REVIEW ARTICLE

Behçet's syndrome in pregnancy

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Summary: Behçet's syndrome (BS), a systemic inflammatory disease characterized by oral and genital ulceration, eye inflammation and arthritis, usually presents in the third and fourth decades of life, but is rare in pregnancy. BS is not usually associated with a detrimental effect on pregnancy outcome. In most women BS is reported to improve in pregnancy, although it may not always follow a similar course in successive pregnancies and it is not possible to predict the course of BS in a particular pregnancy. Many of the drug therapies used to treat BS are safe to use in pregnancy and in the breastfeeding mother. These include corticosteroids, azathioprine, calcineurin inhibitors and probably colchicine. Experience with use of biologics in pregnancy is increasing. Drugs used in the management of BS that should be avoided in women planning a pregnancy include methotrexate, mycophenolate mofetil, thalidomide, cyclophosphamide and chlorambucil.

Keywords: drugs (medication), high-risk pregnancy, rheumatology

INTRODUCTION

Named after the Turkish dermatologist Hulusi Behçet *(pronounced 'bay – chet')*, who, in 1937, described a syndrome of recurrent aphthous ulcers, genital ulcerations and uveitis leading to blindness, Behçet's syndrome (BS) is a systemic inflammatory process affecting the mucous membranes, skin, eyes, gastrointestinal tract, joints, blood vessels and central nervous system.

BS has a worldwide distribution, although most prevalent along what was traditionally the ancient Silk Road running between Asia and the Mediterranean. Estimates of population prevalence in Turkey vary from 80 to 370 cases per 100,000, with prevalence rates in Japan, Korea, China and the Middle East ranging from 13 to 20 cases per 100,000 population.[1] The prevalence in the UK is not known but estimated at about 1 per 100,000.[2]

BS is most commonly diagnosed in the second and third decades of life during the reproductive years. Women appear more commonly affected in Europe. Familial occurrences have been reported[3–7] but are unusual and the aetiology of the syndrome remains unclear. The most widely held hypothesis is that of an inappropriate inflammatory response triggered by an infectious agent in a genetically susceptible host.[8] Supporting this is the consistent association of disease susceptibility with polymorphisms in the human leukocyte antigen complex, particularly HLA-B51. There are several different classification criteria used for BS, although these are primarily directed at selecting patients for research studies. The International Study Group for Behçet Disease (ISGBD) criteria which were revised in 1990, are the most commonly used.[9]

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The International Study Group for Behçet Disease criteria

Recurrent oral ulcerations – at least 3 times in one 12-month period plus 2 of the following:
Recurrent genital ulceration
Uveitis
Cells in the vitreous
Retinal vasculitis
Erythema nodosum
Pseudofolliculitis
Papulopustular lesions
Acne (postadolescent/not on steroids)
+ve Pathergy test (see below)

EFFECT OF PREGNANCY ON BS

Little is known about the influence of pregnancy on BS. In the majority of affected pregnancies there is no deleterious effect on the course of the syndrome, and pregnancy may sometimes ameliorate it. This may be due to key hormonal and immunological changes occurring during normal pregnancy. The inflammation underlying BS is thought to be a cell-mediated immune response,[10–12] which is attenuated in pregnancy as part of the anti-inflammatory state leading to 'tolerance' to the fetus. Additional evidence in support of immune modification during pregnancy comes from Krause *et al.*[13] who reported a depression in neutrophil chemotaxis and adherence. Physiological changes during pregnancy underlying these findings include high levels of oestrogen, which have been shown

to inhibit specific immune activity,[14] as well as a rise in other key pregnancy-related hormones (βHCG, αFP, progesterone) that may also induce antenatal immunosuppression.[15] This is further compounded by a three-fold antenatal rise in the potent anti-inflammatory hormone cortisol.[16]

The precise role that changes in progesterone and other hormone levels related to pregnancy play in BS is unclear. Two case reports of quiescent BS during pregnancy that flared postpartum[17,18] have led some to conclude that high levels of progesterone during pregnancy may act to attenuate the inflammatory response in BS, with exacerbation after delivery as levels fall. A similar mechanism may explain premenstrual flairs of BS.[17,19] However, Jadaon *et al.*[20] observed that the commonly reported antenatal disease remission continued into the puerperium. An alternative theory is that susceptible individuals become sensitized to their own progesterone during pregnancy giving rise to a deterioration; their symptoms resolving only following delivery and the consequent precipitous fall in progesterone levels.[21–23] It should, however, be stressed that the association between progesterone levels and disease activity is speculative and based predominantly on observational evidence only.

There are still many unanswered questions as to why BS may react differently in different women during pregnancy, and why an individual's response in one pregnancy is not always predictive of what will happen in successive pregnancies.[20,24]

A review of the literature regarding BS in pregnancy between 1977 and 2008 includes six small case series in addition to 13 case reports, together comprising 221 pregnancies in 121 patients (Table 1). These data suggest that the majority of women with active BS experienced remission of their disease during pregnancy (62%); however, over a quarter (29%) experienced an exacerbation, with the remainder (9%) having no alteration in their disease activity. Looking specifically at the five case series conducted after the introduction of the ISGBD criteria in 1990, the findings are very similar. Of the 182 pregnancies reviewed, 115 were associated with remission (63%), 47 with exacerbation (26%) and 20 with no change in disease activity (11%).

In a large case-controlled study of BS in pregnancy, published by Jadaon *et al.*, of the 77 pregnancies conceived after the diagnosis of BS, 70% of the women went into remission. The remaining third experienced either exacerbation of the disease (16%) or no change in their condition (14%). Furthermore, the antenatal course of the BS appeared to continue after delivery, with 61% remaining in remission and 17% experiencing a flare, this trend continuing into the puerperal period.[20] Conversely, Chajek and Fainaro[25] published a case of a woman who, despite having quiescent disease during the course of both her pregnancies, experienced persistently active BS during the intervening 20 years. Larsson and Baum[17] and Ferraro *et al.*[18] both reported similar cases of

Table 1 **Effect of pregnancy on course of Behçet's syndrome (English language literature review)**

Author/date	Number of patients	Pregnancies	Clinical manifestations	BS disease activity in pregnancy	Reference
Chajek/1975	1	2		Remission	25
Novak *et al.*/1977	1	1	Dermatological + orogenital ulceration uveitis. Cranial nerve involvment	Remission	26
Berman *et al.*/1979	1	1		Exacerbation	6
Plouvier *et al.*/1979	1	1		Remission	27
Hurt *et al.*/1979	1	1	Orogenital ulcers, arthritis and iridocyclitis	Exacerbation	21
Madkour and Kadwah/ 1978	4	4	Mucocutaneous and arthritic manifestations	Severe and prolonged exacerbation	31
Fam *et al.*/1981	1	2	Oropharyngeal ulcers	*Status quo*	48
Han/1983	1	1		Exacerbation	32
Suchenwirth/1984	1	1	Orogenital ulcers, uveitis and encephalitis	Remission	28
Ferraro *et al.*/1984	1	1		Remission	18
Farrag *et al.*/1987	1	1	Orogenital ulceration	Exacerbation	22
Casanova *et al.*/1987	1	1	Large painful genital ulceration	Remission	29
Larson and Baum	1	1		Remission with postnatal relapse 1/12	17
Hamza *et al.*/1988	8	21	Painful genital ulceration in third trimester	Remissions (12) Exacerbations (9)	33
Bang *et al.*/1997	20	20		Remissions (8) Exacerbations (12)	19
Marsal *et al.*/1997	10	25	Orogenital ulceration, Budd-Chiari in the puerperium	Remissions (23) Exacerbations (2)	38
Gul /2000	16	16	Papulopustular lesions (2) and erythema nodosum (1) Deep genital ulcers (7) oral ulcers (3)	Remissions (7) Exacerbations (9)	30
Uzun *et al.*/2003	28	44	Orogenital ulcers iritis and arthritis	Remissions (23) *Status quo* (9) Exacerbations (12)	24
Jadaon *et al.*/2005	23	77	Orogenital ulceration uveitis arthritis skin lesions vascular disease	Remissions (55) *Status quo* (11) Exacerbations (12)	20
Total	121	221		Remission 136 (62%) *Status quo* 21 (9%) Exacerbation 64 (29%)	

BS = Bechet's syndrome

remission of BS during pregnancy and relapse postpartum. Four additional case reports also described antenatal remission,[26–29] including two with a resolution of neurological symptoms of acute cranial nerve palsies and pyramidal tract involvement[26] and acute encephalitis.[28]

In both case series by Bang *et al.*[19] and Gul,[30] there was a predominance of antenatal disease exacerbation with characteristic signs of activation including mucocutaneous ulceration (both oral and genital) and occasionally skin lesions and uveitis. Five separate case reports describe similar findings.[6,21,22,31,32] Of those individuals in whom BS worsened during pregnancy, details regarding gestational age were often not stipulated. Bang *et al.*[19] reported that in over 75% of women their disease flared during the first trimester. Hamza *et al.*[33] however found exacerbation to be predominately in the third trimester. Termination of pregnancy has occasionally been necessary when BS deteriorated,[19,20] presumably in an attempt to bring about remission and to permit the initiation of potentially teratogenic treatments.

Genital ulceration may be exacerbated during pregnancy but is not an indication for delivery by elective caesarean section. Aggravation of genital ulcers may be explained by an increase in the vascularity and hyperaemia of the surrounding tissues of the perineum and vulva,[34] resulting in an increased inflammatory cell infiltrate, and is not necessarily due to mechanical congestion of venous blood flow due to fetal growth.[19] With careful multidisciplinary planning and the use of regional anaesthetic techniques, vaginal delivery should be the aim unless there are additional obstetric maternal or fetal indications for caesarean section.

Individuals with BS may develop a widespread vasculopathy, and associated endothelial dysfunction[35] with potential qualitative and quantitative changes in key haemostatic factors.[36,37] Behçet's vasculopathy consists of

(1) Superficial and deep vein thrombosis – affecting veins anywhere in the body;
(2) Arterial aneurysms – due to adventitial inflammation;
(3) Pulmonary vasculitis (since pulmonary arteries are in many ways similar to veins with low O_2 concentrations and low pressures).

Pulmonary embolism is disproportionately uncommon in comparison to *in situ* venous thrombosis, possibly because thrombosis in BS is due to thrombophlebitis and clot tends to bind to the vessel wall, making embolism less likely.

Outside pregnancy, the risk of lower limb superficial thrombophlebitis and deep vein thrombosis are reported to be about 25% and 5%, respectively. Additional procoagulant changes occurring during pregnancy, coupled with increased venous stasis in the lower limbs, further compound this risk. Occasionally other atypical sites may be involved, with isolated reports in pregnant patients of Budd Chiari syndrome,[38] superior vena cava thrombosis and pulmonary embolism,[39] iliac and ovarian vein thrombosis[40] and cerebral venous thrombosis.[41] All patients with BS should receive an individualized risk assessment regarding their thrombotic risk and consideration should be given to the use of prophylactic low molecular weight heparin injections both during their pregnancy and in the puerperium.[42]

From this literature review it can be seen that the clinical course of BS is highly variable, both between patients and in successive pregnancies. Overall, the pattern is for pregnancy to result in remission or continued quiescence in about 70% of pregnancies.

EFFECT OF BS ON PREGNANCY

In BS, normal vaginal delivery at term is the aim and would appear to be the usual outcome.[19,24,30,33,38] However, in a large case-control series of BS in pregnancy by Jadaon *et al.*, the rate of obstetric complications was significantly higher in those with BS compared with the control group. The rate of miscarriage was 18% versus 7% (Table 2) and the caesarean section rate was 15% versus 5% (Table 3).[20] This reported increased incidence of miscarriage, although only marginally above that of the normal background population, may be due in part to the inflammatory process in addition to key changes in the coagulation cascade underlying BS.[37] Alternatively impaired function of the vascular endothelium and the presence of antiendothelial cell antibodies seen in BS may also be responsible.[43] In addition, this study demonstrated small but significant increases in the rates of gestational diabetes mellitus and hypertension, as well as increases in the rates of infection, preterm rupture of membranes and preterm delivery (Table 2). However some of these increases may be an iatrogenic effect due to the use of immunosuppressive medication, particularly steroids (used in 29 of the 77 pregnancies) and calcineurin inhibitors. Further work is needed to determine the relative contribution of BS and immunosuppressive medications to these documented small increased risks.

Rarely in pregnancies complicated by BS there may be fetal growth restriction,[44] fetal arterial involvement,[45] direct placental involvement[46] or transient neonatal BS. Neonatal BS is rare but may cause oral and genital ulceration in the baby as well as skin changes. The mucosal and cutaneous lesions of neonatal BS often show similar characteristics to those of the mother and last for up to six to eight weeks postpartum.[47–49] Thought to be the result of a transplacental acquired maternal factor or the passive transfer of immunoglobulins, early recognition of this condition is important in order to ensure appropriate treatment to help avoid permanent cutaneous scarring. Following exclusion of other causes, such as infection with herpes simplex

Table 2 **Pregnancy complications in women with Bechet's syndrome (data from Jadaon *et al.*[20])**

Complications	BS $n = 77$	Controls $n = 288$
Miscarriage	14 (18%)	19 (6.6%)
Hypertension (>140/90)	3 (3.8%)	1 (0.3%)
GDM	7 (9.0%)	2 (0.6%)
Preterm delivery (<37/40)	1 (1.2%)	1 (0.3%)
Infection	2 (2.5%)	0
PROM	1 (1.2%)	0
Thomboembolic events	1 (1.2%)	0

GDM = gestational diabetes mellitus; BS = Behçet's syndrome
PROM = premature rupture of membranes

Table 3 **Indications for caesarean section in women with Bechet's syndrome (data from Jadaon *et al.*[20])**

Caesarean section rates	BS $n = 9/61–15\%$	Control $n = 14/269–5\%$
Fetal distress	3 (5%)	6 (2%)
Breech	1 (1%)	3 (1%)
>2 CS	2 (2%)	2 (0.7%)
Failure to progress	3 (5%)	3 (1%)

BS = Bechet's syndrome; CS = caesarean section

virus, treatment with corticosteroids should be initiated without delay.

After delivery, some women with BS may experience exaggerated cutaneous hyper-reactivity around areas of minor skin trauma such as an episiotomy or caesarean section wound. Referred to as *pathergy*, this aseptic inflammation[50] has important implications with regard to treatment. Although wound healing appears not to be altered, prompt initiation of topical steroids following the exclusion of an infective aetiology may help expedite recovery and help to relieve discomfort, thereby reducing associated morbidity resulting from delayed mobilization after delivery.

DRUG THERAPY FOR BS IN PREGNANCY

For most of the medications used in the treatment of BS, substantial data from their use in transplantation, connective tissue disease, inflammatory bowel disease and other autoimmune conditions in pregnancy provide reassurance regarding safety.

In BS complicated by oral ulceration, treatment with steroid-based creams, mouthwashes or inhalers may be effective.[8] Topical sucralfate is an alternative topical therapy. Both sucralfate and topical steroids are safe in pregnancy.[51,52] Similarly, genital ulceration may respond to topical steroid treatment, although with prolonged uses skin atrophy can occur. Mild ocular inflammation in BS may be managed with tropicamide and corticosteroid eye drops. However, in deteriorating disease additional treatment options should be used.

Prednisolone is the most commonly prescribed immunosuppressive agent in pregnancy and has long-term safety data to support its use.[52] Azathioprine is also safe.[53–55] Cyclosporine,[56,57] tacrolimus[58] and prednisolone, although not detrimental to fetal development, may increase the risk of gestational diabetes and hypertension in genetically susceptible individuals and these complications should be screened for. Outside pregnancy the plant extract colchicine may be effective in the treatment of some female patients with genital ulceration, erythema nodosum and arthritis.[59] There is now growing evidence to support its use in pregnancy,[60–62] with previous concerns regarding an association with fetal chromosomal abnormalities being unsubstantiated. Reports of reduced male fertility secondary to colchicine are well documented.[63,64] However, a possible explanation may lie in the effects of the disease itself resulting in epididymitis and impaired spermatogenesis.[65]

Although not licensed for use in pregnancy, the anti-tumour necrosis factor (TNF) alpha agents, Infliximab, etanercept and adalimumab are being used with increasing frequency in rheumatoid arthritis, other inflammatory arthritides, inflammatory bowel disease and psoriasis in pregnancy. Evidence is accumulating for their safety.[66–73]

There is, however, substantial placental transfer of maternal IgG to the fetus and therapeutic levels of infliximab have been detected in a six-week-old baby following maternal infliximab use in pregnancy.[74] There is therefore the theoretical potential for significant immunosuppression of the neonate and these agents do not have a licence for use in pregnancy. Ideally infliximab, which has a half-life of 9–10 days, should not be used after 30 weeks gestation[75] in order to minimize the risk of the baby being born with significant levels of the drug. Limited data are available concerning the effects of infliximab on semen quality. However, a small retrospective case series provides some evidence and reassurance of normal fetal outcome for male patients treated with the anti-TNF-alpha agents.[76]

The disease-modifying agent, methotrexate, and alkylating agents, chlorambucil and cyclophosphamide, are occasionally used in the treatment of severe inflammatory complications of BS, such as meningoencephalitis or uveitis. These drugs are teratogenic and should be avoided during pregnancy. Methotrexate reversibly inhibits dihydrofolate reductase, with the critical period of exposure thought to be between six and eight weeks of development.[77] The most characteristic malformations induced by methotrexate include craniofacial and limb defects and central nervous system abnormalities, including anencephaly, hydrocephaly and meningomyelocele.[78]

Spermatogenesis is potentially susceptible to methotrexate-induced mutagenesis resulting in chromosomal abnormalities and single gene mutations,[79] in addition to severe reversible oligospermia despite normal gonadotropins and testosterone.[80] However, a case series of 26 male patients exposed to methotrexate found no unfavourable effect on male fertility.[81] Methotrexate should be withdrawn at least three months prior to conception in both women and men.

Mycophenolate mofetil (MMF) is also teratogenic, with one study of transplant patients suggesting a malformation rate of up to 25%, although this is a likely overestimate in view of reporting bias.[82] A specific phenotype has been proposed for MMF – associated embryopathy, whose main features are cleft lip and palate, microtia with atresia of the external auditory canal, micrognathia and hypertelorism.[83] MMF should be reserved for women when no more suitable alternative is available and should be used in pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus. It should be stopped at least six weeks before a planned pregnancy in view of its long half-life and enterohepatic recirculation. If discontinued prior to pregnancy it may be replaced with an alternative agent such as azathioprine.

Thalidomide is a very effective anti-inflammatory agent and is used in the treatment of oral and genital ulceration, but is *absolutely* contraindicated during pregnancy and effective contraception is mandatory. Its effect on human spermatogenesis is unknown; however, mammalian studies show conflicting results regarding teratogenesis.[84,85]

BREASTFEEDING

Breastfeeding in BS is strongly encouraged. Recent data showing zero to minimal levels of azathioprine metabolites in breast milk, with no detectable levels in breastfeeding infants, suggest that this medication is safe to use in the breastfeeding mother.[86,87] Similarly, it is thought that only minimal levels of cyclosporine and tacrolimus appear in breast milk. Neonatal serum levels of tacrolimus and cyclosporin were almost unrecordable in two neonates fully breast fed by mothers receiving these calcineurin inhibitors (Bramham, personal communication). Therefore, women taking these drugs are encouraged to breastfeed, although further studies are needed. The biological agent infliximab also appears safe to use in breastfeeding,[88,89] although this is not recommended by the manufacturer, with unrecordable levels detected in both the breast milk of nursing mothers and in the sera of the newborn. Women should be counselled that the evidence

base is very limited.[90] However, etanercept is secreted in human breast milk[91] and although it is likely that anti-TNF agents and other biologics are digested in the gastrointestinal tract of the infant and therefore not absorbed orally, caution is recommended. There are as yet no data for adalimumab.

CONCLUSION

Although rare, BS is most commonly diagnosed during the reproductive years. For affected women, many questions may arise with regard to the effect of pregnancy on their disease and *vice versa*. Useful patient information concerning BS and pregnancy is freely accessible on the Behçet's Syndrome Society website at http://www.behcets.org.uk

Our review of the literature has demonstrated that in the majority of cases BS improves in pregnancy with no adverse effects on pregnancy outcome or a need for operative delivery. Because of the increased risk of thrombosis in pregnancy, women with BS should be assessed regularly with regard to the presence of other risk factors for thrombosis and their potential need for thromboprophylaxis.[42] Many of the medications used in the management of BS outside pregnancy are safe to use at the time of conception and throughout the antenatal period. Women taking these drugs should be reassured accordingly. The exceptions include cytotoxics, MMF and thalidomide. For women receiving these drugs, planning of pregnancy around necessary alterations to their medications is important.

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