Pregnancy may favour the development of severe autoimmune central diabetes insipidus in women with vasopressin cell antibodies: description of two cases

Giuseppe Bellastella¹, Antonio Bizzarro², Ernesto Aitella², Mariluce Barrasso¹, Domenico Cozzolino², Sergio Di Martino², Katherine Esposito² and Annamaria De Bellis³

Departments of ¹Medical, Surgical, Neurological, Metabolic and Geriatric Sciences, ²Clinical and Experimental Medicine and ³Cardiothoracic and Respiratory Sciences, Second University of Naples, Piazza L. Miraglia 2, 80131 Napoli, Italy

Abstract

Recently, an increased incidence of central diabetes insipidus (CDI) in pregnancy, and less frequently in the post partum period, has been reported, most probably favoured by some conditions occurring in pregnancy. This study was aimed at investigating the influence of pregnancy on a pre-existing potential/subclinical hypothalamic autoimmunity. We studied the longitudinal behaviour of arginine–vasopressin cell antibodies (AVPcAbs) and post-pituitary function in two young women with a positive history of autoimmune disease and presence of AVPcAbs, but without clinical CDI, and who became pregnant 5 and 7 months after our first observation. The behaviour of post-pituitary function and AVPcAbs (by immunofluorescence) was evaluated at baseline, during pregnancy and for 2 years after delivery. AVPcAbs, present at low/middle titres at baseline in both patients, showed a titre increase during pregnancy in one patient and after delivery in the other patient, with development of clinically overt CDI. Therapy with 1-deamino-8-α-arginine vasopressin (DDAVP) caused a prompt clinical remission. After a first unsuccessful attempt of withdrawal, the therapy was definitively stopped at the 6th and the 7th month of post partum period respectively, when AVPcAbs disappeared, accompanied by post-pituitary function recovery, persisting until the end of the follow-up. The determination of AVPcAbs is advisable in patients with autoimmune diseases planning their pregnancy, because they could be considered good predictive markers of gestational or post partum autoimmune CDI. The monitoring of AVPcAb titres and post-pituitary function during pregnancy in these patients may allow for an early diagnosis and an early replacement therapy, which could induce the disappearance of these antibodies with consequent complete remission of CDI.

Introduction

Central diabetes insipidus (CDI) during pregnancy is a rare phenomenon with an estimated incidence between two and six cases per 100 000 pregnancies; however, an increase in the incidence of gestational CDI has been recently reported (¹, ², ³). It can occur at any stage of gestation and more rarely after delivery (⁴, ⁵). Various conditions occurring during pregnancy can favour the development of CDI, such as increased degradation of arginine vasopressin (AVP) by vasopressinase, a placental enzyme that cleaves AVP but not 1-deamino-8-α-AVP (DDAVP) (⁶, ⁷, ⁸, ⁹). Moreover, some cases of CDI in pregnancy may be linked to lymphocytic hypophysitis (LYH), an organ-specific autoimmune disease of the pituitary gland, closely related to pregnancy and the
post partum period (10), especially when the autoimmune inflammatory process involves the infundibulum and neurohypophysis, as occurs in lymphocytic infundibuloneurohypophysitis (11). In previous studies, we had reported that autoimmune CDI is often characterised by the presence of antibodies to AVP-secreting cells (AVPcAbs) and sometimes by a pituitary stalk thickening on magnetic resonance imaging (MRI), suggestive of lymphocytic infundibuloneurohypophysitis (12). However, the influence of pregnancy in women positive for AVPcAbs but without clinical autoimmune CDI has never been investigated. Given the lack of such studies in the literature, we describe the behaviour with the time of post-pituitary function and AVPcAbs during a follow-up of 33 months, including pregnancy and the post partum period, in two cases of pregnant women previously found positive for AVPcAbs but without clinically overt CDI.

Clinical cases

Case 1

A 33-year-old woman with celiac disease, diagnosed in the previous 2 years, was admitted to the Endocrinology Unit of the Second University of Naples for organ-specific antibody screening before planning her first pregnancy. All organ-specific antibodies, including thyroid antibodies, were absent; also anti-endomysial (EMA) IgA and anti-tissue transglutaminase (AtTG) autoantibodies, present at diagnosis of celiac disease, disappeared after prolonged gluten-free diet. Instead, antihypothalamus antibodies (AHAs), identified by four-layer double immunofluorescence as AVPcAbs, were present at titre 1:16. No significant alteration in her water balance was reported. However, she was submitted for further investigations such as urinary specific gravity, basal urinary and plasma osmolality, a dehydration test and the study of plasma AVP concentration, following desmopressin administration. The results were addressed to the diagnosis of autoimmune subclinical CDI, following the criteria described previously (13). The patient became pregnant 5 months later.

Case 2

A 26-year-old woman with euthyroid, untreated Hashimoto’s thyroiditis, positive for antithyroglobulin antibody (TgAb) and antiperoxidase antibody (TPOAb), who was planning her first pregnancy, was submitted to a screening for other organ-specific antibodies, showing only the presence of AHAs at low titre (1:8), identified by double immunofluorescence as AVPcAbs. No significant alteration in her water balance was reported. However, she was submitted for further investigation. On the basis of the results of a complete post-pituitary function evaluation, as described earlier, autoimmune subclinical CDI was diagnosed (Table 1). The patient became pregnant 7 months later.

Methods

In both patients, AVPcAbs and post-pituitary function were evaluated during pregnancy at the 4th, 20th and 28th weeks and then in the post partum period at the 2nd, 4th and 6th weeks, and every 6 months thereafter until the 24th month, together with the determination of EMA (by indirect immunofluorescence) and AtTG (by ELISA) in case 1 and of TgAb and TPOAb (by RIA) in case 2. Moreover, anti-pituitary antibodies (APAs) by immunofluorescence and anterior pituitary function were also evaluated in both patients at 4 weeks of pregnancy and at the onset of clinical CDI.

The determination of AVPcAbs was also crosswisely performed in 30 healthy women (20 in pregnancy and ten in post partum period), 20 women with Hashimoto’s thyroiditis and 15 women with HT and celiac disease, all of them with normal post-pituitary function. Finally, MRI of the hypothalamic–pituitary region was performed at the first observation and at the appearance of clinical CDI. The study was approved by the Local Ethics Committee and both patients gave their informed consent to be enrolled in the study.

AHA, AVPcAb and APA evaluation

AHAs and APAs were detected by simple indirect immunofluorescence method on cryostat sections of young baboon hypothalamus and pituitary, respectively, supplied by Biosystem Italia Srl (San Martino Buon Albergo, VR, Italy), as described previously (14, 15). In particular, FITC conjugated with goat anti-human IgG was used to detect the presence of AHAs and APAs. Sera of patients positive for AHAs were re-tested by four-layer double immunofluorescence to verify whether the hypothalamic cells targeted by AHAs were AVP-secreting cells (12, 13, 14). For this purpose, in a second step, the same hypothalamus section was tested consecutively against the patient’s serum and the rabbit antiserum anti-AVP, followed by rhodamine goat sera anti-rabbit IgG. The different colours of anti-Ig conjugate against the human
serum and against the animal serum, green (FITC) and red (rhodamine) respectively, allowed for direct visual assessment of whether the patient’s serum and the animal’s ant-AVP serum stained the same or different hypothalamic cells. AVPcAbs were considered positive starting at a dilution of 1:8 (15).

**Posterior pituitary function**

The diagnosis of CDI was suspected on the basis of evidence of polyuria, polydipsia and urinary and plasma osmolality. To confirm the diagnosis of CDI, patients underwent a dehydration test followed by a desmopressin administration test. A ratio of urinary osmolality to plasma osmolality of one or less was taken to indicate the presence of complete CDI and a ratio of more than 1.0 but < 1.4 was taken to indicate partial CDI (16). Moreover, an increase in urinary osmolality of more than 50%, or from 10 to 50%, after desmopressin injection allowed for the diagnosis of complete or partial CDI respectively. Patients underwent these tests at the first observation (before pregnancy).

The diagnosis of complete CDI in pregnancy was suspected from the presence of severe polydipsia–polyuria syndrome with urinary specific gravity below the normal range, and when plasma sodium level was above 145 mEq/l and the basal urine osmolality < 300 mOsm/l and lower than plasma osmolality, and when plasma AVP levels were low and plasma osmolality high. As a water deprivation test cannot be performed in pregnancy, a definite diagnosis of CDI was sought when a prompt decrease in oral fluid intake and urine output, and

### Table 1 Behaviour of vasopressin cell antibodies and post-pituitary function at baseline and during the pregnancy and in the post partum period in case 1 and case 2 patients.

<table>
<thead>
<tr>
<th></th>
<th>AVPcAb titre</th>
<th>Basal urinary osmolality (mOsm/kg)</th>
<th>Basal plasma osmolality (mOsm/kg)</th>
<th>AVP (pg/ml)</th>
<th>Water deprivation test</th>
<th>Desmopressin test</th>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Urinary osmolality</td>
<td>Plasma osmolality</td>
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<td>(mOsm/kg)</td>
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<tr>
<td>Case 1</td>
<td>5 months before pregnancy</td>
<td>1:16</td>
<td>308</td>
<td>280</td>
<td>–</td>
<td>300</td>
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<td></td>
<td>Pregnancy</td>
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<tr>
<td>4th week</td>
<td></td>
<td>1:8</td>
<td>302</td>
<td>285</td>
<td>1.5</td>
<td>–</td>
</tr>
<tr>
<td>20th weeka</td>
<td></td>
<td>1:256</td>
<td>110</td>
<td>294</td>
<td>0.3</td>
<td>–</td>
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<tr>
<td>28th week</td>
<td></td>
<td>1:128</td>
<td>590</td>
<td>273</td>
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<tr>
<td>Post partum</td>
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<tr>
<td>2nd week</td>
<td></td>
<td>1:128</td>
<td>620</td>
<td>280</td>
<td>–</td>
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</tr>
<tr>
<td>4th weekb,c</td>
<td></td>
<td>1:64</td>
<td>190</td>
<td>291</td>
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<tr>
<td>6th monthd</td>
<td></td>
<td>0</td>
<td>360</td>
<td>283</td>
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<td>800</td>
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<tr>
<td>12th month</td>
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<td>0</td>
<td>790</td>
<td>278</td>
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<td>815</td>
<td>282</td>
<td>4.2</td>
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<tr>
<td>Case 2</td>
<td>7 months before pregnancy</td>
<td>1:8</td>
<td>320</td>
<td>290</td>
<td>–</td>
<td>280</td>
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<tr>
<td></td>
<td>Pregnancy</td>
<td></td>
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<tr>
<td>4th week</td>
<td></td>
<td>1:8</td>
<td>370</td>
<td>293</td>
<td>1.8</td>
<td>–</td>
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<tr>
<td>20th week</td>
<td></td>
<td>1:16</td>
<td>350</td>
<td>291</td>
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<tr>
<td>28th week</td>
<td></td>
<td>1:16</td>
<td>300</td>
<td>295</td>
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<td>Post partum</td>
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<td>2nd weeka</td>
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<td>1:256</td>
<td>120</td>
<td>297</td>
<td>0.4</td>
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<tr>
<td>6th weekb,c</td>
<td></td>
<td>1:128</td>
<td>190</td>
<td>296</td>
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<tr>
<td>7th weekd</td>
<td></td>
<td>0</td>
<td>450</td>
<td>282</td>
<td>–</td>
<td>920</td>
</tr>
<tr>
<td>12th month</td>
<td></td>
<td>0</td>
<td>960</td>
<td>284</td>
<td>4.2</td>
<td>–</td>
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<td>24th month</td>
<td></td>
<td>0</td>
<td>750</td>
<td>278</td>
<td>3.8</td>
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AVP, arginine–vasopressin; AVPcAbs, arginine–vasopressin cell antibodies; DDAVP, 1-deamino-8-arginine–vasopressin.

aStart DDAVP therapy.
bFirst interruption of DDAVP therapy.
cDDAVP therapy again.
dSuspension of DDAVP therapy.
recovery of urinary osmolality to the normal range, was induced by DDAVP therapy (3, 17).

Results

The behaviour of AVPcAbs in relation to the post-pituitary function in patients is depicted in Fig. 1. At 4th week of pregnancy, both patients showed presence of AVPcAbs at low titres (1:16 and 1:8 respectively) accompanied by mild polyuria and polydipsia and by urinary osmolality and plasma osmolality and AVP values suggestive of subclinical autoimmune CDI. With regard to case 1 (Table 1), the course of pregnancy was normal until the 20th week. At this time, the patient was urgently admitted to the Endocrinology Unit because of a dramatic increase in her urinary output to 8500 ml/day and her oral water intake (7–8 l/day). At the time of admission, her laboratory tests were as follows: urinary analysis was negative for glucose; the specific gravity was 1002; urinary and plasma osmolality was 110 and 294 mOsm/kg, respectively; serum sodium level was 150 mEq/l and basal plasma AVP level was 0.3 pg/ml despite high plasma osmolality. An increase in AVPcAbs to high titres (1:256), accompanied by dramatic worsening of symptoms and signs, suggested a presumptive veering to complete autoimmune CDI. Liver function was normal. Hypothalamic–pituitary MRI was normal showing neither pituitary gland swelling nor pituitary stalk thickening: moreover, the high-intensity signal in the posterior lobe in T1 sequence was still present. A complete study of basal anterior pituitary function did not show any significant alterations nor presence of APAs. Therapy with 20 µg twice/daily of intranasal DDAVP was commenced. Following this therapy promptly, urine output significantly decreased and osmolality of serum and urine recovered to the normal range; at the 28th week of pregnancy, during DDAVP therapy, the AVPcAb titre decreased to 1:128. Thus, intranasal DDAVP therapy was reduced at the dose of 10 µg twice/daily. At the 36th week, she had spontaneous delivery (2.5 kg female infant) and subsequently normal and complete lactation. At the 4th week of the post partum period, a DDAVP therapy withdrawal was attempted but severe polyuria and polydipsia immediately reappeared; AVPcAb titre was 1:64. Therefore, DDAVP therapy was restarted and administered until the 6th month of the post partum period, when it was interrupted again, because she became AVPcAb negative. Off therapy, her oral intake and urinary output remained normal, her sodium level was 134 mEq/l and basal urine and plasma osmolality were 390 and 383 mOsm/kg respectively; re-evaluation of water deprivation test showed an urinary osmolality of 750 mOsm/kg, a plasma osmolality of 374 mOsm/kg and AVP levels of 3.7 pg/ml. During the remaining follow-up, at 12th and 24th months of the post partum period, post-pituitary function remained persistently normal and AVPcAbs, as well as EMA and AtTG, persistently negative.

With regard to case 2 (Table 1), between the 20th and the 28th week of pregnancy, AVPcAbs were present at a titre of 1:16 accompanied by mild polyuria and mild polydipsia. At the 36th week, she spontaneously delivered a 2800 g male infant and subsequently she showed a normal and complete lactation. At the 2nd week after delivery the patient was admitted to our Endocrinology Unit because of increasingly severe polyuria and polydipsia.
A 24-h urine volume of 9870 ml and water intake of 9 l/day, urinary specific gravity of 1002, basal urinary osmolality of 120 mOsm/kg, basal plasma osmolality of 297 mOsm/kg and AVP values of 0.4 pg/ml were found. The titre of AVPcAbs increased to 1:256. Hypothalamic–pituitary MRI was normal with a high-intensity signal in the posterior lobe in T1. A complete study of basal anterior pituitary function did not show any significant alterations nor presence of APAs. A presumptive diagnosis of complete CDI was made and she started therapy with DDAVP 20 µg twice/daily intranasal. After this therapy, urinary output significantly decreased and serum and urine osmolality recovered to the normal range. At the 6th week post partum period, DDAVP therapy was stopped but severe polyuria and polydipsia immediately reappeared; AVPcAb titre was 1:128. Intranasal DDAVP therapy at a lower dose (10 µg twice/day) was restarted and continued for 6 months and then it was stopped, because of disappearance of AVPcAbs. Her oral intake and urinary output remained normal, her sodium level was 134 mEq/l, basal urinary and plasma osmolality were 390 and 383 mOsm/kg respectively; after water deprivation, a urinary osmolality of 750 mOsm/kg, a plasma osmolality of 374 mOsm/l and AVP levels of 3.7 pg/ml were observed.

During the following 2 years, post-pituitary function remained persistently normal and AVPcAbs persistently negative; instead TgAb and TPOAb persisted positive but without worsening of thyroid function.

Finally, none of all healthy women, of women with HT and of those with HT and celiac disease, showed presence of AVPcAbs nor alterations of post-pituitary function.

**Discussion**

This study describes two female patients, positive for AVPcAbs at low titres but without clinically overt CDI, showing an increase in AVPcAbs to high titres accompanied by a worsening to severe clinical CDI during the second trimester of pregnancy in the first case and at the 2nd week of post-delivery period in the other. After an improvement following early therapy with DDAVP, a relapse occurred after the first attempt of therapy withdrawal, and therefore this therapy was restarted. However, during the subsequent follow-up, at the 6th and the 7th month after delivery respectively, when the therapy was definitively stopped because of disappearance of AVPcAbs in both patients, a normalisation of post-pituitary function was observed, which persisted until the end of the follow-up. It has been well demonstrated that some patients with pre-existing subclinical CDI, idiopathic CDI or CDI secondary to transsphenoidal surgery, craniopharyngioma, pituitary prolactin-secreting microadenomas, may develop a clinical phase of CDI during pregnancy (18, 19, 20, 21, 22). This worsening may occur for the physiological osmo-regulatory adaptations of pregnancy, including decreased thresholds for both thirst and AVP secretion and increased metabolic clearance rate of AVP. This may be due to excessive vasopressinase activity, a placental enzyme that degrades AVP, because hyper-production of this enzyme in the large volume placentas of women with multiple pregnancies, or to its decreased hepatic degradation, was related to liver damage in patients with pre-eclampsia and HELLP syndrome (8, 23, 24). Moreover, Wallia et al. (25) have recently reported the onset of acute post partum CDI 12 h after Caesarean section, caused by the release of placental vasopressinase into the blood, due to placenta abruption. Usually, all patients with increased vasopressinase activity show transient CDI that regresses spontaneously a few days or weeks after delivery.

In our study, both CDI cases showed a recovery of post-pituitary function occurring not a few days or weeks, but some months, after delivery, most probably favoured by an early therapy with DDAVP. Moreover, both patients had normal pituitary function, normal characteristics of pituitary on MRI and absence of APAs. For these reasons, an increase in vasopressinase activity and an increased volume of pituitary gland-impairing hypothalamic–post-pituitary function, as occurring in LYH, may be excluded as a cause of gestational or post partum CDI in our patients. Another message emerging from our study is that AVPcAbs were still present, with a titre higher than that observed at the start of the study, at the first interruption of the desmopressin therapy initiated after clinical CDI, in both patients. Subsequently, when desmopressin therapy was definitively interrupted, AVPcAb disappearance was accompanied by a recovery of post-pituitary function persisting during the subsequent longitudinal study. Instead, while in the first case, EMA and AtTG previously disappeared on gluten-free diet, and persisted negative in the second case, both anti-thyroid antibodies persisted positive, even if without worsening of thyroid function.

Therefore, our results indicate for the first time that the worsening in pregnancy and in the post partum period to a clinically overt CDI can be due to a direct autoimmune aggression by AVPcAbs to hypothalamic AVP-secreting cells. This assumption seems also supported by the absence of AVPcAbs in healthy women (in pregnancy or in post partum period) and in those with...
HT or with HT and celiac disease, suggesting that the presence of these antibodies in our two cases are not linked specifically to pregnancy or the post partum period nor to the presence of other autoimmune diseases, but they may be considered good predictive markers of subclinical/clinical CDI in these women, especially if present at high titre. Moreover, the relapse of post-pituitary dysfunction after the first interruption of DDAVP in both cases, when AVPcAbs were still present at high titre, suggests that this therapy should not be interrupted until the disappearance of these antibodies.

In our previous longitudinal studies, performed in patients with autoimmune polyendocrine syndromes (APSs), we showed that the natural history of autoimmune CDI seems to evolve through four functional stages in which AVPcAbs are always present (26). This staging of autoimmune CDI is very important for planning a therapeutic strategy, taking into account that the disease could still be reversible, not only in the subclinical stage, but also in the early phase of the clinical stage, when hypothalamic AVP-secreting cells are not completely destroyed. Following the results of these previous studies, we suggest that, in both our cases, autoimmune CDI progressed from a subclinical stage to an early clinical stage, characterised by the presence of AVPcAbs with a titre higher than that found in the previous stages, persistence of hyper-intense signals and normal pituitary stalk on MRI, and AVP plasma levels low but still detectable. Subsequently, the observed recovery of the autoimmune process, with disappearance of AVPcAbs and restoration of posterior pituitary function, was most probably favoured by the early DDAVP therapy, acting as an iso-hormonal therapy, allowing an AVP cell function rest with the consequent recovery.

It is well known that pregnancy is associated with various hormonal and immunological changes that facilitate the survival of a semi-allogenic foetus. These physiological changes influence the activity of various maternal autoimmune diseases during pregnancy and the post partum period (27, 28); therefore, they may have favoured the activation of hypothalamic autoimmunity in our patients, with development of clinically overt CDI. With regard to the persistence of clinical CDI for some months after delivery in both our cases, a particular role could have been played by PRL. In fact, it has been suggested that lactation and the related increased PRL levels may worsen some autoimmune diseases after delivery (28, 29), given the well-known pivotal role played by PRL in the immune system (29). This may explain the prolonged persistence of CDI after delivery in our patients, considering that both cases experienced a normal and complete lactation accompanied by the physiological increase in PRL levels. In conclusion, our results seem to present the following indications:

i) women of fertile age, if positive for AVPcAbs even at low or middle titres, are prone to developing a severe autoimmune CDI during pregnancy or post partum, especially when affected by other autoimmune diseases.

ii) Presence of these antibodies, associated with celiac disease and with HT in our patients, suggests searching for AVPcAbs in patients with APS or with a single autoimmune disease, as an advisable tool, when they are planning their pregnancy, because these antibodies could be considered good predictive markers of future gestational or post partum autoimmune CDI.

iii) Monitoring of AVPcAb titres and post-pituitary function during pregnancy and in the post partum period in these patients may allow for an early diagnosis and an early replacement therapy, which could induce the disappearance of these antibodies with consequent complete remission of CDI.

However, further longitudinal studies on a larger population of women with autoimmune diseases without clinical CDI are needed to confirm our assumptions.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the case report.

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