



Antagonists of TNF α for recurrent miscarriages: 2 Illustrative cases

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ARTICLE INFO

Article history:

Received 20 February 2019

Accepted 26 February 2019

Keywords:

Chronic intervillositis

Miscarriages

Outcome

Adalimumab

ABSTRACT

Approximately 1 to 3% of women have recurrent early miscarriages, defined as ≥ 3 pregnancy losses before 14 weeks of gestation. The immune deregulation and tolerance rupture could be the origin of these miscarriages in at least 30% of these women. Chronic intervillositis of unknown etiology (CIUE) is a rare placental lesion characterized by intrauterine deaths, growth restriction and high recurrence rate. In cases with recurrent obstetrical adverse events and intrauterine deaths, we previously reported the benefit of hydroxychloroquine combination to prednisone. Even few data raised the potential value of TNF antagonists in early recurrent miscarriages, these cases show its potential value in the setting of recurrent refractory chronic intervillositis and unexplained miscarriages.

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Sir,

Approximately 1–3% of women have recurrent early miscarriages, defined as ≥ 3 pregnancy losses before 14 weeks of gestation. The immune deregulation and tolerance rupture could be the origin of these miscarriages in at least 30% of these women [1]. Chronic intervillositis of unknown etiology (CIUE) is a rare placental lesion characterized by intrauterine deaths, growth restriction and high recurrence rate [2,3]. In cases with recurrent obstetrical adverse events and intrauterine deaths, we previously reported the benefit of hydroxychloroquine combination to prednisone [4].

A 37-years old woman have been referred to our university unit for recurrent early miscarriages. Her obstetrical history consisted in a first pregnancy without any adverse obstetrical events, and then 12 early recurrent miscarriages. At least 6 of these miscarriages have been treated, using aspirin and progesterone, with hydroxychloroquine, or with low weighted heparin, prednisone, and preconception intralipids infusions in the last one. Several placental examinations showed chronic intervillositis extensive lesions, with normal karyotype of the fetal loss. For the subsequent pregnancy, adalimumab was initiated 2 months in preconception period, combined to aspirin (100 mg/day) and

prednisone (10 mg/day). The pregnancy outcome was successful and adalimumab was discontinued at 9 weeks of gestation. She delivered a live born baby weighting 2960 g without complications or malformation at 38 weeks of gestation.

A 40-years old woman have been referred to our university unit for early recurrent miscarriages. Her obstetrical history consisted in several early miscarriages in the context of diminished ovarian reserve (AMH levels less than 0.4 pg/ml), despite various treatments during the pregnancies (steroids, progesterone, vitamins combination, aspirin and low molecular weighted heparin). Because of premature ovarian insufficiency, she was directed to oocytes donation, but still experienced recurrent miscarriages despite embryo transfers following egg donation. Endometrial receptivity have been evaluated and showed normal uNK levels, and normal IL18/Tweak and IL15/Fn ratios. We thus considered a possible immune origin combined to premature ovarian insufficiency, because of recurrent miscarriages despite oocytes donation. Adalimumab (40 mg every 2 weeks subcutaneously) was initiated 2 months before the oocytes donation, and continued until the 9 weeks of gestation. Despite this treatment she experienced early miscarriage, and the karyotype of the fetal loss showed the presence of non-viable trisomy 8. The same treatment was used for the next oocytes donation, and as previously discontinued at 9 weeks of gestation expect the low dose aspirin and she delivered a baby at 39 weeks of gestation, without any obstetrical or fetal complications.

In early ≥ 3 unexplained miscarriages, 17 patients treated by adalimumab or etanercept combined with low-dose aspirin, heparin and intravenous immunoglobulins have a live births of

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71%, versus 54% with aspirin, heparin + intravenous immunoglobulins [5]. The safety during pregnancy seem to be good, with good rate of live birth without increased risk of congenital abnormalities among 472 pregnancies under TNF- α antagonists. The rationale for TNF α antagonists use could be raised in recurrent miscarriages because of the increase of TNF α levels in recurrent miscarriages. The management of chronic intervillitis is controversial and no clinical guidelines are actually available. The values of these drugs in recurrent miscarriages seem to be less effective, but in refractory cases there is no data about the use of additional drugs. Even few data raised the potential value of TNF antagonists in early recurrent miscarriages, these cases show its potential value in the setting of recurrent miscarriages with refractory chronic intervillitis.

Disclosures

None to declare for this case.

Conflicts of interest and funding sources

None.

Acknowledgment

None.

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