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Adult onset Still's disease and pregnancy

Dear Editor,

The relationships between pregnancy and Adult Onset Still's Disease (AOSD) is still unclear, due to the scarcity of data in literature, to the difficulties in identifying the role of pregnancy and puerperium on disease course, and, on the other side, to understand the influence of active/inactive disease on pregnancy outcome. We report a case of a pregnant patient with new onset of AOSD, referred to our University Hospital. Furthermore, we provide a review of all cases of AOSD described since 1971 to nowadays.

A Caucasian nulliparous 33-year-old woman was referred to our center, because of the appearance of fever, sore throat and pink-salmon maculo-papular rash. Laboratory investigations revealed anemia (hemoglobin 9.7 g/dL) neutrophilic leukocytosis (WBC 14,950/mm^3, of which 12,060 neutrophils), elevation of C-reactive protein (CRP = 150.7 mg/L); and slightly increased ferritin (295 mg/dL). Moreover, anti-streptolysin title, procalcitonin, blood and urine cultures, pharynx and vaginal swabs were negative. Skin biopsy was executed with no specific findings at the histologic examination. Diagnosis of AOSD was made and treatment with methylprednisolone 40 mg iv/daily was started. Within few days, fever and the skin rash rapidly disappeared. After the sixth day, the patient complained of bilateral knee arthralgia and the ultrasonography examination found a slight swelling of the left semi-membranous bursa. Six days after discharge the patient was admitted again, because the relapse of fever and skin rash despite steroid regimen. Laboratory examination confirmed the presence of leukocytosis with > 80% granulocytes, and a new elevation of CRP (up to 110 mg/L). Therapy with intravenous immunoglobulins 0.4 g/kg daily and methylprednisolone 2 mg/kg iv/daily for five days was administered obtaining rapid resolution of symptoms and normalization of CRP value within five days. Then, the patient was discharged with prednisone 1 mg/kg/daily *per os*, gradual tapered during *puerperium*. At 39 weeks of gestation the patient had an induced vaginal delivery and a healthy female baby of 3000 g was born, breast-fed. One month after delivery the patient was completely asymptomatic, inflammation indexes were negative, and ferritin value was just above the normal range. After 9 months from delivery, no disease relapse occurred.

A literature search found 48 additional cases of AOSD in pregnancy, reported since 1971 to nowadays [Table 1]. According to the timing of disease onset, three different settings were identified. The first group (Group 1) includes women with previous diagnosis of AOSD who became pregnant (n = 21) [1–10], the second group (Group 2) [2,11–23,7,9,present case] includes women with first manifestations of disease during pregnancy (n = 22), and the third group (Group 3) includes women with disease onset occurring after delivery (n = 6) [2,25–27].

In the Group 1, all AOSD patients (n = 21) were in clinical disease remission at the time of conception [5]. Disease relapse occurred in 71.4% (n = 15) [1–10] of patients and it was more frequent during pregnancy (n = 10/15) than after delivery [1,4,5,10]. In the first and second trimester disease relapses (n = 4 [1,9,10] and n = 3 [1,8], respectively) were more frequent than during the third trimester (n = 1) [2]. Only 28.6% of patients remained asymptomatic during all the pregnancy [1,6,10,20]. One case of maternal Hemophagocytic Lymphohistyoyctosis (HLH) was reported [8]. Glucocorticoids were the most commonly used drug to treat relapse (n = 6) [1,8–10], while in resistant or refractory disease synthetic and biologic DMARDs have been used [1,6,9,10,15]. The most frequent obstetrical complications were Intra Uterine Growth Restriction (IUGR) (6/13 = 46.1%) [1,5,8,9,24], and preterm delivery (3/13 = 23.1%) [1,6,8], in 4 cases (30.7%) no obstetrical complications were encountered [2,10,7]. Interestingly, in women who experienced relapse after delivery, 2 IUGR [1,9], and 2 fetal losses [1,10] were described before any evidence of disease relapse. One case of neonatal (HLH) has also been described [6]. In the group with AOSD onset during pregnancy (Group 2) the onset of symptoms during pregnancy occurred in the first trimester in 7 cases [2,7,10,13,14,16,23]; in the second trimester in 10 cases [2,10,12,17–19,21], and in the third trimester in 4 cases [15,20,22,present case]. Among the 18 patients whose treatment was reported, steroids represented the initial therapy (PDN-equivalent 0.3–1 mg/kg) [2,7,10,12–14,17–23,present case], failing to achieve symptoms control in 8 cases [10,14,17,18,21,23,present case], so requiring additional therapies [present case,7,10,14,17,21,23]. Relapse rate through pregnancy was 35.0% (n = 7/20): all after 20 weeks of gestation [2,10,16,17,23,present case], and only one case in the *puerperium* [10]. One pregnancy was complicated by Macrophage Activation Syndrome (MAS) [18]. Among 17 patients whose pregnancy outcome has been reported [2,7,10,12,14,16–19,21,22,present case], 22.2% of pregnancies were uncomplicated [2,10,present case]; there were 1 fetal loss in early pregnancy [14] and 1 neonatal death [12]. The pregnancy complications observed were preterm delivery (68.7%) [7,10,12,16,17–19,21–23], IUGR (18.7%) [6,16,24], preterm-PROM (18.7%) [10,21], and oligohydramnios (12.5%) [2,10]. There was also 1 case of pre-eclampsia with placenta abruption in a patient not treated with steroids [15]. HLH occurred in 1 neonate [21]. The last group (Group 3) includes six cases of women having AOSD within 3 months after delivery. In one case the disease appeared after miscarriage [27]. Steroids were the most used starting therapy [2,25–27]. One pregnancy was complicated by IUGR [5].

Taking together all these data, it can be argued that women with pregnancy-revealed AOSD have higher risk of obstetrical complications; moreover, an additional risk due to pharmacological therapy can also be considered. No obstetrical problems were observed only in the minority of cases (26.5%) and the risk of poor obstetrical outcome seems to be particularly high when AOSD was diagnosed during pregnancy (76.5% in Group 2 *versus* 66.7% in Group 1). Furthermore, the rate of IUGR appears to be higher in Group 1, suggesting that placental

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Table 1
Review of cases with AOSD in pregnancy, according to the time onset of the disease.

Case no	Authors, year	Age at dg	Timing at onset/ relapse	Symptoms	Treatment	Obstetrical complications
Disease onset before pregnancy (Group 1) n = 21						
1	Bywaters, 1971 [3]	34	unk	F, A, R	Gold	unk
2	Parry, 1992 [4]	27	12 wks Pp	Coronary thrombosis	unk	unk
3	Le Loët, 1993 [2]	25	6 mths	unk	unk	unk
4	Mok, 2004 [1]	30	17 wks	A, R	PDN 5 mg/day,HCQ	IUGR, PTD(35 wks)
5	Mok, 2004 [1]	24	1st trimester	unk	unk	Pregnancy loss (1st trimester)
6	Mok, 2004 [1]	24	Healthy	None	None	GDM
7	Mok, 2004 [1]	24	21 weeks	F, A, R	PDN 60 mg/day	None
8	Mok, 2004 [1]	22	2 mths Pp	A, R	NSAIDs	IUGR
9	Berger, 2009 [5]	33	4 mths Pp	unk	Anakinra 100 mg/day	IUGR
10	Sayarlioglu, 2010 [6]	19	unk	None	Leflunomide 20 mg/day and MTX 20 mg/wks until 7 wks, Oral cholestyramine 8 g/3 times daily at 8 wks and at 22 wks	p-PROM
11	Fischer-Betz, 2011 [7]	25	unk	A transient	Anakinra 100 mg/day	None
12	Dunn T, 2012 [8]	Unk	19 wks (twin pregnancy)	F, R, HLH	PDN 40 mg/day, solumedrol 1 g/day for 3 days	IUGR, PTD (30 wks)
13	Shimizu, 2012 [9]	19	7 wks	unk, 6 flares from 7 wks to 28 wks	PDN 10 mg/day untill 28 wks then 20 mg/day, Cyclosporin A 150 mg/day until 20 wks, Etanarcept 25 mg/wk. from the 16th wks	IUGR, neonatal serum IL-18 levels' elevation at birth, and persisted for about 1 mth.
14	Gerfaud-Valentin, 2013 [10]	29	5 mths Pp	F, A, R, LAD, WL	unk	None
15	Gerfaud-Valentin, 2013 [10]	23	Healthy	None	None	unk
16	Gerfaud-Valentin, 2013 [10]	23	Healthy	None	None	unk
17	Gerfaud-Valentin, 2013 [10]	23	8 mths Pp	F, PA, SR, pleuritis, L	PDN 10 mg, IVIg, HCQ	unk
18	Gerfaud-Valentin, 2013 [10]	26	Healthy	None	NSAIDs, IVIg	“Non-evolutive pregnancy”
19	Gerfaud-Valentin, 2013 [10]	26	2 mths	F, SR	NSAIDs, IVIg, NSAIDs during Pp	unk
20	Gerfaud-Valentin, 2013 [10]	21	11 wks	F, A, R, SR, LAD, L	PDN 1 mg/kg/day	None
21	Park, 2014 [24]	unk	Healthy	None	None	IUGR, HLH
Disease onset during pregnancy (Group 2) *n* = 22						
22	Kaplinsky, 1980 [11]	25	unk	F, A, R, SM, L, PE	Aminopyrine, gold salt	unk
23	Green, 1982 [12]	23	21 wks	F, A, R	PDN 60 mg/day	ND at 28 wks
24	Yebra Bango, 1985 [13]	19	1st trimester	F, A, R, SR, arthritis of wrist	PDN	unk
25	Le Loët, 1993 [2]	27	5 mths	F, A, R	PDN 60 mg/day	TOHA
26	Le Loët, 1993 [2]	30	2 mths	unk	PDN until 3rd mth	unk
27	Le Loët, 1993 [2]	24	5 mths	F, A, R, 1 flare (8 mths)	PDN 20 mg/day	None
28	Falkenbach, 1994 [14]	25	8 wks	F, A	PDN, IVIg	“Termination”
29	Mahmud and Hughes, 1999 [58]	33	30 wks	unk	unk	unk
30	Liozon, 1999 [16]	28	10 wks	F, A, R, SR, cervical LAD, synovitis of wrists, knees, mediotarsal and metacarpophalangeal joints, 1 flare (22 wks)	Salicylates 3 g/24 h at 10 wks and 22 wks, IVIg 1 g/kg/day for 2 days at 22 wks and 31 wks	Pre-eclampsia, placenta abruption, PTD
31	Pan, 2003 [17]	31	20 wks	F, R, headache, non-productive cough, A, SR, odynophagia, pleuritic chest pain, meningeal symptoms of neck pain	PDN 30 mg/day at 20 wks, 1 flare (25 wks)PDN 60 mg/day, HCQ at 25 wks, AZA at 32 wks, MTX during Pp	IUGR, PTD
32	Pan, 2003 [18]	38	22 wks	F, A, R, SR, bilateral knee effusion, lung bibasal infiltrates	PDN 60 mg/day discontinued at 32 wks	None
33	Yamamoto, 2011 [19]	28	21 wks	F, A, R, cervical LAD, PA (wrist, knees), bilateral pleuritis, MAS	PDN 60 mg/day, plasma exchange,, Cyclosporine, dexamethasone	IUGR, PTD
34	Fischer-Betz, 2011 [7]	29	12 wks	F, A, R, HSM, SR, L	PDN 60 mg/day, Anakinra 100 mg/day	PTD

(*continued on next page*)

Table 1 (*continued*)

Case no	Authors, year	Age at dg	Timing at onset/ relapse	Symptoms	Treatment	Obstetrical complications
35	Gerfaud-Valentin, 2013 [10]	33	10 wks (twin pregnancy)	F, A, R, submandibular LAD, 1 flare (1 mth Pp)	PDN 0,7 mg/kg/day	p-PROM
36	Gerfaud-Valentin, 2013 [10]	27	14 wks	F, R, PA (fingers wrists knees ankles), SR, SM, 2 flares (Pp 1 & 3 mths)	PDN 1 mg/kg/day, IVIg NSAIDS (2 mths)	TOHA, p-PROM
37	Gerfaud-Valentin, 2013 [10]	36	14 wks	F, A of knees, R, SR, LAD, SM	PDN 0,5 mg/kg/day	None
38	Hammammi, 2013 [19]	32	22 wks	F, A, R, WL, purpura, LD, pericarditis	PDN 1 mg/kg/day	PTD
39	Moussa, 2014 [20]	25	26 wks	F, A, WL, HM, R	PDN 60 mg/day	unk
40	Odai, 2015 [21]	32	14 wks	F, A, R, MAS	PDN 25 mg/day and then 50 mg/day, leukocytapheresis twice a wk. for 12 wks	p-PROM, IUGR
41	Lin, 2016 [22]	unk	32 wks	F, A, R, LAD, TTP, HSM	unk	PTD, HLH
42	Plaçais, 2017 [23]	38	12 wks	F, LD, SR, abdominal pain, cholestasis, HM, pericarditis, PA, PE (flares at 20 wks, at 28 wks, severe sepsis at 34 wks)	PDN 1 mg/kg, colchicine, IVIg, anakinra 100 mg/day	PTD
43	Present case	33	27 wks	F, R, A, L,1 flare (29 wks)	metilprednisolon 40 mg/day, IVIg	None
Disease onset after pregnancy (Group 3) n = 6						
44	Katz, 1990 [25]	32	2 wks Pp	A, R	NSAID	unk
45	Katz, 1990 [25]	35	2 mths Pp	F, R	PDN 40 mg/day	unk
46	Leff, 1990 [26]	23	unk	F, A, R	PDN 20 mg/day	unk
47	De Miguel, 1992 [27]	38	3 mths Pp	F, A, R	PDN 30 mg/day;AZA	unk
48	De Miguel, 1992 [27]	40	Post abortion	unk	MTX	Miscarriage
49	Le Loët, 1993 [2]	24	unk	R	PDN 10 mg/day	IUGR

Dg = diagnosis; Unk = unknown; Wks = weeks; Mths = months; Pp = post-partum; F = fever; A = arthralgia; PA = polyarthritis; R = rash; SR = sore throat; HM = hepatomegaly; LD = liver disfunction; SM = splenomegaly; HSM = hepatosplenomegaly; L = leukocytosis; LAD = lymphadenopathy; WL = weight loss; TTP = thrombocytopenia; PDN = prednisone; AZA = azathioprine; MTX = methotrexate; IVIg = intravenous immunoglobulin; IUGR = intra uterine growth restriction; p-PROM = preterm Premature Rupture of Membranes; PTD = pre-term delivery; HCQ = hydroxychloroquine; MAS = Macrophage Activation Syndrome; HLH = Hemophagocytic Lymphohistyoyctosis; PE = polyciclic evolution; GDM = gestational diabetes mellitus; ND = neonatal death; TOHA = transient oligohydramnios.

function was impaired in almost half of cases.

Moreover, pregnancy could be a trigger for disease relapse in patients in clinical remission. More than one third of cases (35.0%) diagnosed during pregnancy experienced one or more relapse during gestation or in *puerperium* (higher risk of polycyclic evolution?) and one case of MAS was described in this group. The treatment of AOSD during pregnancy could be challenging, particularly in steroid and pregnancy-compatible DMARDs refractory disease, as therapy with bDMARDs is not recommended. However, intravenous immunoglobulins are safe and can be considered in presence of severe and/or life-threatening AOSD.

A multidisciplinary management by rheumatologist, obstetrician and family physician is suggested before, during and after pregnancy. Moreover, an accurate counseling about the increased risk for obstetrical complications has to be performed in all patients with AOSD. Further, to clarify the optimal management a multicenter, prospective study is advocated.

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