Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Obstetrics Gynecology

Adult-Onset Still's Disease in Pregnancy Treated by Anti-TNF Drugs: Case Report and Literature Review

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DOI: 10.36347/sjmcr.2022.v10i10.021 | **Received:** 26.08.2022 | **Accepted:** 01.10.2022 | **Published:** 30.10.2022

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Abstract **Case Report**

Adult onset Still's illness is a non-hereditary auto inflammatory disease that affects a small number of people. From fever with arthralgia and maculopapular eruption to life-threatening symptoms such as secondary lymphohistiocytosis are all possible clinical signs. The causes of AOSD are unknown; however it appears to be linked to NK cell malfunction and the release of pro-inflammatory cytokines such as IL-1ß, IL-6, and IL-18 [1]. AOSD has been reported to occur during pregnancy, particularly in the first and second trimesters, and there is still discussion about whether it can affect the pregnancy result. We report a case of 29 years old women with Still's disease on anti TNF alpha and the follow-up during her pregnancy.

Keywords: Adult-onset still's disease /AOSD/ Pregnancy/Fetal outcome/Maternal outcome/ anti-TNF.

INTRODUCTION

Adult-onset still's disease (AOSD), first described by Bywaters in 1887, and is a systemic inflammatory disorder of unknown etiology. AOSD is uncommon with an estimated prevalence of less than one case per 100, 000 people which predominantly affects young adults [2]. The effect of pregnancy on disease activity and maternal and fetal outcome in patients with adult onset still's disease (AOSD) has not been well addressed. We describe a case of 29 years old women with (AOSD) who had exacerbation of disease in pregnancy.

THE OBJECTIVE

Report a case of Adult-onset Still's disease in pregnancy.

CASE REPORT

A 29-year-old patient, 2nd Gestity 2nd Parity 1 living child followed in internal medicine since 2015 for Still's disease in front of:

- Prolonged fever + Alteration of the general state.
- Symmetric polyarthritis.
- Polyadenopathy (lymph node biopsy: non-specific reactive adenitis).
- Hyperleukocytosis with neutrophilic polynucleosis.
- Ferritinemia at 6924, glycosylated fraction < 7%.
- Negative immunological assessment (AAN, Anti-DNA, FR, ACPA).
- Negative serology (hepatitis B C, toxoplasmosis, CMV, VEB, rubella, syphilis, HIV).

Therapeutically:

- **Corticosteroid Therapy:** solumedrol 240 mg/day for 3 days, then relay PO 1 mg/kg/day, on admission 7.5 mg/day.
- **Nsaids:** indomethacin.
- **Methotrexate:** 25 mg/week from 2015 => 06/2016, no improvement.
- **Tocilizumab (Actemra):** 4 courses (20/05/2016 => 26/09/2016), Stopped following an allergic reaction requiring transfer to intensive care.
- **Cyclophosphamide:** 6g (10/2016 => 23/02/2017), without clinical and biological improvement.
- **Azathioprine:** 150mg/d, (2017=>2018), Without clinical-biological improvement.
- Etanercept (enbrel) since 11/2018
  - 25 mg x2/week for 2 years, then 50 mg/10 days.
  - Good clinical and biological evolution.

Followed in our training for pregnancy follow-up estimated at 10SA:

- During the monitoring, the patient presented a relapse made by inflammatory polyarthralgia

(hands, wrists, knees, shoulders) in a context of fever amounting to 38.3° C.

- Assessment carried out during his hospitalization.

CBC	Hb :10,1 WBC :8080 Pq:267000	MCV : 76,5 NEU :7050	MCH :24,9 LYM :610	
Inflammatory assessment	CRP: 66,1	Sed Rate: 69	ASO: negative	SF :250
Hepatic check	ALT:44	AST: 53	Alk Phos: 78	GGT: 33
PCR covid	Negative			
Serology	Negatives			
Obstetric ultrasound	Ongoing pregnancy, 10 Week of Amenorrhea			

The decision of the staff meeting was to resume etanercept:

- **Final Treatment:** etanercept (enbrel 50 mg/10 days), corticosteroid therapy 0.5 mg/kg/d (20mg/d), APA (kardegic) 160 mg/d, folic acid (yofolvit 1cp/d) and martial treatment (tardyferon B9 1cp x2/d).

During obstetric monitoring, intrauterine growth restriction< 3% with IR at 0.65 and oligoramnios was observed, without any other associated disorder.

The decision of the obstetrical staff was the expectation with clinical and ultrasound monitoring with corticosteroid therapy consisting of 2 boluses of betamethasone 12mg/24h for lung maturation.

An extraction programmed at 37 SA. At 37 weeks the patient admitted to our department. The clinical examination objectified a uterine height of 26 cm outside labor.

Obstetric ultrasound showed an evolving monofetal pregnancy with oligoamnios and growth restriction<3% with an estimate of fetal weight at 2100 and RI at 0.63.

Labor was induced by Foley catheter and during the partogram monitoring the patient showed no labor abnormalities which resulted in delivery of a female newborn Apgar 10/10 with a birth weight of 2300g.

Neonatal Examination

No rush was showed

The breathing rate was 30/min, with a strong heart sound, a heart rate of 140 bpm, and no murmur evident. Neonatal blood routine: white blood cell count (WBC) = 30.5 G/L; neutrophil ratio (NE) = 58.9%; hemoglobin (HGB) = 20.1 g/L; platelet (PLT) = 225.0 G/L; and C-reactive protein (CRP) = 3.00 mg/L. The newborn was transferred to the pediatric Department of Pediatrics due to suspected infection.

DISCUSSION

Adult-onset Still's disease (AOSD) is a multigene auto inflammatory illness that was originally described in 1887 [1]. It is defined as a systemic inflammatory sickness with uncertain etiology. The disease's etiology and pathogenesis are still unknown. Serum interleukin (IL)-6, IL-8, IL-18, IL-1, tumor necrosis factor (TNF), interferon (IFN), soluble IL-2 receptor, and macrophage colony-stimulating factor (M-CSF) levels are all high, resulting in fever, rash, arthralgia, and elevated ferritin levels in the blood.

In 1980, the recurrence of AOSD during pregnancy was described for the first time. Le Lot *et al.*, reported five pregnancies in four AOSD patients, two of whom were diagnosed with the condition. They discovered that pregnancy had no negative impact on AOSD and that AOSD had no bearing on pregnancy outcomes [3].

Pregnancy-related AOSD is still uncommon. The age distribution of AOSD is bimodal, with peaks at 15 to 25 and 36 to 46 years of age. In a case series published locally, the age range was between 21 and 48 years (mean age, 35) [4]. Our patient's symptoms were similar to those described in a case series of patients who developed AOSD during pregnancy and had fever, arthralgia, and sore throat; 80% of those patients had a rash, which was not present in our patient, though the rash may be more difficult to detect in dark-skinned people [4].

The following are some of the clinical manifestations of AOSD:

1. **Onset:** Fever and rash are the most prevalent onset symptoms, and fever, rash, and arthralgia are subsequent symptoms. Without antipyretic medication, body temperature can drop to normal levels by the next morning.
2. **Transient Erythema:** Erythema that changes with body temperature can occur. It might be millet-like or scratchy, and it commonly appears on the face, trunk, and limbs. It can also appear as maculopapules.
3. **Arthritis:** Almost every patient has joint discomfort, and about 90% of patients have

arthritis. Joint stiffness and deformity may develop in the later stages of the disease if the cartilage and bone of the concerned joints have erosive damage. In addition, roughly 80% of patients complain of muscle soreness.

4. **Pharyngeal Discomfort:** most patients experience pharyngeal pain in the early stages of the sickness, which might last for the duration of the illness but may subside after a fever. Swab culture of the pharynx is negative, and antibiotic therapy is ineffectual.
5. **Furthermore:** The initial treatment can help with pharyngeal pain.

In the active phase of the disease, routine blood tests reveal that:

1. The neutrophil count is high in more than 90% of patients, possibly due to orthocytochrome anemia, and almost all patients have a rapid increase in ESR.
2. Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) levels in the liver increase somewhat in some patients, especially in cases of fever.
3. Bacterial culture of the blood is negative.
4. Rheumatoid factor (RF) and antinuclear antibody (ANA) are negative, and only a few people with normal or high complement levels get a slightly positive result.
5. The level of serum ferritin (SF) is also significantly elevated, which is helpful for differential diagnosis. We found that the level of SF was positively correlated with the activity of the disease.

Currently, there are two types of treatments: pharmacological therapy and surgical treatment:

1. **Medication:** There is no complete treatment for AOSD. Nonsteroidal anti-inflammatory medicines, glucocorticoids, anti-rheumatics such methotrexate, gold preparations, azathioprim, and cyclosporine A are some of the most widely used medications. The use of several Chinese herbal treatments, as well as intravenous gamma globulin injections, is still contentious. AOSD can also be treated with plasma exchange. In recent years, antagonists of IL-1, IL-6, and TNF- have been found to be employed in the therapy of these patients. According to reports, the patients' clinical problems can be treated quickly [5].
2. **Surgical Treatment:** Patients with arthritis as the primary symptom should have X rays of the affected joints done on a regular basis. Patients with joint erosion, destruction, or deformity should seek arthroplasty if the damage is severe, but this can typically be avoided with early intervention with immune modifying medicines [5].

Relationship between AOSD and pregnancy outcome

According to limited research, the beginning of AOSD in pregnancy is most likely in the third trimester, next in the first trimester and finally in the postpartum period. Patients with AOSD in relative remission had a lower risk of pregnancy problems and unfavorable pregnancy outcomes than those who do not have excellent illness control.

Obstetrical disorders appeared to be common, as 50% of pregnancies resulted in preterm, and 15% of pregnancies were complicated by intrauterine growth restriction, even though some of them could be linked to steroid therapy side effects. Although the pathophysiological link is elusive, new research has found elevated amounts of IL18 during pregnancy, which could function as a trigger for a previously latent disease and cause pregnancy-induced AOSD [6].

according to A Cohort Study From China the remission in medicine-free wasat conception, an exacerbation occurred in the fourth and fifth months of gestation and during the postpartum period, the study reported that estrogens could activate macrophages to produce tumor necrosis factor (TNF-a), IL-6, and IL-1It could also boost the expression of IL-1 mRNA through monocytes as well as increase several aspects of endothelial-cell biological functions, such as adhesion to matrix proteins, migration and cell differentiation, and promoting inflammation [7].

The treatment of AOSD during pregnancy is challenging. Glucocorticoids are a mainstay of treatment for patients with AOSD; despite the potential increased risk of gestational diabetes, arterial hypertension, intrauterine growth restriction, or pre-term premature rupture of membranes. Intravenous immunoglobulin (IVIG) has been reported for the management of AOSD during pregnancy, especially for the life-threatening complications. Recently, Smith reported Anakinra was successfully used in five patients during pregnancy with no serious complications or adverse pregnancy outcomes [8]. Which provided alternative therapies for pregnancy related AOSD?

In recent years, it has been reported that antagonists of IL-1, IL-6 and TNF-_ have been used in the treatment of these patients. Reports suggest that the clinical symptoms of the patients can be relieved rapidly [5].

The register of the English Society of Rheumatology which includes 11,473 patients treated with anti-TNF agent reported largest series of pregnancies on anti-TNF agents with 32 patients with inflammatory arthritis [9]. However, only 23 of them were still exposed to an anti-TNF agent (17 etanercept, 3 infliximab, and 3 adalimumab) at the time conception and 11 were taking MTX or leflunomide in association. Only two patients continued their anti-TNF treatment

during the first trimester (until the20 week for a patient and throughout the pregnancy for the second). In this series, live newborns displayed 61% of cases (14 out of 23). Six patients had a miscarriage (4 were taking etanercept, one adalimumab, one infliximab and three of them were taking of MTX concomitantly) and three interruptions pregnancy volunteers had been chosen (three were taking etanercept, two were taking MTX in combination) [9]. He no increase in maternal quality or foetus, nor of obvious fetal malformation, especially in the patient who used etanercept and leflunomide in combination at the time of conception [9].

However The High Authority of French health has established recommendations for the proper use of anti-TNFs.

A woman on anti-TNF wishing to conceive, after consulting the specialist prescribing the anti-TNF, contraception can be stopped while continuing the anti-TNF until conception. As soon as the pregnancy is confirmed, it is recommended to stop the anti-TNF therapy.

On a case-by-case basis, and in consultation with the patient and the gynecologist-obstetrician, continuation of anti-TNF treatment can be discussed until the completed second trimester of pregnancy, whether the activity of the disease is such that it poses a risk severe for the mother or for the evolution of the pregnancy.

In the 3rd trimester of pregnancy, it is not recommended to continue the use of anti-TNF. In the event of a pregnancy occurring under anti-TNF treatment, it is there is no reason to recommend termination of pregnancy.

The frequency of systematic monitoring of pregnancy does not take place to be modified in a patient treated with anti-TNF.

Due to the induced immunosuppression, special attention regarding the risk of maternal-fetal infection is recommended, in particular because of the possible absence of fever.

If anti-TNF therapy has been instituted or continued for pregnancy, all those involved with the newborn should be warned in order to adapt his care, in particular in relation to the risk of infection and in anticipation of the calendar vaccination of the child.

CONCLUSION

In conclusion, the diagnosis of a pregnancy complicated by AOSD is still not clear, and it often depends on an exclusionary diagnosis. There is a high rate of clinical misdiagnosis because AOSD has a wide range of clinical manifestations. Pregnancy is one of the variables that predispose someone to developing AOSD, according to nationally and internationally literature. Its clinical symptoms, which affect different systems, include arthritis, arthromyalgia, fever, pharyngitis, and others. For this condition, there is no relevant field's technique for laboratory testing or imaging. AOSD is a set of unusual clinical disorders, and the mechanism linking pregnancy to AOSD is currently remaining unclear.

However there is still no evidence that anti-TNF agents can be used without risk during pregnancy, as less than 30 mothers continued their treatment during the second and/or third trimester. This is why practitioners should always declare to their patients to stop anti-TNF agents before starting pregnancy. Conversely, there is still no evidence that exposure to anti-TNF treatments during conception only significantly increases the risk of malformations fetal. In order to better assess the risk associated with exposure to anti-TNF agents at the time of conception or pregnancy, any new pregnancy while taking these medications anti-TNF should be declared and/or reported.

A trace long-term treatment of these children could make it possible to exclude minor forms of VATER syndrome, which can pass unnoticed on ultrasound [11] or at birth, and which associate costovertebral or axial skeletal malformations. With this in mind, it should be emphasized that a follow-up long-term of these children has only been described in a few cases and was rather short.

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