Pregnancy management in Behçet's disease treated with uninterrupted infliximab. Report of a case with fetal growth restriction and mini-review of the literature

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Summary

Background: The mutual impact of Behçet's disease (BD) and pregnancy is variable and still unclear. Among the safe drugs administered, the newer infliximab (IFX) was rarely experienced in pregnancy, particularly in the third trimester. *Case:* The authors report a pregnancy with fetal growth restriction at 36 weeks in a 31-year-old primigravida with symptomatic BD, treated with uninterrupted monthly IFX and daily enoxaparin. The patient was induced at 38 weeks and had an uneventful vaginal delivery of a healthy baby. The postpartum period and following six months were uneventful for mother in terms of BD exacerbation, and newborn in terms of potential risks of neonatal BD and/or infections due to late immunosuppressive IFX administration. *Conclusion:* Because of the inconstant mutual impact, BD pregnancies should be precautionary considered at "potential high-risk" and need a careful and close monitoring by a multidisciplinary team with specific expertise.

Key words: Behçet's disease; Vasculitis; Infliximab; Pregnancy; Obstetric outcome; Fetal growth restriction.

Introduction

Behçet's disease (BD) is a relapsing multisystemic vasculitis first described in 1937 as a distinct clinical entity characterized by the clinical triplet: oral aphthous ulcers, genital ulcers, uveitis [1]. Since then, additional features such as arthritis, thrombophlebitis, erythema nodosum, gastrointestinal lesions, central nervous system lesions, vascular injuries, and hypercoagulability have been included in the variable pattern of the disease [2].

Although the unknown etiology of BD, autoimmune and microbial origin have been suggested in terms of an autoimmune reaction (HLA-B5 and HLA-DR5 alloantigens) set off by infectious agents such as Herpes Simplex Virus 1 or Streptococcus species in genetically predisposed individuals [3].

Behçet's disease begins in the third decade and occurs endemically in the Mediterranean regions, Middle East, and Far East: highest prevalence in Turkey (80-370 cases per 100,000); middle prevalence in Japan, Korea, China, Iran, and Saudi Arabia (13.5 - 20 cases per 100,000); low prevalence in Western countries (0.12 - 0.33 per 100,000 in the USA) [3].

The incidence of BD in childbearing age suggests a careful management of maternal course and obstetric outcome in pregnant patients, however, the mutual influence of BD and pregnancy is variable and still unclear. Generally, BD tends toward remission during pregnancy, but the overall risk of poor obstetric outcome could be relatively increased. Both the largest and the most recent reviews of the literature reported an improvement of BD in up to 60% of pregnant women and about 30% of relapses of various severity, with rare cases of maternal venous thrombosis. Concerning obstetric outcome, the same two reviews showed 9-30% of fetal losses, with less than 5% of intrauterine growth retardation (IUGR) and preterm birth [4, 5].

Among the safe drugs commonly used to treat BD in pregnancy (corticosteroids, colchicine, cyclosporine, azathioprine), the newer infliximab (IFX) appear to be safe in the first two trimesters [6], but very rare experiences for uninterrupted treatments up to third trimester are reported [7, 8].

Due to increasing awareness of the risks of pregnancy in BD, the authors report a case of a pregnancy with late fetal growth restriction in a 31-year-old woman with symptomatic disease treated with uninterrupted IFX. Moreover, a mini-review of the literature on the maternal effects and the obstetric outcome in BD pregnant women is performed. Finally, the safety of IFX treatment in pregnancy is briefly reviewed and discussed.

Case Report

In 2009, a diagnosis of BD was made in a 27-year-old woman for an episode of oral ulceration plus left uveitis and positive pathergy test, according to the International Study Group criteria for the diagnosis of BD: recurrent oral ulceration plus at least two of recurrent genital ulceration, eye lesions, skin lesions, or positive pathergy test [9]. Furthermore, a transient ischemic right pyramidal syndrome with aphasia was contextually detected. Therefore, a BD therapy with monthly intravenous IFX 5 mg/kg was instituted and a remission of the disease was achieved.

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In 2012, the 31-year-old case-patient (eumenorrheic, gravida 0) spontaneously conceived (singleton), with uninterrupted maintenance of monthly IFX therapy and start of daily subcutaneous enoxaparin 4,000 IU. The pregnancy, carefully monitored in the present hospital outpatient by both obstetrician and rheumatologist, uneventfully coursed for mother and fetus until the hospitalization at 36 weeks plus two days of anamnestic gestational age for maternal vagal syncope symptoms, paresthesia on face and upper extremity, and episodic obscuring of vision (neurological consult: no focal signs of central nervous system involvement and negative EEG; cardiologic consult: no cardiocirculatory alterations and negative ECG). Fetal surveillance by ultrasound revealed a fetus on cephalic presentation with growth restriction of more than two weeks (abdominal circumference 290 mm), but a normal and normally inserted placenta (Grade 2), normal amniotic fluid (Amniotic Fluid Index 12.1), and normal pulsatility index (PI) of umbilical artery at Doppler study (0.89). Maternal blood samples showed mild anemia (hemoglobin 9.4 g/dl) and moderate neutrophilia (neutrophils 13,020 / mm^3), with normal values of biochemical tests, including clotting profile, erythrocytes sedimentation rate (ESR), and C-reactive protein (CRP).

The pregnant was closely monitored during the following two weeks, until the ultrasonographic suggestion, at 38 weeks plus four days, of stopped fetal growth (abdominal circumference 304 mm), with decrease of amniotic fluid (Amniotic Fluid Index 9.9) and umbilical PI (0.80). Therefore, the patient was induced and had an uneventful vaginal delivery of female healthy baby weighing 2,400 kg (Apgar score 9-10 at 1-5 minutes, pH 7.32, pCO_2 41.0 mmHg). A normal placenta was detected and a second-degree vaginal tear was sutured without pathergy-like inflammatory reaction around the site and/or wound healing alterations.

Postpartum period was uneventful, and mother and newborn were discharged at three days from delivery. Afterwards, patient continued to be monitored closely for eight weeks for the risk of BD flares, and heparin was given for additional four weeks for thromboembolic prophylaxis. At present six-month follow-up, the mother continues IFX therapy and does not present BD exacerbation, and the infant is normal without any sign of BD and/or infections.

Discussion

BD is a heterogeneous vasculitis with a broad spectrum of clinical presentations, and its reciprocal influence with pregnancy is relatively variable between patients and even during different pregnancies in the same patient. These controversial outcomes during pregnancy could reflect the protean nature of BD and the different ethnic study groups, but also the pregnancy-induced immunosuppression, also explaining the remissions during gestation [10]. Generally, pregnancy does not have a deleterious effect on the course of BD and may improve it, however, BD may adversely affect pregnancy with a variably increased rate of miscarriage and IUGR, as reported in the present case.

In particular, in the largest case-control study (31 BD patients, 77 pregnancies), remissions were significantly more frequent during both pregnancy and postpartum periods (70.1% and 61.0%, respectively), while exacerbations were observed only in 15.6% and 16.9%, respectively ($p < 0.001$) [2]. Rather similar conclusions were achieved by three different case series (sum: 48 BD patients, 115 pregnancies) reporting approximately half entered remission during pregnancy, whereas a third-quarter of patients experienced disease flares [11-13]. Moreover, these data were confirmed by the largest (131 BD patients, 229 pregnancies) and the most recent (published on February 2013) reviews of the literature, respectively: improvement of BD in up to 60% of pregnant women (mostly limited to non-severe cases), about 30% of relapses of various severity (especially around delivery) [4, 5]. On the other hand, two series (sum: 43 BD pregnancies) reported the opposite effect and 56-66% of their patients worsened during pregnancy, whereas 33-44% improved [10,14]. Anecdotally maternal thromboembolic events as cerebral venous thrombosis [15], superior vena cava thrombosis and pulmonary embolism [16], fatal colonic perforation [17], inferior vena cava and suprahepatic venous thrombosis (Budd-Chiari syndrome) in the puerperium were described [12].

Concerning obstetric outcome, in the aforementioned large case-control study, pregnancy complications (26.2% vs. 1.9%, $p < 0.001$) and miscarriage (20.8% vs. 6.6%, $p = 0.020$) rates were significantly higher in the study group, but not significantly higher gestational hypertension (3.8% vs. 0.3%) [2]. However, a large series (59 BD patients, 144 pregnancies) did not report an increased risk of pregnancy complications compared with 20 healthy pregnant women [12]. The two aforementioned reviews of the literature showed 9-30% of fetal losses (9.2% in the systematic review), with less than 5% of IUGR and preterm birth (0.8% and 1.3%, respectively, in the systematic review) [4, 5]. Finally, neonatal outcome was good and did not differ from the controls [2, 12]. Minor and transient neonatal disease (commonly cutaneous and/or oral aphthous lesions), probably caused by transplacental passage of maternal antibodies, were rarely described only in symptomatic mothers [18-20].

Among the drugs commonly used to treat BD [21], only corticosteroids, colchicine, cyclosporine, and azathioprine are considered safe at conception and throughout pregnancy [22]. Recently, newer agents such as the anti-TNF-alpha monoclonal antibody IFX, also used in the present case also, have been used to treat other inflammatory conditions in pregnancy and appear to be safe. Data on more than 300 pregnancy showed that IFX carries low fetal risk during conception and the first two trimesters, and suggest to consider discontinuation in the early third trimester in order to minimize late fetal exposure for the risk of neonatal immunosuppression [6]. Nevertheless, in a small retrospective series on inflammatory bowel disease, IFX treatment during pregnancy revealed to be safe for the mother and the fetus for uninterrupted treatments also [7]. To date, the present authors found only a very recent paper in the literature reporting a case of safe and successful treatment with repeated IFX 5 mg/kg in a woman diagnosed with BD at 12 weeks of pregnancy, with improvement of all symptoms and normal full-term delivery [8]. In the present authors' opinion, both the effective and safe use of IFX in BD pregnancy up to third trimester, therefore, render this present case report particularly interesting.

In this case, a 31-year-old primigravida with asymptomatic BD uninterruptedly treated with monthly IFX had an uneventful pregnancy, until 36 weeks of gestation when maternal disorders and fetal IUGR were detected, as sometimes reported in the literature [4,5]. Labor was induced at 38 weeks of gestation with an uneventful vaginal delivery of female healthy baby weighing 2,400 kg (caesarean section was not considered for the absence of any genital ulceration). A normal placenta was detected, without any sign of necrotizing villitis and/or decidual vasculitis, in fact rarely reported in the literature [23]. The vaginal tear did not present pathergy-like inflammatory reaction and/or wound healing alterations, as sometimes reported as a result of excessive action of white blood cells mimicking the signs of infection.

On the contrary of other reports, maternal clotting profile, ESR, and CRP were normal, although the pathogenesis of thromboembolic events in BD patients is still unclear, and conflicting results about the role of thrombophilic parameters such as protein C, protein S, antiphospholipid antibodies, and factor V Leiden have been reported [24]. Nevertheless, thromboembolic prophylaxis with daily subcutaneous low-molecular-weight heparin was started at conception, given throughout pregnancy, and continued for four weeks after delivery, as sometimes recommended in women with previous ischemic thrombosis.

The postpartum period and the closely monitored follow-up six months were uneventful for mother, considering the risk of flares shortly after delivery [25], and for the newborn, considering the potential risks of neonatal BD [18-20] and/or infections due to IFX late immunosuppression [6].

Conclusions

BD is a very heterogeneous syndrome and, similarly, the reciprocal impact with pregnancy is variously reported: in most cases, pregnancy does not have a deleterious effect on the clinical course of BD, however, the disease can adversely affect the obstetric outcome, with increased risk of fetal loss and IUGR. Because of these unclear and inconstant course of gestation and disease, these pregnancies should be considered at "potential high-risk" and, therefore, they require the knowledge of the possible reciprocal impacts, careful planning, and close monitoring by obstetricians, rheumatologists, and internists with specific expertise.

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