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Behçet's disease: clinical course and maternal, fetal and neonatal outcomes

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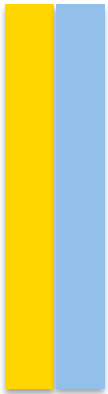

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**

Behçet's disease:
clinical course and maternal, fetal and neonatal outcomes

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

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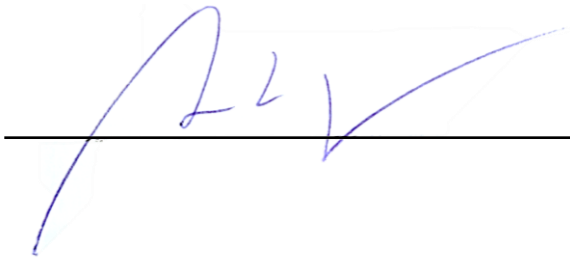

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Maio de 2023

• DEDICATÓRIA •

*Aos **meus pais**, que serão sempre o meu porto-seguro; pelo amor incondicional, pelos sacrifícios, pela força e pela fé inabaláveis.*

*À **minha irmã**, que será sempre a minha pessoa; pelo exemplo que é e pela cumplicidade inexplicável.*

*Aos **meus amigos**, pelo companheirismo, pela confidência, e, especialmente, pela relação que construímos.*

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• RESUMO •

Introdução: A doença de Behçet (DB) é uma vasculite multissistémica rara que afeta habitualmente mulheres em idade reprodutiva (entre a 2.ª e a 4.ª décadas), altura em que a gravidez é um evento esperado. Assim, este estudo tem como objetivo avaliar e caraterizar os desfechos obstétricos e neonatais em doentes com DB, bem como a atividade da doença durante este período.

Materiais e Métodos: Foi realizado um estudo retrospetivo de caso-controlo que incluiu mulheres com DB, seguidas na nossa instituição, entre 2012 e 2022. Os desfechos obstétricos e neonatais foram comparados com um grupo de grávidas saudáveis, num rácio de 3 controlos por caso. A análise estatística foi realizada com recurso ao SPSS 29.0. Para comparar os grupos, foram utilizados o teste do Qui-Quadrado, o teste Exato de Fisher e o Teste-t para amostras independentes. Um valor de $p \leq 0,05$ foi considerado estatisticamente significativo.

Resultados: Foram incluídas 59 gravidezes de 33 mulheres com DB e comparadas com 177 grávidas saudáveis. No grupo das doentes, a prevalência de 2 ou mais abortamentos espontâneos (15,3%, $p<0,05$) e de parto por cesariana (47,1%, $p<0,05$) foi superior à dos controlos. Na gravidez atual, também se verificou uma maior taxa de abortamento (20,3%, $p<0,05$), restrição de crescimento fetal (RCF, 12,8%, $p<0,05$) e hipertensão gestacional (8,5%, $p<0,05$). A taxa de cesarianas por estado fetal não-tranquilizador foi significativamente superior no grupo DB (33,3% vs 18,2%, $p<0,05$). Registou-se uma diferença significativa na idade gestacional média no parto (37,7 vs 38,6 semanas, $p=0,05$), na incidência de complicações neonatais ($p<0,05$) e de admissão na unidade de cuidados intensivos neonatais (UCIN, $p<0,05$). Não houve diferenças estatísticas significativas entre os dois grupos relativamente à taxa de parto pré-termo, diabetes gestacional, pré-eclampsia, descolamento de placenta e peso ao nascimento ($p>0,05$). A DB melhorou em 37,3% das gravidezes, enquanto 28,8% agravou. O puerpério teve efeitos variáveis no curso da DB.

Conclusão: O presente estudo demonstrou que, embora a atividade da doença melhore na gravidez, a DB pode ter um impacto desfavorável nos desfechos obstétricos e neonatais. No grupo de estudo, as taxas de abortamentos espontâneos e de RCF foram significativamente mais elevadas, bem como as taxas de complicações neonatais e de admissão na UCIN.

Palavras-chave: Doença de Behçet; Patologia autoimune; Vasculite; Gravidez; Desfechos obstétricos; Desfechos neonatais.

• ABSTRACT •

Introduction: Behçet's disease (BD) is a rare multisystemic vasculitis that commonly affects women in their reproductive years (between the 2nd and 4th decades), when pregnancy is an expected event. Therefore, this study aims to assess and characterize pregnancy and neonatal outcomes in BD patients, as well as disease activity during this period.

Material and Methods: A retrospective case-control study was conducted and included women with BD, followed in our institution, between 2012 and 2022. Pregnancy and neonatal outcomes were compared with a control group of healthy pregnant women, at a ratio of 3 controls per case. For statistical analysis, SPSS 29.0 was used. The Chi-Square Test, Fisher's Exact Test and the Independent Samples t-Test were used to compare groups. A *p*-value ≤ 0.05 was considered statistically significant.

Results: Fifty-nine pregnancies in 33 women with BD were included and compared with 177 healthy women. Among the study group, the prevalence of 2 or more miscarriages (15.3%, $p<0.05$) and cesarean delivery (47.1%, $p<0.05$) was higher than in controls. In the current pregnancy, there was also a higher rate of miscarriage (20.3%, $p<0.05$), fetal growth restriction (FGR, 12.8%, $p<0.05$) and gestational hypertension (8.5%, $p<0.05$). The cesarean rate due to non-reassuring fetal status was significantly higher in the BD group (33.3% vs 18.2%, $p<0.05$). The mean gestational age at delivery (37.7 vs 38.6 weeks; $p=0.05$), the incidence of neonatal complications ($p<0.05$) and the neonatal intensive care unit admission (NICU, $p<0.05$) differed between groups. There were no significant statistical differences regarding the rate of preterm delivery, gestational diabetes, preeclampsia, placental abruption and the newborns weight ($p>0.05$). BD improved in 37.3% of the pregnancies, while 28.8% exacerbated. The puerperium had variable effects on the BD course.

Conclusion: The current study demonstrated that although the disease course improves during pregnancy, BD may have an unfavorable impact on pregnancy outcomes. Miscarriage and FGR rates were significantly higher in the study group, as well as neonatal complications and NICU admission rates.

Keywords: Behçet's disease; Autoimmune disease; Vasculitis; Pregnancy; Pregnancy Outcomes; Neonatal outcomes.

aβ2GPI	Anti-β2-glycoprotein I
aCL	Anticardiolipin
ACOG	American College of Obstetricians and Gynecologists
ANA	Antinuclear antibodies
anti-La/SSB	Anti-Sjögren's syndrome-related antigen B
anti-Ro/SSA	Anti-Sjögren's syndrome-related antigen A
aPL	Antiphospholipid antibodies
APO	Adverse pregnancy outcomes
APS	Antiphospholipid syndrome
BD	Behçet's disease
CG	Control group
CHUdSA	Centro Hospitalar Universitário de Santo António
CLC	Colchicine
FGR	Fetal growth restriction
GD	Gestational diabetes
HCQ	Hydroxychloroquine
HELLP	Hemolysis, elevated liver enzymes, and low platelet count
HLA	Human leukocyte antigen
LA	Lupus anticoagulant
LDA	Low-dose aspirin
LMWH	Low-molecular-weight heparin
NICU	Neonatal intensive care unit
SD	Standard deviation
SLE	Systemic lupus erythematosus
SPSS	Statistical Package for the Social Sciences
SS	Sjögren's syndrome

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• INTRODUCTION | INTRODUÇÃO •

Behçet's disease (BD) is a rare multisystemic vasculitis mainly characterized by recurrent oral and genital ulcers and uveitis (anterior or posterior).[1–3] Other less common clinical features include arthritis, dermatologic (pseudofolliculitis and erythema nodosum), gastrointestinal, cardiovascular, neurological and vascular manifestations.[4–7] Unlike most vasculitic disorders, it can affect both arteries and veins of all sizes, increasing the risk of thromboembolic events due to endothelial dysfunction and hypercoagulability. However, venous involvement is most frequently reported.[5,6]

Behçet's disease is considered to be an autoimmune disease, although the underlying physiopathology remains unclear.[2,3,8] Nevertheless, it has been strongly suggested that the presence of human leukocyte antigen (HLA)-B51 may predispose BD's development in genetically susceptible individuals. Moreover, it is recognized that other immunological, inflammatory, environmental factors and even infectious agents can play a pathological role.[2,7,9–11]

Geographically, its distribution is worldwide, but it is more common in the Mediterranean, the Middle East and Far East regions – the old Silk Road – with the highest prevalence in Turkey.[4,10,11] The incidence is similar in both males and females, but women in Northern Europe and the United Sates of America seems to be more affected.[11]

The diagnosis relies on clinical findings since there aren't neither pathognomonic manifestations nor specific laboratory tests.[8,11] Consequently, classification criteria, such as the International Study Group for Behçet's Disease 1990 or the International Criteria for Behçet's Disease (ICBD), have been developed to support the establishment of a diagnosis.[12,13]

Disease onset usually is between the second and fourth decades of life, with most diagnoses occurring during the reproductive years.[4,9,14] Even so, evidence on the mutual effect between BD, pregnancy and the puerperium is scarce and conflicting and, to this date, there is only one study that was performed on the Portuguese population.[15,16] Currently, some studies have reported remission or no apparent differences on the course of the disease during pregnancy.[2,17] By contrast, flare-ups including mucosal, neurological and vascular involvement, have also been described.[4,5,9]

Literature concerning pregnancy-related complications in Behçet's disease is limited, mainly consisting in case reports or small sample sized studies.[4,9]

Though some authors suggest no correlation between BD and adverse pregnancy outcomes (APO), others recognize miscarriage, fetal growth restriction (FGR) and caesarean delivery rates to be higher in BD patients.[9,14]

Regarding the therapeutic regimen for BD, most drugs are known to be safe and compatible with pregnancy. Corticosteroids and colchicine (CLC) are the most commonly prescribed, but azathioprine, cyclosporine or infliximab are other options that have also been used.[14,17] However, the impact on disease activity during pregnancy and pregnancy outcome is not yet fully understood.[14,17,18]

Thus, since the course of BD in each pregnancy cannot be predicted and may not always be similar in subsequent pregnancies, further insight into this relationship is required for thorough management and follow-up of the disease's impact in these patients and the fetus.[4,6,17]

Therefore, this study aims to retrospectively assess and characterize pregnancy and neonatal outcomes in BD patients, as well as disease activity during this period.

This is an observational and retrospective case-control study of women who received prenatal and obstetric care in Centro Materno Infantil do Norte Albino-Aroso – Centro Hospitalar Universitário de Santo António (CHUdSA), Porto, Portugal.

A comparison between BD patients and a control group (CG) was conducted to assess for differences regarding maternal and neonatal outcomes.

Study Population, inclusion and exclusion criteria

The study cohort included pregnant women with BD followed in our Centre between January 1, 2012 and December 31, 2022. Each pregnancy was considered an event and exclusion criteria included multiple gestations. Therefore, our sample comprised 59 pregnancies of 33 women.

The CG, randomly selected, included 177 women of the general obstetric population, with low-risk singleton pregnancies, who attended the same hospital (CHUdSA) during the same period for antenatal care and delivery, at a ratio of 3 controls per case.

The patient selection protocol is represented in Figure 1.

Data sources

All data were retrieved from the patients' electronic medical records, through the SClínico® and PCE® platforms. The information was stored and handled anonymously.

Baseline characteristics, clinical background and other covariates

We analyzed the patients according to age at delivery; age at BD diagnosis; years between the BD diagnosis and the ongoing pregnancy; clinical manifestations; vascular events; number of exacerbations until current pregnancy; and treatment for BD at conception and during pregnancy.

The ICBD were used to establish a diagnosis of BD; all patients in the study population fulfilled these criteria.[12,13]

Concerning disease activity, the appearance of new clinical manifestations and/or worsening of pre-existing ones, as well as the requirement to modify the previous therapeutic strategy was defined as a disease flare. On the other hand,

the absence of BD-related symptoms and/or directed treatment was interpreted as patients were in remission.

Previous obstetric data, current pregnancy surveillance, preconceptional history of cardiovascular risk factors and concomitant autoimmune diseases (particularly, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) and Sjögren's syndrome (SS)) were also considered.

In addition, the maternal immunological profile was analyzed and the following antibodies were included: antiphospholipid antibodies (aPL); anti-Sjögren's syndrome-related antigen A (anti-Ro/SSA); anti-Sjögren's syndrome-related antigen B (anti-La/SSB) and antinuclear antibodies (ANA). Considering the increased risk of vascular events (especially thrombotic) in BD and the association of aPL with vascular thrombosis and pregnancy morbidity, the presence of lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β2-glycoprotein I (aβ2GPI) were also evaluated.[19,20]

Outcomes

Obstetric, maternal and fetal outcomes ascertained from the linked dataset included the occurrence of a spontaneous abortion, stillbirth, preterm delivery, FGR, placental abruption, gestational diabetes, hypertensive disorders of pregnancy (chronic hypertension; gestational hypertension; preeclampsia; eclampsia; hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome), and medical termination of pregnancy due to fetal malformation.

Thus, a miscarriage or spontaneous abortion was considered as a non-viable intrauterine pregnancy before 20 weeks of gestation, while a stillbirth was described as fetal death after 20 weeks.[21]

According to the American College of Obstetricians and Gynecologists (ACOG) criteria (2019), a preterm delivery was defined as a labor that occurs before 37 weeks of pregnancy.[22] FGR was defined as an estimated fetal weight below the 10th percentile associated with fetal Doppler parameters alterations.

Placental abruption was defined as premature separation of the placenta from the uterus before delivery.

Gestational diabetes (GD) was defined according to the Portuguese Society of Endocrinology recommendations and the International Association of Diabetes and Pregnancy Study Groups criteria (2011).[23–25] At the first trimester, the diagnosis was made when a fasting glucose value was ≥92 mg/dL and <126 mg/dL. If it was <92 mg/dL, a reassessment was made with an oral glucose tolerance test between

24-28 weeks of gestation and, at least one abnormal value, established the diagnosis.

Hypertensive disorders of pregnancy were defined according to ACOG criteria (2019 and 2020):[26,27]

– Chronic hypertension was diagnosed as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, prior to the 20 weeks of gestation;[26,27]

– Gestational hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (on two occasions, at least 4 hours apart), after 20 weeks of gestation, in a previously normotensive woman; and which resolves within 12 weeks postpartum;[26,27]

– Preeclampsia was characterized by the new-onset of hypertension and proteinuria (defined as urinary excretion of 300 mg or more in a 24-hour urine collection; or protein/creatinine ratio of 0.3 mg/dL or more; or dipstick reading of 2+) or, in the absence of proteinuria, new-onset hypertension with new onset of target organ damage (platelet count <100.000 cells/uL; serum creatinine concentration >1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease; elevated blood concentrations of liver transaminases to twice the upper limit of normal concentration; severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses; pulmonary edema or new-onset headache unresponsive to medication and not accounted for by alternative diagnoses; or visual disturbances);[26,27]

– Eclampsia was defined as the new-onset seizures and/or coma in a patient with preeclampsia, not attributable to any other causes;[26,27]

– HELLP syndrome was diagnosed when analytically there was lactate dehydrogenase ≥600 IU/L, serum aspartate aminotransferase and alanine aminotransferase ≥2 times the upper limit of normal and platelet count <100.000 cells/uL.[26,27]

Delivery-related data (need for medical induction, mode of delivery and cause of cesarean delivery) were also evaluated. Other maternal outcomes included venous and/or arterial thrombosis during pregnancy and/or puerperium and maternal death.

Neonatal outcomes and data concerning the newborn included gestational age at delivery; birthweight; gender; Apgar score[28] at 1 and 5 minutes; neonatal complications (particularly, the need for resuscitation, jaundice and sepsis);

admission to a neonatal intensive care unit (NICU) and neonatal death (in the first 28 days of life).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software, version 29.0 (IBM Corp. Released 2022. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp.) was used for statistical analysis.

A descriptive statistic was performed to summarize baseline characteristics. Categorical variables were described as frequencies and percentages and continuous variables as means and standard deviation (SD). For comparative analysis between the Behçet group and the CG, the Chi-Square Test and Fisher's Exact Test were used to establish associations between categorical data and the Independent Samples t-Test for continuous variables. All reported *P* values are two-tailed, with a p-value ≤ 0.05 indicating statistical significance.

The study was approved by the institutional Ethics Committee, the Department of Clinical Investigation and the Learning, Formation and Investigation Department (reference number 2022.243(190-DEFI/205-CE)).

The study group included a total of 59 pregnancies in 33 women with BD, whereas the control group comprised 177 randomly selected healthy women, with low-risk singleton pregnancies (Figure 1). One comparison table was designed: Table V comparing women with BD vs controls.

Baseline data and clinical background

The demographic and medical characteristics of BD patients are summarized in Table I. The mean age of diagnosis was 24.5 (±4.9) years and the median duration of BD prior to conception was 5.5 years.

As described in Table I, oral and genital ulcerations were the most frequent symptoms in women with BD before pregnancy, with a rate of 98.2% and 67.9%, respectively. Other clinical manifestations included dermatologic involvement in 28.6%, 18.9% with arthritis and 17.9% with uveitis. Previous thrombotic events were also reported: 18.9% venous and 3.4% arterial. Neurological symptoms were only observed in two patients (3.6%).

Besides BD, the study group had a history of concomitant autoimmune diseases: three cases (5.1%) of APS, two (3.4%) of SLE, two (3.4%) of SS and nine (15.3%) of other autoimmune diseases.

When analyzing the immunological profile, 42.4% had ANA antibodies, 10.2% had aβ2GPI antibodies, 8.5% had aCL antibodies, 3.4% had LA, 3.4% had triple aPL positivity (simultaneous presence of LA, aCL and aβ2GPI antibodies) and only 1.7% had anti-SSA and/or anti-SSB antibodies.

Regarding cardiovascular risk factors, the prevalence of obesity was 13.6% and 3.4% of the women suffered from hypertension. Ten women (16.9%) were smokers. None had diabetes or dyslipidemia.

Concerning disease activity, during pregnancy, we observed that 22 women (37.3%) were in remission, 20 (33.9%) remained stable and 17 (28.8%) experienced exacerbation. By contrast, during puerperium, 41 (69.5%) women remained stable, 12 (20.3%) flared up and only 6 (10.2%) were in remission (Table II). Until the current pregnancy, fourteen (23.7%) women had flared up once, since the diagnosis and fifteen (25.4%) had two or more exacerbations (Table I). The number of flare-ups before pregnancy, however, wasn't associated with the rate of exacerbation or remission during this pregnancy (Table III).

The most frequent clinical manifestation, in both pregnancy and the puerperium, was oral ulcerations (16.9% and 11.9%, respectively). Other signs associated with the BD exacerbations were also found such as genital ulcers (6.8% vs 3.4%), dermatologic involvement (5.1% vs 6.8%), arthritis (6.8% in both periods) and thrombotic events (6.8% vs 1.7%). Neurological manifestations (1.7%) were observed only during pregnancy. No ocular involvement was noted during any of the periods. The clinical manifestations of BD are listed in Table II.

As to the targeted therapy for BD (Table IV), comparing the prescription period prior conception and during pregnancy, glucocorticoids (topical, systemic or both) were used in thirty-one patients (52.5%) vs twenty-seven patients (45.8%); CLC in twenty-four (40.7%) vs six (10.2%); hydroxychloroquine (HCQ) in three (5.1%) vs five (8.5%), infliximab in three (5.1%) vs two (3.4%) and azathioprine was used in six patients (10.2%) in both periods.

Furthermore, in Table IV, none of the groups were prescribed with low-dose aspirin (LDA) or low-molecular-weight heparin (LMWH) prior to conception. Nevertheless, during pregnancy, 72.9% of the study group women were medicated with LDA, 35.6% with LMWH and 33.9% with combined treatment (LDA+LMWH). As for the control group, LDA was prescribed to six women (3.4%) and LMWH to three (1.7%). Only two women (1.1%) were under combined treatment. There was a statistically significant difference from the results reported in the study and the control group for all the above variables (p<0.001).

By considering targeted therapy for BD, along with LDA, LMWH or combined treatment, eighteen (30.5%) of the women with BD did not require treatment before pregnancy, but only eight (13.6%) did not require treatment while pregnant. These treatment rates showed statistical significance between the study group and the control group (p<0.001), since 96.0% of the latter required no treatment during pregnancy (Table IV).

Data regarding the clinical background and obstetric history of both groups are described in Table V. The mean age at pregnancy was 31.1 (±5.2) and 30.6 (±5.7) years for the study and control group, respectively. While only 1.1% of the controls recurred to assisted reproductive technology, 11.9% of BD patients conceived with these procedures (p=0.001). The nulliparity rate was 64.4% in the BD women and 53.1% in the CG women, which was not statistically significant. The previous history of one miscarriage was not statistically relevant between groups. Conversely, the rate of two or more miscarriages was significantly higher (15.3% vs

3.4%) in women with BD than in healthy women (p=0.003). Previous voluntary interruption of pregnancy rate was also higher in the study group than in the CG (p=0.001), as well as the percentage of previous cesarean delivery (p=0.005). There was no reported history of stillbirth in any of the groups.

Obstetric outcomes

Pregnancy outcomes and delivery-related data of patients with BD and controls are described in Table V. Of the pregnant women in the BD group, 12 cases of miscarriage (20.3%), 6 cases of FGR (12.8%) and 4 cases of gestational hypertension (8.5%) were observed. One pregnancy (2.1%) was also medically terminated at 22 weeks due to multiple fetal malformations (p=0.210); of note, the patient was in remission and not receiving any medication.

Among the 59 pregnancies in the study group and the 177 in the CG, there was no statistically significant difference in the incidence of preeclampsia (p=1.000), GD (p=0.377) and preterm delivery (p=0.338). Contrarily, the percentages of miscarriage (p<0.001), FGR (p=0.033) and gestational hypertension (p=0.019) were significantly different between groups. Therefore, 47.5% of the pregnancies in the study group had APO (p<0.001).

Placental abruption was reported only in pregnant healthy women, with a percentage of 1.1%. The live birth rate was 78.0% in the study group and 100.0% in the CG, showing a significant difference (p<0.001). There were no cases of eclampsia, HELLP syndrome and stillbirths in either of the groups (Table V).

With respect to delivery-related data, 44.7% and 31.1% cesarean deliveries were performed in the BD and CG, respectively, which was not statistically significant in the current pregnancy (p=0.080). However, the rate of cesarean delivery due to non-reassuring fetal status was higher in pregnant women with BD than in healthy women (p=0.037).

As described in Table VI, no association was found between aPL positivity and thrombotic events (p=0.494), APO (p=0.477) or miscarriage (p=1.000). In Table VII, it is shown that there was no significant difference in the presence of cardiovascular risk factors and the occurrence of thrombotic events (p=1.000) or APO (p=0.598).

Moreover, a comparison between the disease activity, medical therapy and pregnancy outcomes in BD women was performed, as presented in Tables VIII to X. No association was found between obstetric, fetal or neonatal outcomes between

patients who flared-up and those who went into remission (Table VIII). In contrast, as shown in Table IX, patients with no changes in the disease activity had a higher rate of spontaneous abortions when compared to ones who exacerbated (p=0.023). No other associations regarding obstetric, fetal and neonatal outcomes were observed between stable and exacerbated patients (Table IX).

As BD therapeutic regimens, azathioprine, CLC, systemic glucocorticoids and HCQ were not associated with any poor obstetric outcomes (including preterm delivery or FGR), low birth weight or neonatal complications (Table X). Furthermore, there was no statistically significant difference (p=0.787) regarding APO between women with BD under LDA+LMWH and those who were not (Table XI).

Maternal outcomes

Four cases of thrombotic events were recorded during pregnancy and only one during the puerperium in women with BD (Table II). These results showed a statistically significant difference when compared to the CG (Table V), where no thrombotic events occurred (p=0.004) during the current pregnancy. In addition, thrombotic events that occurred in pregnancy were found to be present only in the patients who experienced exacerbations (Table VIII and IX), thus there was an association between disease activity and thrombotic events (p=0.029 and p=0.036).

As presented in Table XI, from the twenty women with BD treated with LDA+LMWH, only four had thrombotic events. However, there was a difference in the development of thrombosis considering the use of this treatment in the study group (p=0.011).

No cases of maternal death were observed (Table V).

Fetal and neonatal outcomes

A comparison of the fetal and neonatal outcomes of the BD and control groups is presented in Table XII. Despite being statistically significant (p=0.005), the mean gestational age at delivery was above 37 weeks (early term) for both groups, with 37.7 (±3.1) weeks in BD group vs 38.6 (±1.6) weeks in CG.

The mean birth weight of newborns pregnant with BD and the CG was 2995.4 grams and 3136.9 grams, respectively; and the rate of male newborns was 43.5% vs 49.2%. There were no significant differences regarding the newborn birth weight (p=0.112) or gender (p=0.493).

The Apgar score was below 7 at the first and fifth minutes in 10.9%/2.2% in BD group and 4.5%/1.1% in the control group. No statistically significance difference was found between groups. Regardless, 28.3% of the newborns from the BD group presented neonatal complications and 10.9% required NICU admission, contrasting to only 9.7% and 1.7% of the newborns of the control group. These results showed a statistically significant difference when comparing the two groups (p<0.001 and p=0.010, respectively).

No neonatal deaths were reported in any group (Table XII).

BD is a rare multisystemic vasculitis that commonly affects women in their reproductive years, when pregnancy is an expected event. In the present study, the mean age of BD diagnosis was 24.5 (±4.9) years, as previously described in literature.[4]

It is, therefore, important to understand the relationship between pregnancy and BD, particularly as current evidence is sparse and contradictory. We retrospectively analyzed and compared the course of the disease and maternal-fetal outcomes of 59 pregnancies in 33 BD women with 177 healthy controls. A higher incidence of miscarriage and FGR was observed in the study group, when compared with the controls, increasing the overall pregnancy complications. Pregnancy had influence on the symptoms of BD and its clinical condition.

Regarding the effects of BD on pregnancy outcomes, in several studies it has been reported that the rate of obstetric and fetal complications ranges from 4 to 27%. Noel *et al.*[4], Nadji *et al.*[29], and Jadaon *et al.*[7] found a complication rate greater than 15% among their pregnant patients with BD, around 16%, 19.5%, and 27%, respectively. By contrast, Marsal *et al.*[30] and Uzun *et al.*[31] did not establish an association between BD and APO. In Iskender *et al.*[9], complications were also not increased and were similar to the general obstetric population for all the different variables (including miscarriage, preeclampsia, FGR, preterm and cesarean delivery). In the present study and the previous one conducted at our centre[8], there were no significant differences in the incidence of preeclampsia and preterm delivery between groups, as reported in the latter series. However, a higher rate of miscarriage and FGR was found, contrary to what was encountered by Iskender *et al.*[9], Marsal *et al.*[30] or Hamza *et al.*[32]

In our sample, besides BD, other autoimmune diseases were present, notably APS, which is associated with thrombotic events and pregnancy morbidity.[19,20] It is possible that the high incidence of miscarriage could be explained by APS and/or APL positivity rather than BD. However, in this study, of the nine women with APL positivity, only three had a previous APS diagnosis, therefore no association was established between APL positivity and APO (including spontaneous abortions). Additionally, the rate of two or more miscarriages was significantly higher (15.3% vs 3.4%) in women with BD than in healthy women (p=0.003). Thus, it is most likely that the high incidence is due to BD.

According to a few studies, miscarriage, FGR and preterm delivery may be associated with the vasculitic and inflammatory process inherent to BD.[5,7,9] Since any vessel can be affected, the placenta is a target tissue. In fact, placental lesions had already been reported in BD patients, particularly necrotizing villi and decidual vasculitis.[9,33,34] As BD placental involvement appears to occur from early gestation stages, vasculitic placental lesions (with neutrophil-dominant infiltration) may account for the unfavorable influence of BD on pregnancy.[7–9,33] Other authors claim that a default trophoblast implantation might explain the occurrence of more miscarriages and cesarean deliveries through association with previous thrombotic events and/or vascular involvement.[4] Furthermore, it should be taken into concern that the hypercoagulable state underlying pregnancy may also potentiate obstetric complications in patients with vascular involvement.[7,8] Thus, appropriate treatment with anticoagulation or thromboprophylaxis for women with BD should be and was considered in this study, with an increased prescription rate of LDA and LMWH.[2,7,35] These therapeutic regimens have also been proven to minimize other obstetric complications, namely preeclampsia, preterm delivery, FGR and miscarriage.[36,37]

Preterm birth rates were increased in BD patients, as it is shown in the studies by Orgul *et al.*[34] and Lee *et al.*[2] Similarly, in Iskender *et al.*[9] a non-significant tendency towards this direction was reported. However, in the present study, there was no association between the disease and preterm delivery. As mentioned above, we did not also find significant differences in the incidence of preeclampsia between the groups, which may be due to the use of LDA and LMWH.[36,37] For thrombotic events, there was a statistically significance as cases were only observed in BD patients using LDA + LMWH. Still, it is likely that this percentage would be higher if they were not undergoing any treatment, given the high risk of vascular involvement in BD.[2,7,35] Regarding APO as a whole, no association was found.

Unlike Barros *et al.*[8], Jadaon *et al.*[7] and Lee *et al.*[2], where there was a statistically significant difference for cesarean delivery, in this study only a non-significant tendency was observed. This tendency may be explained by placental insufficiency in late pregnancy, secondary to BD, which might cause fetal distress.[8] In fact, a high incidence rate of cesarean delivery due to non-reassuring fetal status was observed in BD patients when compared to controls. However, further studies are required to clarify these results. We only observed a statistically significant difference in the rate of cesarean delivery history, which is in a way consistent with previous studies.[2,7,8]

Concerning newborn outcomes, the rate of low birth weight was similar between the groups, supported by the literature.[2,7,8] Conversely, this study showed more neonatal complications (including the need for resuscitation, jaundice, and sepsis) and NICU admission. This may be due to a high ratio of cesarean delivery because of a non-reassuring fetal status, however, the current evidence about the effects of BD including these variables is limited.[1,38] Future studies should be conducted to have a better understanding of these findings.

Bang *et al.*[39] reported that among the 27 women with BD, 18 experienced a clinical exacerbation; and Gul *et al.*[40], found a flare-up ratio of, approximately, 56%, with 9 cases of exacerbation vs 7 cases of remission. On the other hand, there are studies showing that pregnancy had positive rather than adverse impact on the course of BD. In Erenel *et al.*[18], Uzun *et al.*[31] and Hamza *et al.*[32], BD showed a lower rate of flare-up during pregnancy, as well as in the studies conducted by Iskender *et al.*[9] and Orgul *et al.*[34] It is also important to emphasize that the remission rate in Jadaon *et al.*[7] was about five times higher than the exacerbation rate; and Marsal *et al.*[30] found that of the 25 pregnant women, only 2 aggravated. In this study, the majority (71.2%) of our cohort improved or remained with a stable condition during pregnancy. An explanation for this behavior may be associated with hormone-dependent immunomodulatory effects (especially estrogen and progesterone), which are significantly increased during pregnancy.[4,9,34] The BD-associated inflammation might be attenuated by the anti-inflammatory and immunosuppressive state induced by these hormones.[2,7,9,41] Alpha-fetoprotein and human chorionic gonadotropin may also contribute, but the precise role is not yet fully understood.[2,7,8]

The puerperium had variable effects on the disease activity, with no changes in most cases (69.5%). When comparing disease activity in pregnancy and postpartum, we found that only 6 were in remission (10.2%) in the postpartum period vs 22 during pregnancy (37.3%). This finding may be evidence that the immunosuppressive state induced by pregnancy may positively influence the course of the disease, but further studies are needed.[9,29,30]

For the 17 women whose gestation had a negative influence on disease activity, oral ulcerations (16.9%) were the most frequent complications, along with genital ulcers, arthritis and thrombotic events (6.8%), which is consistent with other published data.[18,31,34,35] In Nadji *et al.*[29], ocular involvement appears to be a risk factor for APO.[1,41] In our study, no cases were detected during pregnancy, and thus the poor obstetric outcomes are not attributable to this clinical manifestation.

Additionally, we sought to understand whether disease course influenced obstetric, fetal and neonatal outcomes, as well as thrombotic events.[9] It was only identified a significant relationship between disease activity and thrombotic effects, both in exacerbation vs remission and in exacerbation vs stable disease, which was expected. Curiously, we found that the spontaneous abortion rate was higher in patients with stabilized disease, compared to patients who experienced exacerbations during pregnancy.

The literature reports that it is quite challenging to predict the effect of the disease on pregnancy outcomes and the effect of pregnancy on the disease course and symptoms.[1,17,31,41] Hamza *et al.*[32], found that 4 of the 8 pregnant women in the study had different disease courses during their pregnancies. It means that the same patient may be in remission in one pregnancy, while in a subsequent pregnancy she may have an outbreak, for example. Perhaps, the variability in disease behavior (in obstetric or non-obstetric periods) is due to the involvement of different organs and tissues and, consequently, the various clinical manifestations presented.[1,41]

Ideally, in an autoimmune disease, pregnancy should be planned towards a remission phase of the disease.[6,42] It would be expected that if the disease was stable or in remission before conception, it would be less likely to experience an exacerbation during pregnancy. Indeed, Noel *et al.*[4], demonstrated that the flare up rate before pregnancy was correlated with the same rate during pregnancy. Nevertheless, a similar association was not found in our study. Also, in Nadji *et al.*[29], clinical manifestations prior to pregnancy did not influence the exacerbation of the disease during pregnancy, again demonstrating, the unpredictable nature of this disease.[42]

The management of BD before and during pregnancy included glucocorticoids, CLC, HCQ, azathioprine and infliximab. CLC is one of the most frequently prescribed, along with glucocorticoids.[18] Of the 24 women taking CLC before pregnancy, only 6 maintained this therapeutic option; perhaps because they didn't need it or because of its antimitotic effects, even though prospective studies have demonstrated its safety.[4,43] In Orgul *et al.*[34], CLC demonstrated an increased risk of preterm delivery and low birth weight. In the present study, there were no obstetric, fetal or neonatal complications associated with any of the prescribed therapies. These findings have been evidenced in other studies.[18,41]

Cardiovascular risk factors have also been associated with an increased risk of adverse pregnancy outcomes.[44,45] Of the 59 women with BD, 15 had modifiable

cardiovascular risk factors (including hypertension, obesity, and smoking), but we found no association between an increased rate of APO or thrombotic events in our cohort. Hence, we have excluded the possibility of bias in the interpretation of our results.

There are a few limitations in the present study. We acknowledge that the most relevant are due to its retrospective nature and to the relatively small cohort size, which may not be representative of the Portuguese population.

The information available in medical records is limited and often incomplete, and it is not always possible to collect all the necessary data. Therefore, confounding factors and inherent risk of drawbacks (including selection, recall and information biases) may be present in this study. In addition, because each pregnancy was considered an event, multiparous women were also part of the study, which could represent a bias. However, no association between the number of pregnancies and disease outcome has been found in the current literature.[41]

As this was a single center study of a rare disease, it was expected that the number of cases would be reduced. Nevertheless, despite the small data pool, it was possible to obtain statistically significant results in different variables. It is also noteworthy that since the data collected comes from a single institution, there is a certain consistency in the patients' management and follow-up.

Finally, to expand the sample size and ensure more accurate results leading to an improved medical care, large-scale prospective multicenter controlled studies should be conducted.

• CONCLUSION | CONCLUSÃO •

In conclusion, the current study demonstrated that although the disease course improves during pregnancy, BD may have an unfavorable impact on pregnancy outcomes. Miscarriage, FGR and thrombotic events rates were significantly higher in the study group, increasing the overall adverse pregnancy outcomes. Neonatal complications and NICU admission incidence were also higher, which could be related to increased ratio of cesarean delivery due to a non-reassuring fetal status.

During pregnancy, 37.3% of the patients experienced disease remission, whereas 33.9% remained stable. These results support the theory of pregnancy-induced disease remission and are consistent with other studies. The puerperium had variable effects on the BD course.

Hence, close surveillance by a multidisciplinary and specialized team along with appropriate treatment are necessary for a successful pregnancy and management of BD.

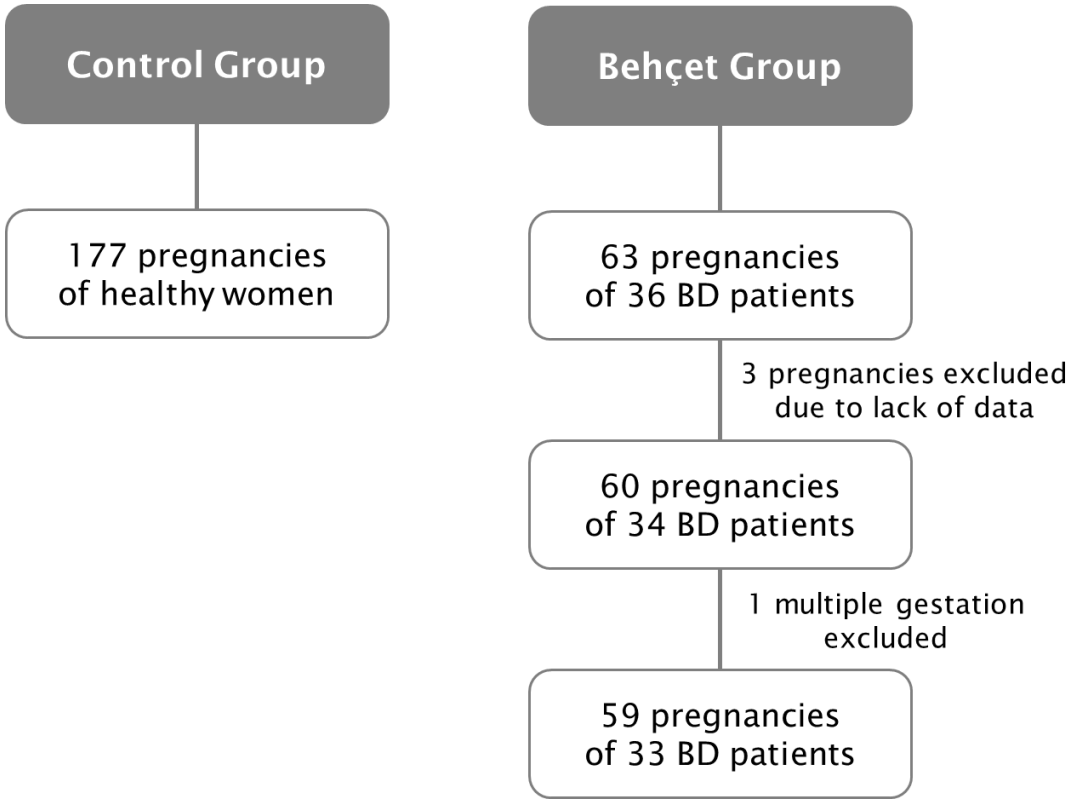

Figure 1: Patient selection protocol
BD – Behçet's Disease

Table I: Characteristics of the Patients with Behçet's Disease.

	Behçet's Disease (n=59)
Age at BD diagnosis[a] (years) – mean (±SD)	24.5 (±4.9)
Duration of disease[a] (years) – median (IQR)	5.5 (5.3)
Age at pregnancy (years) – mean (±SD)	31.1 (±5.2)
Symptoms until current pregnancy[a]	
Oral ulcers – n (%)	55 (98.2)
Genital ulcers – n (%)	38 (67.9)
Dermatologic involvement – n (%)	16 (28.6)
Ocular involvement – n (%)	10 (17.9)
Joint involvement – n (%)	11 (18.9)
Neurological involvement – n (%)	2 (3.6)
Vascular involvement: venous – n (%)	11 (18.9)
Vascular involvement: arterial – n (%)	2 (3.4)
Medical history	
Chronic hypertension – n (%)	2 (3.4)
Diabetes mellitus – n (%)	0 (0)
Obesity – n (%)	8 (13.6)
Dyslipidemia – n (%)	0 (0)
Smoking – n (%)	10 (16.9)
Systemic lupus erythematosus – n (%)	2 (3.4)
Antiphospholipid syndrome – n (%)	3 (5.1)
Sjögren's syndrome – n (%)	2 (3.4)
Other autoimmune diseases – n (%)	9 (15.3)
Number of exacerbations since diagnosis until current pregnancy[a]	
1 – n (%)	14 (23.7)
2 or more – n (%)	15 (25.4)
Immunological profile[a]	
Lupus anticoagulant – n (%)	2 (3.4)
Anticardiolipin – n (%)	5 (8.5)
Anti-β2-glycoprotein I – n (%)	6 (10.2)
Triple aPL positivity[b] – n (%)	2 (3.4)
Anti-Ro/SSA and/or Anti-La/SSB – n (%)	1 (1.7)
Antinuclear antibodies – n (%)	25 (42.4)

BD – Behçet's disease | *SD* – Standard deviation | *IQR* – Interquartile Range | *aPL* – Antiphospholipid antibodies | *Anti-Ro/SSA* – Anti-Sjögren's syndrome-related antigen A | *Anti-La/SSB* – Anti-Sjögren's syndrome-related antigen B.

[a]1 missing value for age at BD diagnosis and duration of disease; 3 missing values for oral ulcers and genital ulcers; 3 missing values for dermatologic, ocular and neurological involvement; 1 missing value for joint and vascular involvement; 2 missing values for number of exacerbations until current pregnancy; 3 missing values for anti-Ro/SSA and/or anti-La/SSB antibodies.

[b]Includes simultaneous presence of lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein I antibodies.

Table II: Characterization of disease activity during pregnancy and puerperium.

	Behçet's Disease (n=59)
Disease activity during pregnancy	
Remission – n (%)	22 (37.3)
Exacerbation – n (%)	17 (28.8)
Stable disease – n (%)	20 (33.9)
Disease activity during puerperium	
Remission – n (%)	6 (10.2)
Exacerbation – n (%)	12 (20.3)
Stable disease – n (%)	41 (69.5)
Symptoms in patients during pregnancy	
Oral ulcers – n (%)	10 (16.9)
Genital ulcers – n (%)	4 (6.8)
Dermatologic involvement – n (%)	3 (5.1)
Ocular involvement – n (%)	0 (0)
Joint involvement – n (%)	4 (6.8)
Neurological involvement – n (%)	1 (1.7)
Vascular involvement – n (%)	4 (6.8)
Symptoms in patients during puerperium	
Oral ulcers – n (%)	7 (11.9)
Genital ulcers – n (%)	2 (3.4)
Dermatologic involvement – n (%)	4 (6.8)
Ocular involvement – n (%)	0 (0)
Joint involvement – n (%)	4 (6.8)
Neurological involvement – n (%)	0 (0)
Vascular involvement – n (%)	1 (1.7)

Table III: Association between the number of exacerbations prior conception and disease activity during pregnancy.

	2 or more exacerbations (n=15)	**No exacerbations (n=42)**	***p*-value**
Exacerbation during current pregnancy – n (%)	5 (33.3)	12 (28.6)	0.751
Remission during current pregnancy – n (%)	3 (20.0)	18 (42.9)	0.115

Table IV: Characterization of the therapy prescribed before and during pregnancy.

	Behçet's Disease (n=59)	**Control Group (n=177)**	***p*-value[1]**
Before pregnancy			
No treatment – n (%)	18 (30.5)	-	-
Medication			
Azathioprine – n (%)	6 (10.2)	-	-
Colchicine – n (%)	24 (40.7)	-	-
Glucocorticoids (topical, systemic or both) – n (%)	31 (52.5)	-	-
Hydroxychloroquine – n (%)	3 (5.1)	-	-
Infliximab – n (%)	3 (5.1)	-	-
Low-dose aspirin – n (%)	0 (0)	-	-
Low-molecular-weight heparin – n (%)	0 (0)	-	-
LDA + LMWH – n (%)	0 (0)	-	-
During pregnancy			
No treatment – n (%)	8 (13.6)	170 (96.0)	**<0.001**
Medication			
Azathioprine – n (%)	6 (10.2)	-	-
Colchicine – n (%)	6 (10.2)	-	-
Glucocorticoids (topical, systemic or both) – n (%)	27 (45.8)	-	-
Hydroxychloroquine – n (%)	5 (8.5)	-	-
Infliximab – n (%)	2 (3.4)	-	-
Low-dose aspirin – n (%)	43 (72.9)	6 (3.4)	**<0.001**
Low-molecular-weight heparin – n (%)	21 (35.6)	3 (1.7)	**<0.001**
LDA + LMWH – n (%)	20 (33.9)	2 (1.1)	**<0.001**

LDA – Low-dose aspirin | *LMWH* – Low-molecular-weight heparin | [1]*p*-values ≤ 0.05 are bolded.

Table V: Comparison between pregnant women with Behçet's disease and the control group.

	Behçet's Disease (n= 59)	**Control Group (n=177)**	***p*-value**[1]
Age at pregnancy (years) – mean (±SD)	31.1 (±5.2)	30.6 (±5.7)	0.538
Obstetric history			
Nulliparity – n (%)	38 (64.4)	94 (53.1)	0.130
Previous miscarriage			
1 – n (%)	11 (18.6)	37 (20.9)	0.709
2 or more – n (%)	9 (15.3)	6 (3.4)	**0.003**
Previous voluntary interruption of pregnancy – n (%)	7 (11.9)	2 (1.1)	**0.001**
Assisted reproductive technology pregnancy – n (%)	7 (11.9)	2 (1.1)	**0.001**
Previous fetal growth restriction – n (%)	2 (5.6)	-	-
Previous preterm delivery – n (%)	3 (8.3)	-	-
Previous cesarean delivery – n (%)	8 (47.1)	12 (14.5)	**0.005**
Previous stillbirth – n (%)	0 (0)	0 (0)	-
Pregnancy outcomes			
Adverse pregnancy outcomes[a] *– n (%)*	28 (47.5)	34 (19.2)	**<0.001**
Gestational hypertension – n (%)	4 (8.5)	2 (1.1)	**0.019**
Preeclampsia – n (%)	1 (2.1)	3 (1.7)	1.000
Eclampsia – n (%)	0 (0)	0 (0)	-
HELLP syndrome – n (%)	0 (0)	0 (0)	-
Placental abruption – n (%)	0 (0)	2 (1.1)	1.000
Gestational diabetes – n (%)	2 (4.3)	16 (9.0)	0.377
Fetal growth restriction – n (%)	6 (12.8)	7 (4.0)	**0.033**
Miscarriage – n (%)	12 (20.3)	0 (0)	**<0.001**
Stillbirth – n (%)	0 (0)	0 (0)	-
Medical termination of pregnancy – n (%)	1 (2.1)	0 (0)	0.210
Live birth rate – n (%)	46 (78.0)	177 (100.0)	**<0.001**
Preterm delivery – n (%)	5 (10.6)	11 (6.2)	0.338
Maternal outcomes			
Thrombotic events – n (%)	4 (6.8)	0 (0)	**0.004**
Maternal death – n (%)	0 (0)	0 (0)	-
Delivery-related data			
Induced labor[b] *– n (%)*	23 (48.9)	-	-
Vaginal delivery or assisted vaginal delivery – n (%)	26 (55.3)	122 (68.9)	0.080
Cesarean delivery – n (%)	21 (44.7)	55 (31.1)	0.080
Cesarean delivery for non-reassuring fetal status – n (%)	7 (33.3)	10 (18.2)	**0.037**

SD – Standard deviation | *HELLP* – Hemolysis, elevated liver enzymes, and low platelet count.
[1] *p*-values ≤ 0.05 are bolded.
[a]Includes gestational hypertension, preeclampsia, eclampsia, HELLP syndrome, placental abruption, gestational diabetes, fetal growth restriction, miscarriage, stillbirth and preterm delivery.
[b]2 missing values for induced labor.

Table VI: Association between aPL positivity and pregnancy outcomes.

	aPL positivity (n=9)	**No aPL positivity (n=50)**	***p*-value**
Thrombotic events – n (%)	1 (11.1)	3 (6.0)	0.494
Adverse pregnancy outcomes[a] – n (%)	3 (33.3)	25(46.3)	0.477
Miscarriage – n (%)	2 (22.2)	10 (20.0)	1.000

aPL – Antiphospholipid antibodies.
[a]Includes gestational hypertension, preeclampsia, eclampsia, HELLP syndrome, placental abruption, gestational diabetes, fetal growth restriction, miscarriage, stillbirth and preterm delivery.

Table VII: Association between cardiovascular risk factors and pregnancy outcomes.

	Cardiovascular risk factors (n=15)	**No cardiovascular risk factors (n=44)**	***p*-value**
Thrombotic events – n (%)	1 (6.7)	3 (6.8)	1.000
Adverse pregnancy outcomes[a] – n (%)	8 (53.3)	20 (45.5)	0.598

[a]Includes gestational hypertension, preeclampsia, eclampsia, HELLP syndrome, placental abruption, gestational diabetes, fetal growth restriction, miscarriage, stillbirth and preterm delivery.

Table VIII: Association between disease activity (exacerbation vs remission) and pregnancy outcomes.

	Exacerbation (n=17)	**Remission (n=22)**	***p*-value[1]**
Thrombotic events – n (%)	4 (23.5)	0 (0)	**0.029**
Adverse pregnancy outcomes[a] – n (%)	9 (52.9)	9 (40.9)	0.455
Fetal growth restriction[b] – n (%)	4 (25.0)	2 (10.5)	0.379
Miscarriage – n (%)	1 (5.9)	3 (13.6)	0.618
Preterm delivery[b] – n (%)	2 (12.5)	3 (15.8)	1.000
Cesarean delivery[b] – n (%)	8 (50.0)	8 (42.1)	0.640
Cesarean delivery for non-reassuring fetal status[c] – n (%)	4 (50.0)	3 (37.5)	1.000
Low birth weight (<2500 grams)[d] – n (%)	3 (18.8)	2 (11.1)	0.648
Neonatal complications[d,e] – n (%)	5 (31.3)	5 (27.8)	1.000

[1] *p*-values ≤ 0.05 are bolded.
[a]Includes gestational hypertension, preeclampsia, eclampsia, HELLP syndrome, placental abruption, gestational diabetes, fetal growth restriction, miscarriage, stillbirth and preterm delivery.
[b]Exacerbation n=16 and remission n=19 (miscarriages excluded).
[c]Exacerbation n=8 and remission n=8 (vaginal delivery or assisted vaginal delivery excluded).
[d]1 missing value for low birth weight and neonatal complications.
[e]Includes the need for resuscitation, jaundice and sepsis.

Table IX: Association between disease activity (exacerbation vs stable disease) and pregnancy outcomes.

	Exacerbation (n=17)	**Stable disease (n=20)**	***p*-value[1]**
Thrombotic events – n (%)	4 (23.5)	0 (0)	**0.036**
Adverse pregnancy outcomes[a] – n (%)	9 (52.9)	10 (50.0)	0.858
Fetal growth restriction[b] – n (%)	4 (25.0)	0 (0)	0.113
Miscarriage – n (%)	1 (5.9)	8 (40.0)	**0.023**
Preterm delivery[b] – n (%)	2 (12.5)	0 (0)	0.492
Cesarean delivery[b] – n (%)	8 (50.0)	5 (41.7)	0.662
Cesarean delivery for non-reassuring fetal status[c] – n (%)	4 (50.0)	0 (0)	0.085
Low birth weight (<2500 grams)[b] – n (%)	3 (18.8)	0 (0)	0.238
Neonatal complications[b,d] – n (%)	5 (31.3)	3 (25.0)	1.000

[1] *p*-values ≤ 0.05 are bolded.
[a]Includes gestational hypertension, preeclampsia, eclampsia, HELLP syndrome, placental abruption, gestational diabetes, fetal growth restriction, miscarriage, stillbirth and preterm delivery.
[b]Exacerbation n=16 and stable disease n=12 (miscarriages excluded).
[c]Exacerbation n=8 and stable disease n=6 (vaginal delivery or assisted vaginal delivery excluded).
[d]Includes the need for resuscitation, jaundice and sepsis.

Table X: Association between medical therapy and pregnancy outcomes.

	Azathioprine (n=6)	**No azathioprine (n=53)**	***p*-value**
Adverse pregnancy outcomes[a] – n (%)	2 (33.3)	26 (49.1)	0.673
Preterm delivery[b] – n (%)	1 (16.7)	4 (9.8)	0.511
Fetal growth restriction[b] – n (%)	2 (33.3)	4 (9.8)	0.162
Low birth weight (<2500 grams)[b] – n (%)	2 (33.3)	3 (7.5)	0.120
Neonatal complications[b,c] – n (%	3 (50.0)	10 (25.0)	0.330
	Colchicine (n=6)	**No colchicine (n=53)**	***p*-value**
Adverse pregnancy outcomes[a] – n (%)	3 (50.0)	25 (47.2)	1.000
Preterm delivery[b] – n (%)	0 (0)	5 (11.9)	1.000
Fetal growth restriction[b] – n (%)	1 (20.0)	5 (11.9)	0.511
Low birth weight (<2500 grams)[b] – n (%)	1 (20.0)	4 (9.8)	0.453
Neonatal complications[b,c] – n (%)	1 (20.0)	12 (29.3)	1.000
	Glucocorticoids (n=25)	**No glucocorticoids (n=34)**	***p*-value**
Adverse pregnancy outcomes[a] – n (%)	13 (52.0)	15 (44.1)	0.549
Preterm delivery[b] – n (%)	1 (5.9)	4 (13.3.)	0.640
Fetal growth restriction[b] – n (%)	2 (11.8)	4 (13.3)	1.000
Low birth weight (<2500 grams)[b] – n (%)	1 (5.9)	4 (13.8)	0.637
Neonatal complications[b,c] – n (%)	4 (23.5)	9 (31.0)	0.739
	Hydroxychloroquine (n=5)	**No hydroxychloroquine (n=54)**	***p*-value**
Adverse pregnancy outcomes[a] – n (%)	2 (40.0)	26 (48.1)	1.000
Preterm delivery[b] – n (%)	0 (0)	5 (11.9)	1.000
Fetal growth restriction[b] – n (%)	1 (20.0)	5 (12.2)	0.511
Low birth weight (<2500 grams)[b] – n (%)	0 (0)	5 (12.2)	1.000
Neonatal complications[b,c] – n (%)	2 (40.0)	11 (26.8)	0.612

[a]Includes gestational hypertension, preeclampsia, eclampsia, HELLP syndrome, placental abruption, gestational diabetes, fetal growth restriction, miscarriage, stillbirth and preterm delivery.
[b]1 missing value for preterm delivery, fetal growth restriction, low birth weight and neonatal complications.
[c]Includes the need for resuscitation, jaundice and sepsis.

Table XI: Association between LDA plus LMWH treatment and pregnancy outcomes.

	LDA plus LMWH (n=20)	**No LDA plus LMWH (n=39)**	***p*-value**[1]
Thrombotic events – n (%)	4 (20.0)	0 (0)	**0.011**
Adverse pregnancy outcomes[a] *– n (%)*	9 (45.0)	19 (48.7)	0.787

LDA – Low-dose aspirin | *LMWH* – Low-molecular-weight heparin | [1] *p*-values ≤ 0.05 are bolded.
[a]Includes gestational hypertension, preeclampsia, eclampsia, HELLP syndrome, placental abruption, gestational diabetes, fetal growth restriction, miscarriage, stillbirth and preterm delivery.

Table XII: Neonatal outcomes characterization.

	Behçet's Disease (n= 59)	**Control Group (n=177)**	***p*-value[1]**
Gestational age at delivery (weeks) – mean (±SD)	37.7 (±3.1)	38.6 (±1.6)	**0.005**
Birth weight[a] (grams) – mean (±SD)	2995.4 (±664.2)	3136.9 (±498.0)	0.112
Low birth weight[a] (<2500) – n (%)	5 (10.9)	14 (7.9)	0.554
Normal birth weight[a] (2500-4000) – n (%)	40 (87.0)	159 (89.8)	0.595
Male gender[a] – n (%)	20 (43.5)	87 (49.2)	0.493
Apgar score 1 minute < 7[a] – n (%)	5 (10.9)	8 (4.5)	0.153
Apgar score 5 minute < 7[a] – n (%)	1 (2.2)	2 (1.1)	0.508
Neonatal complications[a,b] – n (%)	13 (28.3)	17 (9.7)	**<0.001**
Admission to a NICU[a] – n (%)	5 (10.9)	3 (1.7)	**0.010**
Neonatal death – n (%)	0 (0)	0 (0)	-

SD – Standard deviation | *NICU* – Neonatal Intensive care unit | [1] *p*-values ≤ 0.05 are bolded.
[a]1 missing value for birth weight (including low and normal birth weight), male gender, Apgar score 1 and 5 minute < 7, neonatal complications and admission to a NICU.
[b]Includes the need for resuscitation, jaundice and sepsis.

• REFERENCES | REFERÊNCIAS BIBLIOGRÁFICAS •

1. Chan TM, Chiou MJ, Kuo CF. Adverse pregnancy outcomes in women with Behçet's disease: population-based registry linkage study in Taiwan. *Clin Rheumatol*. 2021;40(10):4135-4142. doi:10.1007/s10067-021-05688-6.

2. Lee S, Czuzoj-Shulman N, Abenhaim HA. Behcet's disease and pregnancy: Obstetrical and neonatal outcomes in a population-based cohort of 12 million births. *J Perinat Med*. 2019;47(4):381-387. doi:10.1515/jpm-2018-0161.

3. Gilio M, Tramontano G, D'Angelo S, *et al*. FRI0252 Behcet's Disease and Pregnancy: What is the Relationship? *Ann Rheum Dis*. 2015;74(Suppl 2):516-516. doi:10.1136/ANNRHEUMDIS-2015-EULAR.3438.

4. Noel N, Wechsler B, Nizard J, *et al*. Behçet's disease and pregnancy. *Arthritis Rheum*. 2013;65(9):2450-2456. doi:10.1002/art.38052.

5. Gungor ANC, Kalkan G, Oguz S, *et al*. Behcet disease and pregnancy. *Clin Exp Obstet Gynecol*. 2014;41(6):617-619. doi:10.12891/CEOG16762014/PDF.

6. Gomes V, Mesquita A, Capela C. Autoimmune diseases and pregnancy: Analysis of a series of cases. *BMC Res Notes*. 2015;8(1):1-7. doi:10.1186/s13104-015-1177-x.

7. Jadaon J, Shushan A, Ezra Y, Sela HY, Ozcan C, Rojansky N. Behçet's disease and pregnancy. *Acta Obstet Gynecol Scand*. 2005;84(10):939-944. doi:10.1111/j.0001-6349.2005.00761.x.

8. Barros T, Braga A, Marinho A, Braga J. Case Series Behçet's Disease and Pregnancy: A Retrospective Case-Control Study. *Yale J Biol Med*. 2021;94(4):585-592.

9. Iskender C, Yasar O, Kaymak O, Yaman ST, Uygur D, Danisman N. Behçet's disease and pregnancy: A retrospective analysis of course of disease and pregnancy outcome. *J Obstet Gynaecol Res*. 2014;40(6):1598-1602. doi:10.1111/jog.12386.

10. Marshall SE. Behçet's disease. *Best Pract Res Clin Rheumatol*. 2004;18(3):291-311. doi:10.1016/j.berh.2004.02.008.

11. Smith, EL, Yazici, Y. Clinical manifestations and diagnosis of Behçet syndrome. (Internet). Waltham, MA: Merkel PA, ed. *UpToDate*. Available from: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-behcet-syndrome?search=behcet%20tratamento&source=search_result&selectedTitle=2~141&usage_type=default&display_rank=2. Accessed May 10, 2023.

12. Kiafar M, Faezi ST, Kasaeian A, *et al*. Diagnosis of Behçet's disease: clinical characteristics, diagnostic criteria, and differential diagnoses. *BMC Rheumatol*. 2021;5(1):1-7. doi:10.1186/s41927-020-00172-1.

13. Davatchi F, Assaad-Khalil S, Calamia KT, *et al*. The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol.* 2014;28(3):338-347. doi:10.1111/jvd.12107.

14. Merlino L, Del Prete F, Lobozzo B, Priori R, Piccioni MG. Behcet's disease and pregnancy: a review of the literature. *Minerva Ginecol*. 2020;72(5):332-338. doi:10.23736/S0026-4784.20.04564-5.

15. Mainini G, Di Donna MC, Esposito E, *et al*. Pregnancy management in Behçet's disease treated with uninterrupted infliximab. Report of a case with fetal growth restriction and mini-review of the literature. *Clin Exp Obstet Gynecol*. 2014;41(2):205-207. doi:10.12891/CEOG17642014/PDF.

16. Ross C, D'Souza R, Pagnoux C. Pregnancy Outcomes in Systemic Vasculitides. *Curr Rheumatol Rep*. 2020;22(10):63. doi:10.1007/s11926-020-00940-5.

17. Martineau M, Haskard DO, Nelson-Piercy C. Behçet's syndrome in pregnancy. *Obstet Med*. 2010;3(1):2-7. doi:10.1258/om.2009.090033.

18. Erenel H, Alici Davutoglu E, Ozel A, Karsli F, Ozge Korkmaz S, Madazli R. Pregnancy and Behcet's Disease: Obstetric outcomes of 33 patients. *Sisli Etfal Hastan Tip Bul.* 2017;51(4):318-321. doi:10.5350/semb.20170725042231.

19. Sammaritano LR. Antiphospholipid syndrome. *Best Pract Res Clin Rheumatol*. 2020;34(1):101463. doi:10.1016/j.berh.2019.101463.

20. Arslan E, Branch DW. Antiphospholipid syndrome: Diagnosis and management in the obstetric patient. *Best Pract Res Clin Obstet Gynaecol*. 2020;64:31-40. doi:10.1016/j.bpobgyn.2019.10.001.

21. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. *Obstet Gynecol.* 2018;132(5):e197-e207. doi:10.1097/AOG.0000000000002899.

22. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 171: Management of Preterm Labor. *Obstet Gynecol.* 2016;128(4):e155-e164. doi:10.1097/AOG.0000000000001711.

23. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, *et al*. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010;33(3):676-682. doi:10.2337/DC09-1848.

24. Ferreira AF, Silva CM, Antunes D, Sousa F, Lobo AC, Moura P. Gestational diabetes mellitus: Is there an advantage in using the current diagnostic criteria? *Acta Med Port*. 2018;31(7-8):416-424. doi:10.20344/amp.10135.

25. Dores J, Magalhães Â, Carvalheiro M, *et al*. Consenso "Diabetes Gestacional": Atualização 2017. *Rev Port Diab*. 2017;12(1):24-38.

26. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. *Obstet Gynecol*. 2019;133(1):e26-e50. doi:10.1097/AOG.0000000000003020.

27. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 222: Gestational Hypertension and Preeclampsia. *Obstet Gynecol*. 2020;135(6):e237-e260. doi:10.1097/AOG.0000000000003891.

28. Watterberg KL, Aucott S, Benitz WE, *et al*. The Apgar Score. *Pediatrics*. 2015;136(4):819-822. doi:10.1542/PEDS.2015-2651.

29. Nadji A, Shahram F, Jamshidi AR, Davatchi F. Behcet's disease and pregnancy. *Acta Med Iran*. 2004; 42(6): 415-418.

30. Marsal S, Falgá C, Simeon CP, Vilardell M, Bosch JA. Behçet's disease and pregnancy relationship study. *Br J Rheumatol*. 1997;36(2):234-8. doi: 10.1093/rheumatology/36.2.234.

31. Uzun S, Alpsoy E, Durdu M, Akman A. The Clinical Course of Behçet's Disease in Pregnacy: A Retrospective Analysis and Review of the Literature. *J Dermatol*. 2003;30(7):499-502. doi:10.1111/j.1346-8138.2003.tb00423.x.

32. Hamza M, Elleuch M, Zribi A. Behçet's disease and pregnancy. *Ann Rheum Dis*. 1988;47(4):350. doi:10.1136/ard.47.4.350-a.

33. Hwang I, Lee CK, Yoo B, Lee I. Necrotizing villitis and decidual vasculitis in the placentas of mothers with Behçet disease. *Hum Pathol*. 2009;40(1):135-138. doi:10.1016/j.humpath.2008.04.021.

34. Orgul G, Aktoz F, Beksac MS. Behcet's disease and pregnancy: what to expect? *J Obstet Gynaecol.* 2018;38(2):185-188. doi:10.1080/01443615.2017.1336614.

35. Xu C, Bao S. Behcet's disease and pregnancy-a case report and literature review. *Am J Reprod Immunol*. 2017;77(1):1-4. doi:10.1111/aji.12530.

36. Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev*. 2019;2019(10). doi:10.1002/14651858.CD004659.pub3.

37. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol*. 2018;218(3):287-293.e1. doi:10.1016/j.ajog.2017.11.561.

38. Chen JS, Roberts CL, Simpson JM, March LM. Pregnancy outcomes in women with rare autoimmune diseases. *Arthritis Rheumatol*. 2015;67(12):3314-3323. doi:10.1002/art.39311.

39. Bang D, Chun YS, Haam IB, Lee ES, Lee S. The influence of pregnancy on Behçet's disease. *Yonsei Med J.* 1997;38(6):437-443. doi:10.3349/YMJ.1997.38.6.437.

40. Gül Ü. Pregnancy and Behçet Disease. *Arch Dermatol*. 2000;136(8):1063-1064. doi:10.1001/archderm.136.8.1063.

41. Ben-Chetrit E. Behçet's syndrome and pregnancy: course of the disease and pregnancy outcome. *Clin Exp Rheumatol*. 2014;32(4 Suppl 84):S93-S98.

42. Pagnoux C, Mahendira D, Laskin CA. Fertility and pregnancy in vasculitis. *Best Pract Res Clin Rheumatol*. 2013;27(1):79-94. doi:10.1016/j.berh.2013.02.002.

43. Diav-Citrin O, Shechtman S, Schwartz V, *et al*. Pregnancy outcome after in utero exposure to colchicine. *Am J Obstet Gynecol*. 2010;203(2):144.e1-144.e6. doi:10.1016/j.ajog.2010.02.063.

44. Lumsden RH, Pagidipati N. Management of cardiovascular risk factors during pregnancy. *Heart*. 2022;108(18):1438-1444. doi:10.1136/heartjnl-2021-319606.

45. El-Shebiny E, El-Fakharany A, Zahran E, et al. Modifiable cardiovascular risk factors in patients with Behçet's disease: a multicenter experience. *Egypt J Intern Med*. 2019;31(4):726-732. doi:10.4103/ejim.ejim_112_19.