Behçet's syndrome and pregnancy: course of the disease and pregnancy outcome

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ABSTRACT

Objective. *To review the current available literature on the mutual effect of pregnancy or contraceptives and Behçet's disease (BD) in order to guide our patients more wisely before they take contraceptives or decide to conceive.*

Methods. *We performed a systematic review of the literature regarding the above issues using PubMed, Cochrane and EMBase databases.*

Results. *We have found 21 case reports and 11 series dealing with the mutual effect of pregnancy or contraceptives and Behçet's disease and 5 case reports dealing with BD and contraceptives. In most cases the course of BD was ameliorated or unchanged during pregnancy. The outcome of pregnancy in BD patients was poorer than that in healthy individuals. Contraceptives have various effects on the course of BD.*

Conclusions. *Despite the above impression, it is quite difficult to predict the course of the disease during pregnancy in an individual BD patient. Patients with BD and a history of thrombosis are recommended to avoid contraceptive pills.*

Introduction

Behçet's syndrome is a systemic vasculitis characterised by recurrent oral and genital ulcers and ocular inflammation (1). This multisystem disease may also involve the joints, skin, central nervous system and gastrointestinal tract. Disease onset is usually around the third decade of life (2, 3). This means that most Behçet's disease (BD) patients at disease onset are in their reproductive years. Since about half of the patients with BD are women, the mutual effect of pregnancy and BD raises interest and concern at the same time. Furthermore, since Behçet's disease may manifest with thrombotic events due to endothelitis, a question is raised regarding the safety of taking contraceptive pills which may further contribute to the hyper-coagulability state of these patients (4).

There are some case reports and series dealing with the above issues with different findings and outcomes. Some of them claim that pregnancy or contraceptive pills adversely affect BD. Others report that the disease remitted or ameliorated during pregnancies or following treatment with contraceptives. (4-42)

In the present paper, the current available literature on the mutual effect of pregnancy or contraceptives and Behçet's disease is reviewed, with the aim of obtaining a better insight into these issues in order to guide BD patients more wisely before they take contraceptives or decide to conceive.

Methods

We performed a systematic review of the literature using the key words: pregnancy, contraceptives, birth control and Behçet's disease or syndrome. We tried to find all the published series and cases about pregnancy or contraceptive use in women with BD, using Pubmed, Cochrane and EMBase databases. We also looked at publications written in languages other than English.

We limited our analysis of the effect of pregnancy on BD only to the period of pregnancy in patients already known to have the disease prior to conception. We excluded cases where BD was diagnosed during pregnancy or cases where flare-ups or remissions occurred during the post-partum period. Regarding contraception, we included only cases dealing with pills but not those with mechanical measures of contraception.

Search results

Regarding contraceptive pills and BD, we found only 5 case reports but not even a single series (4-8). Regarding the mutual effect of pregnancy and BD, we found 11 series from Tunisia,

Turkey, Spain, France, Iran, Israel and South Korea, some of which were published in Turkish ((9-19). We also found 21 case reports from different countries dealing with pregnancy in BD (20-40). All the studies reported were retrospective. Some described only the effect of pregnancy on the disease while others added details about the effect of BD on pregnancy outcome. We decided to include in our analysis only BD patients who fulfilled the International Study Group (ISG) criteria (41). Thus, in our analysis, one can find different numbers of BD patients compared with those of the original publications.

Table I. Behçet's disease course during pregnancy according to published case reports.

Study number	no. of Patients	no. of Pregnancies	Remission	Exacerbation	No change	Reference
1	1	2	2	_	_	Chatjek *et al*. 1975
2	1	1	_	1	_	Novak *et al*. 1977
3	4	4	_	4	_	Madkuor *et al*. 1978
4	1	1	_	1	_	Hurts *et al*. 1979
5	1	3	3	_	_	Plouvier *et al*. 1979
6	1	1	_	1	_	Berman L *et al*. 1983
7	1	1	1	_	_	Ferraro *et al*. 1984
8	1	1	1	_	_	Suchenwirth *et al*. 1984
9	1	1	1	_	_	Larsson *et al*. 1987
10	1	1	_	1	_	Farrag *et al*. 1987
11	1	1	_	1	_	Wechsler *et al*. 1995
12	1	1	_	1	_	Guzelian *et al*. 1997
13	1	1	_	_	1	Prada *et al*. 1997
14	2	5	3	2	_	Hermas *et al*. 1997
15	1	1	1	_	_	Taguchi *et al*. 1999
16	1	1	_	1	_	Fotaki P *et al*. 2002
17	1	1	_	1	_	El Hajoui *et al*. 2002
18	1	1	1	_	_	Yamada *et al*. 2003
19	1	1	_	1	_	Sumita *et al*. 2006
20	1	1	_	1	_	Kale A *et al*. 2006
21	1	1	1	_	_	Palla *et al*. 2009
Total	25	31	14	16	1	

Results

Contraceptives and BD

Only five case reports were found dealing with the course of BD and contraceptive use (4-8). In 2 cases, the disease was improved following birth control ingestion, since this treatment suppressed the outbreaks of their oral, genital ulcers and erythema nodosum-like lesions. (5, 6) . In one of these cases, the author cited an additional case of a young woman who experienced oral and genital ulcers each at menses which improved immediately following the use of contraceptives (42). On the other hand, cases of Budd-Chiari syndrome or long saphenous vein thrombosis appearing following contraceptive use were also reported (7, 8). Although we know that BD by itself can lead to these thrombotic events, it was suggested that the use of contraceptive pills contributed an additional hit for hypercoagulation.

Effect of pregnancy on BD course

Reviewing the medical literature (including languages other than English) we found 21 case reports dealing with the effect of pregnancy on BD course in an already BD diagnosed women (Table I) (20-40). Many reports that described BD which was diagnosed during pregnancy or BD flares ups during the post-partum period were excluded from our analysis. Among 25 patients with 31 pregnancies (in the 21 case reports) there were 16 (51.6%) exacerbations, 14 (45%) remissions and a single pregnancy with no change in the course of the disease. This result shows that pregnancy may improve or adversely affect the disease course of BD in an almost equal rate. Of course the third possibility is that pregnancy has no appreciable effect on BD.

Table II summarises the results from eleven series dealing with the effect of pregnancy on Behçet's disease (9-19). Of the 568 pregnancies (in 339 patients) collected from the 11 series, 296 (52%) BD patients improved during pregnancy whereas 154 (27%) exacerbated. One hundred and eighteen (21%) patients did not have any change in their disease course. It was also found that in the same patient the course of the disease could be different in subsequent pregnancies.

In a single study by Noel *et al*. they compared the flare-up rate in the periods before gestation with the rate during pregnancy. They found that this rate was significantly lower during pregnancy, suggesting a favourable effect of pregnancy on BD (18). In most studies 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. However, Noel *et al*. found that the shorter duration of the disease prior to conception, the higher the rate of exacerbation (18). Moreover, they added that treatment with colchicine was associated with lesser flares during pregnancy. In a comment letter Seyahi *et al*. claim that since BD becomes less severe with the passage of time it is expected to see less flares with long disease duration (42). Furthermore, patients who were treated only with colchicine had probably a milder disease and therefore experienced less flares during pregnancy.

The main manifestations of exacerbations during pregnancy, in most studies included oral aphthosis, genital ulcers and erythema nodosum. Very rarely there were thrombotic events such as Budd-Chiari syndrome, ocular involvement or cerebral sinus vein thrombosis (18, 21). Of note is the observation published in two Japanese case reports about the favourable effect of pregnancy on Behçet's uveitis during pregnancy (34, 37). This observation was not shared by other case reports or series.

Effect of Behçet's disease on pregnancy outcome

Table III summarises the outcome of pregnancies in BD patients. As shown, the rate of complications ranges be-

Table II. Behçet's Disease course during pregnancy according to published series.

Study number	Country of origin	no. of Patients	Mean age (range or average)	no. of Pregnancies	no. of Remissions (%)	no. of Exacerbations (%)	no. of Patients with no change	Reference
1	Tunisia	8	ND	21	12 (57)	9 (43)	_	Hamza *et al*. 1988
2	Spain	10*	21±6.3	25	23 (92)	2 (8)	_	Marsal *et al*. 1997
3	South Korea	20*	23.5±3.8 (28.5)	20	8 ((40)	12 (60)	_	Bang *et al*. 1997
4	Turkey	16	(19-37) (28)	16	7 (43)	9 (53)	_	Gul *et al*. 2000
5	Turkey	50	ND	50	50 (100)	_	_	Kose *et al*. 2003
6	Turkey	28	28.7±8 (18-44)	44	23 (52)	12 (27)	9 (21)	Uzun *et al*. 2003
7	Iran	69	22.6±5.1	77	21 (28)	25 (32)	31 (40)	Nadzi *et al*. 2004
8	Israel	31	24.4±8.8	77**	54 (70)	12 (16)	11 (14)	Jadaon *et al*. 2005
9	Tunisia	46	ND	147	35 (24)	53 (36)	59 (40)	Olfa *et al*. 2010
10	France	37**	22.8±3.9 (28.4)	67**	49 (73)	18 (27)	_	Noel *et al*. 2013
11	Turkey	24	28.6±4.4 (12-35)	24	14 (58.3)	2 (8.3)	8 (33.3)	Iskender *et al*. 2014
Total		339		568	296	154	118	

*Included only BD patients who fulfilled the International Study Group (ISG) criteria; **Included only pregnancies in already diagnosed BD patients. ND: No data.

tween 4 and 20% of pregnancies in different studies. Only the studies by Marsal *et al*. Jadaon *et al*. and Iskender *et al*. compared their study groups with healthy controls (10, 16, 19). In the paper by Marsal *et al*. the pregnancy outcome of BD patients was better than that of the healthy controls (10). In the study of İskender *et al*. the rates of stillbirth, pre-eclampsia, preterm delivery and Caesarean deliveries did not differ between the groups (19). However, in the report by Jadaon *et al*. the rate of complications was the highest (20%) of the studies and significantly more than in the healthy controls (16). Noel *et al*. and Nadzi *et al*. reported an almost similar rate of complications (16–19%) among their BD pregnant patients (15, 18). Of note is the relatively high rate of miscarriages and the high number of deliveries by Caesarean section required in these patients.

It should be emphasised that in the early papers the rate of complications was relatively low or close to zero, whereas these complications are mentioned mainly in the later studies. This observed difference is surprising since it is expected that due to improvement in health services over the years one would see less complications such as miscarriages or the need for Caesarean sections.

Nadzi *et al*. claimed that the presence of ocular involvement was associated with a higher risk for complicated outcomes of pregnancy in BD patients (15). Noel *et al*. noted that a history of previous deep vein thrombosis (DVT) or other thrombotic event was also predictive for poor outcome or obstetric complications (18). However, these observations were not shared by the other studies. Furthermore, the outcome of pregnancies varied even during different pregnancies in the same BD patient, suggesting that it is not invariably related to the disease. No associations were found between the outcomes of pregnancies and the age of disease onset, disease duration and the age of the patient at gestation.

Table III. Pregnancies outcomes in BD according to published series.

Study number	no. of Patients	no. of Pregnancies	no. of Complicated pregnancies (%)	Type of complication	Reference
1	8	21	none	_	Hamza *et al*. 1988
2	10	25	1 (4)	miscarriage	Marsal *et al*. 1997
3	16	16	none	_	Gul *et al*. 2000
4	28	44	3 (7)	3 miscarriages	Uzun *et al*. 2003
5	69	77	15 (19)	13 miscarriages 1 stillbirth 1 premature delivery	Nadzi *et al*. 2004
6	31	77	16 (20)	16 miscarriages* 9 Caesarean deliveries**	Jadaon *et al*. 2005
7	46***	76	12 (16)	5 miscarriages 3 Caesarean deliveries 2 terminations of pregnancies 1 HELLP 1 Thrombocytopenia	Noel *et al*. 2013
8	24	49		8 miscarriages 17 Caesarean deliveries	Iskender *et al*. 2014

*Significantly more Caesarean sections compared with healthy controls; **Nine Caesarean sections out of 61 pregnancies (not 77); ***Included also 9 BD patients diagnosed during pregnancy.

Discussion

Rheumatic and vasculitic diseases often affect women during their childbearing years, when pregnancy is an expected event. During pregnancy, immune and endocrine systems undergo profound changes involving both hormone profiles and cytokine microenvironment. Cortisol, progesterone, estradiol and testosterone increase physiologically during gestation and seem to favour

Th-2 cytokine polarisation at the systemic level (44-46). Such immunological changes may suggest a natural improvement of primarily TH-1 mediated diseases such as rheumatoid arthritis (RA) or Behçet's syndrome and a worsening of Th-2 derived diseases such as systemic lupus erythematosus (SLE) or polyangiitis with granulomatosis. (Wegener's disease) (47).

Indeed, the first observation that the symptoms of RA often ameliorate during pregnancy dates back to the landmark publication of Hench in 1938 (48). Since that publication, several studies have confirmed the observation about spontaneous improvement of RA during pregnancy and increased risk of flare-ups after delivery (49-52).

In the UK, a nationwide prospective study of 140 pregnant women with RA, recruited during pregnancy and followed until 6 months post partum, reported improvement in joint swelling and pain in about two-thirds of patients. However, the extent of improvement was limited, with only 16% of women reaching remission during pregnancy (52). A Dutch study prospectively evaluated disease activity in pregnant RA patients (53). They found that the mean disease activity scores significantly decreased during pregnancy and increased post partum. Overall, 39% of patients improved during pregnancy, mirrored by flares observed in 38% of patients from 12 to 26 weeks post-partum. The relationship between lupus activity and pregnancy is more debatable (54). Up until now seven prospective comparative studies using non-pregnant SLE patients as controls have been published. The conclusion of three of them was that SLE flares up more during pregnancy (55-57), whereas the conclusion of the other four was quite the opposite, i.e. SLE does not flare up more during pregnancy (58-61). In general, there is a tendency for mild to moderate flares, especially during the second half of pregnancy and the post-partum period. However, a prolonged period of clinical remission before conception decreases the chance of a flare-up during pregnancy (54).

Similarly, it is quite difficult to predict what effect pregnancy will have on the symptoms and course of Behçet's disease and which effect the disease will have on the outcome of pregnancy in the individual patient. The impression though is that the effect of pregnancy on the clinical course of RA is much more marked as compared with that of pregnancy in BD.

Following our review and analysis of the published series and case reports, several points should be emphasised and addressed:

First is the issue of contraceptive use. Data are scarce on this subject and we cannot draw firm conclusions about the best policy concerning their use in BD. Indeed, there are three case reports suggesting that the contraceptive pill may ameliorate oral and genital ulcers in BD patients. Still other reports and additional discussions from multiple forums on the internet claim that these symptoms flared up in BD patients who took birth control pills. Furthermore, one cannot ignore the risk of increasing coagulability in those taking contraceptive pills especially in BD patients who are *a priori* in a high coagulable state. Therefore, it may be suggested that BD patients who have already experienced a thrombotic event should avoid using birth control pills. For patients with BD without a history of thrombotic events and who have a justified indication for pills, it is suggested to use those containing a minimal dose of oestrogen and more progesterone. The risk of venous thromboembolism is not thought to be increased with the use of progestogen-only contraceptives. However, shorter-acting methods such as the progestogen-only pill have higher failure rates associated with typical use than longer-acting methods and therefore may be less favourable.

The second question is why there is such a discrepancy between the results which we found in the case reports and those from the series dealing with BD and pregnancy. In the case reports most of the patients (although not big difference) experienced an exacerbation of the disease during pregnancy (16 versus 14 remissions). The findings from the series disclosed that the number of BD patients who were improved during pregnancies doubled the number of those who exacerbated during pregnancy. It seems that the most plausible explanation for this discrepancy is that the normal course of BD during pregnancy does not justify a published report or article, while exacerbation is more impressive and merits publication. That is why there are more cases reporting on BD exacerbation during pregnancy. This kind of publication-selection bias puts in doubt our ability to draw firm conclusions from case reports about the course of BD during pregnancy.

A third question is why the results differ so much among the various series. The most plausible answer is the differences in study design and the different definitions for the outcomes and complications in the various studies. Furthermore, since all the studies dealing with BD and pregnancy were retrospective, there is always an inherent risk of selection bias, recall bias with information bias and a lack of appropriate controls. Thus, in different studies the authors could be exposed to different data. Yet it should be emphasised that despite the presence of prospective studies in SLE, the question regarding the course of the disease during pregnancy remained inconclusive. Thus, prospective studies in BD may not solve the problem of variability. It is most probable that due to the diverse course of BD among different individuals with the various clinical presentations and organ involvement, the disease course will differ – in some the disease will exacerbate and in others it will go into remission during pregnancy. In others, pregnancy does not affect the course of the disease at all.

The variability in disease course during pregnancy is not limited to different patients. Even in the same patient, in one pregnancy the disease may exacerbate while in a subsequent one the course of the disease may remain stable. There was no association between the number of the pregnancy (first, second or third) and the course of the disease. For example, Hamza *et al*. reported that 4 out of the 8 patients in their study had different influences of their pregnancy on their disease during each pregnancy (9). Still the question raised is whether there are predictive signs or findings for BD exacerbation in the course of the disease

prior to conception. In a relatively large study by Nadzi *et al*. no association was found between disease manifestations prior to pregnancy and the exacerbation of the disease during pregnancy (15). Bang *et al*. found that in BD patients with normal CRP at conception, the disease tended less to exacerbate during pregnancy (11). Noel *et al*. observed that treatment with colchicine protected the patients from flares during pregnancy (18). There was no association with underlying carriage of HLA- B51 or positivity of pathergy test. However, each of these observations was mentioned in a single study and was not confirmed or mentioned in the other studies. Therefore, the strength of these findings is relatively weak.

Regarding the time of exacerbations, the results were also inconsistent. In the study by Hamza *et al*. exacerbation occurred mainly in the third trimester while in the study of Bang *et al*. most exacerbations occurred during the first trimester (9, 11). In the study by Kose *et al*. remissions occurred in the second and third trimesters in pregnant BD patients (13).

Regarding pregnancy outcome, it seems that BD patients are at a higher risk for miscarriages and Caesarean deliveries. Ocular involvement and a history of thrombotic events prior to conception are risk factors for obstetric complications. The high rate of miscarriages may reflect thrombotic events in the patients' placenta. Still, the question remained as to why there is a high rate of Caesarean sections in BD patients. A possible answer is that vaginal delivery may exacerbate a major inflammatory response in the genital area, especially if there is birth trauma to the perineum. Therefore, it is possible that the reason for the increased rate of Caesarean section among BD patients is due to their physicians' (gynaecologists) preference rather than due to an urgent clinical indication.

As already mentioned, increase in oestrogen and progesterone levels during pregnancy may play an indirect role with their effect on the immune response (44-47). The combined effect of increased levels of cortisol, oestrogen and vitamin D has been implicated in lowering the pro-inflammatory cytokines, IL-12 and TNF-α, during pregnancy (62). However, their effect may vary among different patients and diseases and may be influenced by other environmental and genetic factors leading to the great differences of their outcomes.

The main limitation of the current analysis is derived from the fact that the studies included are retrospective – the type of study with built-in drawbacks. Nevertheless, if we combine the data from all the published series we can draw the following conclusions: More than 50% of the BD patients will improve or go into remission during pregnancy. A few will experience exacerbations of their disease, while others will remain in the same clinical condition. Generally, there are no clear predictive signs or findings for exacerbation or remission during pregnancy. Nevertheless, the better the disease condition prior to conceiving, the lesser chance for exacerbation during pregnancy.

Since the populations described in the various papers represent different areas (North Africa, Turkey, Iran, Israel and East Asia), it seems that the results found in the different studies may be applied to BD patients throughout the world.

Key points

1. Most BD patients will experience a better or unchanged disease course during pregnancy.
2. Disease course may differ in different pregnancies in the same BD patient.
3. Controlling BD prior to conception will lead to a better course of the disease during pregnancy.
4. Generally, outcome of pregnancies in BD patients is poorer compared with healthy controls – more miscarriages and more Caesarean deliveries.
5. It is possible that the higher rate of Caesarean deliveries results from the preference of gynaecologists who want to avoid local trauma to the perineum in vaginal delivery.
6. Contraceptive pills have diverse effect on BD course in different patients.
7. Contraceptive pills should not be used in BD patients who have a history of thrombotic event.

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