Pregnancy-Associated Onset of Adult-Onset Still's Disease

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Abstract

Objective This study aims to elucidate the clinical manifestations, diagnostic challenges, and management strategies of adult-onset Still's disease (AOSD) during pregnancy, leveraging a case series overview and a detailed case report from our center.

Study Design A comprehensive review of 21 published case reports on AOSD diagnosed during pregnancy was conducted, alongside a detailed case report of a patient diagnosed and managed at our center. This study emphasizes the importance of recognizing AOSD in pregnant patients, outlines the therapeutic challenges encountered, and discusses the potential complications arising from the disease and its treatment.

Results The onset of AOSD during pregnancy predominantly occurs in the first or second trimester, with a polycyclic disease course observed in most cases. Management primarily involves corticosteroids and immunosuppressive medications, balancing the disease control with potential pregnancy complications. The case report highlights the complex interplay between AOSD, hemophagocytic lymphohistiocytosis, and pregnancy, illustrating a multidisciplinary approach to management that ensured favorable maternal and fetal outcomes despite the significant challenges.

Conclusion AOSD presents unique diagnostic and therapeutic challenges during pregnancy, requiring careful consideration of maternal and fetal health. Early diagnosis, a multidisciplinary approach to care, and judicious use of immunosuppressive therapy are critical for managing AOSD flares and associated complications. Further research is necessary to optimize care for this rare condition in the context of pregnancy.

Keywords
- adult-onset Still's disease
- management of AOSD during pregnancy
- rheumatology
- disorders
- Anakinra and pregnancy
- hemophagocytic lymphohistiocytosis
- pregnancy complications
- macrophage activation syndrome

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AOSD diagnosis in pregnancy is complex. Early diagnosis of AOSD leads to better outcomes, and a multidisciplinary approach is key in AOSD care. Adult-onset Still's disease (AOSD), characterized by fevers, arthralgia or arthritis, and evanescent rash[1–5] stands as an enigmatic autoinflammatory disorder of uncertain etiology, predominantly afflicting individuals of childbearing age.[6,7] Despite its rarity, with an estimated prevalence ranging from 1 to 34 cases per million people,[8] its occurrence during pregnancy introduces unique clinical challenges.

The diagnosis of AOSD lacks a definitive test, making it particularly challenging to identify. The widely recognized Yamaguchi criteria,[4] established for its diagnostic sensitivity (96.2%) and specificity (92.1%), advocate for a diagnostic approach that necessitates meeting at least five of the outlined criteria, including two major ones, contingent upon the exclusion of similar presenting conditions such as infections, malignancies, and other rheumatic diseases (►**Table 1**). Our objective is to provide clinicians with a detailed overview of AOSD diagnosed during pregnancy, offering insights into effective management strategies that carefully balance maternal and fetal health considerations.

Methods

We have conducted a comprehensive analysis, pooling data from 21 published case reports of AOSD identified during pregnancy, alongside an in-depth case report of a patient managed at our center. This patient, diagnosed with AOSD during gestation, consented for her case to contribute to our research, thereby enriching our study with valuable, firsthand clinical insights. To collect the 21 published case reports on AOSD diagnosed during pregnancy, we systematically searched multiple electronic databases, including PubMed, MEDLINE, Embase, and Google Scholar. Keywords used in our search strategy encompassed "Adult-Onset Still's Disease," "AOSD," "pregnancy," "gestation," "Hemophagocytic Lymphohistiocytosis," "(HLH)," "Anakinra and pregnancy," and "case reports." We refined our search by applying filters for English language and publication dates up to the current year to ensure relevancy and comprehensiveness. Each identified case report was then reviewed for relevance based on predefined inclusion criteria, focusing on cases diagnosing AOSD during pregnancy. A critical aspect of our selection process was the exclusion of patients who had received a diagnosis of AOSD prior to pregnancy. This decision was driven by our objective to isolate and examine the unique challenges and management strategies pertinent to the onset of AOSD during pregnancy. Data extraction from these reports included patient demographics, clinical presentations, management approaches, and pregnancy outcomes, forming the basis of our analysis.

Table 1 Diagnostic criteria for AOSD by Yamaguchi et al

Major criteria	1. Fever ($\geq$ 39°C or higher $\geq$ 1 wk) 2. Arthralgias lasting $\geq$ 2 wk 3. Typical rash[a] 4. Leukocytosis ($\geq$ 10,000/mm^3 or more) including 80% more of granulocytes
Minor criteria	1. Sore throat 2. Lymphadenopathy and/or splenomegaly 3. Liver dysfunction[b] 4. Absence of RF and ANA

Abbreviations: ANA, antinuclear antibody; AOSD, adult-onset Still's disease; RF, rheumatoid factor.

Notes: Diagnosis of AOSD necessitates the fulfillment of five or more criteria, of which at least two must be major. Additionally, it is imperative to exclude other clinical conditions that may present with similar symptoms to AOSD.

[a]Rash identification: The characteristic rash of AOSD, a macular or maculopapular nonpruritic salmon-pink eruption, typically accompanies fever.

[b]Liver dysfunction assessment: Defining liver dysfunction involves elevated transaminase and/or lactate dehydrogenase levels not attributable to drug allergies, toxicity, or other liver conditions. Prior to applying this criterion, it is advisable to assess whether liver function normalizes after stopping any hepatotoxic medications, thereby ruling out drug-induced effects.

An Analysis of Clinical Manifestations, Treatment Efficacies, and Obstetric Challenges—A Case Series Overview

We investigated the relationship between AOSD and pregnancy, analyzing data from 22 cases where AOSD was identified during gestation, inclusive of the case presented herein (►**Tables 2**–**4**). The ages of the patients ranged from 19 to 38 years, with a median age of 28 years. Our review indicates that AOSD onset during pregnancy predominantly occurs in the first or second trimester. Specifically, the initial flare was observed in the second trimester in 59.09% of cases, the first trimester in 31.82%, with the onset remaining unspecified in 9.09%.

The clinical spectrum of AOSD in these pregnant patients primarily encompassed fever, observed in almost all cases, followed by arthritis or arthralgia, rash, and polyarthralgia or polyarthritis, with leukocytosis and splenomegaly also frequently reported.

The course of AOSD in these pregnant patients demonstrated a predominance of the polycyclic pattern, with 63.16% (12 out of 19 cases with specified disease course) experiencing recurrent flares. In contrast, a monocyclic disease course was noted in 36.84% (7 out of 19 cases) of patients.

Corticosteroids emerged as the principal therapeutic intervention, employed in 81.82% of instances, with prednisone being the preferred agent at a dosage of 0.5 to 1 mg/kg body weight. Intravenous immunoglobulin (IVIG) was administered in 13.64% of the cases.

Additional treatments, including nonsteroidal anti-inflammatory drugs, leukocytapheresis, tacrolimus (TAC), colchicine, azathioprine, gold, hydroxychloroquine, plasma exchange, and cyclosporine, were reported in 4.55% of the cases.

Adverse obstetric outcomes, defined as any maternal, fetal, or neonatal complications that arose during pregnancy, delivery, or throughout the postpartum period, were

Table 2 Clinical characteristics, treatment modalities, and obstetric outcomes in pregnant patients with adult-onset Still's disease onset in pregnancy: a case series overview

Case	Source reference	Age at Dx	Parity	Disease onset	Clinical presentations	Treatment	MOD	GA at delivery (wk)	Adverse obstetrical outcomes	Disease course	Postpartum
A01	Kaplinsky et al (1980)[42]	34	G5P4	Unk	F, PA, R, SM, ↑ WBC	Gold	Unk	Unk	None	Polycyclic	Worsening of disease
A02	Green et al (1982)[43]	23	Unk	Second tri	F, A, R, HM, SM	PDN	Unk	28	PTD, neonatal death due to prematurity	Polycyclic	Worsening of disease
A03	Yebra Bango et al (1985)[44]	19	Unk	First tri	A, anorexia, HM, R, SM, ST	PDN	VD	Unk	None	Monocyclic	No flare-ups
A04	Le Loët et al (1993)[45]	27	Unk	Second tri	A, F, LAD, pharyngitis, R	PDN	Unk	Unk	Transient Olig	Polycyclic	Unk
A05	Le Loët et al (1993)[45]	30	Unk	First tri	Unk	PDN	Unk	Unk	Unk	Unk	Unk
A06	Le Loët et al (1993)[45]	24	Unk	Second tri	A, F, LAD, pharyngitis, myalgias, R	PDN	VD	Unk	None	Polycyclic	Unk
A07	Falkenbach et al (1994)[46]	25	G1P0	First tri	A, F, headache, myalgias, LAD, SM, HM, ST, ↑ WBC	IVIG, PDN	N/A	N/A	ETOP	Polycyclic	Unk
A08	Liozon et al (1999)[47]	28	G1P0	First tri	F, LAD, PA, R, ST, ↑ WBC, ↑ Ferritin, ↑ AST/ALT	Salicylates 3 g/24 h, IVIG, PDN	C/S	36	PEC, placenta abruption, PTD	Polycyclic	Flare at 5 mo
A09	Pan et al (2003)[48]	21	G2P1	Second tri	F, A, R, malaise, cough, headaches, myalgias, odynophagia, ↑ AST&ALT, ↑ Ferritin	PDN, HCQ	VD	34	IUGR (IOL)	Polycyclic	Persistence of symptoms
A10	Pan et al (2003)[48]	38	G3P1	Second tri	F, A, malaise, cough, ST, ↑ ferritin	PDN	VD	FT	None	Monocyclic	No flare-ups
A11	Fischer-Betz et al (2011)[25]	29	G2P1	First tri	F, PA, HM, pharyngitis, myalgias, SM, R, ↑WBC, ↑ Ferritin	PDN, anakinra	C/S	36	PTD	Polycyclic	Flare after few months
A12	Yamamoto et al (2012)[49]	28	G0P0	Second tri	F, ST, LAD, R, PA, synovitis, pleural effusion, ↑ ferritin, ↑ WBC, ↑ AST and ALT	PSL, plasma exchange, cyclosporine, dexamethasone	C/S	33	HLH, oral ulcers induced by CMV, IUGR	Monocyclic	No flare-ups
A13	Hammami et al (2013)[50]	32	G1P0	Second tri	F, PA, R, SM, weight loss, ↑ ferritin	PDN	VD	34	PTD	Monocyclic	No flare-ups
A14	Gerfaud-Valentin et al (2014)[51]	33	Unk	First tri	F, erythema, LAD, PA, ↑ WBC	PDN	Unk	34	PPROM	Polycyclic	Flare at 1 mo
A15	Gerfaud-Valentin et al (2014)[51]	27	Unk	Second tri	F, PA, erythema, SM	PDN + IVIG + NSAIDs	Unk	32	PTD, oligo	Polycyclic	Flare at 1 and 3 mo

(*Continued*)

Table 2 (*Continued*)

Case	Source reference	Age at Dx	Parity	Disease onset	Clinical presentations	Treatment	MOD	GA at delivery (wk)	Adverse obstetrical outcomes	Disease course	Postpartum
A16	Gerfaud-Valentin et al (2014)[51]	36	Unk	Second tri	F, PA, erythema, pharyngitis, LAD, SM	PDN	Unk	FT	None	Monocyclic	Unk
A17	Moussa and Hassan (2014)[52]	25	G1P0	Second tri	F, A, malaise, HM, SM, ↑ WBC, ↑ ferritin	PDN	Unk	Unk	Unk	Unk	Unk
A18	Odai et al (2015)[53]	32	Unk	Second tri	F, R, LAD, PA, ST, ↑ WBC, ↑ ferritin	PSL, LCAP twice weekly × 12 wk	C/S	34	PPROM	Monocyclic	No flare-ups
A19	Lin et al (2016)[16]	Unk	Unk	Third tri	F, A, HM, SM, R, LAD, TTP	Unk	Unk	Unk	PTD, neonatal HLH	Unk	Unk
A20	Nakamura et al (2016)[28]	22	G1P0	Second tri	F, R, PA, ↑WBC, ↑ferritin	PSL, tacrolimus	Unk	38	None	Monocyclic	No flare-ups
A21	Plaçais et al (2018)[54]	38	Unk	First tri	F, myalgias, PA, HM, ST, ↑ ferritin, ↑ AST and ALT	PDN, colchicine, IVIG	Unk	34	Acute agranulocytosis (related to colchicine) c/b severe sepsis	Polycyclic	Disease persisted despite delivery and sepsis control; addition of anakinra allowed rapid remission
A22	Present case	29	G3P2	Second tri	F, headaches, vomiting, ↑AST and ALT	Methylprednisolone, azathioprine, anakinra	C/S	32	HLH, acute agranulocytosis (related to anakinra) c/b severe sepsis, placental abruption, GDM	Polycyclic	No flare-ups

Abbreviations: A, arthralgia/arthritis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C/S, cesarean section; CMV, cytomegalovirus; CS, corticosteroids; Dx, diagnosis; ETOP, elective termination of pregnancy; F, fever; FT, full-term; GDM, gestational diabetes mellitus; HCQ, hydroxychloroquine; HLH, hemophagocytic lymphohistiocytosis; HM, hepatomegaly; IOL, induction of labor; IUFD, intrauterine fetal demise; IVIG, intravenous immunoglobulin; LAD, lymphadenopathy; LCAP, leukocytapheresis; MOD, mode of delivery; N/A, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; Olig, oligohydramnios; PA, polyarthralgia/polyarthritis; PDN, prednisone; PSL, prednisolone; PTB, preterm birth; PTD, preterm delivery; R, rash; SM, splenomegaly; ST, sore throat; tri, trimester; Unk, unknown; VD, vaginal delivery; WBC, white blood cell count.

Table 3 Obstetrical complications associated with adult-onset Still's disease onset in pregnancy (total cases: 22)

Complication	Frequency	Percentage of cases
Preterm delivery	11	50%
Intrauterine growth restriction	2	9.09%
Preterm premature rupture of membranes	2	9.09%
Neonatal hemophagocytic lymphohistiocytosis	1	4.55%
Medication-induced acute agranulocytosis	2	9.09%
Neonatal death	1	4.55%
No complications observed	6	27.27%

prevalent in 72.73% of the cases (16/22), with only 27.27% (6/22) reporting no adverse effects. Preterm birth emerged as the most frequent complication, affecting 50% of the cohort (11/22) (►**Table 3**). The mode of delivery was equally divided between vaginal delivery and cesarean section, each constituting 50% of the known outcomes.

Less frequently, intrauterine growth restriction and preterm premature rupture of membranes were each documented in 9.09% of pregnancies. Notably, medication-related acute agranulocytosis, specifically from the recombinant interleukin (IL)-1 receptor antagonist anakinra, and colchicine, led to sepsis in 9.09% of pregnancies. There were two cases of HLH identified within the cohort, accounting for approximately 9.09% of the total cases analyzed.

Moreover, the cohort included one instance of neonatal death due to prematurity, accounting for 4.55% of cases, alongside a case of neonatal HLH. Elective termination of pregnancy was a chosen course of action in one instance.

Postpartum analysis revealed considerable variation in outcomes, with 31.82% of patients experiencing no flare-up, while another 36.36% faced a flare-up or worsening condition, with the absence of documented postpartum outcomes in 31.82% of cases.

Case Report

A 29-year-old pregnant woman, gravida 3, para 2, presented at 16 weeks' gestation with severe headaches, malaise, sore throat, and persistent vomiting. Initial evaluation revealed significant transaminitis with aspartate aminotransferase (AST) at 353 U/L and alanine aminotransferase (ALT) at 255 U/L, alongside a urinary tract infection caused by *E. faecalis*, for which nitrofurantoin was prescribed. Her condition deteriorated, marked by high-grade fever (103°F), tachycardia (150 bpm), hypoxemia (SpO_2 92%), with chest X-ray confirming pulmonary edema. Examination and ultrasonography identified hepatosplenomegaly. Subsequent laboratory findings revealed further deterioration of liver function (AST > 2,000 U/L, ALT > 600 U/L), marked hyperferritinemia (ferritin > 100,000 ng/mL), and leukocytosis (white blood cell [WBC] count 15,000/mm^3), leading to an initial consideration of pyelonephritis, which rapidly progressed to a suspicion of urosepsis, prompting an urgent transfer to the intensive care unit (ICU) for escalated care.

Table 4 Summary of results: clinical manifestations, treatment efficacies, and obstetric outcomes in AOSD diagnosed during pregnancy—a case series analysis

Total cases analyzed	22
Age range of patients	19–38 y
Median age	28 y
AOSD onset during pregnancy	First trimester: 31.82%, second trimester: 59.09%, unspecified: 9.09%
Clinical presentation	Fever, arthritis or arthralgia, rash, polyarthralgia or polyarthritis, leukocytosis, splenomegaly
Disease course	Polycyclic: 63.16%, monocyclic: 36.84%
Principal treatment	Corticosteroids (prednisone 0.5–1 mg/kg body weight) in 81.82% of cases
Additional treatments	IVIG: 13.64%, others (NSAIDs, LCAP, tacrolimus, colchicine, azathioprine, gold, HCQ, plasma exchange, cyclosporine): 4.55%
Adverse obstetric outcomes	72.73% experienced adverse outcomes
Most frequent obstetric complication	Preterm birth: 50%
Mode of delivery	Vaginal delivery and cesarean section: 50% each
Less frequent complications	IUGR and PPROM: 9.09% each, medication-related acute agranulocytosis leading to sepsis: 9.09%, HLH: 9.09%, neonatal death: 4.55%
Postpartum outcomes	No flare-up: 31.82%, flare-up or worsening condition: 36.36%, unspecified outcomes: 31.82%

Abbreviations: AOSD, adult-onset Still's disease; HCQ, hydroxychloroquine; HLH, hemophagocytic lymphohistiocytosis; IUGR, intrauterine growth restriction; IVIG, intravenous immunoglobulin; LCAP, eukocytapheresis; NSAIDs, nonsteroidal anti-inflammatory drugs; PPROM, preterm premature rupture of membranes.

Despite exhaustive evaluations, no infectious etiology could be identified. Rheumatology, hematology, and infectious disease specialists were consulted. Screening for autoimmune markers, including antinuclear antibodies, rheumatoid factor, and antineutrophil cytoplasmic antibodies, returned negative. Bone marrow biopsy demonstrated trilineage hematopoiesis with hemophagocytosis, absence of increased blasts, and additional laboratory evaluation revealed an elevated soluble IL-2 receptor (sIL-2R) level (2,311 U/mL), elevated IL-18 (179,892 pg/mL), and hypertriglyceridemia (584 mg/dL), collectively suggesting a diagnosis of AOSD complicated by HLH. Echocardiographic findings revealed global cardiac hypokinesis with a reduced ejection fraction of 45%, which significantly improved to 65% following administration of high-dose corticosteroids (1 mg/kg).

Opting to continue the pregnancy despite the significant risks involved, the patient was managed on an outpatient basis with a regimen comprising methylprednisolone (24 mg orally daily), azathioprine (25 mg orally daily), anakinra (100 mg subcutaneously daily), ursodiol (300 mg orally twice daily), and atovaquone (1,500 mg orally daily) for *Pneumocystis jirovecii* pneumonia prophylaxis.

At 23 weeks of gestation, the patient experienced a disease flare despite treatment with anakinra, azathioprine, and methylprednisolone, evidenced by periodic fevers, nausea and vomiting, significant elevations in liver enzymes (ALT more than AST) and hypoalbuminemia. She was managed in the antepartum unit with antenatal corticosteroids for fetal lung maturation and an increased dosage of corticosteroid therapy (methylprednisolone 48 mg intravenously daily) to address the AOSD flare. Azathioprine, anakinra, and atovaquone were temporarily discontinued due to concerns of potential drug-induced liver injury, as advised by the rheumatology and hepatology teams. Cytomegalovirus (CMV) polymerase chain reaction testing yielded a low-positive result (62 copies) against a background of previously positive CMV immunoglobulin G antibodies, indicating nonprimary CMV shedding. This did not warrant treatment, given the lack of active infection or risk to the fetus.

By 24 weeks of gestation, with liver enzymes showing continual improvement, anakinra therapy was reinstated.

Further complications arose at 26 weeks of gestation when the patient developed neutropenic fever and sepsis, necessitating another admission to the ICU. This episode required comprehensive support, including the administration of intravenous norepinephrine bitartrate and a blood transfusion to address severe anemia. The neutropenia, believed to be induced by medication, led to a pause in Anakinra treatment and the commencement of broad-spectrum antibiotics and a 7-day regimen of Neupogen (filgrastim), resulting in a significant improvement in the WBC count and overall clinical condition.

In the critical juncture of this complex case, a meticulous plan was devised for the planned delivery at 32 weeks of gestation, a decision underscored by the interdisciplinary team's commitment to prioritizing both maternal and fetal health.

The journey toward delivery at 32 weeks was characterized by diligent monitoring and management of maternal and fetal health. Despite encountering challenges, such as gestational diabetes induced by steroids, the prenatal care team successfully navigated these complexities, ensuring the safety and well-being of both the mother and fetus.

At 30 weeks of gestation, fetal assessment via ultrasound demonstrated normal growth, amniotic fluid volume, and the absence of anatomical abnormalities.

The case culminated in a successful delivery at 32 weeks of gestation via cesarean section, necessitated by the acute onset of symptoms indicative of placental abruption, including active and profuse vaginal bleeding accompanied by diffuse uterine tenderness. This intervention was crucial for the well-being of both mother and child, resulting in favorable outcomes for both. The newborn had an Apgar score of 9 at 1 minute and 9 at 5 minutes, and the birth weight was 1,088 g. Following delivery, the newborn was transferred to the neonatal ICU for prematurity-related care. Postpartum, the patient was managed for presumed endometritis and transiently elevated liver enzymes, with a successful transition back to oral methylprednisolone (8 mg orally daily) and azathioprine (50 mg orally daily).

At a 2-month postpartum follow-up, the patient's condition had notably improved, with normalized liver enzyme levels and overall good health. She opted for the etonogestrel subdermal implant for contraception, closing a chapter on a challenging yet ultimately successful pregnancy and postpartum period.

Association with Hemophagocytic Lymphohistiocytosis

Our exploration of AOSD during pregnancy places significant emphasis on its link with HLH, an aggressive and potentially fatal syndrome marked by excessive immune activation. HLH, triggered by overactive immune responses and often associated with infections, malignancies, or inflammatory conditions such as AOSD, can be challenging to diagnose due to its symptomatic overlap with other conditions.[9–11]

The case study by Awoyemi et al illustrates the complexities of AOSD diagnosis and management in the postpartum period, where symptoms of AOSD and macrophage activation syndrome (MAS), a condition closely related to HLH, can mimic infectious conditions, demanding astute clinical judgment for accurate diagnosis and management. Their report on a young postpartum woman, who presented with symptoms typically associated with AOSD and was further complicated by MAS, emphasizes the diagnostic complexity due to symptom overlap with common postpartum conditions. The successful management of this case with corticosteroids and anakinra not only illustrates the effectiveness of these treatments in controlling MAS during pregnancy but also highlights the critical need for heightened clinical vigilance and the consideration of HLH in differential diagnoses when confronted with fever, liver dysfunction, and rash in pregnant patients.[9]

The case report by Peters and Prickett presents a distinctive scenario of AOSD manifesting as MAS during the third trimester of pregnancy, underlining the onset of AOSD during pregnancy and its symptomatic overlap with other peripartum disorders. The response of the patient to immunosuppressive therapy highlights the significance of considering AOSD in the differential diagnosis of pregnant patients with unexplained fever and multiorgan dysfunction, thereby contributing valuable insights into the potential severe manifestations of AOSD, including pulmonary involvement and systemic inflammation, during pregnancy.[12]

Yip et al's study highlights the diagnostic challenges of HLH during pregnancy, emphasizing its symptomatic overlap with common conditions in pregnancy such as fever and liver dysfunction and the importance of considering HLH in the differential diagnoses. In their study, they described a case of a 23-year-old pregnant woman diagnosed with HLH at 22 weeks of gestation. The patient was successfully managed with corticosteroids and anakinra, leading to the resolution of symptoms and normalization of ferritin levels, highlighting the effectiveness of these treatments in managing HLH during pregnancy.[10]

In addition, the study by Liu et al offers invaluable insights into the management of HLH in pregnant patients, underscoring the effectiveness of early diagnosis and the pivotal role of corticosteroids in treatment. Their comprehensive analysis of 13 cases emphasizes the effective use of corticosteroids as a primary treatment, highlighting a nuanced approach to balancing maternal and fetal health risks.[11]

The article by Wise and Zell provides a comprehensive case-based review of AOSD complicated by MAS during pregnancy. It highlights the rarity and severity of AOSD with MAS presenting in pregnant patients, discussing two cases that required critical immunosuppressive therapy. Both cases demonstrated the challenge of diagnosing and managing AOSD and MAS during pregnancy due to their severe presentations but ultimately had favorable maternal outcomes. This review underscores the importance of considering anti-IL-1 therapy for such life-threatening conditions and the need for a multidisciplinary approach in managing these complex clinical scenarios.[13]

Dunn et al reported a case of HLH in a 41-year-old pregnant woman with twins, who initially presented with symptoms consistent with HLH and a history of Still's disease. The patient showed a favorable response to high-dose corticosteroids.[14] This case underscores the potential of corticosteroids as a safe and effective therapy for HLH during pregnancy, offering a promising alternative to more aggressive standard treatments which may pose risks to the fetus.

A particularly noteworthy case by Watanabe et al presents AOSD during pregnancy resulting in neonatal HLH and severe liver failure, requiring a liver transplant.[15] Lin et al also documented a compelling case involving a preterm delivery with severe HLH in an infant born to a mother with AOSD.[16] The neonate exhibited a constellation of symptoms mirroring those of the mother during late pregnancy, including fever, generalized lymphadenopathy, transient erythematous skin rash, hepatosplenomegaly, ascites, pancytopenia, marked hyperferritinemia, and hypofibrinogenemia.[16] Treatment with dexamethasone, etoposide, and cyclosporin A led to a prompt response in the infant, obviating the need for bone marrow transplantation.[16] These cases suggest a possible vertical transmission of autoantibodies, antigens, or inflammatory mediators from the mother to the fetus, precipitating intense inflammation in the neonate. They serve as poignant reminders of the grave consequences AOSD can pose to both pregnancy and offspring, underscoring the imperative for clinicians to remain vigilant for potential neonatal HLH, particularly in the presence of fever, cytopenia, and hepatosplenomegaly.

Collectively, these studies emphasize the need for vigilant management of AOSD alongside HLH and highlight the value of a multidisciplinary approach in addressing these complex clinical challenges. The absence of standard care for HLH in pregnant women can lead to serious, even life-threatening, complications, thus the necessity for treatments such as corticosteroids and anakinra in suspected HLH cases is paramount.

Discussion

In our comprehensive study, we explore the diagnostic and therapeutic challenges associated with the management of AOSD during pregnancy, presenting through both a broad review of case reports and an in-depth case study from our own institution. Our research brings to light the complex interaction between AOSD and gestation, notably identifying that the onset of AOSD during pregnancy typically occurs during the first or second trimester and is characterized by a polycyclic disease course in a significant majority of cases. Through our detailed case report, we demonstrate the successful multidisciplinary management of a patient with AOSD complicated by HLH, resulting in favorable maternal and fetal outcomes despite significant challenges. Our study offers vital insights into the clinical manifestations, diagnostic challenges, and management strategies of AOSD during pregnancy, emphasizing the importance of early diagnosis, a multidisciplinary approach to care, and the careful use of immunosuppressive therapy to manage AOSD and associated complications during pregnancy.

Central to the diagnostic challenge of AOSD in pregnancy is the identification of its hallmark nonpruritic salmon-pink rash, requiring careful differentiation from pregnancy-specific dermatological conditions. Similarly, interpreting leukocyte counts in the context of AOSD necessitates an understanding of normal leukocytosis during pregnancy, ensuring that physiological changes associated with gestation are considered in the diagnostic process. It is important to note that the neutrophil count begins to rise as early as the second month of pregnancy, typically plateauing in the second or third trimester, with WBC counts ranging between 9,000 and 15,000 cells/μL.[17] This knowledge is crucial for distinguishing between normal gestational leukocytosis and the leukocyte elevations indicative of AOSD. Additionally, assessing liver dysfunction in pregnant patients requires distinguishing AOSD-related impairments from

conditions unique to pregnancy, such as intrahepatic cholestasis.

Our case study emphasizes the necessity for multidisciplinary management involving rheumatology, hematology, and maternal–fetal medicine. The diagnosis of AOSD was established in this patient based on the fulfillment of the Yamaguchi criteria, inclusive of major criteria (fever and leukocytosis), and minor criteria (sore throat, splenomegaly, elevated liver function tests, with the absence of rheumatoid factor and antinuclear antibodies), further complicated by HLH during pregnancy. This was evidenced by elevated sIL-2R levels and a bone marrow biopsy revealing hemophagocytic cells.

In this case report, the critical role of elevated levels of sIL-2R in the diagnosis and management of HLH during pregnancy is highlighted. This aligns with established literature, where elevated sIL-2R levels are recognized for their role in indicating excessive T-cell activation, a central feature of HLH pathophysiology.[18] The incorporation of sIL-2R into the HLH-2004 diagnostic guidelines by the Histiocyte Society underscores its diagnostic importance.[19,20] Elevated sIL-2R not only aids in diagnosing HLH but also provides insight into the disease's severity and progression, guiding the multidisciplinary team in crafting a tailored treatment strategy.

In their seminal work, Gerfaud-Valentin et al and Mathieu et al[21,22] provide a comprehensive overview of myocarditis associated with AOSD. The study involves a case series of 57 patients with AOSD, with a specific focus on four cases of myocarditis identified within this cohort. Additionally, 20 cases of myocarditis-complicated AOSD from a literature review were analyzed. The findings indicate that myocarditis in AOSD typically manifests early in the disease course, often at onset or within the first year after the disease onset, affecting younger patients, and is symptomatic in most cases, presenting with nonspecific electrocardiographic abnormalities and reduced ejection fraction ($\leq$ 50%) in a significant proportion of cases. Steroids alone were effective in 50% of patients with myocarditis. Additionally, other immunomodulatory drugs were often effective in managing myocarditis in AOSD. Accordingly, myocarditis linked to AOSD, while potentially fatal, generally forecasts a favorable prognosis if promptly and effectively addressed. The authors acknowledge the utility of IVIG from their clinical experience, though they concede that definitive conclusions cannot be drawn from their retrospective analysis. In our case study, the patient demonstrated clinical manifestations indicative of compromised cardiac function, notably tachycardia and pulmonary edema, alongside global cardiac hypokinesis and a diminished left ventricular ejection fraction of 45%. Following administration of high-dose corticosteroids alone, a significant improvement in cardiac function was observed. This positive outcome emphasizes the importance of early diagnosis and aggressive treatment to mitigate the risks associated with myocarditis in AOSD.

A notable aspect of this case is the application of an interdisciplinary treatment regimen that included methylprednisolone, azathioprine, and anakinra. This approach reflects the complexities inherent in treating AOSD in pregnant patients, particularly due to the limited data on the safety profiles of various disease-modifying antirheumatic drugs during pregnancy.[23] The challenge is further pronounced by the associated risks of corticosteroids, such as gestational diabetes, which our patient developed, highlighting a pressing need for treatment options that balance maternal and fetal well-being.

The recombinant IL-1 receptor antagonist, anakinra, has been documented for its capacity to manage refractory AOSD. Described in the literature, a case study of a 33-year-old woman with AOSD treated with the recombinant IL-1 receptor antagonist, anakinra, throughout pregnancy and breastfeeding demonstrates the drug's capacity to manage her refractory AOSD, which had not responded to prednisone, either as monotherapy or in combination with azathioprine or etanercept, without adverse effects on fetal development or the health of the child postdelivery.[24] The child demonstrated normal psychomotor development and weight progression during early childhood. Complementing this narrative, Fischer-Betz et al shared insights from successfully treating two pregnant women suffering from intractable AOSD with anakinra, resulting in the birth of healthy infants devoid of congenital anomalies, thereby corroborating its efficacy and safety in maternal care.[25] In a broader analysis, anakinra was administered in 24 pregnancies among women with autoinflammatory conditions, encompassing nine instances where the treatment was continued throughout gestation.[26] Notably, in a twin pregnancy, one fetus exhibited renal agenesis leading to in utero demise, attributed to an inherited genetic anomaly. However, the other twin and the remainder of the births proceeded without complications. In a study conducted by Youngstein et al, favorable outcomes were reported for 21 of 23 pregnancies exposed to anakinra,[27] thus providing additional substantiation of anakinra's safety and effectiveness in managing AOSD during pregnancy. Despite these documented cases of successful AOSD management in pregnancy using anakinra, our patient encountered anakinra-induced agranulocytosis, necessitating the discontinuation of this treatment.

Significant contributions to the field include the work of Nakamura et al, who investigated TAC for its effectiveness in treating refractory AOSD cases.[28] Notably, a pregnant patient who did not respond to corticosteroid monotherapy found success with a combination of TAC and corticosteroids (as detailed in ►**Table 2**, A20).[28] In addition, evidence from teratogenicity studies in animal models suggests a negligible risk of congenital malformations associated with TAC administration.[29,30] Although definitive, controlled studies in human pregnancies are absent, anecdotal use of TAC across a spectrum of cases has yielded favorable outcomes, thereby affirming its clinical viability.[31,32] Most pregnancies subjected to TAC therapy frequently incorporate corticosteroids and additional immunomodulatory agents. Despite the predominately normal outcomes in TAC-exposed pregnancies, there exists an elevated occurrence of hypertensive disorders, pre-eclampsia, and preterm delivery, and the birth weight for gestational age was lower than normal.[31,33–35]

Moreover, the utilization of tocilizumab, an antagonist of the IL-6 receptor, represents an innovative approach to the management of AOSD during pregnancy. A clinical report on a 23-year-old primigravida illustrated the efficacy of tocilizumab in moderating disease activity in a patient previously intolerant to anakinra due to a severe allergic response.[36] This patient experienced a significant exacerbation of her condition in her first pregnancy upon cessation of tocilizumab. However, during her next pregnancy 2 years later, she maintained a stable condition throughout gestation on continued tocilizumab therapy, resulting in normal fetal development and the birth of a healthy, full-term infant. Notably, a comprehensive 2022 review of 610 tocilizumab-exposed pregnancies revealed outcomes largely consistent with those expected in the general population.[37] Specifically, the review highlighted that the rate of congenital malformations observed in tocilizumab-exposed pregnancies did not exceed the baseline risk anticipated in the general population. This finding is particularly reassuring, considering the heightened concern for teratogenic effects associated with many immunomodulatory therapies. However, the review did indicate a slight increase in the incidence of miscarriage and preterm deliveries among the cohort. It is crucial to note that this increase could not be directly attributed to tocilizumab therapy. Instead, the review suggests that these outcomes may be more closely related to the effects of concomitant medication use or the underlying disease activity in the pregnant population studied.[37] Furthermore, data from a pharmacovigilance database did not demonstrate a correlation between tocilizumab use and adverse fetal or neonatal outcomes.[38]

Our patient's experience with AOSD during pregnancy showcases a polycyclic disease course, highlighting the notable occurrence of recurrent episodes in a significant proportion of pregnant patients diagnosed with AOSD. Our literature review reveals a 63.16% recurrence rate, with postpartum assessments showing 36.36% of patients experiencing flare-ups or condition deterioration, suggesting pregnancy may act as a catalyst for disease relapse, even in previously stable patients. This observation aligns with findings by De Carolis et al,[39] further affirming the relationship between pregnancy and AOSD flare-ups. Following childbirth, our patient resumed treatment with azathioprine and, fortunately, experienced an uneventful postpartum recovery.

Although we did not monitor disease activity using IL-18 levels in our case, the potential role of IL-18 during pregnancy emerges as a critical area of interest, with its elevated levels being potentially indicative of AOSD exacerbations, thus pointing to a significant interaction between AOSD activity and pregnancy influenced by IL-18 modulation. This premise gains support from recent studies highlighting the crucial role of cytokines, particularly IL-18, in the pathogenesis of AOSD.[40] These findings advocate for the utilization of IL-18 and other cytokines as biomarkers to guide the monitoring, management, and prognosis of AOSD during pregnancy.

The management of our patient also highlights the significant impact of AOSD on pregnancy outcomes, including the risk of preterm delivery and the need for intensive neonatal care. The successful delivery of a healthy neonate at 32 weeks of gestation, following a carefully monitored pregnancy complicated by AOSD flares, sepsis, and gestational diabetes, exemplifies the potential for positive outcomes with comprehensive, specialized care.

The discussion of this case would be incomplete without acknowledging the research conducted by Jia et al,[41] which suggests a possible role of CMV infection in triggering or exacerbating inflammatory responses in AOSD. Their findings of elevated levels of anti-CMV antibodies and increased CMV DNA load in individuals with AOSD, particularly among those with active disease symptoms, provide a compelling argument for the interplay between viral infections and AOSD pathophysiology. In our case, the indication of CMV shedding in the patient might not only trigger AOSD flares but also substantiate the hypothesis that viral infections, especially CMV, play a role in the disease's pathogenesis. This insight suggests future directions for AOSD management, including the potential for viral screenings to enable more targeted therapeutic interventions. Such strategies could mitigate disease activity and enhance patient outcomes by addressing underlying viral triggers.

Our study, while providing valuable insights into the management of AOSD during pregnancy, is not without its limitations. Chief among these is the inherent rarity of AOSD diagnosed during gestation, which significantly constrains our ability to assemble large cohorts for more robust statistical analysis. Such constraint may affect the generalizability of our observations, suggesting caution when applying these insights to broader patient populations. These limitations highlight the necessity for further research, ideally through larger, possibly multicentric studies, to validate and extend our observations.

Conclusion

In conclusion, our study adds valuable insights into the complex interplay between AOSD, pregnancy, and HLH, demonstrating the potential for successful maternal and fetal outcomes with an individualized, multidisciplinary care approach. It reinforces the importance of early diagnosis, the judicious use of immunosuppressive therapy, and the need for ongoing research to optimize care for this rare and challenging condition.

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Consent Statement

Informed consent was obtained from the patient for publication of this article after the nature and possible consequences of the study had been fully explained.

Authors' Contribution

All authors have made substantial contributions to the conception, design, acquisition of data, and analysis and

interpretation of the case report. Specifically, each author was involved in reviewing radiologic and pathological findings and synthesizing the article into a comprehensive report for academic dissemination. All authors contributed to drafting the manuscript and revising it critically for important intellectual content. They have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability

All relevant data are within the article and its supporting information files.

Conflict of Interest

None declared.

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References

1 Wang Z, Chi H, Feng T, et al. Pregnancy outcomes in patients with adult-onset Still's disease: a cohort study from China. Front Med (Lausanne) 2020;7:566738
2 Mok MY, Lo Y, Leung PY, Lau CS. Pregnancy outcome in patients with adult onset Still's disease. J Rheumatol 2004;31(11): 2307–2309
3 Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. Autoimmun Rev 2014;13(07):708–722
4 Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19(03): 424–430
5 Katz WE, Starz TW, Winkelstein A. Recurrence of adult Still's disease after pregnancy. J Rheumatol 1990;17(03):373–374
6 Cagatay Y, Gul A, Cagatay A, et al. Adult-onset Still's disease. Int J Clin Pract 2009;63(07):1050–1055
7 Zeng T, Zou YQ, Wu MF, Yang CD. Clinical features and prognosis of adult-onset Still's disease: 61 cases from China. J Rheumatol 2009; 36(05):1026–1031
8 Magadur-Joly G, Billaud E, Barrier JH, et al. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. Ann Rheum Dis 1995;54(07):587–590
9 Awoyemi T, Conti A, Aguilar FG. Adult-onset Still's disease complicated by macrophage activation syndrome. Clin Case Rep 2023; 11(09):e7825
10 Yip KP, Ali M, Avann F, Ganguly S. Pregnancy-induced haemophagocytic lymphohistiocytosis. J Intensive Care Soc 2020;21(01): 87–91
11 Liu C, Gao J, Liu J. Management of hemophagocytic lymphohistiocytosis in pregnancy: case series study and literature review. J Obstet Gynaecol Res 2022;48(03):610–620
12 Peters AT, Prickett MH. Adult-onset Still's disease presenting as macrophage-activation syndrome with critical illness in the third trimester of pregnancy: a case report. Crit Care Explor 2021;3 (05):e0440
13 Wise L, Zell M. Adult-onset Still's disease complicated by macrophage activation syndrome during pregnancy: a case-based review. Clin Rheumatol 2023;42(11):3159–3166
14 Dunn T, Cho M, Medeiros B, Logan A, Ungewickell A, Liedtke M. Hemophagocytic lymphohistiocytosis in pregnancy: a case report and review of treatment options. Hematology 2012;17(06):325–328
15 Watanabe E, Sugiyama Y, Sato H, et al. Adult-onset Still's disease during pregnancy that delivered a neonate with haemophagocytic lymphohistiocytosis and severe liver failure requiring liver transplantation: a case report and literature review. Mod Rheumatol Case Rep 2022;6(02):260–265
16 Lin A, Ma TPY, Cheng FWT, Ng PC. Neonatal haemophagocytic lymphohistiocytosis associated with maternal adult-onset Still's disease. Neonatology 2016;110(04):267–269
17 Kuvin SF, Brecher G. Differential neutrophil counts in pregnancy. N Engl J Med 1962;266:877–878
18 Dik WA, Heron M. Clinical significance of soluble interleukin-2 receptor measurement in immune-mediated diseases. Neth J Med 2020;78(05):220–231
19 Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48(02):124–131
20 Lehmberg K, Ehl S. Diagnostic evaluation of patients with suspected haemophagocytic lymphohistiocytosis. Br J Haematol 2013;160(03):275–287
21 Gerfaud-Valentin M, Sève P, Iwaz J, et al. Myocarditis in adult-onset Still disease. Medicine (Baltimore) 2014;93(17): 280–289
22 Jamilloux Y, Gerfaud-Valentin M, Henry T, Sève P. Treatment of adult-onset Still's disease: a review. Ther Clin Risk Manag 2014; 11:33–43
23 Fautrel B, Patterson J, Bowe C, et al. Systematic review on the use of biologics in adult-onset Still's disease. Semin Arthritis Rheum 2023;58:152139
24 Berger CT, Recher M, Steiner U, Hauser TM. A patient's wish: anakinra in pregnancy. Ann Rheum Dis 2009;68(11):1794–1795
25 Fischer-Betz R, Specker C, Schneider M. Successful outcome of two pregnancies in patients with adult-onset Still's disease treated with IL-1 receptor antagonist (anakinra). Clin Exp Rheumatol 2011;29(06):1021–1023
26 Chang Z, Spong CY, Jesus AA, et al. Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS). Arthritis Rheumatol 2014;66(11):3227–3232
27 Youngstein T, Hoffmann P, Gül A, et al. International multi-centre study of pregnancy outcomes with interleukin-1 inhibitors. Rheumatology (Oxford) 2017;56(12):2102–2108
28 Nakamura H, Odani T, Shimizu Y, Takeda T, Kikuchi H. Usefulness of tacrolimus for refractory adult-onset Still's disease: report of six cases. Mod Rheumatol 2016;26(06):963–967
29 Farley DE, Shelby J, Alexander D, Scott JR. The effect of two new immunosuppressive agents, FK506 and didemnin B, in murine pregnancy. Transplantation 1991;52(01):106–110
30 Saegusa T. Reproductive and developmental studies of tacrolimus (FK506) in rats and rabbits. The Journal of Basic and Clinical Medicine 1992;26:969–981
31 Kainz A, Harabacz I, Cowlrick IS, Gadgil SD, Hagiwara D. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. Transplantation 2000;70(12):1718–1721
32 Alsuwaida A. Successful management of systemic lupus erythematosus nephritis flare-up during pregnancy with tacrolimus. Mod Rheumatol 2011;21(01):73–75
33 Armenti VT, Radomski JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2005;19:69–83
34 Jain A, Venkataramanan R, Fung JJ, et al. Pregnancy after liver transplantation under tacrolimus. Transplantation 1997;64(04): 559–565
35 Christopher V, Al-Chalabi T, Richardson PD, et al. Pregnancy outcome after liver transplantation: a single-center experience of 71 pregnancies in 45 recipients. Liver Transpl 2006;12(07): 1138–1143

36 Martinez-King C, Chung SH, McCartney SA. Adult-onset Still's disease in pregnancy: lessons learned and an approach to subsequent pregnancies. Reprod Sci 2023;30(12):3515–3519
37 Jorgensen SCJ, Lapinsky SE. Tocilizumab for coronavirus disease 2019 in pregnancy and lactation: a narrative review. Clin Microbiol Infect 2022;28(01):51–57
38 Dernoncourt A, Liabeuf S, Bennis Y, et al. Fetal and neonatal adverse drug reactions associated with biologics taken during pregnancy by women with autoimmune diseases: insights from an analysis of the world health organization pharmacovigilance database (VigiBase((R))). BioDrugs 2023;37(01):73–87
39 De Carolis S, Cianci F, Del Sordo G, et al. Adult onset Still's disease and pregnancy. Autoimmun Rev 2019;18(09):102356
40 Kadavath S, Efthimiou P. Adult-onset Still's disease-pathogenesis, clinical manifestations, and new treatment options. Ann Med 2015;47(01):6–14
41 Jia J, Shi H, Liu M, et al. Cytomegalovirus infection may trigger adult-onset Still's disease onset or relapses. Front Immunol 2019; 10:898
42 Kaplinsky N, Pras M, Frankl O. An adult form of juvenile rheumatoid arthritis. Arch Intern Med 1980;140(08):1073–1074
43 Green J, Kanter Y, Barzilai D. Adult Still's disease associated with pregnancy. Isr J Med Sci 1982;18(10):1037–1039
44 Yebra Bango M, García Paez JM, Solovera JJ, Merino MF, Girón González JA. Adult-onset Still's disease: a case with onset during pregnancy. Arthritis Rheum 1985;28(08):957
45 Le Loët X, Daragon A, Duval C, Thomine E, Lauret P, Humbert G. Adult onset Still's disease and pregnancy. J Rheumatol 1993;20 (07):1158–1161
46 Falkenbach A, Lembcke B, Schneider M, Wigand R, Mulert-Ernst R, Caspary W. Polyserositis in adult Still's disease with onset during pregnancy [corrected]. Clin Rheumatol 1994;13(03): 513–517
47 Liozon E, Ly K, Aubard Y, Vidal E. Intravenous immunoglobulins for adult Still's disease and pregnancy. Rheumatology (Oxford) 1999;38(10):1024–1025
48 Pan VL, Haruyama AZ, Guberman C, Kitridou RC, Wing DA. Newly diagnosed adult-onset Still disease in pregnancy. Obstet Gynecol 2003;101(5 Pt 2):1112–1116
49 Yamamoto M, Tabeya T, Suzuki C, et al. Adult-onset Still's disease in pregnancy. Mod Rheumatol 2012;22(01):163–165
50 Hammami S, Barhoumi A, Loussaief C, Mahjoub S, Chakroun M. [Adult-onset Still disease in pregnancy]. Presse Med 2013;42(01): 114–116
51 Gerfaud-Valentin M, Hot A, Huissoud C, Durieu I, Broussolle C, Seve P. Adult-onset Still's disease and pregnancy: about ten cases and review of the literature. Rheumatol Int 2014;34(06): 867–871
52 Moussa M, Hassan MF. Newly diagnosed adult-onset Still's disease with pure red cell aplasia in pregnancy. Arch Gynecol Obstet 2014;290(01):195–198
53 Odai T, Isozaki T, Kasama T, Ogata H, Kinugasa E. Therapeutic efficacy of leukocytapheresis in a pregnant woman with refractory adult-onset Still's disease. Intern Med 2015;54(17): 2261–2266
54 Plaçais L, Mekinian A, Bornes M, et al. Adult onset Still's disease occurring during pregnancy: case-report and literature review. Semin Arthritis Rheum 2018;47(04):575–577