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CASE REPORT

Adverse Pregnancy Outcomes in an IVF Patient with Anti-Synthetase Syndrome: Insights From a Rare Case

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Abstract: Anti-synthetase syndrome (ASS) is a rare autoimmune condition characterized by the presence of anti-aminoacyl tRNA synthetase (ARS) antibodies and systemic features such as interstitial lung disease and myositis. Although autoimmune disorders are known to affect fertility, the impact of ASS on assisted reproductive technology (ART) outcomes remains largely unexplored. We present the case of a 36-year-old woman with primary infertility and no prior autoimmune diagnosis. She underwent six in vitro fertilization (IVF) cycles marked by recurrent fertilization failure, cleavage-stage arrest with high fragmentation and poor grading and oocytes exhibiting a waxy zona pellucida (ZP). Her diminished ovarian reserve (DOR) (anti-Müllerian hormone: 0.351 ng/mL; antral follicle count: 5) was documented prior to ART. Following a rare successful embryo transfer, she developed severe ASS at 20 weeks of gestation, characterized by acute interstitial lung disease (ILD), anti-PL-12 antibody positivity, and myositis. These conditions progressed to life-threatening complications, ultimately necessitating pregnancy termination. This case suggests a possible link between ASS and ovarian dysfunction, potentially mediated by autoimmune injury to follicular structures, cytokine dysregulation, or anti-zona pellucida antibody interference. Moreover, pregnancy-associated immune shifts may exacerbate latent autoimmune activity. Screening for anti-synthetase antibodies could be beneficial in patients with unexplained infertility or recurrent ART failure.
Keywords: anti-synthetase syndrome, assisted reproduction, infertility, ovarian reserve, autoimmune infertility, pregnancy complications

Introduction

Anti-synthetase syndrome (ASS), a rare systemic autoimmune disorder and a subtype of idiopathic inflammatory myopathies (IIMs), is clinically characterized by myositis, interstitial lung disease (ILD), Raynaud's phenomenon, mechanic's hands, fever, and arthritis. Its hallmark is the presence of anti-aminoacyl tRNA synthetase (ARS) antibodies, most commonly anti-histidyl-tRNA synthetase (anti-Jo-1), along with other synthetase antibodies. The estimated global incidence is 1–9 per 100000 individuals, with a female predominance and mean onset age of 40–55 years.

Autoimmune diseases (AIDs) contribute to infertility and pregnancy complications. However, direct evidence linking ASS to reproductive dysfunction is limited, with only sporadic case reports.[1] Within IIMs, chronic inflammation and immune dysregulation have been associated with diminished ovarian reserve (DOR) and reduced assisted reproductive technology (ART) success.[2] Successful pregnancy requires finely tuned maternal immune adaptation, including Treg

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expansion, Th2/Th17 balance, NK cell modulation, and controlled cytokine signaling.[3–5] Autoimmune activation can disrupt these processes, leading to infertility, implantation failure, miscarriage, and adverse obstetric outcomes.[6,7]

Here, we report a woman with recurrent fertilization failure and multiple ART attempts who was diagnosed with ASS during pregnancy and subsequently experienced adverse obstetric outcomes. This case highlights potential mechanisms by which ASS may impair ovarian function, fertilization, implantation, and early embryonic development, and illustrates the bidirectional interaction between pregnancy and disease activity. Our findings underscore the reproductive implications of ASS and emphasize the importance of early autoimmune evaluation in women undergoing fertility treatment. This case report has been approved by the Ethics Committee of Sichuan Provincial Women and Children's Hospital (Approval No. 20250222–22), including approval of the study protocol and permission to publish the case details.

Case Presentation

A 36-year-old woman with a 10-year history of primary infertility was evaluated in February 2023. She had regular unprotected intercourse across two marriages (remarried for 5 years) without conception. Hysterosalpingography (HSG) in 2016 revealed a normal uterus, right tubal patency, and left tubal obstruction. Three cycles of ovulation induction (protocols unspecified) with confirmed ovulation failed to achieve pregnancy.

Her reproductive history included bilateral tubal surgery and a failed in vitro fertilization (IVF) attempt in 2017. In 2022, she underwent laparoscopic bilateral tubal repair and salpingostomy, but natural conception remained unsuccessful.

At the time of evaluation, she was diagnosed with DOR, evidenced by an anti-Müllerian hormone (AMH) level of 0.351 ng/mL and an antral follicle count (AFC) of 5. Endocrine assessment revealed well-controlled hypothyroidism and insulin resistance. Cytogenetic analysis showed normal karyotypes for both partners (46, XX and 46, XY). Semen analysis of the male partner revealed a normal sperm concentration (89×10^6/mL), progressive motility of 52%, non-progressive motility of 4%, and a high rate of teratozoospermia, with 95% of sperm exhibiting abnormal morphology. Sperm DNA fragmentation and infection screening were normal.

She underwent six ART cycles—one IVF and five intracytoplasmic sperm (ICSI) cycles, as shown in Table 1. Across all cycles, oocytes consistently showed a "waxy" zona pellucida (ZP) with normal cytoplasm, resulting in suboptimal

Table 1 Comparison of ART Cycle Outcomes

Cycle	Protocol	Oocytes Retrieved (MII)	Fertilization Method	2PN Zygotes	Embryo Quality (Day 3)	Outcome
1	GnRH antagonist	5 (3)	IVF	0	9 cells, Grade 3	Transfer failed
2	Mild stimulation	2 (2)	ICSI	0	8 cells, Grade 3	Cryopreserved
3	GnRH antagonist	4 (2)	ICSI	1	8 cells, Grade 2	Transferred 2 embryos, resulting in clinical pregnancy (terminated at 13 weeks plus 4 days due to fetal cardiac malformation)
4	Luteal phase stimulation	1 (1)	ICSI	0	–	No viable embryos
5	Luteal phase stimulation	1 (1)	ICSI	1	6 cells, Grade 3	Cryopreserved
6	GnRH antagonist	4 (3)	ICSI	2	7 cells, Grade 2; 5 cells, Grade 4	Fresh transfer → clinical pregnancy (terminated at 21 weeks due to ASS exacerbation)

Notes: Embryo Grading Criteria: Grade 1: No fragmentation; Grade 2: <10% fragmentation; Grade 3: 10–25% fragmentation; Grade 4: >25% fragmentation.
Abbreviations: MII, Metaphase II oocytes; 2PN, Two-pronuclei zygotes; ICSI, Intracytoplasmic Sperm Injection; GnRH, Gonadotropin-Releasing Hormone.

fertilization. A clinical pregnancy in Cycle 3 ended at 13 weeks plus 4 days due to fetal cardiac anomalies (whole-exome sequencing was normal), and a second pregnancy occurred in Cycle 6 following fresh embryo transfer.

At 5 weeks of gestation in the second pregnancy, she developed cough and throat discomfort, initially managed conservatively. Vaginal bleeding was treated with progesterone. At 18 weeks of gestation, the patient developed worsening respiratory symptoms and fever; by 19 weeks plus 4 days, persistent fever, lower limb rash, and thigh pain led to hospitalization for suspected pneumonia, but empirical antibiotic treatment was ineffective. At 20 weeks, she was referred to Sichuan Provincial Women's and Children's Hospital, where physical examination revealed bilateral lower limb rash and indurated erythema at injection sites. During hospitalization, progressive dyspnea, myalgia, and fatigue prompted immunological workup for connective tissue disease. Results showed anti-PL-12 positivity, high antinuclear antibodies (ANA) titer (1:1280, speckled), anti-SSA (60kD) positive, and elevated KL-6 (769 U/mL), while other myositis-specific antibodies were negative. Absence of skin ulcers, rapid muscle necrosis, high-titer anti-dsDNA, or hypocomplementemia excluded alternative myositis or lupus. Combined with the triad of myositis, ILD, and arthritis during pregnancy, these findings confirmed ASS.

Treatment included methylprednisolone (1 mg/kg/day) and hydroxychloroquine (0.2 g twice daily). Retrospective history revealed a two-year course of intermittent, mild arthralgia (knees, shoulders) and diffuse myalgia, self-limited and non-inflammatory, which had not prompted medical attention, suggesting latent ASS prior to pregnancy. Due to rapid disease progression, the pregnancy was terminated at 21 weeks, as shown in Figure 1. The baseline clinical and laboratory characteristics of the patient are summarized in Table 2.

Discussion

ASS and Its Potential Reproductive Implications

Infertility can be male-factor, female-factor, combined, or unexplained. Despite regular unprotected intercourse over two marriages and prior male fertility, the couple failed to conceive; semen analysis revealed only teratozoospermia (95% abnormal morphology), insufficient to explain infertility.

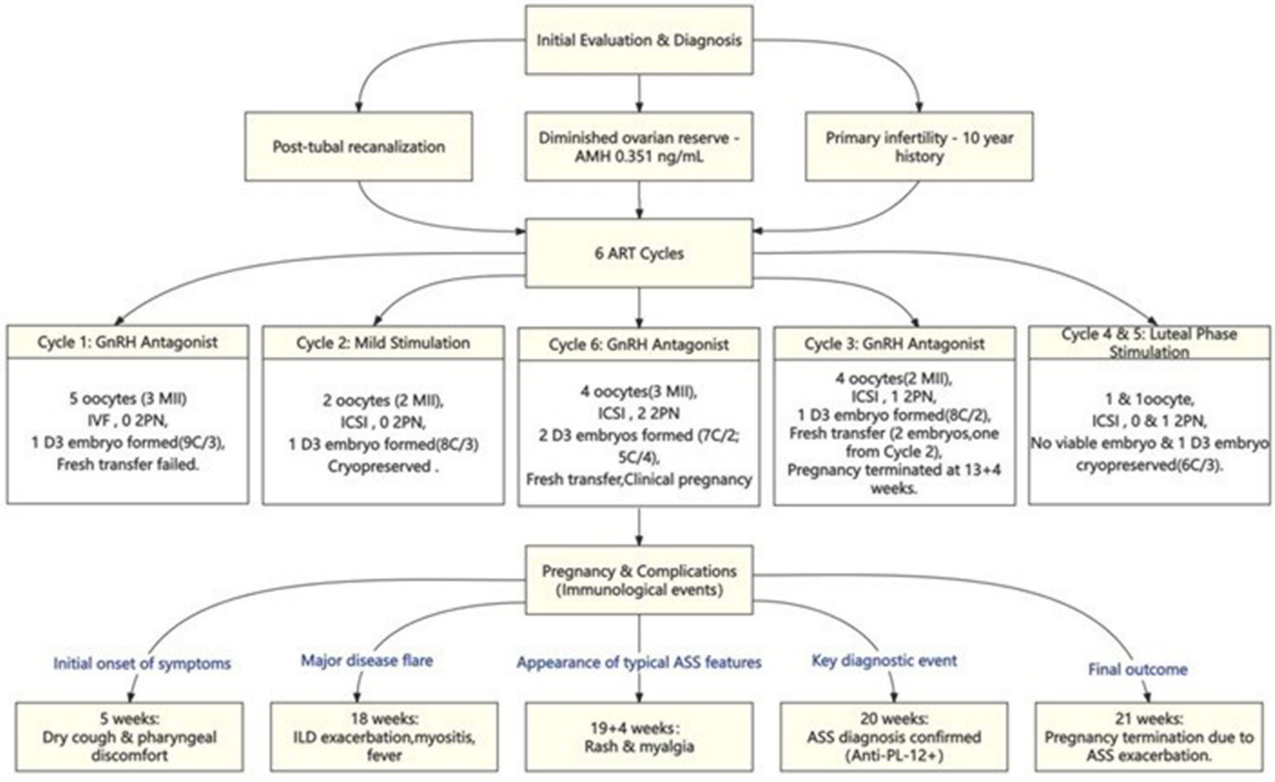

Figure 1 Timeline of Diagnosis and Pregnancy Course.

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Table 2 Baseline Clinical and Laboratory Characteristics of the Patient

Characteristic	Result	Reference Range / Comment
Age (years)	36	–
Height (cm)	159	–
Weight (kg)	60	–
Body mass index (BMI, kg/m²)	23.73	Normal (18.5–24.0)
Blood pressure (mmHg)	106/70	Normal (<130/80)
Thyroid function	TSH: 2.2 mIU/L	Within normal limits (0.4–4.0)
	FT4: 18.8 pmol/L	Within normal limits (11.2–23.8)
Glucose metabolism	Fasting glucose: 5.1 mmol/L	Normal (<6.1)
	Fasting insulin: 12.5 μIU/mL	Normal (2.2–24.9)
Lipid profile	Total cholesterol: 2.64 mmol/L	Normal (<5.2)
	Triglycerides: 1.2 mmol/L	Normal (<1.7)
Complete blood count	Hemoglobin: 122 g/L	Normal (115–150)
	WBC: 6.8 $\times 10^9$/L	Normal (4.0–10.0)
	Platelets: 215 $\times 10^9$/L	Normal (150–400)
Reproductive hormones	AMH: 0.351 ng/mL	Diminished ovarian reserve
	Antral follicle count: 5	Diminished ovarian reserve
Karyotype	46, XX (female), 46, XY (male partner)	Normal

Female factors considered included ovulatory dysfunction, tubal or uterine abnormalities, endometriosis, endocrine or autoimmune disorders, and age-related decline.[8] The patient had confirmed ovulation, a normal uterus on ultrasound, and bilateral tubal surgery (salpingostomy and adhesiolysis) with postoperative right tubal patency and partial left recanalization, excluding major anatomic causes.

The main finding was DOR. Evaluation showed: (1) age-related decline unlikely at 35 years; (2) normal karyotype (46, XX) and no family history of chromosomal disorders, and whole-exome sequencing revealed no pathogenic variants; (3) no ovarian surgery, chemotherapy, or radiation history; (4) negative genital infection screening; (5) no smoking, toxins, or known environmental exposures.

ASS, a subset of IIMs, is defined by ARS antibodies, including anti-Jo-1 and anti-PL-12 in this patient, and manifests variably with myositis, ILD, arthritis, Raynaud's phenomenon, fever, and "mechanic's hands".[9,10] While direct reproductive effects of ASS are poorly documented, related AIDs such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis (SSc) can impair ovarian reserve via chronic inflammation, cytokine dysregulation, and autoimmune oophoritis;[11–18] polymyositis and dermatomyositis have been linked to gonadal dysfunction,[19,20] and mitochondrial tRNA synthetase mutations—functionally related to ARS—are associated with ovarian failure.[21]

In this case, marked DOR without identifiable non-immune causes, poor oocyte quality across ART cycles, and eventual ASS diagnosis suggest a potential link between anti-PL-12 autoimmunity and reproductive dysfunction. Given the ubiquitous expression of tRNA synthetases in immune signaling and antigen presentation, off-target ovarian injury is plausible. Early recognition and immunologic evaluation may inform fertility preservation strategies in women with unexplained DOR and subtle autoimmune features.

Potential Influence of ASS on Fertilization, Implantation, and ART Outcomes

This case highlights a potential link between ASS and impaired ART outcomes. In the first IVF cycle, poor fertilization occurred despite normal semen parameters. Oocytes consistently exhibited a "waxy" ZP, microscopically characterized by thickening, increased refractivity, and rigidity, in contrast to the normal translucent and pliable ZP.[22,23] Such morphology resembles ZP dysmorphisms caused by ZP glycoprotein mutations that impair fibril assembly and produce a fertilization-incompetent, non-hatchable ZP.[24,25] Whole-exome sequencing revealed no pathogenic variants, which reduces but does not exclude non-exonic, structural, or mosaic mutations. Therefore, alternative mechanisms, such as autoimmune interference, should be considered.

Although direct evidence linking ASS-specific antibodies to ZP abnormalities is lacking, generalized autoimmunity and cross-reactivity could alter zona structure and function. Anti-ZP antibodies have been implicated in infertility through zona hardening, impaired sperm binding, and defective embryo hatching.[26–28] In autoimmune contexts, molecular mimicry or epitope spreading may generate antibodies targeting zona proteins, thereby compromising oocyte quality and fertilization competence.[29–31] Consistent with this, all cycles showed developmental arrest before blastulation, a hallmark of abnormal ZP integrity, as thickened or irregular ZP may disrupt cortical granule exocytosis, leading to zona hardening, fertilization failure and aberrant cleavage division.[23,32–34] ICSI failed to normalize fertilization rates, ruling out sperm- or technique-related causes and reinforcing the hypothesis of an intrinsic oocyte defect.

The patient's serology further supports immune involvement: positivity for anti-PL-12, anti-SSA, and ANA suggests pathogenic autoantibody activity. ANA can penetrate embryos and impair mitosis or DNA replication.[35–38] Anti-SSA /SSB antibodies have been associated with elevated TNF-α and IL-17A, reduced NK cell cytotoxicity, and lower oocyte retrieval and blastocyst development rates.[39] Kubota et al demonstrated that anti-dsDNA induces embryonic DNA fragmentation,[40] with similar findings in ART cohorts.[41]

Beyond oocyte morphology, maternal immune regulation via Tregs, uNK cells, and a balanced Th1/Th2 cytokine milieu is crucial for implantation and pregnancy maintenance.[3–5] Autoimmune dysregulation—through autoantibodies, pro-inflammatory cytokines (eg, TNF-α, IL-17), or impaired Tregs—may disrupt these processes, contributing to implantation failure, miscarriage, or preeclampsia.[42–44] In this case, coexistence of anti-PL-12 and anti-SSA antibodies likely reflects immune-mediated injury to embryonic and placental development, underscoring the importance of immunological evaluation in women with unexplained infertility or recurrent ART failure.

Interplay Between Pregnancy and ASS

This case suggests that pregnancy, especially following ART, may unmask or exacerbate ASS. The patient developed ILD and myositis symptoms during early gestation, progressing to classic ASS by 18 weeks. Although pregnancy usually favors immunotolerance, hormonal and immune shifts can trigger autoimmunity in predisposed women.[4,45,46]

The effect of pregnancy on AIDs differs—SLE often worsens, RA improves, and limited reports indicate ASS may also flare during gestation.[47–51] Saikumar et al[52] reported a similar case of gestational ASS exacerbation, but ours is the first reported case following ART. Ovarian stimulation, embryo transfer, and pregnancy may have collectively disrupted immune homeostasis and revealed latent ASS.

In this case, the first pregnancy ended in fetal abnormality despite normal genetics; the second resulted in a structurally normal fetus. Whether ASS contributed remains unclear but may involve ILD-related hypoxia, systemic inflammation, or autoantibody effects on the placenta. These findings underscore the need for early diagnosis and immune monitoring in pregnant women with suspected autoimmunity, especially in ART populations. Although guidelines do not recommend routine autoimmune screening in ART, selective testing for ANA, anti-SSA/SSB, and myositis-specific antibodies may be warranted in women with unexplained infertility or atypical systemic features. Pre-ART immune evaluation could enable earlier diagnosis, tailored immunotherapy, and reduced risk of gestational complications.

Conclusion

This case highlights a potential link between ASS and reproductive dysfunction, including DOR, abnormal oocyte morphology, impaired fertilization, and adverse pregnancy outcomes. Early autoimmune evaluation may aid diagnosis and guide individualized ART and pregnancy management. Future studies should clarify the mechanisms by which ASS-associated antibodies affect ovarian and embryonic function and assess whether immunomodulatory strategies can improve ART success. Greater awareness of the reproductive implications of ASS may ultimately enhance fertility counseling and optimize maternal–fetal outcomes.

Abbreviations

AFC, Antral follicle count; AIDs, Autoimmune diseases; AMH, Anti-Müllerian hormone; ANA, Anti-nuclear antibodies; ARS, Anti-aminoacyl tRNA synthetase; ART, Assisted reproductive technology; ASS, Anti-synthetase syndrome; DOR,

Diminished ovarian reserve; GnRH, Gonadotropin-Releasing Hormone; HSG, Hysterosalpingography; ICSI, Intracytoplasmic Sperm Injection; IIMs, Idiopathic inflammatory myopathies; ILD, Interstitial lung disease; IVF, In vitro fertilization; MII, Metaphase II; PN, Pronuclei; RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus; SSc, Systemic sclerosis; ZP, Zona pellucida.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding authors on reasonable request.

Ethics Approval and Consent to Participate

This study protocol and publication of the case details were approved by the Ethics Committee of Sichuan Provincial Women and Children's Hospital (Approval No. 20250222-22) and written informed consent form was obtained from the patient. All methods involving human data in this study were performed in accordance with the institutional guidelines or the Declaration of Helsinki.

Consent for Publication

Written informed consent for publication of clinical details and associated data was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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