Chapter

Behçet's Disease and Pregnancy

Gökçe Işıl Kurmuş and Erol Koç

Abstract

Behçet's disease (BD) is a rare, chronic, multisystemic, vasculitic disease of unknown etiology. BD is characterized by recurrent oral and genital ulcers and ocular inflammation. This systemic vasculitis may also involve the joints, skin, vascular, gastrointestinal, urogenital, and central nervous system and is associated with hypercoagulability. Disease onset is commonly around the third decade of life and has a higher prevalence along the ancient "silk route." Because the disease is often diagnosed in women of childbearing age, disease activity during pregnancy and any adverse effect on obstetric and neonatal outcomes deserve special attention. Previous retrospective studies have demonstrated that BD activity usually regresses in pregnancy because of the immunomodulatory effects of both estrogen and progesterone. Furthermore, previous reports from different countries indicate that the disease course of BD during pregnancy may vary from patient to patient and even during different pregnancies in the same woman. In this chapter, we emphasize the course of the BD and pregnancy outcomes.

Keywords: Behçet's disease, pregnancy, vasculitis, clinical course, colchicine

1. Introduction

Behçet's disease (BD) is a rare, chronic, relapsing, multisystemic, and inflammatory disorder involving the oral and genital mucosa, eyes, joints, gastrointestinal, urogenital, vascular, and central nervous system [1–3]. It commonly occurs between the ages of 18 and 40, mainly affects young men, and tends to affect individuals with "silk road" bloodlines (corresponding the ancient route between the Mediterranean, the Middle East, and the Far East) [2–5]. Although the etiopathogenesis of the disease still remains unknown, it has been hypothesized as a genetic predisposition determined by the human leucocyte antigen-B51 (HLA-B51) allele. Infectious agents such as herpes simplex virus 1 or *Streptococcus* species may play a role as pathogenic triggers in genetically predisposed individuals [4–12]. BD is characterized by histopathologic vasculitic changes and thrombogenicity, which are common to all involved organs. Vessels of all sizes are affected, both in the arterial and venous systems, with venous involvement being more common than arterial involvement [1, 4].

Most BD patients at disease onset are in their reproductive ages. Since about half of the patients with this disease are women, BD activity during pregnancy, and obstetric and neonatal outcomes must be carefully researched. Any possible interaction between this two multisystemic condition deserves special attention [1, 13, 14]. Very little is known about the influence of BD and pregnancy to date. In few anecdotal case reports and retrospective small sample studies, both remissions and flares during pregnancy have been reported, and the effect of the disease on pregnancy remained unclear [1–4, 13–22]. Based on previous studies, it can be concluded that disease activity usually regresses during pregnancy.

2. Discussion

The variability in the activity of BD in different pregnancies may be associated with various immunomodulatory effects of estrogen and progesterone, which are significantly elevated during pregnancy. Pregnancy has been associated with suppression of humoral and cellular-mediated immunological functions [23–26]. Estrogen may have anti-inflammatory actions by stimulating anti-inflammatory interleukin (IL)-10 production and counteracting the effects of IL-12, antigen-presenting capacity, and tumor necrosis factor [26–32]. Progesterone may induce the inhibition of T cell, macrophage, and natural killer cell activity during pregnancy [24, 28–31]. Progesterone can enhance both Th2 cell polarization and Treg cell production [24–30]. Oh et al. reported the case of a young woman who experienced flares of BD during every premenstrual period [33]. This condition dramatically improved when the patient received oral contraceptive therapy. As a result, it is suggested that steady-state levels of estrogen and progesterone, during pregnancy or oral contraceptive treatment, may play a role in the suppression of BD exacerbations. Krause et al. reported that neutrophil functions such as chemotaxis and adherence were depressed during pregnancy, and this was associated with an improvement in autoimmune diseases [34]. It may be the reason for the reduced number of BD flares during pregnancy, because excessive neutrophil activation has been involved in BD pathogenesis. Ferraro et al. reported an almost complete absence of autoantibodies during pregnancy in a recent study [35].

In an extensive review of the literature, both remissions and exacerbations of BD were investigated during pregnancy, and it has been reported that disease activity may differ between pregnancies in the same women [13, 15, 35–47]. The current data is limited to retrospective studies and individual case reports. Hurt et al. reported a case of severe, recurrent, oral, and genital mucosal ulcerations and iridocyclitis during the second trimester of pregnancy [46]. Madkour and Kudwah reported prolonged mucocutaneous and articular exacerbations during pregnancy and during treatment with oral contraceptive pills, in four women with BD [47]. Farrag et al. described one case of severe vaginal and cervical ulcers in the third trimester of pregnancy, treated by prednisolone [48]. Bang et al. reported on 20 pregnancies with BD, in which 12 became exacerbated [15]. The most common lesions were oral and genital ulcers in Bang's study. Similarly, in the series of Gürler and Erdi, exacerbations were observed in most of the cases [49].

In recent studies, the main symptoms during BD flares were oral ulceration and genital ulceration, followed by skin lesions and ocular inflammation; no neurological or gastrointestinal symptoms were observed during pregnancy [3, 13, 36, 38, 46–48]. The most serious manifestations of the exacerbation were vascular complications such as Budd-Chiari syndrome and deep vein thrombosis (DVT) [3, 36, 49]. Some case reports that have been reported are severe disease flares such as DVT with nephrotic syndrome, superior vena cava thrombosis, dural sinus thrombosis, or intracardiac thrombosis [16, 19, 50, 51].

Conversely, some authors reported remissions during pregnancy in BD patients. Hamza et al. studied 21 pregnancies in eight women with BD and found remissions in 12 pregnancies [38]. In this study mainly genital ulcers were seen in nine flares during the last trimester, despite systemic corticotherapy. Marsal et al. studied 25 pregnancies in 10 women and reported 23 remissions and only 2 flares [36]. Chajek and Fainaro reported a woman with persistent BD who had remissions only during her pregnancies over a 20-year follow-up [43]. Ferraro et al. and Larsson and Baum reported two similar cases with complete remissions

during pregnancy with a flare after delivery [35, 45]. In a recent study, Uzun et al. reported on 44 pregnancies in 28 women and found remission rate to be 52.3%, while exacerbation rate was 27.3% [13]. In this study in nine pregnancies, there were no changes in the clinical course of BD.

In a single retrospective study by Noel et al., the authors compared the frequencies of BD exacerbations in the periods before gestation with the rate during pregnancy [3]. They observed that the annual incidence of BD flares per patient was lower during pregnancy than during the nonobstetric period. In most series there was no association between the pregnant woman's ages, the age at onset of Behçet's disease, and the course of the disease during pregnancy. Noel et al. found that the shorter duration of BD prior to conception had the higher rate of exacerbation. In addition, they investigated that the treatment with colchicine was associated with lesser exacerbations during pregnancy. On the other hand, Seyyahi et al. considered that since BD becomes less severe with the passage of time, it is also expected to see less flares with long disease duration [52]. Moreover, patients who were treated only with colchicine had probably a milder disease, and hence, they experienced less flares during pregnancy.

In a review Ben-Chetrit reported the rate of complications ranges between 4 and 20% of pregnancies in eight different studies [14]. In these studies only Marsal et al., Jadaon et al., and Iskender et al. compared their study groups with healthy controls [1, 2, 36]. Marsal et al. reported no significant differences in the incidence of maternal and fetal complications (abortions, congenital abnormalities, perinatal death, etc.) between BD patients and healthy controls [36]. In the series of Iskender et al., the frequencies of stillbirth, preeclampsia, preterm delivery, and cesarean deliveries did not differ between groups [1]. Jadaon et al. reported the highest rate of complications (20%) of these studies and significantly more than control groups [2]. The authors considered that especially the higher rate of miscarriage, but also the elevated pregnancy complication rate, may be explained by the vasculitic process underlying the pathogenesis of BD, as well as by hypercoagulability during pregnancy in BD patients. There was no difference of the neonatal outcomes such as intrauterine growth restriction, congenital abnormalities, neonatal weight, APGAR score at 1 and 5 min, respiratory distress syndrome, intraventricular hemorrhage, convulsions, prematurity, and perinatal death between the study and control groups [2]. In the reports by Noel et al. and Nadzi et al., the rate of complications was similar (16–19%) among their BD pregnant patients [3, 53]. In these studies, the high rate of miscarriages and the high number of deliveries by cesarean section were reported. Noel et al. observed a significant association between a history of DVT in BD and the risk of obstetric complications (miscarriages and cesarean deliveries) [3]. They found that the previous venous involvement due to BD increased obstetric complications, as previously suggested by Jadaon et al. [2]. All of such patients in their cohort had experienced prior DVT, and two had associated cerebral venous thrombosis. The main obstetric complications were miscarriages for these patients. The authors considered that there was a link between venous thrombosis and the risk of default in trophoblast implantation [3]. They suggested that the antiphospholipid syndrome must be ruled out. The risk of fetal loss in BD is, however, lower than the risk in antiphospholipid syndrome [54]. Jadaon et al. thought that the presence of anti-endothelial cell antibodies in the sera of patients with BD and impaired function of vascular endothelial cells may explain the high rate of miscarriages and pregnancy complications in BD patients [2, 55, 56]. However, these observations were not reported by other retrospective studies. In addition, the outcome of pregnancies varied even during different pregnancies in the same BD patient, suggesting that it is not invariably related to BD.

Jadaon et al. observed the rate of BD patients in which patients who went into remission was significantly higher than the number of patients who had exacerbations in the postpartum period [2]. In this case control study, it was shown that patients, who went into remission or exacerbation during pregnancy, tend to continue in the same direction after delivery. When the rate of remissions and exacerbations during pregnancy and postpartum period was compared, they found that the difference between the rate of remissions and exacerbations during pregnancy and postpartum for each of the women was not significant. They reported that there was no difference in disease activity during pregnancy and postpartum between HLAB51-positive and HLAB51-negative BD patients. In this study the number of pregnancies that were conceived under treatment was as follows: 29 of 77 patients with corticosteroids, 1 with colchicine, 1 with insulin, and 5 with heparin [2]. Hamza et al. reported exacerbations of BD in nine pregnancies despite corticosteroid treatment (10–15 mg/day) but no significant obstetric complications [38]. In a 20 case series reported by Marsal et al., 3 patients with corticosteroids, 1 patient with colchicine, and 1 patient with cyclosporine all discontinued the treatments at the onset of the pregnancy, due to concerns regarding adverse effects [36].

Many of the medications used in the treatment of BD are safe to use during pregnancy. These include corticosteroids, cyclosporine, and azathioprine. There is now growing evidence to suggest that colchicine is also safe to use in pregnancy, and previous concerns about associations with fetal chromosomal abnormalities have not been proven. The question of whether colchicine treatment is safe during pregnancy is important, because colchicine crosses the human placenta [3]. Despite the antimitotic effects of colchicine, the safety of this drug during pregnancy was recently assessed in a prospective comparative cohort study in which 238 colchicine-exposed pregnancies were followed up [57]. Increase in teratogenicity or congenital abnormalities was not observed. This finding is consistent with previous reports and underlines the safety of colchicine during pregnancy [58]. There is no agreement on the therapy of deep venous thrombosis and PE in BD [16]. Systemic anticoagulation with conventional agents including aspirin and low-molecular-weight heparin (LMWH) is usually applied because of hypercoagulability of pregnancy, but lack of response or recurrence may occur if immunosuppressive therapy is not continued [59].

New agents such as the anti-TNF-alpha monoclonal antibodies such as infliximab and etanercept have been used to treat inflammatory conditions in pregnancy and appear safe. There is no report that exposure to TNF inhibitors is toxic to the developing fetus. However, due to the limitations of available data and lack of controlled trials, there is not sufficient evidence to demonstrate the safety of the fetus exposed to TNF inhibitors during pregnancy. Moreover, the long-term safety of the infant is uncertain. If possible, discontinuation of the TNF inhibitor is desirable during pregnancy. If it appears to be necessary to use a TNF inhibitor to control the disease activity during mid and late pregnancy, then inoculations of live vaccine after birth pose a problem [20, 60]. It was reported that an infant born from a patient with Crohn's disease and exposed to infliximab during pregnancy died due to disseminated BCG because of a live vaccine received at 3 months of age [61]. Therefore, any infant exposed to anti-TNF monoclonal antibody in the uterus should be protected from the administration of a live vaccine until at least 6 months from birth or until the drug disappears from the serum [20]. Data on more than 300 pregnancies showed that infliximab carries low fetal risk during conception and the first two trimesters but suggests considering discontinuation in the early third trimester to minimize late fetal exposure to the risk of neonatal immunosuppression [62]. However, if treatment needs to be continued to keep the BD controlled, then the advantages probably outweigh the theoretical disadvantages. In a case

report, a 30-year-old woman diagnosed with BD at 12 weeks of pregnancy was successfully treated with infliximab, 5 mg/kg repeated dosages after 18 weeks of pregnancy, with improvement in all symptoms and normal full-term delivery [21]. A 36-year-old Japanese woman with intestinal BD (a recurrent ileocecal ulcer) was treated with adalimumab [20]. In this case, infliximab treatment showed secondary failure, so infliximab was switched to adalimumab. After the third injection of adalimumab, the patient was unexpectedly 4-week pregnant. Adalimumab was continued until the 20 weeks of pregnancy. Remission of the disease activity during pregnancy, the disappearance of ileocecal ulcer after delivery was reported, and the birth was uneventful in this case. It was also reported that adalimumab was detected in the umbilical blood after 119 days from the last infusion. The placental transition and timing of neonatal vaccination should be considered in cases of pregnancy with TNF antibody therapy [20].

Thalidomide is an effective treatment of oral and genital ulceration in BD but should never be used in pregnancy or in the absence of effective contraception because of its teratogenicity. Mycophenolate mofetil may also cause fetal malformations and should ideally be discontinued prior to pregnancy. It may sometimes be replaced with azathioprine. Disease-modifying drugs such as low-dose methotrexate and cytotoxic drugs such as chlorambucil and cyclophosphamide used in BD to treat inflammation of the brain and eye should also be avoided when planning a pregnancy as these medications may cause fetal abnormalities. These drugs should be discontinued at least 3 months prior to conception and alternative safe medications commenced if necessary [63].

During lactation the risk of taking medication that may suppress neonatal immune system must be balanced against the many benefits that breast milk confers and the risk of disease relapsing if medication is not taken. Prednisolone and azathioprine are safe to use during lactation, and only low concentrations of cyclosporine are transferred to the breast milk, so these may be safe as well. Similarly colchicine, which is secreted into breast milk, has had no adverse side effects associated with its use in lactation [57]. Other agents such as infliximab and etanercept are not thought to be secreted in breast milk, but there are as yet no data on whether these drugs are safe to use in lactation [20, 21].

3. Conclusions

It seems that pregnancy in general does not have harmful effects on the natural course of BD at all, though the limited number of cases reported and the lack of prospective studies. When the data from all the published series were analyzed, it has been considered that more than 50% of BD patients will improve remission during pregnancy. However, the BD activity usually regresses during pregnancy, and it is more recommended that due to the diverse course of the disease among different patients with the various clinical presentations and organ involvement, the disease course will differ. In some patients, the disease will go into remission, and in others, it will exacerbate during pregnancy. The variability in BD course during pregnancy is not limited to different patients. Even in the same patient, in one pregnancy, the disease may remain stable, while in a subsequent one, the disease exacerbates. There was no association between the number of pregnancy and the natural course of the disease.

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