Case Report

Pregnancy Outcome in Patients with Adult Onset Still's Disease

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ABSTRACT. Pregnancy outcome of patients with adult onset Still's disease (AOSD) has not been addressed. We report the maternal and fetal morbidity of 5 pregnancies from 3 Chinese patients with AOSD and review another 17 pregnancies from 14 patients reported in the English literature. Nine patients had their first manifestation in the 5th to 6th gestational month. Disease relapse in patients with known AOSD occurred most commonly in the post-partum period. Most did not respond satisfactorily to nonsteroidal antiinflammatory agents alone, but responded to administration of corticosteroids, especially in high doses. (J Rheumatol 2004;31:2307–9)

Key Indexing Terms:
EXACERBATION FETAL OUTCOME MATERNAL OUTCOME

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 pregnancies from 3 Chinese patients with AOSD and review the pregnancy outcome of patients satisfying the classification criteria for AOSD[1,2] (Table 1) reported in the English literature[3-12].

CASE REPORTS

Case 1. A 30-year-old woman presented in April 1995 with low grade fever, weight loss, cervical lymphadenopathies, urticaria-like rashes, and polyarthritis affecting her fingers, wrists, and knees. Skin biopsy showed leukocytoclastic vasculitis. Blood tests revealed leukocytosis (24.6×10^9/l), elevated erythrocyte sedimentation rate (ESR; 60 mm/h), and C-reactive protein (CRP) 13.5 mg/dl (normal < 0.6 mg/dl). There were also abnormal liver function tests [alkaline phosphatase (ALP) 167 U/l, ALT 38 U/l, AST 43 U/l] and hyperferritinemia (3985 ng/ml). Immune profiles including antinuclear antibodies and rheumatoid factor and septic examination were negative. AOSD was diagnosed and she was treated with methotrexate (MTX) 12.5 mg/wk, prednisolone 15 mg, and indomethacin 25 mg twice daily, with satisfactory response.

Relapse of polyarthritis and urticarial rash occurred at the 17th gestational week in October 1999. Blood tests showed leukocytosis (15.6×10^9/l) and elevated ESR (30 mm/h) and CRP (4.7 mg/dl). Oral prednisolone 5 mg and hydroxychloroquine 200 mg daily were restarted. She had a premature delivery at the 33rd gestational week because of spontaneous rupture of the amniotic membrane. She remained well in the post-partum period.

Case 2. A 24-year-old woman was diagnosed with AOSD in October 1996, when she presented with high swinging fever, polyarthralgia, and urticarial and maculopapular rash at peaks of temperature. She was found to have leukocytosis (21.3×10^9/l), hyperferritinemia (3990 ng/ml), elevated ESR (101 mm/h) and CRP (11 mg/dl), and negative septic investigations. She responded well to prednisolone 20 mg, hydroxychloroquine 200 mg, and indomethacin 50 mg 3 times daily, which were then stopped in late 1997.

She had one first-trimester miscarriage in March 1998 and a full-term normal delivery one year later. She had impaired glucose tolerance in the latter pregnancy. At the 21st gestational week of her third pregnancy in March 2003, she developed urticarial rash, polyarthralgia, and high fever. Blood tests showed leukocytosis (12.2×10^9/l), abnormal liver function (ALP 96 U/l, ALT 35 U/l, AST 86 U/l), hyperferritinemia (3210 ng/ml), and elevated ESR (107 mm/h) and CRP (13 mg/dl). Septic investigation was negative. She was treated with prednisolone 60 mg daily with gradual tapering in dose. She delivered uneventfully at full-term with no relapse afterwards.

Case 3. A 22-year-old woman was diagnosed with angioimmunoblastic lymphoproliferative disease in February 1994, when she presented with high fever, polyarthralgia, cervical lymphadenopathies, splenomegaly, and maculopapular and urticaria-like rash. Three courses of chemotherapy were given, to no avail. Symptoms relapsed in January 1995 with leukocytosis (15.6×10^9/l), abnormal liver function (ALP 229 U/l, ALT 41 U/l, AST 24 U/l), and elevated ESR (80 mm/h) and CRP (8 mg/dl). Exhaustive septic investigations and immune profiles were negative. Skin biopsy showed leukocytoclastic vasculitis. She was treated with prednisolone 60 mg, hydroxychloroquine 400 mg, and MTX 15 mg/week, with satisfactory response.

Her first pregnancy, in August 2001, was complicated by intrauterine growth restriction (IUGR). At 38 weeks' gestation, the baby was delivered by cesarean section after transient paroxysmal atrial tachycardia was detected. Anti-Ro/SSA antibodies were not present in the maternal serum by countercurrent electrophoresis. Immunoblotting did not show reactivity towards Ro52 and Ro60 peptides. She developed transient arthritis of the right wrist 2 months after delivery and was managed with naprosyn.

DISCUSSION

The role of hormonal factors was first postulated to influence disease susceptibility in AOSD when Bywaters[13] noted a slight female predominance. Indeed, our literature review identified 10 patients with first manifestations and 7 exacerbations in 12 pregnancies in patients with known AOSD. Although only 3 pregnancies were reported to be uneventful, it is likely that good pregnancy outcomes from patients with established AOSD are under-reported.

First manifestations mostly occurred in the 5th to 6th gestational months (Table 1, Patients 5a, 6, 9, 11, and 12). Three

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Table 1. Our cases and previous reported pregnancies in adult onset Still's disease.

Patient	Reference	Age, yrs	FM, K	Treatment at Conception	Onset of Symptoms: G, PP, (E)	Symptoms	Treatment	Response to Treatment	Fetal Outcome	Maternal Outcome
1*		30	K	—	G17w (E)	A, R	P 15 mg QD, HCQ 200mg QD	Satisfactory	Prematurity (G33w)	—
2a*		24	K	—	—	—	—	—	Fetal loss (G6w)	—
2b*		24	K	—	—	—	—	—	—	IGT
2c*		27	K	—	G21w (E)	A, R, F (G23w)	P 30mgQD	Partial satisfactory to P 60mg QD given 3 days later	—	—
3*		22	K	—	PP	A (Transient)	Naprosyn 250mg tds p.r.n.	—	Transient irregular heartbeat IUGR	—
4a	3	32	FM	—	PP2w (E)	R, A (PP2m)	Aspirin	Resolved in 4 months	—	—
4b	3	35	K	—	PP2m (E) PP5m	F, J, L, R Persistent symptoms	Naprosyn 375mg BD P 40mg QD	Partial, satisfactory	—	—
5a	4	27	FM	—	G5m (E) PP	A, F, L, LN, R, ST J (Transient)	P 30mg QD	Partial, increased to P 60mg QD 3 days later with satisfactory response	Transient oligo-hydramnios	—
5b	4	30	K	P 2mg QD to G3m	—	—	—	—	—	—
6	4	24	FM	—	G5m (E) G8m	A, F, L, R, ST J, R (Transient)	P 20mg QD	Satisfactory	—	—
7	4	24	K	P 10mg QD	Throughout PP	J J, R (Transient)	P 10mg QD	—	Prematurity (G36w)	—
8	4	25	K	—	G6m	J	—	—	—	—
9	5	23	FM	—	G25w (E)	A, F, HS, LN, R	Amidopyrine 1.2g QD	Poor	Prematurity (G28w)	—
				—	G28w PP3w	Persistent symptoms A, F, HS	Indomethacin P 60mg QD	Poor Satisfactory	Neonatal death	—
10	6	28	FM	—	G10w (E)	A, F, L, LN, R, ST	Salicylates 3 gm QD	Partial	—	PET
					G22w	NM	Salicylates 3 mg QD, IVIg	Partial		
					G31w PP5m (E)	A NM	IVIg IVIg, pulse methylpred (15 mg/kg), then P 15mg QD	Satisfactory Satisfactory		
11	7	21	FM	—	G20w (E)	F, J, L, Meningism, myalgia, S, ST	P 30mg QD	Partial	Prematurity (G34w), IUGR	—
					G23w PP	F, J, R F, J	P 60mg QD, HCQ P, HCQ, MTX	Partial Satisfactory		
12	7	38	FM	—	G22w (E)	A, F, R	P 60mg QD	Satisfactory Taken off at G32w	-1	—
13	8	25	FM	—	G8w (E) Post-TOP	A, F, LN F, J, HS, L, S, ST, LN, Diarrhoea	— P (high dose), CTX 1.5gm × 6 doses	Satisfactory	TOP	
14a	9	38	K	—	PP3m (E)	A, F, R, ST	Gold salts, NSAID	Poor, P 30mg QD, aza 150mg QD started 6 months later with satisfactory response	—	—
14b	9	40	K	P 5mg alt days	Post abortion (E)	NM	MTX 7.5mg/wk, indomethacin 25mg QD	Satisfactory	Fetal loss (G8w)	—

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Table 1. Continued.

Patient	Reference	Age, yrs	FM, K	Treatment at Conception	Onset of Symptoms: G, PP, (E)	Symptoms	Treatment	Response to Treatment	Fetal Outcome	Maternal Outcome
15	10	19	FM	—	First trimester (E)	A, F, HS, R, ST	NSAID	Poor, became steroid-dependent in PP	—	—
16	11	23	K	—	PP3 days (E)	A, F, R	Salicylates 4mg QD	Partial, finally responded to P 20mg QD	—	—
17	12	34	FM	—	G? (E) PP	A, F, LN, R Worsened	Aminopyrine 0.6gm QID Intramuscular gold	Partial Satisfactory	NM	NM

* Our cases; [a] first pregnancy; [b] second pregnancy; [c] third pregnancy; A: Arthritis; aza: azathioprine; CTX: cyclophosphamide; E: exacerbation; F: fever; FM: first manifestation; G: gestational; HS: hepatosplenomegaly; HCQ: hydroxychloroquine; IGT: impaired glucose tolerance; J: arthralgia; K: known AOSD; L: lymphadenopathies; m: month, MTX: methotrexate; NM: not mentioned; P: prednisolone; PET: preeclampsia; PP: post-partum; R: rash; S: serositis; ST: sorethroat; w: week; TOP: termination of pregnancy.

patients manifested AOSD in the first trimester (Patients 10, 13, 15), one in the post-partum period (Patient 4a), and the timing of one was not mentioned (Patient 17). Exacerbations occurred despite inactive disease at conception, mostly in the post-partum period (Patients 4b, 14a, 16) from 3 days to 5 months after delivery or even following spontaneous abortion (Patient 14b). Two other exacerbations developed in the 4th to 5th gestational months (Patient 1, 2c). All episodes were classical acute systemic manifestations, except for one (Patient 4a) with an insidious onset of rash and arthritis. Elective termination of the pregnancy at the time of relapse did not result in ablation of disease activity (Patient 13). Transient articular symptoms of mild severity were also frequent complaints (Patients 3, 5a, 6, 7, 8).

Multiple exacerbations in the same pregnancy were not common (Patient 10). Rather, most symptoms resulted from incomplete treatment of an earlier exacerbation. Salicylates and nonsteroidal antiinflammatory drugs (NSAID) showed initial response, but there was a subsequent resurgence of symptoms within weeks (Patients 4b, 9, 10, 15, 16, 17). One patient with no systemic complaint (Patient 1) fared well with low dose prednisolone. Complete (Patients 6, 14a, 16) and partial (Patients 2c, 5a, 11) responses were achieved with moderate doses (≤ 0.5 mg/kg/day) of prednisolone. High dose prednisolone (1 mg/kg/day) was successful (Patients 2c, 4b, 9, 12, 13) and without adverse event. Pulse methylprednisolone, intravenous immunoglobulin (IVIG; Patient 10), and pulse cyclophosphamide (given after elective termination, Patient 13) were also reported to be efficacious. Disease modifying agents including hydroxychloroquine, gold salts, MTX, and azathioprine were used as maintenance therapy after delivery, with variable response.

Unfavorable pregnancy outcomes including spontaneous abortion (Patients 2a, 14b), prematurity (Patients 1, 7, 9, 11), and IUGR (Patients 3, 11) were occasionally observed. It is likely that prematurity and IUGR occur more commonly in pregnancies complicated by disease exacerbation. Maternal morbidities were not common. Impaired glucose tolerance (Patient 2b) and preeclampsia (Patient 10) were among those reported.

Patients with AOSD may experience exacerbation of disease in pregnancy. Corticosteroid therapy is generally safe and can achieve satisfactory response and perhaps better fetal outcome. Longterm data are needed for management of these patients.

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