Behcet’s disease is a multisystemic inflammatory chronic vasculitis of unknown etiology characterized by recurrent oral ulcers, genital ulcers, eye lesions, and dermatological manifestations that is usually diagnosed during the reproductive years. There is limited information about the effects of Behcet’s disease on pregnancy and vice versa, but in most women, it appears to improve during this period. However, cases of activation or exacerbation of the disease in pregnancy are not uncommon and they are mainly manifested by oral ulcers, genital ulcers, and skin lesions. Corticosteroids and topical sucralfate are safe to use in pregnancy and while breastfeeding to treat oral ulcerations. The purpose of this study is to synthesize available information about Behcet’s disease oral manifestations in pregnancy, diagnosis, and treatment.

**Keywords:** Behçet disease, pregnancy, oral manifestations, diagnosis, treatment

**INTRODUCTION**

First described in 1937 by Hulusi Behçet, a Turkish dermatologist, as a triad of recurrent aphthous oral ulcers, genital ulcers, and relapsing uveitis that can lead to blindness [1,2], Behçet's syndrome (BS) is a multisystemic inflammatory chronic disorder [3], that can affect mucous membranes, skin, eyes, joints, blood vessels, central nervous system (CNS), and/or gastrointestinal system [2,4].

Despite its undetermined etiology, histopathological vasculitis abnormalities are common findings in all afflicted organs, and involvement of small vessels is thought to cause many of the problems that this disease is associated with [3,5]. Behçet's disease (BD), unlike other vasculitis conditions, can affect both arterial and venous systems, as well as vessels of various diameters [2], and can cause thrombotic complications, which may harm the pregnancy [6,7].

Although familial cases have been reported [8], they are rare, and the most prevailing theory remains that of an infectious pathogen that causes an abnormal inflammatory response in a genetically vulnerable host [1,9]. This theory is supported by the consistent link between the human leukocyte antigen (HLA)-B51 and Behçet's disease [10,11]. HLA-B51-positive people have a higher risk of Behçet's disease [12]. This link is more prevalent in the region comprising southwest Asia and northeast Africa, Mediterranean region and Japan, and is less common in Western countries. In addition, HLA-B51-positive patients appear to have a worse prognosis [13].

BS is diagnosed in the fertile years of life, especially during the second and third decades. In Europe, women seem to be more affected. It is distributed worldwide, but it is most common along what was formerly the ancient ‘Silk Routes’ that connect-
ed Asia and the Mediterranean [1]. Population prevalence rates in Turkey range from 80 to 370 cases per 100,000, while rates in East Asia and the Mideast range from 13 to 20 cases per 100,000 [1,3,14]. The prevalence in the United Kingdom is unknown, however it is thought to be around 1 per 100,000 [15].

MATERIAL AND METHODS

Even though Behçet syndrome is usually diagnosed during the fertile years of life, little is known about the impact of BS on pregnancy outcomes and the implications of pregnancy on the disease. Case reports and small sample-sized studies make up the majority of the literature on this topic. We have used keywords such as ‘Behçet disease’, ‘pregnancy’, ‘oral manifestations’, ‘diagnosis of Behçet disease’, ‘treatment of Behçet disease’, and we have searched articles through PubMed, UpToDate, Medscape, and Medicine, to seek out and synthesize available information on Behçet’s disease oral manifestations during pregnancy, diagnostic criteria, and treatment.

DIAGNOSIS OF BEHÇET’S DISEASE

There are no specific tests that may be used to confirm a Behçet’s disease diagnosis, which is mainly established on clinical criteria. All of the main symptoms of the disease may take months or years to emerge, making it difficult to obtain a firm diagnosis. The signs and symptoms of the disease, as well as positive clinical criteria known as ‘The International Clinical Criteria for Behçet’s Disease classification’, are used to confirm the diagnosis (Table 1) [5,16].

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<th>TABLE 1. The International Clinical Criteria for Behçet’s Disease classification [16]</th>
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<td>Recurrent oral ulcerations a minimum of 3 times in 12 months plus two additional criteria:</td>
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<td>• Relapsing ulceration of the genitalia</td>
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<td>• Eye lesions (inflammation of the eye layers or vessels)</td>
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<tr>
<td>• Skin lesions (panniculitis, folliculitis, acne-like lesions, acneiform nodules)</td>
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<td>• Positive Pathergy test</td>
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The Pathergy reaction involves inserting a tiny, sterile needle into the forearm skin. A positive result is defined as the appearance of a tiny erythematous induration at the site of skin trauma in the first two days following the pathergy test. The presence of pathergy indicates that the immune system is reacting excessively to a mild insult, and it can help in the diagnosis of Behçet’s disease, but only a minor percentage of Behçet’s patients exhibit the pathergy phenomena. Inhabitants of the Mediterranean area are more prone to have a positive pathergy reaction. On the other hand, only 50% of patients in the Mideast and Japan present a positive pathergy test. In the United States, this reaction is significantly less common. Furthermore, other illnesses might occasionally cause positive pathergy tests, so the test is not 100% specific [5].

When it comes to the oral manifestations of Behçet’s disease, mouth ulcers are the earliest and most frequent, being experienced by 98% of the patients, and represent a sine-quâ-non feature of BD, according to International Study Group criteria [16].

These are painful lesions that typically affect the gingival, buccal, and labial mucosa, as well as the tongue, while they can also arise in the soft and hard palate, oropharynx, and tonsils [17,18]. It can occur alone or in clusters, often after local trauma or dental procedures [17]. The typical ulcer is spherical, encircled by a raised erythematous border, and has a yellowish pseudomembrane covering the bottom [2,17]. Minor ulcers (less than 1 cm in diameter) are the most common type of recurrent oral aphthous ulcers (80-85%). They are small shallow ulcers that range in number from one to five, are mildly painful, and heal without scarring in four to fourteen days [19,20]. Major ulcers, a less common type, are more painful and heal in two to six weeks with scarring. The least common type of ulcer is the herpetiform ulcer, which consists of multiple small (2-3 mm) and painful sores that may consolidate. Patients may arrive with a mixed pattern, which is uncommon [17].

The histological appearance is unspecific, with a mixed inflammatory infiltration near the ulcer’s base. A leukocytoclastic and lymphocytic vasculitis might be seen in more severe instances. [2,21].

Recurrent oral aphthous ulcers caused by Behçet’s disease should be distinguished from those caused by other diseases associated with recurrent oral ulcers. Trauma, recurrent aphthous stomatitis (RAS), infections (herpes simplex, syphilis, HIV, primary herpetic gingivostomatitis, and hand-foot-mouth disease), mucocutaneous disease (lichen planus, erythema multiforme), immunobullous disease (pemphigus), squamous cell carcinoma, drugs, and systemic disorders, are all frequent cause of mouth lesions [22-24]. Oral ulcers can also be caused by systemic lupus erythematosus, MAGIC syndrome, Reiter’s syndrome, and Sweet’s syndrome, or they can be caused by hematological/nutritional deficiencies (iron, vitamin, and B12 deficiency, folic acid deficiency, celiac disease) and hematological diseases (cyclic neutropenia, lymphoma) [18,22]. Inflammatory bowel illness, particularly Crohn’s disease, and ulcerative colitis, to a lesser extent, can cause oral mucosa ulcers (Table 2) [17].

EFFECTS OF PREGNANCY ON BEHÇET’S DISEASE MANIFESTATIONS

Variability in Behçet’s disease activity among pregnancies could be linked to several immunologi-
cal and hormonal changes brought on by pregnancy. Remissions during pregnancy may be attributed to pregnancy-induced immunosuppression, according to one theory [3]. The inflammation that causes BS is assumed to be based on cell-mediated immunity [1,25,26]. Cellular immunity is suppressed throughout pregnancy as a part of the immunological changes that lead to fetus ‘tolerance’. Krause et al. [27] provided more evidence in support of immunological changes during pregnancy, including a decrease in neutrophil chemotaxis and adherence. High levels of estrogen, that can decrease particular immunological activity [28], alongside a rise in other critical pregnancy hormones (βHCG, αFP, progesterone) that may also promote prenatal immunosuppression [29], are among the physiological modifications supporting these findings.

Six small case series and 13 case reports, totaling 221 pregnancies in 121 women, were included in a literature review on BS in pregnancy between 1977 and 2008. According to these findings, 62% of the women presenting with active disease had their condition go into remission during pregnancy, nearly a quarter (29%) had an exacerbation, and the remaining 9% had no change in their disease’s activity [1].

Furthermore, nine case reports and two studies revealed primarily remissions in BD patients during pregnancy. Chajek et al. [30] described a woman with chronic BD who only had remissions during her two pregnancies throughout a 20-year follow-up. Ferraro et al. [31] described two cases that had remissions during pregnancy but then relapsed after birth. Uzun et al. [32] studied 44 pregnancies in 28 women and observed a 52.3 % remission rate (23 pregnancies), a 27.3 % exacerbation rate (12 pregnancies), and nine pregnancies that remained unaffected.

Flares of disease were described in four case reports and two small studies. In pregnancy, Madkour et al. [33] found severe and long-lasting mucocutaneous and articular exacerbations. There was a predominance of prenatal disease exacerbation with typical mucocutaneous ulcers (oral and genital) in a case study by Bang et al. [34]. Hamza et al. [35] studied 21 pregnancies from eight patients and found that while 12 of the pregnancies were in remission, nine of them had exacerbations. Buccal aphthosis and dermatological signs were most frequently observed during exacerbations.

Another study on 16 pregnant women with Behçet’s disease diagnosed before, during, and after pregnancy revealed that BD was triggered in four cases before pregnancy, nine cases during pregnancy, and three cases afterward. Remission was observed in 12 cases before pregnancy, 7 cases during pregnancy, and 13 cases postpartum. Before pregnancy, oral and genital ulcers were the most common signs of activation. During pregnancy, there were deep vaginal ulcers, severe mouth ulcers, papulopustular lesions, and erythema nodosum. Oral ulcers, vaginal ulcers, and erythema nodosum were also frequent after pregnancy [36].

Neonatal BD is a relatively uncommon complication that is almost invariably associated with active maternal disease. Oral ulcers, skin lesions, fever, and leukocytosis are the main symptoms [37].

### TREATMENT OF BEHÇET’S DISEASE IN PREGNANCY

Behçet’s disease with oral ulceration can benefit from treatment with topical steroids available in creams, mouthwashes, or inhalers [9]. Topical sucralfate can be a substitute. According to the literature, both options are safe during pregnancy [38,39].

### CONCLUSIONS

Despite its rarity, Behçet’s disease is most usually diagnosed during the reproductive years. Many questions may arise for the affected women regarding the impact of pregnancy on their condition and vice versa. According to our review of the literature, BD improves in most patients during pregnancy, but there are also cases of activation or exacerbation of the disease. Most frequently, these are manifested by oral aphthosis, genital ulcers and dermatological signs. Topical steroids and topical sucralfate are safe to use during pregnancy to treat oral manifestations of Behçet’s disease.

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