Table 1. The influence of pregnancy on Behçet's disease in 27 pregnant women with Behçet's disease according to the classification by the Behçet's Disease Research Committee of Japan and by Lehner

BD Research committee classification	Group		Lehner Classification	Group	
	Deteriorated	Improved		Deteriorated	Improved
Complete	1	1	Mucocutaneous	13	3
Incomplete	5	7	Arthritic	3	5
Suspected	12	1	Ocular	2	1
Possible	–	–	Neurologic	–	–
Total(%)	18(66.7)	9(33.3)		18(66.7)	9(33.3)

Laboratory tests

We performed complete blood counts, routine urinalysis, blood chemistries, renal function tests, antistreptolysin-O, C-reactive protein, VDRL, antinuclear antibody, rheumatoid factor, pathergy test, and DNCB test for each patient at the first visit while follow-up tests were performed at 2-to-6 month intervals.

Analysis

Data were analyzed using contingency tables and significance was determined using the χ^2 test.

RESULTS

Among the 27 pregnant women with Behçet's disease (BD), the disease became exacerbated in 18 (66.7%) and improved in 9 women (33.3%). According to the criteria of the Behçet's Disease Research Committee of Japan (1974), the 18 patients who deteriorated were classified as complete type in 1 case, incomplete type in 5, and suspected type in 12; while the 9 improved patients were classified as complete type in 1 case, incomplete type in 7, and suspected type in 1 (Table 1). Using Lehner's (Lehner and Barnes, 1979) classification, the 18 patients who worsened were classified as mucocutaneous type in 13 cases, arthritic in 3, and ocular in 2; while the 9 improved patients were classified as mucocutaneous type in 3 cases, arthritic in 5, and ocular in 1 (Table 1).

Table 2. Stage of pregnancy when the patient's symptoms got worse

Stage of pregnancy	Number of cases(%)
First trimester	14 (77.8)
Second trimester	3 (16.7)
Third trimester	1 (5.5)
Total	18(100.0)

In the deteriorated group, clinical exacerbation of BD occurred during the first trimester in 14 patients (77.8%), during the second trimester in 3 (16.7%), and during the third trimester in 1 (5.5%)(Table 2). In view of the aggravated symptoms, 12 patients experienced deterioration of oral ulcers and 10 patients experienced progression of genital ulcers (Table 3).

All 9 patients who improved during pregnancy noted exacerbations closely related to menstruation, especially premenstrual. However, among the 18 patients whose BD worsened, only 2 patients showed menstruation-related exacerbations (Table 4). Therefore, it is possible to hypothesize that the hormones which influence menstruation also contributed to the pathogenesis of BD in the improved group ($p<0.05$).

The results of the C-reactive protein (CRP) tests performed in 21 patients at the first visit, turned out to be negative in 7 women from the improved patients' group and to be positive in 9 patients from the deteriorated group (Table 5).

The DNCB sensitization test was performed in 14 patients, showing a positive reaction in 9 patients (64%); among them, 4 (44%) from the deteriorated group and 5 (56%) from the improved group (Table 6).

By the diagnostic criteria of the International Study Group for BD (1990), 7 patients were excluded. Among the 20 remaining patients, the disease became exacerbated in 12 (60%) and improved in 8 (40%)(Table 7).

Four pregnancies were terminated artificially due to clinical exacerbation of BD. Otherwise, the newborn infants from mothers with BD were all healthy.

Table 3. Aggravated symptoms of Behçet's disease during pregnancy

Aggravated symptoms	Number of cases
Genital Ulcer*	2
Oral Ulcer**	3
Skin Lesion	1
Genital* + Oral**	4
Genital* + Skin	2
Oral** + Skin	3
Genital* + Oral** + Skin	2
Skin + Uveitis	1

*: Number of exacerbated genital ulcers : 10
**: Number of exacerbated oral ulcers : 12

Table 4. Relationship of menstrual cycle in Behçet's disease

	Deteriorated group	Improved group
Menstruation-related exacerbation	2	9
No relationship	16	–

The improved group showed a statistically significant relationship with menstruation when compared with the deteriorated group($p<0.05$).

DISCUSSION

Pregnancy is associated with complex alterations in the physiology of women. Some of the known vascular changes occurring during pregnancy are related to dilation, fragility, and proliferation of small cutaneous blood vessels. Therefore, it can be

Table 5. Relationship of CRP and clinical course of Behçet's disease in pregnancy

CRP	Deteriorated group	Improved group
Positive	9	–
Negative	5	7
N-D*	4	2

*: CRP was not checked in these patients.

Table 6. Results of DNCB test

DNCB	Deteriorated group	Improved group
Positive	4	5
Negative	5	0

The difference in DNCB results between the improved group and the deteriorated group was statistically not significant($p>0.05$).

Table 7. Comparison of the criteria of the Behçet's Disease Research Committee of Japan and criteria for diagnosis of Behçet's disease by International Study Group for Behçet's disease (ISGBD)

No. of patients	Complete or incomplete (with Pathergy)	Suspected + Pathergy	Total No. of BD approved by ISG
Deteriorated Group(18)	6 (1)	6	12
Improved Group(9)	8 (2)	–	8

assumed that some of these changes can influence the course of Behçet's disease (BD) in pregnancy.

The relationship of subtypes of BD and pregnancy and menstrual cycle

Although there have been some reports of cases of BD associated with pregnancy, the influence of the menstrual cycle and pregnancy on BD has not been thoroughly studied. There have been conflicting papers about the exacerbation (Han *et al.* 1983) or improvement (Ferraro *et al.* 1984) of BD during pregnancy. Hamza *et al.* reported 8 BD patients who became pregnant and concluded that the influence of BD on pregnancy varied among patients and even during different pregnancies in the same patient with exacerbations usually occurring in the form of painful genital ulcerations in the third trimester (Hamza *et al.* 1988). Marsal *et al.* reported that BD was not significantly affected by pregnancy and pregnancy outcome was not influenced by BD (Marsal *et al.* 1997). In our study, 18 pregnancies (66.7%) were characterized by exacerbations, with the most common complaint being oral and genital ulcers. These findings may be related to the fact that the suspected type and mucocutaneous type made up an overwhelming majority of the deteriorated group. During pregnancy, there is an increase in vascularity and hyperemia of the skin and muscles of the perineum and vulva with softening of the connective tissue of the surrounding structures, which leads to aggravation of genital ulcers in pregnancy (Cunningham *et al.* 1997). Most of our patients showed exacerbations during the first trimester indicating that edema and mechanical congestion of venous blood flow due to fetal growth is not directly related to the clinical course of BD.

The etiology of BD is not yet clear, but in view of the deteriorated group in pregnancy, it is probable that the patient becomes sensitized to her own progesterone. The dramatic healing of mucosal ulcerations, arthritis, and uveitis immediately after delivery may be due to progesterone withdrawal (Hurt *et al.* 1979).

Larsson and Baum reported cases of BD which improved during pregnancy and became aggravated after delivery and during the premenstrual period (Larsson and Baum, 1987). These findings have similar characterisitics to those of the improved group in our study, suggesting that female sex hormones regulating the menstrual cycle and parturition may have influence on the course of BD.

The main determinant of the onset of menstruation is an abrupt decline in the release of progesterone: progesterone withdrawal (Cunningham *et al.* 1997). In human and other primates, progesterone withdrawal in pregnancy occurs only after delivery, which leads to the belief that progesterone is an important factor influencing the course of BD in pregnancy. The level of progesterone is maintained at a very high level during pregnancy and because patients improve during pregnancy and worsen in the premenstrual period, exacerbation is likely to be related to progesterone withdrawal.

Generally, pregnancy has been associated with suppression of humoral and cellular-mediated immunological functions to accomodate the "foreign" semiallogenic fetal graft, but the underlying reason is not yet clearly defined. Estradiol has been reported to suppress cellular immune response, possibly by causing an alteration in the responsiveness of the regulatory cells of the cellular immune system. The human T lymphocyte is one of the major cellular components of the host defense response to foreign antigens. The total T-cell count falls during gestation; CD4 cells decrease and CD8 cells increase toward the end of pregnancy, resulting in a decrease in the CD4/CD8 cell ratio. Studies of NK cells during gestation show that although the number of these cells decrease, their level of activity is probably unchanged (Landers *et al.* 1991). Hence, decreased cellular immunity with an increased estrogen level during pregnancy may be an aggravating factor in BD during pregnancy.

Krause *et al.* reported that the functions of polymorphous nuclear leukocytes, such as neutrophil chemotaxis and adherence function, were depresssed in pregnant women and this was associated with an improvement in autoimmune diseases (Krause *et al.* 1987). Cortisol is unlikely to contribute to the course of BD during pregnancy because, although the blood levels are elevated due to decreased clearance caused by increased cortisol-binding protein, the net production remains the same. Therefore the clinical remission which occurs in these patients during pregnancy is probably explained by modi-

fication of the immunohumoral picture. In fact, Ferraro *et al.* observed that during pregnancy, patients show a normal level of immunoglobulin and complement with an almost complete absence of autoantibodies (Ferraro *et al.* 1984). The assays performed after delivery revealed significant antibody change, especially in regard to IgA and the appearance of autoantibodies such as anti-smooth muscle antibody, anti-mitochondrial antibody, anti-n-DNA-antibody, and anti-gastric cell antibody. The maternal immunosuppression during pregnancy may be induced by alpha-feto protein (AFP), progesterone, and human chorionic gonadotrophin (HCG) (Landers *et al.* 1991). Furthermore, experiments on rats have shown that during fetal and neonatal life, there exist groups of cells which have an immunosuppressive function, i.e. fetal suppressor cells (FSC). In the improved group, such humoral factors probably influenced the course of BD, directly or indirectly.

The relationship of CRP and the clinical course of BD during pregnancy

The C-reactive protein (CRP) is an acute phase reactant that increases within 6 to 24 hours of active infection or collagen disease and decreases within 24 hours of recovery. However, CRP has other immunologic actions, such as immunodepression, and is positive in 20-60% of pregnancies (Adinolfi and Lehner, 1976). In Oshima's series, 45% of BD patients had an elevated CRP and clinical disease activity was accompanied by slight-to-moderate rises in CRP in many patients (Oshima *et al.* 1963). None of the patients in "complete remission" was noted to have an elevated CRP level. Our study revealed initial negative CRP results in all 7 patients whose disease improved during pregnancy. Among the 14 patients in the deteriorated group whose CRP levels were measured, 9 patients were positive. In follow-up tests, CRP became positive in 5 of the 7 patients in the improved group. The meaning of these results is unclear, but it is unlikely that the increase in CRP was a manifestation of an increase as an acute-phase reactant. The presence of high molecular glycoproteins such as CRP could possibly exert an inhibitory effect on immune responses.

The results of DNCB test

DNCB is occasionally used as a measurement for cell-mediated immunity in various diseases. In Korea, Lee *et al.* reported that 96-100% of verruca patients were sensitized by a DNCB application (Lee *et al.* 1985). Bang *et al.* observed that the overall DNCB positive rate in Korean patients with BD was 51% with the positivity rate according to the specific types of BD as follows: possible type (65%), suspected type (60%), incomplete type (37%), and complete type (37%)(Bang *et al.* 1985). Impairment of the lymphocyte transformation test in the negative responders to DNCB was also noticed and the proportion of helper T-cells were significantly decreased. In our study, the DNCB test results at the first visit were positive in 5 patients of the improved group and positive in 4 patients of the deteriorated group. This data had no statisitical significance ($p>0.05$), but cell-mediated immunity is probably related in some way to the pathogenesis of BD, especially in the improved group.

Comparison of the criteria of the Behçet's Research Committee of Japan and the diagnostic criteria of the International Study Group for BD(ISGBD)

Only 20 patients fulfilled the criteria of ISG and among them 12 patients deteriorated and 8 patients improved during pregnancy. Pathergy reflects a mucocutaneous reaction of hyperirritability or hyperreactivity induced by minor trauma with resultant papules or aseptic pustules (Sobel *et al.* 1973). Since the inflammatory cells in early lesions are polymorphonuclear leukocytes and those of late lesions are lymphocytes, immune-complex Arthus-type reactions and delayed-type hypersensitivity may explain the pathogenesis of early and late reactions, respectively. The neutrophils of BD show increased chemotaxis and similar data have been obtained with studies of mononuclear cells. Thus, these data may be of immunopathogenic importance in cutaneous manifestations of BD, including the phenomenon of pathergy (O'Duffy *et al.* 1983). In our cases, 7 patients in the deteriorated group showed a positive reaction, but only 2 patients in the improved group were positive. Yoon *et al.* reported the positive rate

of the pathergy test in Korea as follows: 48.4% (complete type), 43.8% (incomplete type), 29.3% (suspected)(Yoon *et al.* 1987). Our data somewhat conflicts with the previous report and though the number of our cases is too small for valid statistical analysis, they may serve as a guideline in the relationship of the pathergy test and the course of BD in pregnancy.

The new born infants of mothers with BD

Fam *et al.* reported neonatal BD in an infant of a mother with the disease (Fam *et al.* 1981). The finding of circulating immune complexes in the mother's serum gives some support to the hypothesis that the infant's transient illness was caused by transplacental passage of maternal antibodies. BD did not induce premature delivery or spontaneous abortion in this study, though 4 pregnancies were terminated because of aggravated genital ulcers. We did not perform any studies on the aborted embryos and further prospective investigations should be carried out to determine the true existence of neonatal BD and the relationship between BD and the outcome of pregnancy.

The pathogenesis of BD is still an engima and by this study, we can assume that the pathogenesis varies, as one group improved dramatically and another deteriorated during pregnancy. The deteriorated group is probably not directly affected by hormonal changes as there was no relationship between menstruation and exacerbation of symptoms. Judging by the fact that most patients were of the suspected type and oro-genital ulcers were the most common complaint, local factors such as increased vascularity, loosening of connective tissue in the perineum, or alteration of cell-mediated immunity may play a role in this group. On the other hand, hormonal changes are likely to be directly involved in the pathogenesis of the improved group as there were premenstrual exacerbations. Almost all patients of this group were of the incomplete or complete type, and of the arthritic or ocular type. A certain humoral factor affected by ovarian or adrenal hormones is suspected to exert influence upon patients with BD during the premenstrual and pregnancy period. The etiologic factors and characteristics of systemic lupus erythematosus are similar to BD in some aspects (Talal, 1987). Gilliam and Sontheimer propsed that cell-mediated immune injury and antibody or immune-complex-mediated injury play a major role in chronic cutaneous lupus erythematous and systemic lupus erythematosus, respectively (Gilliam and Sontheimer, 1981). Similarly, BD may have a diffuse spectrum with 2 polar groups each having either cell-mediated immunity or immune-complex-mediated injury as its pathogenic factor. It is likely that these polar groups represent an exacerbation or an improvement in response to the hormonal changes occurring during pregnancy. More prospective studies - such as for the presence of circulating immune complexes and autoantibodies; for polymorphonuclear leukocyte chemotaxis and adherence function; and for alterations of cell-mediated immunity - should be undertaken before, during, and after pregnancy to investigate the exact mechanism of hormonal influence of pregnancy on BD.

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