

# Behçet's disease and pregnancy: retrospective study and updated review of the literature

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## Abstract Objective

Behçet's disease (BD) is a rare, chronic-relapsing multisystem vasculitis of unknown aetiology, typically presenting with bipolar aphthosis (oral and genital), cutaneous lesions, and ocular involvement. It is most often diagnosed during reproductive age and its coexistence with pregnancy is therefore not uncommon. The interaction between BD and pregnancy is complex and bidirectional: pregnancy can modulate disease activity, while the disease itself may influence maternal, foetal, and neonatal outcomes. Current literature remains limited and frequently yields inconsistent conclusions regarding this relationship. In light of these considerations, this study aims to evaluate the impact of BD on pregnancy outcomes and to characterise the disease course during pregnancy in a cohort of affected patients.

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## Methods

We retrospectively analysed data from 25 patients with a confirmed diagnosis of BD and a total of 48 pregnancies, followed at the outpatient clinics of Policlinico Umberto I, Rome, Italy. Clinical records were reviewed and supplemented with telephone interviews to ensure accuracy and completeness of information. Additionally, a literature review was conducted using major databases such as PubMed, Cochrane and Google Scholar to provide context and comparison with previously published findings.

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## Results

Contrary to the prevailing consensus in the literature, which often reports increased disease activity during pregnancy, our findings indicate that in 80% of cases it remained stable, with no significant differences compared to the pre-pregnancy period. When flares did occur, they primarily involved oral aphthosis, aligning with previously reported patterns. Pregnancy outcomes were generally favourable, with an overall live birth rate of 89.58%. Complications were observed in 13 pregnancies (27.08%), mostly in pregnancies that occurred before BD diagnosis (21%). The most common were spontaneous miscarriage and deep vein thrombosis. Other complications, each occurring in one case, included threatened miscarriage, preterm delivery, low birth weight, gestational diabetes, gestational hypertension, and premature rupture of membranes.

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## Conclusion

Our findings suggest that Behçet's disease does not usually worsen during pregnancy and that favourable pregnancy outcomes are achievable. Nonetheless, the risk of complications, although relatively low, supports the need for preconception counselling and close multidisciplinary monitoring. This study contributes new insights from a specialised referral centre to the limited body of evidence available on this topic.

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## Key words

Behçet's disease, vasculitis, pregnancy

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## Introduction

Behçet's disease (BD) is a chronic inflammatory vasculitic disorder of uncertain origin that primarily affects young adults (1). Its prevalence shows marked geographic variation, with higher rates along the ancient Silk Road, spanning the Mediterranean basin, the Middle East, and East Asia (2). The disease is characterised by systemic vasculitis with multisystem involvement, most commonly affecting the oral and genital mucosa, but also potentially involving the eyes, joints, central nervous system, and the vascular system, which is associated with increased morbidity (1, 5). BD typically presents in the third decade of life, placing most patients within their reproductive years at the time of onset. Given that approximately half of those affected are women (6), the interplay between pregnancy and BD is both clinically relevant and a subject of concern.

Although this, the bidirectional interaction between the disease and pregnancy remains poorly defined. To date, available data in the literature on this relationship are limited and inconclusive. The aim of this study is, therefore, to provide an updated overview of the existing literature about the disease and its potential maternal/foetal complications, and to compare it with the clinical experience of a multidisciplinary referral centre.

## Material and methods

A retrospective study was conducted in the multidisciplinary referral centre of Policlinico Umberto I, in Rome, Italy, where obstetricians, rheumatologists and ophthalmologists collaboratively manage patients with BD.

Medical records of female patients diagnosed with BD, according to the International Criteria for Behçet's Disease (ICBD) (7), were reviewed and integrated with data collected through a telephone questionnaire. Exclusion criterion included: nulli-gravidity, incomplete clinical records and lack of consent to participate.

Exacerbation is defined as the appearance or worsening of symptoms and/or modification of current treatment compared to the pre-pregnancy period.

Remission refers to a state in which the patient exhibits a resolution or major improvement of symptoms in comparison to the pre-pregnancy period. Stable disease is characterised as a clinical state in which the disease activity is minimal or well-controlled over a sustained period, with no significant flares or progression of symptoms.

Collected data included demographic characteristics, disease duration and activity, treatments received before and during pregnancy, pregnancy outcomes (e.g. miscarriage, preterm birth, intrauterine growth restriction), and BD flares. In parallel, a systematic literature review was conducted to identify studies focusing on BD and pregnancy. Searches were performed in major databases including PubMed, Cochrane Library, and Google Scholar, using the following keywords: "*Behçet's disease*" OR "*Behçet's syndrome*" AND "*pregnancy*". Eligible studies included case reports, case series, retrospective and prospective cohort studies, case-control studies, published in English up to July 2025. Duplicates were removed, and the remaining articles were screened based on title and abstract. Full texts were reviewed to extract data on maternal outcomes, foetal outcomes, and the clinical course of BD during pregnancy.

## Results

### *Description of our cohort*

Only 25 out of the 86 female patients initially screened met the inclusion criteria and were included in the final analysis. The demographic and clinical features of the patients included in our single-centre retrospective analysis are included in Table I.

All 25 enrolled patients were of Caucasian ethnicity. The mean age at data collection, age at diagnosis, and age at first pregnancy were  $59.76 \pm 10.47$  years,  $40.32 \pm 11.25$  years, and  $25.75 \pm 4.46$  years, respectively.

Among the 25 patients enrolled in our study, HLA-B51 typing was available for only 12 patients; of these, 11 (91.7%) tested positive for HLA-B51 and 1 (8.3%) tested negative. Although the disease presented sporadically in most cases, a positive family history was identified in 3 cases (12%).

Competing interests: none declared

**Table I.** Demographic and clinical characteristics of enrolled patients.

| Variable                              | Patients (n=25)        |
|---------------------------------------|------------------------|
| Demographic characteristics           |                        |
| Ethnicity                             | Caucasian 25/25 (100%) |
| Age at data collection; mean $\pm$ SD | 59.76 $\pm$ 10.47      |
| Age at diagnosis; mean $\pm$ SD       | 38.66 $\pm$ 12.03      |
| Age at first pregnancy; mean $\pm$ SD | 25.75 $\pm$ 4.46       |
| Clinical characteristics              |                        |
| HLA-B51 positive; n (%) <sup>*</sup>  | 11/12 (91.7%)          |
| Family history; n (%)                 | 3/25 (9.38%)           |
| Oral ulcers; n (%)                    | 25/25 (100%)           |
| Genital ulcers; n (%)                 | 19/25 (76%)            |
| Cutaneous lesions; n (%)              | 16/25 (64%)            |
| Ocular involvement; n (%)             | 19/25 (76%)            |
| Other manifestations; n (%)           | 16/25 (64%)            |
| Previous treatments <sup>§</sup>      |                        |
| Corticosteroids; n (%)                | 19/23 (82.61%)         |
| Colchicine; n (%)                     | 1/23 (4.783%)          |
| Conventional DMARDs; n (%)            | 13/23 (56.52%)         |
| Biologic DMARDs; n (%)                | 0/23                   |

SD: standard deviation; DMARD: disease-modifying anti-rheumatic drugs.

<sup>\*</sup>Data available for 12 out of 25 patients enrolled in the study.

<sup>§</sup> Data available for 23 out of 25 patients enrolled in the study.

**Table II.** Disease activity during pregnancy and postpartum period.

| Disease Activity      | Pregnancies (n=20) |
|-----------------------|--------------------|
| Remission; n (%)      | 0/20 (0%)          |
| Exacerbation; n (%)   | 4/20 (20%)         |
| Stable disease; n (%) | 16/20 (80%)        |

Regarding the clinical features of the disease, 100% of patients developed oral aphthae, 76% had genital ulcers, 64% presented with cutaneous lesions (erythema nodosum and/or pseudofolliculitis), 76% had ocular involvement (anterior uveitis, posterior uveitis and/or panuveitis), and 64% exhibited other manifestations (mainly articular, but also neurological, vascular and/or gastrointestinal).

In terms of pharmacological therapy administered during disease flare-ups over the course of their clinical history, 23 (92%) of the 25 patients enrolled in the study received one or more medications, while the remaining 2 patients (8%) had never undergone any pharmacological treatment for BD. A total of 82.61% of patients were treated with topical and/or systemic corticosteroids, 47.83% with colchicine and 56.52% with conventional DMARDs (primarily azathioprine, cyclosporine and/or methotrexate). None of the patients received biological DMARDs.

Among the 25 primiparous and multiparous patients included in the study,

16 (64%) were diagnosed as BD after pregnancy. Of these, 2 reported the onset of symptoms shortly after their first and only pregnancy. The first patient developed oral ulcers, erythema nodosum, and pseudofolliculitis; the second experienced oral and genital ulcers.

In the remaining 9 patients (36%), the diagnosis of BD preceded pregnancy. For these patients and their 20 pregnancies, it was possible to assess disease activity during pregnancy and the postpartum period in terms of exacerbation, remission, or maintenance of baseline disease status, as described in Table II. No cases of remission were observed, even when the disease was active prior to pregnancy. In 4 pregnancies (20%), BD flared, despite being in remission prior to conception. In 16 pregnancies (80%), the disease remained stable throughout gestation and puerperium. Exacerbation occurred during pregnancy in only 1 case, whereas in the remaining 3, flares were observed during the postpartum period. The most frequent manifestation during disease flares was oral ulcers. Others reported

symptoms included genital ulcers, erythema nodosum, and arthritis.

Among the 48 pregnancies reported in patients with Behçet's disease, the overall live birth rate was high (89.58%), reaching 100% in pregnancies occurring after BD diagnosis and 82% in those before diagnosis. Overall, maternal, foetal, and/or neonatal complications were observed in 13 pregnancies (27.08% of pregnancies), with a higher frequency in pregnancies preceding the diagnosis (36% vs. 15% after diagnosis).

Specifically, 5 cases (10.42%) of spontaneous miscarriage were reported, all occurring before BD diagnosis (four in the first trimester and one in the second). Other complications included one case (2.08%) of first-trimester vaginal bleeding due to threatened miscarriage, one case (2.08%) of preterm delivery, one case (2.08%) of low birth weight (<2500 g), one case (2.08%) of gestational diabetes, one case (2.08%) of gestational hypertension, one case (2.08%) of premature rupture of membranes (PROM), and two cases (4.17%) of deep vein thrombosis (DVT), also exclusively observed in pregnancies before diagnosis.

No cases of intrauterine growth restriction (IUGR), neonatal BD, or neonatal complications were recorded. The caesarean section rate (26% overall) was not increased compared with the regional average reported in the Lazio region over the last four decades (38%) (5). Mean birth weight was within the normal range (3340 $\pm$ 329 g), with no significant differences between groups.

#### Literature review

As of July 2025, a total of 34 articles published in English were included: 17 case reports and 17 clinical studies (among which 8 case-control studies), encompassing a total of 708 patients. Table III summarises the main conclusions drawn from these publications (9-42).

Overall, the remission rate appears to be higher than both the exacerbation rate and the rate of disease stability during pregnancy. When exacerbation does occur, it predominantly presents as a flare of oral and/or genital aphthosis. Cutaneous lesions, ocular involvement, arthri-

**Table III.** Review of the literature.

| Study                       | Year | Study design                     | Country of origin (patients) | n. of patients                                                                | n. of pregnancies                                                | Clinical features                                                                                     | Impact of pregnancy on BD                                                              | Impact of BD on pregnancy                                                                                       |
|-----------------------------|------|----------------------------------|------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Chajek <i>et al.</i> (9)    | 1975 | Case report                      | Iraq                         | 1                                                                             | 2                                                                | Arthritis, Mucocutaneous lesions                                                                      | Remission                                                                              | NS                                                                                                              |
| Madkour & Kudwah (10)       | 1978 | Case report                      | Saudi Arabia                 | 4                                                                             | NS                                                               | Mucocutaneous lesions, Arthritis                                                                      | Exacerbation                                                                           | NS                                                                                                              |
| Plouvier <i>et al.</i> (11) | 1979 | Case report                      | France                       | 1                                                                             | 3                                                                | NS                                                                                                    | Remission                                                                              | NS                                                                                                              |
| Hurt <i>et al.</i> (12)     | 1979 | Case report                      | USA                          | 1                                                                             | NS                                                               | NS                                                                                                    | Exacerbation                                                                           | NS                                                                                                              |
| Fam <i>et al.</i> (13)      | 1981 | Case report                      | Canada                       | 1                                                                             | 2                                                                | Recurrent oral ulcers                                                                                 | Status quo                                                                             | Neonatal BD in one newborn                                                                                      |
| Ferraro <i>et al.</i> (14)  | 1984 | Case report                      | Italy                        | 1                                                                             | 1                                                                | Bilateral vision loss                                                                                 | Improvement of visual functions during pregnancy, followed by postpartum exacerbation  | Spontaneous vaginal delivery, no evident foetal malformation                                                    |
| Farrag <i>et al.</i> (15)   | 1987 | Case report                      | Egypt                        | 1                                                                             | 2 (first pregnancy without complications)                        | Genital ulcers                                                                                        | Exacerbation                                                                           | C-section (due to multiple infected ulcers), no evident fetal malformation                                      |
| Larsson <i>et al.</i> (16)  | 1987 | Case report                      | USA                          | 1                                                                             | 1                                                                | Mucocutaneous lesions, Arthritis                                                                      | Pregnancy: Remission post-partum: Exacerbation                                         | Spontaneous vaginal delivery, no evident foetal malformation                                                    |
| Hamza <i>et al.</i> (17)    | 1988 | Case series                      | Tunisia                      | 8                                                                             | 21                                                               | Mucocutaneous lesions, Ocular lesions, Arthritis                                                      | Remission 12/21 (57%)<br>Exacerbation 9/21 (43%) – mainly in the third trimester       | No influence of the disease on pregnancy                                                                        |
| Wechsler <i>et al.</i> (18) | 1995 | Case report                      | France                       | 1                                                                             | 1                                                                | Mucocutaneous lesions, Cerebral venous thrombosis                                                     | Exacerbation                                                                           | C-section (due to foetal conditions), no evident foetal malformation                                            |
| Stark <i>et al.</i> (19)    | 1997 | Case report                      | UK                           | 1                                                                             | 2 (first pregnancy without complications)                        | Mucocutaneous lesions                                                                                 | Exacerbation (diagnosis during pregnancy)                                              | Neonatal BD in one newborn                                                                                      |
| Marsal <i>et al.</i> (20)   | 1997 | Retrospective case-control study | Spain                        | 10 (patients with BD diagnosed prior to pregnancy)                            | 25                                                               | Mucocutaneous lesions, Budd-Chiari syndrome in post-partum                                            | Remission 23/25 (92%)<br>Exacerbation 2/25 (8%)                                        | No influence of the disease on pregnancy                                                                        |
| Bang <i>et al.</i> (21)     | 1997 | Retrospective study- Case series | South Korea                  | 20 (only patients with a diagnosis of BD according to international criteria) | 20                                                               | Mucocutaneous lesions, Ocular lesions                                                                 | Remission 8/20 (40%)<br>Exacerbation 12/20 (60%) - 78% of cases during first trimester | No influence of the disease on pregnancy, 4 medical terminations due to exacerbation                            |
| Guzelian (22)               | 1997 | Case report                      | USA                          | 1                                                                             | 1                                                                | Oro-genital ulcers, abdominal pain                                                                    | Exacerbation                                                                           | IUGR                                                                                                            |
| Gül (23)                    | 2000 | Case series                      | Turkey                       | 16 (patients with BD diagnosed prior to pregnancy)                            | 16                                                               | Mucocutaneous lesions                                                                                 | Remission 7/16 (43%)<br>Exacerbation 9/16 (57%)                                        | No influence of the disease on pregnancy                                                                        |
| Jog <i>et al.</i> (24)      | 2001 | Case report                      | NS                           | 1                                                                             | 5 (4 abortions)                                                  | Mucocutaneous lesions, Arthritis, colitis, lower limb thrombophlebitis, frequent spontaneous abortion | NS                                                                                     | Neonatal BD                                                                                                     |
| Uzun <i>et al.</i> (25)     | 2003 | Retrospective study- Case series | Turkey                       | 28                                                                            | 44                                                               | Mucocutaneous lesions, Ocular lesions, Arthritis                                                      | Remission 23/44 (52%)<br>Exacerbation 12/44 (27%)<br>Status quo 9/44 (21%)             | No influence of the disease on pregnancy                                                                        |
| Nadji <i>et al.</i> (26)    | 2004 | Retrospective study              | Iran                         | 69                                                                            | 77                                                               | Mucocutaneous lesions, Ocular lesions, Arthritis                                                      | Remission 21/77 (27%)<br>Exacerbation 25/77 (33%)<br>Status quo 31/77 (40%)            | Abortion 19.5%,<br>Delivery at term: 80.5%                                                                      |
| Jadaon <i>et al.</i> (27)   | 2005 | Retrospective case-control study | Israel                       | 31                                                                            | 77 (includes only patients with BD diagnosed prior to pregnancy) | Mucocutaneous lesions, Ocular lesions, Arthritis, Vascular involvement                                | Remission 54/77 (70%)<br>Exacerbation 12/77 (16%)<br>Status quo 11/77 (14%)            | Statistically significant increase in the risk of pregnancy complications, spontaneous abortion, and C- section |

| Study                                  | Year | Study design                     | Country of origin (patients) | n. of patients | n. of pregnancies                         | Clinical features                                                                           | Impact of pregnancy on BD                                                                 | Impact of BD on pregnancy                                                                                                                                                            |
|----------------------------------------|------|----------------------------------|------------------------------|----------------|-------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kale <i>et al.</i> (28)                | 2006 | Case report                      | Turkey                       | 1              | 4                                         | Superior vena cava thrombosis, pulmonary embolism                                           | Exacerbation                                                                              | NS                                                                                                                                                                                   |
| Takayama <i>et al.</i> (29)            | 2013 | Case report                      | Japan                        | 1              | 1                                         | Mucocutaneous lesions, Ocular lesions, Arthritis, neuro-Behçet                              | Exacerbation (diagnosis during pregnancy)                                                 | Spontaneous vaginal delivery, no evident fetal malformation                                                                                                                          |
| Antonelou et Braha (30)                | 2013 | Case report                      | UK                           | 1              | 1                                         | Oro-genital ulcers, Arthritis                                                               | Status quo                                                                                | Neonatal BD                                                                                                                                                                          |
| Noel <i>et al.</i> (31)                | 2013 | Retrospective study- Case series | France                       | 46             | 76                                        | Mucocutaneous lesions, Ocular lesions                                                       | No Exacerbation 49/76 (64.5%)<br>Exacerbation 27/76 (35.5%)                               | Increased risk of spontaneous abortion in patients with a history of vascular involvement.                                                                                           |
| Iskender <i>et al.</i> (32)            | 2014 | Retrospective case-control study | Turkey                       | 24             | 63                                        | Mucocutaneous lesions, Ocular lesions                                                       | Remission 14/24 (58%)<br>Exacerbation 2/24 (8%)<br>Status quo 8/24 (34%)                  | Higher rate of vascular complications                                                                                                                                                |
| Gungor <i>et al.</i> (33)              | 2014 | Retrospective case-control study | Turkey                       | 94             | 298                                       | Diagnosis according to international criteria for BD                                        | Remission 2/94 (2.7%)<br>Exacerbation 18/94 (19.1%)<br>Status quo 74/94 (78.2%)           | Increased risk of spontaneous abortion/LBW                                                                                                                                           |
| Fernández-Fructuoso <i>et al.</i> (34) | 2016 | Case report                      | Spain                        | 1              | 2 (first pregnancy without complications) | Oro-genital ulcers                                                                          | Exacerbation                                                                              | Neonatal BD                                                                                                                                                                          |
| Xu et Bao (35)                         | 2016 | Case report                      | China                        | 1              | 3 (2 abortions)                           | Mucocutaneous lesions, Oral lesions, infertility                                            | Status quo                                                                                | C- section (due to podalic presentation), no evident fetal malformation                                                                                                              |
| Orgul <i>et al.</i> (36)               | 2017 | Retrospective study              | Turkey                       | 26             | 66                                        | Mucocutaneous lesions, Ocular lesions                                                       | Remission 60/66 (91%)<br>Exacerbation 6/66 (9%)                                           | Increased risk of preterm birth and low birth weight in patients with active symptomatic disease treated with colchicine                                                             |
| Lee <i>et al.</i> (37)                 | 2019 | Retrospective case-control study | USA                          | 144            | 144                                       | Diagnosis according to international criteria for BD                                        | Remission NS<br>Exacerbation NS<br>Statistically significant increase in the risk of VTE. | Statistically significant increase in the risk of preterm birth/C- section                                                                                                           |
| Barros <i>et al.</i> (38)              | 2021 | Retrospective case-control study | Portugal                     | 27             | 49                                        | Mucocutaneous lesions, Ocular lesions, Arthritis, Neurological Manifestation                | Remission 29/49 (67%)<br>Exacerbation 14/49 (33%)                                         | Statistically significant increase in the risk of spontaneous abortion, IUGR, C- section                                                                                             |
| Chan <i>et al.</i> (39)                | 2021 | Retrospective case-control study | Taiwan                       | 99             | 99                                        | Diagnosis according to international criteria for BD                                        | Remission NS<br>Exacerbation NS                                                           | No impact of the disease on pregnancy (except for a higher risk of postpartum cerebrovascular disorders and gestational diabetes), with no increased risk of adverse foetal outcomes |
| Arbrile <i>et al.</i> (40)             | 2022 | Retrospective study              | Italy                        | 16             | 33                                        | Mucocutaneous lesions, Ocular lesions, Arthralgia, Neurological and vascular manifestations | Remission 9/11 (80%)<br>Exacerbation 2/11 (18%)                                           | Overall pregnancy morbidity rate: 36%                                                                                                                                                |
| Keles <i>et al.</i> (41)               | 2022 | Retrospective case-control study | Turkey                       | 26             | 63                                        | Mucocutaneous lesions, Ocular lesions, Neurological manifestations                          | Remission 14/26 (54%)<br>Exacerbation 12/24 (46%)                                         | Higher risk of preterm delivery and LBW                                                                                                                                              |
| Beça <i>et al.</i> (42)                | 2024 | Retrospective study              | Spain                        | 4              | 7                                         | Diagnosis according to international criteria for BD                                        | Remission 0/7<br>Exacerbation 2/7<br>Status quo 5/7                                       | Higher risk of pre-eclampsia, IUGR, preterm delivery and LBW                                                                                                                         |

NS: not specified; BD: Behçet's disease; C-section: Caesarean Section; LBW: low birth weight; IUGR: Intra Uterine Growth Restriction; VTE: venous thrombo-embolism.

tis, and neurological manifestations are generally less common during pregnancy, while no gastrointestinal symptoms have been reported. Vascular complications described by some authors, such as

cerebral venous thrombosis and Budd-Chiari syndrome, represent some of the most severe disease flares.

In the study by Hamza *et al.* (17), exacerbations occurred primarily in the third

trimester, whereas in the study by Bang *et al.* (21), most flares occurred during the first trimester.

The duration of the disease prior to pregnancy may also influence disease

activity during gestation, regardless of the immunological and hormonal changes associated with pregnancy. Most studies have found no association between maternal age at conception, age at disease onset, and disease activity during pregnancy. However, Noel *et al.* (31) reported a correlation between shorter disease duration before conception and a higher rate of exacerbation during pregnancy. Seyahi *et al.* (43) suggested that the lower flare rate in patients with long-standing disease may be due to the natural decrease in disease aggressiveness over time.

Besides disease duration, other pre-conception factors have been evaluated as potential predictors of disease exacerbation during pregnancy. In the study by Nadji *et al.* (26), no association was found between pre-pregnancy disease manifestations and flare-ups during gestation. Bang *et al.* (21) observed that patients with normal-range C-reactive protein levels at conception experienced fewer flares during pregnancy. Noel *et al.* (31) found that treatment with colchicine appeared to protect against disease exacerbation during pregnancy. No association was found with HLA-B51 positivity or with a positive pathergy test.

Similarly to the literature on the effect of pregnancy on the clinical course of the BD, data on pregnancy complications and neonatal outcomes associated with BD are also inconsistent.

In the literature, an increased risk has primarily been reported for the following pregnancy outcomes: spontaneous abortion, preterm birth, intrauterine growth restriction, low birth weight, caesarean section, vascular complications (including deep vein thrombosis, pulmonary embolism, Budd-Chiari syndrome, and cerebral venous thrombosis). These vascular complications might be sign of an increased BD activity.

Other complications, such as gestational hypertension and/or preeclampsia, gestational diabetes, premature rupture of membranes, infections and placental abruption, have been reported sporadically. No cases of foetal malformations have been described, and no associations have been found between pregnancy outcomes and age at disease

onset, disease duration, or maternal age at the time of pregnancy.

These complications may be attributed both to the hypercoagulable state of pregnancy and to the vasculitic damage associated with BD, which may also involve the placenta. In this regard, Hwang *et al.* (44) reported two cases of patients with BD showing focal necrotising villitis with predominant neutrophilic infiltration and decidual neutrophilic vasculitis, both typical histological lesions of BD.

Regarding the high rate of caesarean delivery, it has been suggested that vaginal delivery may be associated with an increased risk of genital ulcers, particularly in cases involving perineal trauma. Therefore, the elevated caesarean section rate among patients with BD may be partially linked to physicians' preference to prevent local recurrence by avoiding perineal injury, rather than to urgent clinical indications (45).

## Discussion

BD and pregnancy represent two immunologically dynamic conditions that may mutually influence one another.

This retrospective study aimed to evaluate their interaction, with a specific focus on disease activity during pregnancy and associated obstetric outcomes.

According to the published literature, evidence regarding the bidirectional interaction between disease and pregnancy remains heterogeneous. Overall, BD remission is predominantly reported, with no significant interaction with pregnancy outcomes. However, some authors, such as Ben-Chetrit *et al.*, have reported remission rates comparable to those observed in our study (46).

Although our findings are consistent with the literature in showing no significant correlated pregnancy complications, they differ about disease course. The evidence from our study, indeed, indicates a general maintenance of disease status with no significant changes observed during pregnancy compared to the pre-pregnancy period. This stability may be partially explained by the fact that most patients included in our cohort were already in clinical remission prior to conception.

The tendency for disease quiescence

during pregnancy may be attributed to hormone-driven immunomodulation. Elevated levels of pregnancy-associated hormones, particularly progesterone, contribute to an anti-inflammatory state through immunosuppressive mechanisms.

Interestingly, many patients who experienced remission during pregnancy subsequently developed premenstrual or postpartum flares, periods characterised by a sudden drop in progesterone levels. This observation suggests that progesterone may be the principal hormone influencing the course of BD. Additionally, disease remission during pregnancy may be related to decreased neutrophil chemotaxis and adhesion capacity, both of which are reduced during pregnancy and are known contributors to vascular and tissue damage (47, 48). Nevertheless, four disease exacerbations were observed in our cohort, one during pregnancy and three in the postpartum period, manifesting predominantly as oral aphthous ulcers. These findings are in line with existing literature and suggest that the abrupt decline in progesterone levels after delivery may play a role in reactivating inflammatory processes. In our study, some patients had a known history of premenstrual exacerbations, including manifestations such as bipolar aphthosis, arthralgia, erythema nodosum and pseudofolliculitis, further supporting the hypothesis of hormone-related disease modulation.

Our study did not identify pre-conceptual predictors of disease flare during pregnancy, nor was there an apparent association between disease duration and flare occurrence.

Concerning the obstetric outcomes, prior studies have reported an increased risk of complications in pregnancies among patients affected by BD, including spontaneous abortion, preterm delivery, intrauterine growth restriction, low birth weight, vascular events, and, more rarely, hypertensive disorders, gestational diabetes, and neonatal BD. These outcomes are generally attributed to the vasculitic nature of the disease, which can involve placental vasculature and impair maternal-foetal circulation.

In our cohort of 48 pregnancies in women diagnosed with BD, pregnancy outcomes were, in general, favourable and the overall live birth rate was close to 90%. Interestingly, all pregnancies occurring after the diagnosis of BD resulted in live births (100%), whereas a lower live birth rate was observed in those occurring prior to diagnosis (82%). Although this difference did not reach statistical significance, it suggests a potential clinical trend.

The same pattern is recognisable when analysing pregnancy complications. Although overall complications occurred in less than one third of cases when considering all pregnancies, a rate comparable to that of the general population (48), subgroup analysis showed a lower complication rate in pregnancies after BD diagnosis (15%) compared to those before diagnosis (36%), even though this difference was not statistically significant.

One possible explanation could be that women with an established BD diagnosis may benefit from closer monitoring and tailored management during pregnancy, potentially improving outcomes. However, due to the relatively small sample size, these findings should be interpreted with caution and warrant confirmation in larger studies.

Several limitations should be acknowledged, pertaining both to the literature review and to the present study. The literature largely consists of case reports, which are inherently subject to publication bias, as unexpected events are more likely to be reported. Consequently, the available evidence may reflect a worst-case scenario. About our study, the relatively small sample size reflects the rarity of the disease, and the retrospective nature of the study may introduce recall bias, particularly given that data were collected via telephone interviews often conducted several years after the index pregnancy. Moreover, the mean age at diagnosis of BD was higher than the mean age at first pregnancy, indicating that many women were diagnosed only after childbirth, despite reporting symptoms consistent with the disease prior to pregnancy. This diagnostic delay, common in rare diseases, was considered by analysing disease activity only in

pregnancies occurring after a formal diagnosis (20 pregnancies in 9 patients), while pregnancy outcomes were assessed in the full cohort of 48 pregnancies from 25 women. This broader inclusion allowed a more comprehensive evaluation of obstetric events.

In conclusion, our findings suggest that pregnancy does not significantly alter the clinical course of BD in most patients, and that maternal and foetal outcomes are generally favourable. While disease flares may occur, particularly in the postpartum period, they are often mild and manageable. These results support the view that pregnancy should not be considered contraindicated in women with BD. Nevertheless, given the potential for disease activity and obstetric complications, preconception counselling and close multidisciplinary monitoring throughout gestation remain essential.

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