axial disease and 23 with axial and peripheral disease). Hundred-eleven pregnancies were registered in the couples and 99 children were born. Forty-two men (55.26%) with AS onset fathered 58 children and 34 (44.73%) men fathered 41 children before AS onset. Five (6.57%) men fathered children both before and after disease onset. Twenty-three men fathered more than 1 child (30.66%). Fifty-one men fathered 1 child, 16 men fathered 2 children, 4 men fathered 3 children and one fathered 4 children; 4 men did not father children.

Twelve men with AS onset have fathered more than 1 child while 11 men without AS onset fathered more than 1 child (52.17% vs 47.82%).

No statistic significant difference was found in the mean age between men that conceived during the disease course or before (30 ± 4.64 vs 30 ± 5.49 years). No statistic difference was found between the 2 sub-groups when average number of children/family was compared (1.38 for men with AS onset vs 1.20 for men without AS onset). Fourteen/42 (33.33%) men with AS onset at conception were counseled (eg. medical staff, family, friends) not to have children or to limit the family size, as AS would be inherited by the next generation. Statistic significant difference of $p=0.02$ was found between the 2 groups when decision to limit family size analysis was made.

Exposure to medication was present only in men conceiving after disease onset. In this sub-group, NSAIDs prescription was recorded, but schedule of administration, type and dosage could not be accurately determined. Five patients recalled continuous SSZ treatment at the time of conception; they fathered 5 children and one couple recalled TTP >12 months.

Overall, 27 patients (35.52%) recalled a decrease in sexual desire. The phenomenon was identified as being intermittent and recognized as being “from

time to time” or “sometimes”. In 19 (25%) patients, this phenomenon was linked to the disease burden. Decrease of sexual desire in the 2 groups showed a borderline statistic significant difference, $p=0.051$.

Fourteen smokers were identified among the fathers' with AS onset, representing 60.86% of the total smokers. No erectile or other organic sexual relationship dysfunction was identified. BASDAI was available in 5 patients showing active disease in 3 of them. TTP > 12 months was 5.17 % in the couples where the father was already diagnosed with AS vs 7.31% in the couples with healthy males. No statistic significant difference was obtained when TTP in the two groups were compared. One woman received fertility treatment. Her partner had normal sperm parameters.

DISCUSSION

We performed a retrospective interview-based analysis on fertility in AS men. To our knowledge, this is the first population-based study in Romania. Regardless of the fact that conception took place before or after disease onset, our study showed an overall lower average number of children/family (1.32) in comparison to general population.

Official European organizations report a decrease in the average number of children in married couples from 2.33 in 1960 to 2.01 in 1977, reaching a level of 1.9 in 2017 (19). In the United States, the same parameter dropped from 2.3 in 1970 to 1.9 in 2017 (20). In Romania, the National Institute of Statistics (INS) reports identify an average number of children in families of 2.19 in 1989 with a decrease to 1.4 in 2013 (21).

Studies reviewing men infertility meta-analysis and population-based analyses found that geographic distribution of couples infertility due to male factor ranged from 20% to 70% while the percentage of infertile men ranged from 2-5% to 12%. The highest rates were identified in Africa and Central/Eastern Europe (18).

Surprisingly, in our study, men conceiving before disease onset had a lower fertility (1.20) in comparison to those conceiving after AS onset (1.38). One third of the fathers with AS onset at conception recognized external influence on the couple decision to have children and this parameter showed to be statistically significant. Indeed, 27 (35.52%) patients in the entire group recalled a decrease in sexual desire from time to time. The majority (19/27) of patients

linked this phenomenon to the disease burden. A borderline statistical significance was obtained for this parameter analysis, but the number of included patients was low. At this point, one could hypothesize that sexual desire decrease and family size restriction counseling could have been some of the trigger factors for a lower number of children in the family in our groups. In addition, we may speculate that AS onset after the first child could have negatively influenced the couples' decision to have more children (risk of inheritance).

It is known by now, that sexual relationships can be affected in patients with inflammatory rheumatic diseases and this may impact fertility and fecundity. In a study on 612 AS patients (72% men), 38% of them reported a disease impact, ranging from moderate to extreme, on the sexual relationship. Other identified concurrent factors were pain, poor physical function, higher disease activity, anxiety and depression, unemployment and poor self-efficacy (22). Apart from the lower sex desire, none of the above mentioned factors were mentioned by our group; possibly our study groups were younger and had a more recent disease onset in comparison to other studies.

Indeed, no specific erectile dysfunction was identified through interview, regardless of the group affiliation. In other studies, sexual dysfunction was found to affect about 20-50% of the general population and is related to older age (23).

Other known concurrent factors impacting fertility would be disease activity, therapy exposure and history of comorbidities like varicocele or urinary virus infection in adulthood (4,14).

In our study, we could not appreciate the impact of active AS on the group fertility. Not all clinical records certifying AS activity evaluation were available for the purpose of this study. Hypothetically, some of the men with AS onset at conception could have had a pre-conception high disease activity. We were able to find BASDAI records in only 5 patients, 3 of them showing an active disease status. Disease activity scoring was done within a range of 2-4 months pre-conception.

In inflammatory conditions, higher TNF alpha concentrations are detected in the seminal fluid and adverse effects on spermatogenesis have been reported but information is controversial (24-27). A study performed *in vitro*, showed that sperm cell exposure to high concentrations of TNF alpha may induce an important loss of their functional and ge-

netic integrity (25). In contrast to this, another prospective study conducted by Micu et al on 20 active AS patients (high activity documented in the last 6 months) who were selected to receive TNFi therapy, showed similar sperm parameters with the control group, consisting of healthy age matched sperm donors (28). Indeed, chronic inflammation may affect the hypothalamic-pituitary-gonadal axis and subsequently the gonadal function (29,30). Normal gonadal function was found in men with AS, with the exception of patients with varicocele, who showed multiple sperm abnormalities (31-33). In our group, just 1 patient recalled an episode of infectious parotitis in adulthood. Varicocele diagnosis was not confirmed in any of the groups.

Fourty-two men diagnosed with AS before conception recalled NSAIDs exposure but medical records including the type, dosage and administration regimens were missing. Whether NSAIDs can in fact impair fertility in men with rheumatic diseases has not been completely clarified, the number of studies showing no harmful impact on spermatogenesis being small (4). In a prospective longitudinal controlled study, AS patients were exposed to continuous regimen of different NSAIDs, daily administration and highest tolerated dose, for at least 6 months prior to sperm analysis. Twelve patients were exposed to NSAIDs mono-therapy, 7 had additional therapy with Sulfasalazine (SSZ) and 4 a combination of SSZ and Methotrexate (MTX). Sperm analysis showed comparable results in patients and healthy age matched controls (28). The same conclusions are supported by another study on 20 AS patients treated with NSAIDs, where sperm parameters were normal (31). In contrast with this data, an observational study performed on 1376 men attending an infertility clinic, detected a NSAIDs (mainly Aspirin) dose-dependent decrease in seminal volume, sperm concentration, quality and motility (34).

In our group, only 5 patients recalled continuous SSZ treatment at the time of conception. They fathered 5 children and 1 couple recalled TTP >12 months. Overall, TTP > 12 months was present in 6 (6.06%) pregnancies, equally divided between the 2 sub-groups. SSZ can produce temporary oligospermia, but this phenomenon was mostly observed in inflammatory bowel disease (IBD) patients. After 2-3 months of medication cessation, spermatogenesis recovers, and in some cases successful conception can be achieved (35-40). In animal studies, the

sulfapyridine metabolite showed to induce transient infertility in a dose dependent way. Infertility was not influenced by folic acid supplementation (35). However, our previous prospective controlled study on AS patients showed no alteration of sperm parameters during longstanding therapy with SSZ in 11 patients with active AS (3 g/daily for 2 years), (28).

Our study was the first one to evaluate fertility in AS patients showing a lower rate in comparison to general population in this group. Psychological factors and reduced sexual desire showed to play a more important role in family size restriction, in comparison to other factors.

The limits of the study were the retrospective collection of interview-based data and the small number of patients. Delivered information may have been biased by errors in recalling the facts.

In conclusion, a lower fertility in AS patients was described in our group in comparison to general population and this phenomenon could be linked mostly to psychological factors impacting family size decision. No correlation between the low fertility and disease presence at conception was found. Future prospective controlled studies on larger AS patient cohorts are required for a thorough fertility evaluation.

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