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Letter to the editor

Running title: Adult Still disease during pregnancy

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Rheumatology key message

Pregnancy-revealed AOSD is a specific subset with early pregnancy flares and impaired obstetrical outcome.

SIR,

Adult onset Still's disease is a rare affection classified among non-hereditary autoinflammatory diseases. The clinical presentation goes from fever with arthralgia and maculopapular eruption to life-threatening manifestations such as secondary lymphohistiocytosis. The mechanisms of AOSD remains unclear, but seems implicate NK cells dysfunction with pro-inflammatory cytokines secretion including IL-1ß, IL-6 and IL-18 [1]. Several reports mentioned AOSD occurring during pregnancy, mostly in first and second trimester and there is still a debate on whether it could compromise or not the pregnancy outcome. We here report a case of AOSD revealed during pregnancy with a life-threatening presentation along with a review of 19 cases from literature.

A 38-years old woman was treated in our department for diffuse systemic sclerosis and associated Sjögren syndrome. Both diseases were quiescent at the time of the report and none required immunosuppressive therapy. In May 2016 she was pregnant at 12 weeks of gestation and presented with acute fever without any associated features. Laboratory data revealed mild liver cytolysis (AST and ALT x4N) but a large screening for infectious and auto-immune diseases was negative and hepato-biliar imaging was normal. Fever and cytolysis spontaneously regressed in 3 days. Two month later, she was hospitalized again for intense fever, sore throat and abdominal pain. Laboratory analysis revealed liver cytolysis (ALT and AST x10N) with cholestasis, elevated bilirubin and increased C-reactive protein levels (53mg/L). Ferritin plasma levels were slightly high (657 ng/mL). Extended screening for infection remained negative and symptoms spontaneously regressed and she was discharged without any treatment. One month later she was admitted again for fever and arthromyalgia at 28 weeks of gestation. Laboratory data showed increased C-reactive protein levels (163 mg/L) associated with liver cytolysis (x2N), and ferritin levels at 371 mg/l. Cervico-thoraco-abdominal imaging revealed mild non-compressive pericarditis and persistent homogenous hepatomegaly (22cm of great axis). Because of persistent fever and polyarthralgias, after exclusion of active infection, steroids were started (prednisone 1 mg/kg) associated with colchicine, which allowed clinical remission and C-reactive protein significant decrease. When decreasing steroids at 12.5 mg/day, she again experienced fever and arthralgias recurrence and intravenous immunoglobulins were started. Just before intravenous immunoglobulins, acute agranulocytosis occurred and was considered related to colchicine. The agranulocytosis was complicated with severe sepsis from urinary tractus infection, so foetal extraction was decided and realized at 34 weeks of gestation. Despite foetal extraction and sepsis control, the fever and

polyarthralgias persisted, associated with severe cholestasis (x15N) and C-reactive protein levels at 320 mg/l. Ferritin levels were thus at 41 000 ng/mL with glycosylated ferritin less than 5%. The diagnosis of AOSD was stated according to Yamaguchi and Fautrel criteria [2 ; 3] and steroids were associated with anakinra (100 mg/day) allowing rapid clinical and biological remission.

AOSD can be revealed by pregnancy as first suggested in a case report from 1982 [4] eleven years after the first disease's description. We gathered data about 19 additional cases from the literature of AOSD revealed during the pregnancy **[Table 1]**. All cases concerned women from 19 to 38 years old (median age 28.6). Upon 18 pregnancies, median term at first flare was 16.77 weeks of gestation. Most women were in their first and second trimester (from 8 to 26 weeks of gestation). Clinical features mostly included arthritis and arthromyalgia, hectic fever and pharyngitis. Ferritin levels ranged from 1311 to 41 424 ng/mL. Most patients required steroids (n=16/20), and two were treated by intravenous immunoglobulins. All patients had systemic involvement and none presented as a chronic articular form. There were no obvious differences between the monocyclic and polycyclic forms. Obstetrical complications were frequent (n=11/20) mostly showing up as prematurity (n=10/20) though ours was due to foetal extraction and three of them could be linked to pre-term premature rupture of membranes potentially induced by the steroid regimens. There were three cases with intrauterine growth restriction, two with oligohydroamnios and one with neonatal death. In pregnancy-revealed AOSD, flares seemed to appear in first and second trimester earlier than in known AOSD [5]. Obstetrical complications seemed to be frequent as 50% of the pregnancies ended up with prematurity and 15% complicated by intra-uterine growth restriction even though some could be related to steroid therapy adverse events. The pathophysiological link isn't clear but recent studies showed high levels of IL18 during pregnancy [6] that could act as a trigger to a previously latent disease and be responsible for pregnancy-induced AOSD. The treatment of AOSD during pregnancy could be challenging. Steroids can be used, but may be associated with adverse events, like gestational diabetes, arterial hypertension. Intravenous immunoglobulins can be used if necessary in presence of life-threatening AOSD [7]. The use of other agents, like anakinra and tocilizumab cannot be recommended during pregnancy [8]. In conclusion, pregnancy-revealed AOSD appears to be a specifical subset of the disease with a systemic course, flares on first and second trimester, obstetrical complications such as prematurity and IUGR sometimes leading to life-threatening situations requiring parenteral corticotherapy and intravenous immunoglobulins.

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Table 1. AOSD revealed during pregnancy: cases from the literature review.

Year / Author	Age	Time of pregnancy (wg)	AOSD features	Ferritin levels / GF levels	Treatment	AOSD outcome during the pregnancies	Adverse Obstetrical outcome
1980, Kaplinsky [1]	34	Unknown	A, F, LN, E	NA/NA	Aminopyrine, gold salt	Polycyclic (PP)	None
1982, Green [2]	23	25 wg	A,F, HSMG, LN, E	NA/NA	NA	Polycyclic (28wg, PP)	Neonates death, prematurity at 28wg
1985, Yebra Bango [3]	19	12 wg	A,F, HSMG, E, Pha	NA/NA	Prednisone	Monocyclic	0
1990, Katz [4]	32	PP 2 m	E, A	NA/NA	NSAID	Monocyclic	0
1993, Le Loët [5]	27	20 wg	A, F, L, E, Pha,	NA/NA	Prednisone 1 mg/kg/d	Polycyclic	OHA
1993, Le Loët	24	20 wg	A, F, L, E, Pha, AM	NA/NA	Prednisone 20 mg/d	Polycyclic	0
1994, Falkenbach [6]	25	8 wg	A, F, L, AM, HSMG, S, Pha,	NA/NA	High dose prednisone, EDX	Polycyclic (suites de couches)	FE

1999, Liozon [7]	28	10 wg	A, F, L, E, Pha.	NA/NA	NA	Polycyclic (22wg, 31wg, PP 5m)	Pre-eclampsia
2003, Vivien [8]	21	20 wg	F, AM, L, S, Pha, E	NA/NA	Prednisone 1mg/kg + HCQ	Polycyclic (23wg, PP)	Prematurity at 34 wg, IUGR
2003, Vivien	38	22 wg	A, F, E	NA/NA	Prednisone 1mg/kg/d	Monocyclic	None, 41 wg birth
2003, Vivien	21	20 wg	F, A, Pha.	33 900/NA	Prednisone 0.5mg/kg/d	Monocyclic	IUGR, Prematurity at 34 wg
2011, Fischer-Betz [9]	29	12 wg	F, A, HSMG, E, Pha	>40 000/ NA	Prednisone 100 mg/day, Anakinra	Polycyclic	Prematurity at 36 wg
2011, Yamamoto M [10]	28	21 wg	F, E, A, AM, L, S, HLH	24883/NA	Methylprednisone, Ciclosporine	Monocyclic	Prematurity at 33 wg, IUGR
2013,Hammami S [11]	32	22 wg	F, A, E, AM, SMG, S	12957/NA	Prednisone 1mg/kg	Monocyclic	Prematury at 34 wg
2014, Mahmoud M [12]	25	26 wg	F, A, pancytopenia	1733/NA	Prednisone 60mg/j	Monocyclic	NA
2014, Gerfaud-Valentin [13]	33	10 wg	F, A, E	3592/1%	Prednisone 0.7mg/kg/d	Flare at 1 month PP, polycyclic course	Prematurity at 34 wg, PPRM

2014, Gerfaud-Valentin	27	14 wg	F, A, SMG, E	4124/12%	Prednisone 1mg/kg/d + Ig IV	Flare at 1 and 3 month, polycyclic	0
2014, Gerfaud-Valentin	36	14 wg	F, AM, E, L	1311/12%	Prednisone 0.5mg/kg/d	Monocyclic	Prematurity at 32.5 wg, PPRM, OHA
2015, Tsuyoshi [33]	32	14 wg	F, L, A, E, Pha	2920/NA	Prednisone 1mg/kg/d, LCAP	Monocyclic	Prematurity at 34 wg, PPRM
2016, present case	38	12 wg	F, HSMG, A, Pha	41000/<5 %	Prednisone 1 mg/Kg/d, Iv IG	Polycyclic	Prematury at 34 wg, fœtal extraction

Wg : weeks of gestation ; A : arthritis, E : erythema, F : fever, L : lymphadenopathy, S : seritis, AM : arthromyalgia, FE : foetal extraction, Pha : pharyngitis, OHA : oligohydroamnios, SMG : splemomegalia, HSMG : hepatosplenomegalia, IUGR : intrauterine growth restriction, LCAP : leucocytapheresis, PPRM : preterm premature rupture of membranes, Iv IG : intravenous immunoglobulins, PP : post partum.