Pregnancy outcomes in mixed connective tissue disease: a multicentre study

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a multicentre study

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Key Messages

1. In our multicentre cohort, women with mixed connective tissue disease(MCTD) had a live-birth-rate of 72%.

2.Pregnancy counseling should be considered in women withanti-U1RNP positivity.

Abstract

Objectives

In this study, we aimed to investigate fetal and maternal pregnancy outcomes from a large multicentre cohort of women diagnosed with Mixed Connective Tissue Disease(MCTD) and the presence of anti-U1RNP antibodies.

Methods

This multicentre retrospective cohort study describes the outcomes of 203 pregnancies in 94 consecutive women ever pregnant who fulfilled the established criteria of MCTD with confirmed U1RNP positivity.

Results

The fetal outcomes in 203 pregnancies were as follows: 146(71.9%) live births, 38(18.7%) miscarriages (first trimester pregnancy loss of <12 weeks' gestation), 18(8.9%) stillbirths (pregnancy loss after 20 weeks' gestation), 11(5.4%) cases showed intrauterine growth restriction (IUGR). Maternal pregnancy outcomes were as follows: eight(3.9%) cases developed pre-eclampsia, two(0.9%) cases developed eclampsia, 31(15.3%) women developed gestational hypertension and three(1.5%) developed gestational diabetes. Women with MCTD and antiphospholipid antibodies and pulmonary or muscular involvement had worse fetal outcomes compared to those without.

Moreover, we report a case of complete CHB (0.45%) and a case of cutaneous NL, both born to a mother with positive isolated anti-U1RNP and negative anti-Ro/SSA antibodies.

Conclusion

In our multicentre cohort, women with MCTD had a live-birth-rate of 72%. While the true frequency of heart block associated with anti-U1RNP remains to be determined, this study

might raise the consideration of echocardiographic surveillance in this setting. Pregnancy counselling should be considered in women with MCTD.

1.0 Introduction

Mixed connective tissue disease (MCTD) is classified by the presence high titers of antibodies to U1-ribonucleoprotein (RNP) in patients with 'puffy hands', Raynaud's phenomenon, arthritis and myositis[1–3]. Testing for extractable nuclear antibodies (ENA) is mandatory to classify patients suspected with connective tissue diseases (CTD).

In patients with any known CTD, specific situations such as the planning of a pregnancy, requires ENA profiling as the presence of maternal anti-Ro/SSA is strongly associated with the development of neonatal cutaneous lupus and fetal complete congenital heart block (CHB)[4].

However, little is known about the maternal and fetal pregnancy outcomes in women with anti-U1RNP. A recent interesting observation was a case of CHB in a fetus born to a mother with MCTD with isolated high titre anti-U1RNP, who was persistently negative for anti-Ro/SSA and anti-La/SSB[5]. The autopsy report of the child, who died 28 days post-partum due to several complications, confirmed loss and calcification of the myocytes in the bundle of His extending into the Purkinje fibres' with AV node sparring[5]. While the histopathology of this anti-U1RNP associated case of heart block did not reveal the characteristic fibrosis of the AV node, a similar result has been reported for two post-natal deaths associated with autoimmune CHB[6].

Herein, we report pregnancy outcomes from a large multicentre cohort of anti-U1RNP positive women and present the results of a systematic review of the literature.

2.0 Methods

This multicentre retrospective cohort study describes the fetal and maternal outcomes of 203 pregnancies in 94 women ever pregnant, who attended the S. Giovanni Bosco Hospital and Sant' Anna University Hospital, Turin, Italy, the Lupus Unit, Department of

Rheumatology at St Thomas' Hospital, London, UK, Hospital das Clínicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil, Hospital Reina Sofia de Córdoba, Spain, ASST SpedaliCivili di Brescia, Brescia, Italy.

Data collection was performed retrospectively from patient notes, pregnancies occurred in the time range 2000 – 2017. Autoantibody detection and laboratory profile were measured before conception, as per standard care of all centers of the study.

Inclusion criteria: Women ever been pregnant who fulfilled the established criteria of MCTD with confirmed anti-U1RNP positivity [1,3,7].

2.1 Statistics:

Categorical variables are presented as number (%) and continuous variables are presented as mean (S.D.). The significance of baseline differences was determined by the chi-squared test, Fisher's exact test or the unpaired t-test, as appropriate. A two-sided P-value <0.05 was statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

2.2 Systematic review:

A structured search for publications on Neonatal Lupus (NL) with anti-U1RNP antibodies positive patients in the absence of anti-Ro/SSA was undertaken in PubMed using the following search criteria: ("ribonucleoproteins"[MeSHTerms] OR "ribonucleoproteins"[AllFields] OR "ribonucleoprotein"[AllFields]) AND ("antibodies"[MeSHTerms] OR "antibodies"[AllFields]) AND ("infant, newborn"[MeSHTerms] OR ("infant"[AllFields] AND "newborn"[AllFields]) OR "newborninfant"[AllFields] OR "neonatal"[AllFields]). Two-hundred-seventy-six publications were identified and six additional studies were found. Two-hundred-sixty studies were excluded and a total of 22

studies were identified for detailed evaluation by two reviewers (MR and KS). Disagreements were resolved by consensus; if consensus could not be achieved, a third party (SS) would provide an assessment of eligibility. As the data on eligibility were dichotomous (eligible: yes/no), inter rater agreement at both the title and abstract review stage and the full article review stage was determined by calculation of Cohen's kappa coefficient (k=0.92). Fourteen studies were included [5,8–20], the search strategy is presented in Figure 1.

3.0 Results:

3.1 Systematic Review

Fourteen studies, including a total of 17 patients with NL born to women carrying positive anti-U1RNP antibodies in the absence of anti-Ro/SSA, were retrieved from the literature search(5.8–20). Table 1 illustrates the main findings of the studies included in the analysis. Briefly, 16 (94.1%) patients presented with skin involvement, two patients (11.7%) with heart involvement (two cases of congenital atrioventricular heart block) and seven patients (41.1%) with potentially related systemic involvement in addition to the characteristic skin rash (two cases of thrombocytosis, two cases of thrombocytopenia, one case of anaemia, one case of hypotonia and one case of hepatomegaly). The maternal diagnosis was SLE in seven cases, MCTD in ten cases and in one case the diagnosis was not specified.

3.2 Patients characteristics of our multicentre cohort

The analysis included 94 consecutive women (mean age at conception 28.9 years, S.D. 6.3; mean age at data collection 45.1 years old, S.D. 10.9; mean disease duration at data collection 12.9 years, S.D. 8.5) who had a total of 203 pregnancies.

All patients were diagnosed with MCTD according to the established criteria [1,2,21]. Thirteen patients tested positive for aPL and, of those, 6 patients also fulfilled the classification criteria for antiphospholipid syndrome (APS) (two women had a previous history of thrombosis and four patients had a previous history of pregnancy morbidity)[22]. Demographic, clinical and laboratory characteristics are summarized in Table 2.

Thirty-two (15.8%) patients received low-dose aspirin (LDA) and fifteen (7.4%) cases were treated with low molecular weight heparin (LMWH) during pregnancy. Thirty-three patients received steroid treatment during pregnancy [median daily dosage 5 mg (range 3.6-40 mg)]. Immunosuppressant treatment with Azathioprine or Cyclosporine-A was given in eleven (5.4%) and two (0.9%) women, respectively. Treatment received by the patients before, during and after pregnancy are outlined in Table 3.

Of the 203 pregnancies analysed the fetal outcomes were as follows: 147 (72.4%) resulted in live births, 38 (18.7%) in miscarriages defined as pregnancy loss of less than 12 weeks gestation, 18 (8.9%) in stillbirths (pregnancy loss after 20 weeks gestation)and eleven(5.4%) cases showed intrauterine growth restriction (IUGR). Maternal pregnancy outcomes were as follows: eight (3.9%) cases developed pre-eclampsia, two (0.9%) cases developed eclampsia, 31 (15.3%) women developed gestational hypertension and three (1.5%) cases were diagnosed with gestational diabetes. When considering the live birth outcomes (147 live births), birth weight was <2500g in 23.6% and <1500g in 5.6%; in 15.7% of cases birth weight was below the 10^{th} percentiles, while 3.4% cases had a birth weight between the 10^{th} and 5^{th} percentile, and 12.4% were under the 5^{th} percentile. When considering gestational length in live births (total 147), 15.5% of all gestations lasted<37 weeks, 9.2% between 37 and 34 weeks, and 6.4% under 34 weeks. The characteristics of fetal and maternal pregnancy outcomes are summarized in Table 4.

Patients with first trimester miscarriages when compared to those without, were significantly less frequently treated with HCQ (before [13% v.s. 42%; p< 0.05], during [13% v.s. 42%; p<0.05] and after [13% v.s. 56%;p< 0.001] pregnancy), low dose aspirin (LDA) (before [0% v.s. 21%; p< 0.001], during [0% v.s. 33%; p< 0.001] and after [0% v.s. 25%; p< 0.001] pregnancy), steroids (before [13% v.s. 40%; p< 0.05], during [7% v.s. 36%; p< 0.05] and after [0% v.s. 31%; p< 0.001] pregnancy) and azathioprine (AZA) (during [0% v.s. 13%; p< 0.05]).

When comparing patients who experienced still births compared to those without stillbirths, the former had a significantly higher frequency of clinical CTD manifestations, such as joints involvement (100% v.s. 69%; p< 0.05), muscular involvement (64% v.s. 31%; p< 0.05), pulmonary involvement (64% v.s. 27%; p< 0.05). The patients who experienced stillbirths had also a higher frequency of concomitant diagnosis of obstetric APS (11% v.s. 1%; p< 0.05) and had a lower rate of renal manifestations (0% v.s. 12%; p< 0.05).

When comparing patients who experienced either miscarriages or stillbirths with patients who did not experience stillbirths, those with fetal death were more likely to have a concomitant diagnosis of obstetric APS (11% v.s. 0%; p< 0.05), muscular involvement (58% v.s. 25%; p< 0.05), pulmonary involvement (50% v.s. 23%; p< 0.05). The patients who did not experience either miscarriages or stillbirths had a higher frequency of previous treatment with LDA (before pregnancy [4% v.s. 22%; p< 0.05], during pregnancy [9% v.s. 34%; p< 0.05]),treatment with HCQ (before [21% v.s. 45%; p< 0.05] and during [27% v.s. 57%; p< 0.05] pregnancy) and treatment with AZA (during [0% v.s. 16%; p< 0.05]).

3.3 Congenital Atrioventricular Heart Block- Case Presentation

A 33-year-old woman from China with no known previous medical history of connective tissue disease was referred to one of our tertiary pregnancy clinic for evaluation and follow-up at 28 weeks' gestation after detection of a decreased fetal heart rate upon routine obstetric ultrasonographic examination. Fetal echocardiography revealed a structurally normal heart with a ventricular rate of 50 to 55 beats/min, an atrial rate of 130 to 140 beats/min, and no pericardial effusion. These findings were compatible with CHB. No extra-cardiac abnormalities were detected at ultrasonographic examination. No infectious pathology, such as parvovirus B19, cytomegalovirus and Epstein-Barr virus, was found.

The female baby, born via caesarean section at 38 weeks of gestation, weighed 2.855 g and was 49 cm in length. After delivery, her heart rate was 70 to 110 beats/min. Electrocardiography revealed complete AV block, with an atrial rate of 140 beats/min and a ventricular rate of 40 to 50 beats/min. Holter monitoring confirmed the complete AV block, and the baby required a pacemaker implantation.

Results of laboratory examination of the baby showed that the haemoglobin level was 14.9 g/dL, and the blood results were negative for anti-nuclear antibodies, anti-double stranded DNA (dsDNA), anti-La/SSB and anti-Ro/SSA antibodies. She tested positive only for anti-U1RNP antibodies (81 UI/mL, cut-off of positivity >5 UI/mL).

There were no skin lesions, no increase in hepatic transaminase levels and no thrombocytopenia. Echocardiographic evaluation showed normal left ventricular systolic and diastolic function.

The mother's blood samples were negative for anti-La/SSB and anti-dsDNA and anti-Ro/SSA but were positive for anti-U1RNP antibodies. Her previous medical history, physical examination and serological profile were unremarkable. There was no previous pregnancy morbidity.

The blood sample was blindly tested in an external laboratory as previously described[23] (see supplementary material)and tested negative for anti-Ro60 native, anti-La recombinant, Ro52 recombinant, anti-Sm and confirmed the positive result for anti-U1RNP antibodies only.

Due to anti-U1RNP antibodies positivity, she had been attending the Rheumatology outpatient clinic for a regular clinical and laboratory follow-up, during which she started to complain about worsening arthralgia and fatigue. About 24 months after her first pregnancy, she presented with puffy hands', and arthritis on MCP joints, and complained about a new onset of Raynaud's phenomenon. These findings were compatible with a diagnosis of MCTD and she was started on low-dose of prednisone. During her second pregnancy, obstetric ultrasonographic examinations and fetal echocardiography performed throughout pregnancy revealed a structurally normal fetal heart with a physiologic ventricular rate. The baby girl, born via caesarean section, weighed 2873 g and was 52 cm in length. After delivery, the neonate's heart rate was normal with no sign of CHB. However, the neonate, at birth, presented with annular erythematosus plaques with a slight scale, which appeared predominately on the scalp, neck, and on the trunk, suggestive of NL. Lesions resolved in a few weeks without scarring and without any specific treatment.

4.0 Discussion:

To the best of our knowledge, this is the first multicentre cohort study to describe the overall fetal and maternal pregnancy outcomes in MCTD women with positive anti-U1RNP antibodies. Moreover, we report the second case of complete CHB in a fetus born to a mother with isolated positive anti-U1RNP in the absence of Ro/SSA antibodies.

Performing a systematic review of the literature of NL in patients with anti-U1RNP in the absence of anti-Ro/SSA is confined to eighteen cases in total since 1987 (including our

reported case)[5,8–19]. Notably, only one case of CHB has previously been reported[5] (Table 4).

Findings of fetal outcomes in our cohort suggest that the live-birth-rate was 71.9%, that 18.7% ended in a first trimester pregnancy loss, 5.4% cases had IUGR and 8.9% of pregnancies ended in a stillbirth. Maternal pregnancy outcomes showed that 3.9% developed pre-eclampsia, 0.9% developed eclampsia, 15.3% of the mothers developed gestational hypertension and 1.5% were diagnosed with gestational diabetes. Of those patients who developed gestational diabetes, only one of the three was treated with steroids during pregnancy.

Much focus has been on fetal and maternal pregnancy outcomes in women with SLE, who until four decades ago were advised against pregnancy due to a high rate of pregnancy morbidity including pregnancy losses, preterm birth and stillbirth[24]. Depending on the studies SLE cohort live birth rates are described as high as 90%, with 30% of miscarriages and preterm delivery rate of 30%. Women are now advised to be in remission prior to conception[25] and the identification of those women with a history of lupus nephritis[26–28] or persistent aPL[27] as risk factors for adverse pregnancy outcomes allow for individual close monitoring.

The pregnancy morbidity in women with SLE has improved over the last five decades from 40% to less than 15% in recent years[29]. The European League against Rheumatism (EULAR) has very recently published their first clinical recommendations for the management of women with SLE and aPL during pregnancy, which is an important step of the international community and aims to provide a uniform approach for the treatment and surveillance of these high risk patients[30].

As CTD's in general have a female preponderance[31–34] and a proportion of CTD's mostly affecting women of childbearing age[31,33,34], it is pertinent to address their effects on pregnancy outcomes. How come that pregnancy in MCTD has received very little attention[35,36]?

Population based Norwegian data suggest a prevalence of MCTD of 3.8/100.000 with an incidence of 2.1/million/year and a female:male ratio as high as 3:1[33,34]. As a comparison the incidence of SLE in the UK according to the Clinical Practice Research Datalink (CPRD) is 8.3/100,000/ year (for females) in the UK(4). The highest incidence rates of MCTD are described in those of African-Caribbean descent, 31.4/100,000/year compared to 6.7/100,000/year for those of white European descent. Overall, the incidence rate for SLE is slightly higher than for MCTD, which may explain that little attention so far has been paid towards pregnancy complications in women with MCTD.

Our results show a relatively high rate of fetal and maternal complications associated in women with MCTD with anti-U1RNP. In more detail, over 10% of the women in our cohort had cardiac involvement and almost one third of the patients had pulmonary involvement. Maternal cardiac involvement was not associated with increased adverse fetal outcomes. Due to a high maternal mortality, women with established cardiac involvement and/or pulmonary hypertension are advised against pregnancy [37]. It might well be that the high rate of pregnancy morbidity in our cohort reflects selection bias in a potentially general sicker MCTD population recruited from our tertiary centres only.

Further, the rate of NL and complete CHB in our cohort is not negligible, being 2/203(1%) and 1/203 (0.5%) pregnancies, respectively. Complete CHB is a rare complication, which when associated with anti-SSA/Ro is most often detected between 18 and 25 weeks of gestation. Complete block (third degree) in the absence of any extra nodal disease is not

reversible and evidence does not support efficacy in the use of fluorinated corticosteroids [38]. In regards to treatments options to improve pregnancy outcomes in women with MCTD, very little is known at this stage.

On the one hand, in a recent study, Sonesson and colleagues[39] suggested that echographic CHB surveillance still allows detection of fetuses with AVB II-III shortly after its development, allowing for timely treatment initiation and potentially better outcome. On the other hand, Evers et al. [40] suggest that a cost-effective strategy should be considered, focusing the fetal surveillance efforts on targeted screening strategies, such as using maternal antibody levels as a cost-effective alternative strategy. Notably, a recent paper by Cuneo and colleagues [41]supports that daily ambulatory fetal heart rate and rhythm monitoring done by the mother may identify blocks during a stage of transition from normal sinus rhythm to second degree block that may be reversible with anti-inflammatory therapy. Importantly this home monitoring was very reassuring it that no mother missed heart block, i.e. there were no false negative results. In our study, the use of azathioprine and steroids was found to be associated with better pregnancy outcomes. Albeit randomized control trials will be needed to specifically investigate the role of those medications in pregnant women with MCTD, one can speculate that agents lowering the disease activity might have affected the pregnancy outcomes. Similarly, the use of LDA was seen to have a protective effect against adverse maternal and fetal outcomes as observed in other connective tissue diseases (e.g., SLE)[42]. A further important question is whether HCQ may play a role in preventing neonatal lupus and especially the recurrence of CHB in the foetus, as demonstrated in women with anti-Ro/SSA[43]. In both anti-U1RNP positive anti-Ro/SSA negative associated complete CHB cases the mother was not exposed to HCQ during pregnancy [5]. Further

studies are urgently required to address the potential role of HCQ in this setting of anti-U1RNP.

This study presents some limitations. First, its retrospective fashion. However, this aspect is counterbalanced by the facts that we report maternal and fetal findings from the largest ever-reported MCTD cohort, especially when taking into account the low prevalence of this condition in the general population. Secondly, treatments before and during pregnancy were based on the treating physician's judgment. Thirdly, previous medical history of MCTD patients was heterogeneous, including different organs' involvement and potentially affecting fetal outcome. In the same line, one could speculate if the current classification criteria for MCTD, heterogeneous and dated more than 30 years, are still the best tool to identify patients with this condition, in both research and clinical settings. Finally, one could wonder if the usual echocardiographic window (16-26 weeks) of screening for CHB in women with anti-SS-A might not be adequate in women with MCTD.

In summary, acknowledging the limitations of retrospective data, our study suggests some important clinical messages: Firstly, women with MCTD should receive a specific counselling when planning a pregnancy. A suggested format could be similar to the pregnancy counselling currently recommended for women with SLE and APS. Secondly, the observed live-birth-rate was 72%, with poorer fetal outcomes observed in MCTD women with aPL and pulmonary or muscular involvement. A closer pregnancy surveillance of these patients may therefore be considered. While the true frequency of heart block associated with anti-U1RNP remains to be determined and prospective studies are highly needed to confirm our findings, our final clinical message is, that women with U1RNP antibodies should be offered echocardiographic surveillance during pregnancy to detect CHB in this setting.

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Legends of Figures and Tables

Figure 1. Search strategy for the Systematic Review

Table 1. Systematic review on cases of Neonatal Lupus born toanti-U1RNP antibodies positive patients

Table 2. Demographic, clinical and laboratory characteristics of the cohort

Table 3.Therapy undertaken by the patients before, during and after pregnancy.

Table 4.PregnancyOutcomes

First Author	Year of publication	Number of cases	Age of onset	Heart Involvement	Skin Involvement	Type	Systemic Involvement	Maternal Diagnosis
Provost et al. [19]	1987	2	8 w ; Birth	-	2	Erythematous annular and targetoid lesions; Scaling and violaceous lesions, oral ulcers, follicular plugging, residual atrophic macules and teleangectasia	-	SLE; SLE
Dugan et al. [9]	1992	2	3 w ; 4 w	-	2	Erythematous annular and polycyclic plaques, teleangectasia; Erythematous annular plaques, scale, residual hyperpigmentation	Thrombocytosis	MCTD; SLE
Rider et al. [10]	1991	1	5 d	-	1	Edema, macular erythema	Hypotonia	SLE
Lepore et al. [20]	1992	1	4 w	-	1	Erythematous papules, annular and reticulate erythema, residual atrophy	Hepatomegaly	SLE
Kaneko et al. [11]	1992	1	8 w	-	1	Annular erythematous plaques	-	MCTD
Sheth et al. [12]	1995	2	9 w ; 7 w	-	2	Annular scaly plaques, hypopigmentation; scaly erythematous patches, reticulate erythema	- ; Thrombocytosis	ND; MCTD
Solomon et al. [13]	1995	1	8 w	-	1	Scaly erythematous patches, scale, teleangectasia	-	SLE
Cimaz et al. [14]	2002	1	Birth	-	1	Erythematous, atrophic lesions, scaling.	-	MCTD
Fujiw aki et al. [15]	2003	1	3.5 w	-	1	Erythematous papules and subsequent discoid rash	-	MCTD
McGeachy et al. [16]	2009	1	Birth	-	1	Scaly plaques	-	MCTD
Penate et al. [17]	2009	1	1 w	-	1	Scaly urticarial lesions	Thrombocytopenia, anemia	MCTD
Acherman et al. [21]	2010	1	8 w gestation	1, CHB (transient 1 degree)	-	-	-	SLE
Helaan et al. [18]	2013	1	Birth	-	1	Erythematous polycyclic scaly plaques, atrophy	Thrombocytopenia	MCTD

Izmirly et al. [6]	2017	1	Birth	1, CHB	-	-	-	MCTD
Current Study	2018	2	Birth	1, CHB	1	annular erythematous plaques with a slight scale	-	MCTD

MCTD – Mixed connective tissue disease; SLE - Systemic Lupus Erythematosus; CHB – cardiac heart block

Table 1. Systematic review on cases of Neonatal Lupus born to anti-U1RNP antibodies positive patients

"Pregnancy in mixed connective tissue disease"

Patients Characteristics	All (94)	%
Age at conception, mean (S.D.), years	28.9 (±6.3)	
Age at data collection, mean (S.D.), years	45.1 (±10.9)	
Ethnicity		
Caucasians, n	64	68.1
Blacks, n	9	9,6
Asians, n	4	4,3
Other, n	17	18
Diagnosis		
MCTD	94	100
Disease duration at data collection, mean (S.D.), years	12.9(±8.5)	
MCTD and aPL	13	13.8
MCTD and APS	6	6.4
Clinical manifestations*		
Haematological, n	36	38.3
Skin, n	57	60.6
Joints, n	65	69.1
Cardiac, n	10	10.6
Renal, n	9	9.6
Muscular, n	31	33
Raynaud, n	66	70.2
Pulmonary**, n	27	28.7
Neurological, n	6	6.4
Cardiovascular risk factors		
History of smoking, n	10	10.6
Arterial Hypertension, n	13	13.8
Hyperlipidemia, n	11	11.7
Diabetes	2	2.1
Laboratory testing		
Low C3 levels , n	28	29.8
Low C4 levels , n	25	26.6
anti-dsDNA positive, n	12	12.8
anti-Ro/SSA and anti–La/SSB, n	4	4.3
anti-Ro/SSA, n	22	23.4
Hypergammaglobulinemia, n	47	50
LA, n	14	14.9
aCL (IgG/IgM), n	11	11.7
anti-β2GPI(IgG/IgM), n	3	3.2

Table 2. Demographic, clinical and laboratory characteristics of the cohort
"Pregnancy in mixed connective tissue disease"

MCTD – Mixed connective tissue disease; aPL – Antiphospholipid Antibodies; APS – Antiphospholipid Syndrome; LA – lupus anticoagulant; aCL – anti-cardiolpin; anti-β2GPI – anti-βeta Glycoprotein I; Ig – Immunoglobulin
*The listed *Clinical manifestations of MCTD occurred at any time during disease course*
*** Including Interstitial lung disease (42%), pulmonary fibrosis (33%) or pulmonary hypertension (25%)*

Therapy	Before pregnancy N(%*)	During Pregnancy N(%*)	After Pregnancy N(%*)
Immunosuppressants			
Azathioprine	8 (3.9)	11 (5.42)	11 (5.42)
Cyclosporine-A	2 (0.98)	2 (0.98)	0
Mycophenolate	6 (3)	0	3 (1.48)
Methotrexate	5 (2.46)	0	6 (2.96)
Cyclophosphamide	7 (3.45)	0	0
Rituximab	3 (1.48)	0	4 (1.97)
Steroids	40 (19.7)	33 (16.26)	29 (14.29)
Other			
Low Dose Aspirin	21 (10.34)	32 (15.76)	22 (10.84)
Low molecular weight Heparin	2 (0.98)	15 (7.4)	12 (5.91)
Vitamin K antagonists	2 (0.98)	0	1 (0.49)
Hydroxychloroquine	40 (19.7)	37 (18.23)	38 (18.72)
Statins	0	0	2 (0.98)
Anti-hypertensive drugs	12 (5.91)	14 (6.9)	24 (11.82)

Table 3.Therapy undertaken by the patients before, during and after pregnancy.

During pregnancy, 5 patients (2.46%) were taking both Azathioprine and Hydroxychloroquine, One patient was taking both Cyclosporine-A and Hydroxychloroquine (0.49%) and 16 were taking both Steroids and Hydroxychloroquine (7.88%). All patients with a previous diagnose of obstetric antiphospholipid syndrome received during pregnancy low dose aspirin, 3 out of 4 were also treated with low molecular weight heparin and one patient additionally received low dose steroids.

rates are calculated based on the number of pregnancies as:* **x/203*100

Pregnancy Characteristics	All (203)	%
Age at conception, mean (S.D.)	28,9 (±6.3)	
Mode of delivery		
Vaginal, n	97	67.8*
Vaginal Spontaneous/induced, %	88/12	
Cesarean section, n	50	34.2*
Outcomes		
Live births	147	72.4
Miscarriages	38	18.7
Stillbirths	18	8.9
Weight at Birth, mean (S.D.), grams	2930.2 (± 917.6)	
Gestation Duration, mean (S.D.), weeks	35.2 (± 7.5)	
Complications		
IUGR	11	5.4
Pre-eclampsia	8	3.9
Eclampsia	2	0.9
Gestational Hypertension	31	15.3
Gestational Diabetes	3	1.5
Other Neonatal and Obstetric Complications		
Respiratory Distress	3	1.5
Septicemia**	1	0.5
Premature Rupture of the Membranes	1	0.5
Absent end-diastolic flow velocity on umbilical artery	1	0.5
Oligohydramnios	2	1
Placental Abruption	2	1

Table 4. Pregnancy Outcomes

"Pregnancy in mixed connective tissue disease"

IUGR – Intrauterine growth restriction;

**Percentages are calculated considering viable babies (total=147)*

*** the episode of Septicemia resulted in death*