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Original article

# No appreciable decrease in fertility in Behçet's syndrome

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## Abstract

**Objectives.** Behçet's syndrome (BS) follows an active course during the childbearing years in both men and women. We formally surveyed the infertility rate and the effect of drugs and types of organ involvement on fertility in BS.

**Methods.** We compared fertility among BS patients with and without major organ involvement with those with FMF, AS and healthy controls. A structured interview was performed and the medical records of the patients were reviewed to confirm the sites of involvement and drugs they used during their entire follow-up.

**Results.** The number of female patients who were not able to ever conceive, who were not able to conceive before or after disease onset or who were able to conceive late or only with assisted reproductive technology was not increased among the BS group. The same was true for the male patients to successfully achieve a conception and/or father a child. The average number of children, miscarriages, terminations and ectopic pregnancies were similar among the groups. Infertility was more common in BS patients with major organ involvement who used cyclophosphamide (CYC) compared with those who did not ($P = 0.009$).

**Conclusion.** Infertility is not appreciably increased among BS patients attending a dedicated outpatient clinic. Major organ involvement does not increase the risk of infertility and CYC is the only drug that seems to compromise fertility in BS.

**Key words:** Behçet's syndrome, co-morbidity, infertility, familial Mediterranean fever.

CLINICAL SCIENCE

## Introduction

Behçet's syndrome (BS) is a multisystemic vasculitis with mucocutaneous, musculoskeletal, ocular, gastrointestinal and neurological findings. The disease is frequently seen in the Mediterranean basin and the Far East with the highest prevalence in Turkey, Iran and Japan. It typically affects young adults in their 20s and 30s, during their childbearing years, with no sex predilection. However, it is very well known that the disease has a more severe course in young males, who tend to present with frequent eye and other major organ involvement.

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Population-based studies indicate that 15% of all couples fail to achieve conception in their first year of attempt. Among these, one-third of infertility cases are attributed to male factor alone, one-third is attributed to female factor alone and one-third is attributed to male plus female factor [1]. Causes of female infertility include ovulatory disorders, tubal factors (injury, blockage or paratubal adhesions, including endometriosis), uterine, cervical and immunological factors [2]. The most common causes of male infertility are varicocele, infections and immunological and congenital factors [1].

Patients with chronic rheumatic diseases might have fewer children when compared with the general population and this may be due to the impact of disease itself or the effects of drugs on fertility. The impact of the disease and drugs on the fertility rate in BS has not been formally investigated before. Patients with RA have an increased rate of infertility and those with SLE had fewer children than they had initially planned [3]. A reduced rate of fertility has also been reported in other chronic inflammatory

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arthritides, including adult patients with JIA [4]. The negative influence of FMF on fertility has clearly been established in both sexes [5]. A recent report suggests an increased rate of sperm abnormalities in patients with AS [6]. The association between the drugs used in the management of these diseases (e.g. colchicine, AZA) and infertility is controversial.

The aim of this study was to investigate the rate of infertility and the effect of drugs and involved sites on the fertility of patients with BS by studying healthy and diseased controls.

## Patients and methods

This study included patients with BS, FMF, AS and healthy controls who were recruited from hospital staff. All of the patients enrolled in the study fulfilled the International Study Group [7], Livneh [8] and modified New York [9] criteria, respectively. Patients with BS were divided into two groups: the first group had only mucocutaneous disease with or without joint involvement during their entire follow-up; the second group had at least one major organ involvement, such as the eye (uveitis, retinal vasculitis), vascular (deep vein thrombosis, arterial aneurysms, vena cava and intracardiac thrombosis), gastrointestinal system or nervous system involvement (parenchymal CNS involvement, dural sinus thrombosis). Written informed consent was obtained from all participants and the study was approved by the Cerrahpasa Medical School Ethical Committee, Istanbul University.

We surveyed BS patients who visited the outpatient clinic for their routine follow-up between February 2012 and August 2012. We included every patient with an even waiting list number and two physicians (C.S. and D.U.) applied a structured interview (see supplementary data, available at *Rheumatology* Online). All FMF and AS patients who visited our clinic during this time interval were included as diseased controls, and the staff working in our internal medicine department were invited for interview. Participants were asked about their marital status, total number of children, miscarriages and terminations, medications at the time of conception, history of assisted reproductive techniques (ARTs) and the health status of their live-born infants. They were also asked to report whether they or their partners had ever failed to conceive in their lifetime despite having unprotected intercourse for at least 1 year. Individuals who had fertility problems were further questioned if they had ever sought medical care and were asked to report their diagnosis that caused infertility. The medical records of the patients were reviewed to confirm the sites of disease involvement and drugs they used during the entire follow-up time. The temporal relationship between the periods of drug use and conception/infertile periods was investigated.

Infertility was defined as the inability to conceive after 1 year of unprotected intercourse. We aimed to compare the difference between the BS and control groups in the proportion of women (i) who had never conceived in their lifetime, (ii) who had a successful conception but became infertile after disease onset and (iii) who conceived late (without ARTs, but after 1 year of unprotected intercourse) or with ARTs, as well as men whose partners (i) had never conceived, (ii) had a successful conception but could not conceive after disease onset in their partners and (iii) conceived late or with ARTs.

After we completed the data collection, we realized that there was a trend towards increased infertility among patients using CYC; however, there were only four patients who had received this therapy. In order to delineate this effect on fertility, we decided to interview an additional group of patients who had received CYC. Among 5900 BS patients followed up in our clinic, 210 had been treated with CYC. We called 62 patients who had a valid phone number in our records, and all of them came to our clinic for interview. We only included BS patients for this part of the study since our AS and FMF patients are not prescribed CYC unless they have a co-morbid disorder.

### Statistical analysis

In order to show a 20% increase in infertility in BS with $\alpha = 0.05$ and 80% power, we calculated that each group should contain at least 125 individuals. Parametric variables were compared with analysis of variance (ANOVA) and non-parametric variables were compared with the chi-square test. In addition, we used univariate and multivariate logistic regressions to examine the relationship between infertility and involved sites, drugs, disease duration and age at conception or infertile period. Only the patients who attempted to have children after disease onset were included in the regression analysis. All statistical analyses were performed using SPSS version 13.0 (SPSS, Chicago, IL, USA) and Stata 10 for Windows (StataCorp, College Station, TX, USA).

## Results

We surveyed 190 BS patients with major organ involvement, 135 patients with mucocutaneous and/or joint disease, 126 patients with FMF, 129 patients with AS and 125 healthy controls. The demographic features of these patients, including their sex, mean age, age at diagnosis and criteria fulfilment, number of patients who attempted to have children and the drugs used by the patients who attempted to have children are given in Table 1. There were significantly more men among patients with BS major organ involvement and AS ($P < 0.0001$). Mean age, age at diagnosis and age at criteria fulfilment were significantly lower in patients with FMF when compared with other groups ($P < 0.05$).

The infertility rate was not increased among BS patients (Table 2). When men and women were analysed separately, the number of women who had never conceived in their lifetime, who had a successful conception but became infertile after disease onset or who conceived late or with ARTs was not increased among BS patients. The same was true for men with BS whose partners had never conceived, had a successful conception but could not conceive after disease onset in the study subject and conceived late or with ARTs. The only difference between

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**Table 1** Demographic features of study groups

| | BS (major organ) | BS (mucocutaneous) | FMF | AS | Healthy | *P*-value |
|---|---|---|---|---|---|---|
| Total, *n* | 190 | 135 | 126 | 129 | 125 | |
| Male/female, *n* | 121/69[a] | 41/94 | 48/78 | 79/50[a] | 43/82 | <0.0001 |
| Age, mean (S.D.), years | 39.6 (11.0) | 39.0 (11.0) | 36.4 (12.0)[b] | 38.3 (10.7) | 42.0 (9.7) | <0.001 |
| Age at diagnosis, mean (S.D.), years | 29.2 (8.6) | 30.8 (9.4) | 28.7 (11.9)[b] | 31.4 (10.5) | NA | 0.012 |
| Age at criteria fulfilment, mean (S.D.), years | 28.6 (8.5) | 29.9 (9.5) | 16.1 (10.1)[b] | 25.8 (9.9) | NA | <0.001 |
| Attempted to have children, *n* | 156 | 108 | 91 | 100 | 103 | 0.219 |
| Drugs, *n*/total *n* | | | | | | |
| Colchicine | 36/88 | 34/49 | — | — | — | — |
| AZA | 38/88 | 3/49 | — | — | — | — |
| CSA | 20/88 | — | — | — | — | — |
| Steroids | 41/88 | 4/49 | — | — | — | — |
| SSZ | 23/88 | — | — | — | — | — |
| IFN | 8/88 | — | — | — | — | — |
| Etanercept | 5/88 | 1/49 | — | — | — | — |
| Infliximab | 3/88 | 3/49 | — | — | — | — |
| Adalimumab | 2/88 | — | — | — | — | — |
| MTX | 5/88 | — | — | — | — | — |
| CYC | 4/88 | — | — | — | — | — |
| NSAIDs | 29/88 | — | — | — | — | — |
| Aspirin | 8/88 | 1/49 | — | — | — | — |

[a]Male/female ratio was significantly higher in patients with BS (major organ involvement) and AS. [b]Patients with FMF had a significantly lower age at interview, diagnosis and criteria fulfilment. BS: Behçet's syndrome.

**Table 2** Infertility rates among study groups

| | BS (major organ) | BS (mucocutaneous) | FMF | AS | Healthy | *P*-value |
|---|---|---|---|---|---|---|
| Never conceived/impregnated despite regular intercourse, *n*/*n* (%) | 4/156 (2.56) | 0/108 (0) | 3/91 (3.29) | 3/100 (3) | 3/103 (2.91) | 0.502 $\chi^2 = 3.339$, df = 4 |
| Male | 3/98 | 0/32 | 0/36 | 2/57 | 1/37 | 0.691 $\chi^2 = 2.243$, df = 4 |
| Female | 1/58 | 0/76 | 3/55 | 1/43 | 2/66 | 0.358 $\chi^2 = 4.373$, df = 4 |
| Failed to conceive/impregnate after disease onset, *n*/*n* (%) | 7/88 (7.95) | 5/49 (10.2) | 6/80 (7.50) | 6/66 (9.09) | NA | 0.950 $\chi^2 = 0.35$, df = 3 |
| Male | 5/63 | 3/20 | 3/33 | 3/45 | NA | 0.732 $\chi^2 = 1.29$, df = 3 |
| Female | 2/25 | 2/29 | 3/47 | 3/21 | NA | 0.727 $\chi^2 = 1.310$, df = 3 |
| Conceived/impregnated late or with ART, *n*/*n* (%) | 10/156 (6.41) | 9/108 (8.33) | 5/91[a] (16.48) | 6/100 (6) | 4/103 (3.88) | 0.0139 $\chi^2 = 12.52$, df = 4 |
| Male | 6/98 | 3/32 | 5/36 | 4/57 | 2/37 | 0.605 $\chi^2 = 2.724$, df = 4 |
| Female | 4/58 | 6/76 | 10/55 | 2/43 | 2/66 | 0.031 $\chi^2 = 10.65$, df = 4 |

[a]Total number of FMF couples who conceived late (naturally, but after 1 year) or required assisted reproductive techniques (ARTs) to conceive was significantly higher when compared with other groups. The number of couples who failed to conceive after disease onset was not significantly different in diseased groups when compared with healthy individuals who never conceived despite regular intercourse ($P = 0.404$, $\chi^2 = 4.016$, df = 4).

the groups was that there were more women with FMF who conceived late or used ARTs to conceive ($P = 0.0308$, $\chi^2 = 10.65$, df = 4). There were no differences among men with FMF compared with the other groups. We also compared the rate of infertility after diagnosis in diseased groups to the rate of infertility in healthy controls. Although there was a trend for an increased rate of infertility after diagnosis in the diseased groups (BS with major organ involvement 7.95%, BS without major organ involvement 10.2%, FMF 7.5%, AS 9.1%) compared with healthy controls (2.9%), the difference was not statistically significant ($P = 0.404$, $\chi^2 = 4.016$, df = 4).

Among 23 of 130 (17.7 %) male patients with BS who had compromised fertility, the most commonly documented aetiology was varicocele ($n = 4$). Abnormal semen analysis was reported by three patients and

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another three patients stated that their partner had been diagnosed with infertility. One patient was operated for cryptorchidism, but the aetiology of infertility was unknown in the majority of patients ($n = 12$). Among 18 of 134 (13.4%) female BS patients with compromised fertility, the aetiology was unclear in most ($n = 14$), one patient had documented pelvic inflammatory disease and three patients reported that their partner had been diagnosed with infertility.

The average number of children, miscarriages, terminations and ectopic pregnancies were not significantly different between patients with BS and controls, except for AS patients, who had fewer children when compared with other groups ($P = 0.013$) (Table 3). Among 17 organ-involved BS patients who had a history of miscarriage after diagnosis, 16 (94.1%) had eye involvement and 1 (5.9%) had vascular involvement. None of them had gastrointestinal (GI) or CNS involvement.

The number of infants with congenital anomalies was not increased among patients with BS when compared with other groups ($P = 0.465$). The most commonly documented anomalies of live-born infants included cardiovascular defects ($n = 3$), cleft lip/palate ($n = 2$), neural tube defects ($n = 1$), haemangioma ($n = 1$), developmental hip dysplasia ($n = 1$), pes equinovarus ($n = 1$) and mental retardation ($n = 1$). Among these BS patients, drugs used at the time of conception were colchicine (two patients), AZA (two patients), steroids (two patients) and ciclosporin (one patient) and five patients were not on any medication.

We performed a multivariate logistic regression to determine the independent predictors of infertility. We first performed a univariate analysis to find variables that showed an association with infertility. None of the drugs used for BS or diseased controls were associated with infertility (data not shown). The age at conception attempt [odds ratio (OR) = 1.15, 95% CI 1.07, 1.24, $P < 0.001$), disease duration after criteria fulfilment (OR = 1.03, 95% CI 1.01, 1.06, $P = 0.01$) and a diagnosis of FMF (OR = 3.45, 95% CI 1.62, 7.34, $P = 0.001$) showed a significant association with infertility in univariate analysis. In multivariate analysis, the only significant predictor of infertility was age at conception attempt (OR = 1.18, 95% CI 1.09, 1.28, $P < 0.001$).

Although logistic regression did not reveal an association between infertility and any of the drugs that were used, among the four patients with a history of CYC use that we included in this study, two had infertility. After this observation we interviewed a separate group of 62 BS patients who had a history of CYC use. Among these, 16 patients had attempted to have a child during or after CYC therapy. Five of the 16 patients (31.3%) in this group, all men, failed to impregnate after therapy, compared with 3 of 60 BS patients (5%) with major organ involvement who had been treated with drugs other than CYC ($P = 0.009$). Moreover, 3 of 16 patients (18.8%) in the CYC group impregnated late or only with ARTs after therapy, while 1 woman out of 60 BS patients (1.6%) with major organ involvement who had received drugs other than CYC conceived late or with ARTs after treatment ($P = 0.028$).

## Discussion

Our results show that overall infertility is not appreciably increased among BS patients. The number of women with BS, or partners of men with BS who conceived late, meaning after 1 year of unprotected intercourse, or who could only conceive with ARTs was also not high when compared with diseased or healthy controls. Moreover, the average number of children, miscarriages, terminations and ectopic pregnancies were similar among BS patients and controls.

Prior studies have revealed that both male and female patients with BS have higher rates of sexual dysfunction [10, 11]. Diminished desire and arousal, and pain due to genital ulceration are more common in female patients, while erectile dysfunction is a significant problem for males. Additionally, BS patients have higher levels of anxiety and depression, especially at young ages [12]. It is thought that the psychological state of the patient has a greater influence on sexual status in the early stages of disease [11]. BS has a negative effect on quality of life, particularly in patients with organ systemic involvement and frequent disease exacerbations [13]. All of these psychosocial factors may have a great impact on family size, even more so than organic causes.

Moreover, our analysis revealed that infertility was not increased in different sites of disease involvement. Genital ulceration, observed in 91% of patients (122 of 134) who attempted to have children after disease onset, is associated with intense pain and decreased self-esteem. However, these are usually well controlled with treatment and do not affect fertility in long-term follow-up. In our

**Table 3** Pregnancy outcomes

| | BS (major organ) | BS (mucocutaneous) | FMF | AS | Healthy | *P*-value |
|---|---|---|---|---|---|---|
| Average number of children | 2.327 | 2.435 | 2.450 | 1.920[a] | 2.476 | 0.013 |
| Average number of miscarriages | 0.429 | 0.315 | 0.176 | 0.380 | 0.398 | 0.088 |
| Average number of terminations | 0.310 | 0.274 | 0.277 | 0.294 | 0.336 | 0.946 |
| Average number of ectopic pregnancies | 0 | 0.014 | 0 | 0.008 | 0 | 0.867 |
| Average number of children with congenital anomalies, *n/n* (%) | 7/156 (4.49) | 2/108 (1.85) | 1/91 (1.1) | 4/100 (4) | 5/103 (4.85) | 0.465 |

[a]Patients with AS had fewer children when compared with other study groups. BS: Behçet's syndrome.

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study group, 11.1% of male patients (9 of 81) who attempted to have children after disease onset had epididymitis. Non-infectious epididymo-orchitis observed in BS patients is characterized by pain, swelling and tenderness that can last for a few days to 2 weeks [14]. Recurrent attacks may cause thickening of the epididymis, but its effects on fertility are limited. In addition, Yilmaz *et al.* [15] reported that BS patients had a higher incidence of varicocele than healthy controls. We have also shown that varicocele is the leading cause of infertility in males with BS, thus it should be evaluated in every patient with fertility problems. Erectile dysfunction was reported to occur in 7.7% of patients in general [16] and 63% of patients with neurological involvement [17]. The aetiology of erectile dysfunction was multifactorial, including mixed-type vasculogenic impotence, arterial insufficiency, veno-occlusive dysfunction and neurogenic impotence. We observed that our patients with major organ systemic involvement did not show a higher incidence of infertility when compared with the mucocutaneous BS group. Therefore, one can conclude that systemic involvement itself is not a risk factor for infertility in BS.

The impact of drugs on the fertility of patients with rheumatic diseases is highly debated. BS patients use a wide spectrum of drugs, including colchicine, immunosuppressives, anti-rheumatic drugs, NSAIDs and anticoagulants. Colchicine is widely prescribed in BS, especially for mucocutaneous and joint disease. Oligozoospermia was reported in 11 of 131 BS patients who received colchicine 1 mg/day for more than 1 year [18]. Later, colchicine-related oligonecrospermia and azoospermia were shown in BS [19]. Nevertheless, Fukutani *et al.* [20] suggested that CYC rather than colchicine impaired spermatogenesis in BS. The effect of colchicine on female infertility in BS has not been studied up to now. Recent reports have indicated that colchicine, at regular doses, has no negative effect on the fertility of patients with FMF [21, 22]. Our results show that colchicine does not seem to have an effect on fertility in BS patients of both sexes. Data regarding the association of AZA with infertility are limited. One report showed that it had no effect on fertility and the risk of abortion [23]. We also failed to demonstrate a relationship between AZA and decreased fertility in BS patients.

CYC was the only drug that appeared to increase the risk of infertility in our patients with BS. Its use is recommended in BS patients with major vascular involvement [24]. A recent report investigated a cohort of young women diagnosed with SLE, vasculitis and scleroderma and indicated that patients who received CYC had higher incidences of amenorrhea, nulliparity and infertility [25]. Moreover, an increased incidence of azoospermia in BS treated with CYC was reported previously [26]. In our study, although the logistic regression analysis did not show an association with any of the drugs that were used—most probably due to the small number of patients who had used CYC in the original group—a separate analysis of BS patients who had used CYC showed that this drug was associated with infertility.

In general, BS was found not to be associated with increased congenital anomalies and anomalies observed in the offspring of these patients were similar to those of general population. In our study group, drugs used in the management of disease were not associated with an increased incidence of congenital malformations. The increased incidence of late conception and the need for ARTs in patients with FMF can be attributed to the peritoneal adhesions or ovulatory dysfunction associated with the disease. In our study group, most FMF patients were diagnosed years after disease onset and started their colchicine treatment very late. This highlights the importance of early diagnosis and treatment in these patients in order to preserve their fertility potential.

This is the first study investigating fertility in BS, however, there are some limitations to our work. First, we did not make a gynaecological or urological evaluation of patients to elucidate the exact cause of infertility. Our results are dependent on a retrospective survey of infertility; extensive laboratory examinations with hormone tests or sperm analysis were not performed. Further studies with detailed clinical and laboratory evaluation of patients may help us understand more precisely the relationship between the disease and infertility. Another limitation could be the inclusion of hospital staff as healthy controls. However, we do not think the infertility rates of hospital staff are different from the general population. Finally, the sample sizes that we calculated by power analysis when designing the study were for the total group of patients, without analysing for men and women separately. Therefore the lack of a significant difference in the number of patients who parented a child late or with ARTs among men with FMF might be due to a type II error.

In conclusion, BS patients do not have an appreciably increased overall incidence of infertility when compared with FMF and AS patients and healthy controls. Major organ involvement does not seem to increase the risk of infertility and CYC is the only drug that seems to impair fertility in BS.

**Rheumatology key messages**

- The rate of infertility does not seem to be increased among Behçet's syndrome (BS) patients.
- Among the drugs that are used in BS patients, only CYC seems to impair fertility.
- FMF patients have a higher frequency of delayed conception and need for assisted reproductive techniques.

*Disclosure statement*: The authors have declared no conflicts of interest.

## Supplementary data

Supplementary data are available at *Rheumatology* Online.

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