

Original article

A multicentre study of 244 pregnancies in undifferentiated connective tissue disease: maternal/fetal outcomes and disease evolution

Massimo Radin ¹, Karen Schreiber^{2,3}, Irene Cecchi¹, Alessandra Bortoluzzi⁴, Francesca Crisafulli⁵, Cristiano M. de Freitas⁶, Beatrice Bacco⁷, Elena Rubini¹, Silvia G. Foddai¹, Melissa Padovan⁴, Silvia Gallo Cassarino⁷, Franco Franceschini⁵, Danieli Andrade⁶, Chiara Benedetto ⁸, Marcello Govoni⁴, Tiziana Bertero⁷, Luca Marozio⁸, Dario Roccatello¹, Laura Andreoli ^{5,*} and Savino Sciascia ^{1,*}

Abstract

Objectives. To investigate fetal/perinatal and maternal outcomes from a large multicentre cohort of women diagnosed with UCTD.

Methods. This multicentre retrospective cohort study describes the outcomes of 224 pregnancies in 133 consecutive women with a diagnosis of UCTD, positive for ANA and aged <45 years old at study inclusion.

Results. Of the 224 pregnancies analysed, 177 (79%) resulted in live births, 45 (20.1%) in miscarriages (defined as pregnancy loss before 12 weeks' gestation), 2 (0.9%) in stillbirths (pregnancy loss after 20 weeks' gestation) and 6 (2.7%) cases showed intrauterine growth restriction. Miscarriages and stillbirths were strongly associated with the presence of aPL and ENA antibodies ($P < 0.05$). Maternal pregnancy complications were as follows: 5 (2.2%) cases developed pre-eclampsia, 11 (4.9%) cases gestational hypertension and 12 (5.4%) cases gestational diabetes. Joint involvement represented the most frequent clinical manifestation of the cohort (57.9%), followed by RP (40.6%), photosensitivity (32.3%) and haematological manifestations (27.1%). The rate of disease evolution of our cohort from a diagnosis of UCTD to a diagnosis of definite CTD was 12% within a mean time of 5.3 ± 2.8 years. With a total follow-up after first pregnancy of 1417 patient-years, we observed the evolution to a defined CTD in one out of every 88 patient-years.

Conclusion. In our multicentre cohort, women with UCTD had a live birth rate of 79%. Women with UCTD should be referred to specialist follow-up when planning a pregnancy. ENA profiling and aPL testing should be mandatory in this setting, and further therapeutic approaches and management should be planned accordingly.

Key words: undifferentiated connective tissue disease, anti-nuclear antibodies, pregnancy, pregnancy complications, autoimmune disease, congenital heart block, neonatal lupus, autoantibodies

¹Center of Research of Immunopathology and Rare Diseases – Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, Department of Clinical and Biological Sciences, and SCU Nephrology and Dialysis, S. Giovanni Bosco Hospital, Turin, Italy, ²Department of Thrombosis and Haemophilia, Guy's and St Thomas' Hospital, London, UK, ³Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, ⁴Department of Medical Sciences, University of Ferrara and Azienda Ospedaliero-Universitaria Sant'Anna, Cona (Ferrara), ⁵Department of Clinical and Experimental Sciences, University of Brescia, Unit of Rheumatology and Clinical Immunology, ASST Spedali Civili, Brescia, Italy, ⁶Department of Rheumatology, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, ⁷Clinical Immunology Department, University of Turin, AO Mauriziano and

⁸Department of Surgical Sciences, Obstetrics and Gynecology, Sant'Anna, University Hospital, University of Turin, Turin, Italy

Submitted 26 August 2019; accepted 7 November 2019

Correspondence to: Savino Sciascia, Center of Research of Immunopathology and Rare Diseases – Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, Department of Clinical and Biological Sciences University of Turin and SCU Nephrology and Dialysis, S. Giovanni Bosco Hospital, Piazza del Donatore di Sangue 3, Turin 10154, Italy.
E-mail: savino.sciascia@unito.it

*Laura Andreoli and Savino Sciascia contributed equally to this paper.

Rheumatology key messages

- Women affected by UCTD are common in clinical practice.
- In our multicentre study of UCTD women we report a live birth rate of 79%.
- Women with UCTD should be referred to specialist follow-up when planning a pregnancy.

Introduction

UCTD describes a condition characterized by clinical and laboratory findings typical for CTD but not fulfilling the classification criteria for definite CTD [1–3].

UCTD is a nosological entity that encompasses a wide spectrum of clinical pictures, starting from mild presentations with arthralgia, arthritis, RP, mucocutaneous manifestations, sicca symptoms and haematological abnormalities, to severe organ involvement such as non-specific interstitial pneumonia [4]. Since the 1980s many studies have been carried out analysing all aspects of UCTD, from incidence, prevalence, clinical and serological profile, to possible evolution over time to a defined CTD. It is now fully accepted that UCTD represents a separate clinical entity and that only up to 30% of UCTD patients will develop a defined CTD in a 5-year time period [5, 6].

In this context, testing for ENA antibodies is crucial, as an anti-ENA profile might be able to predict disease evolution towards specific defined CTD and help the treating clinician to plan an appropriate clinical and serological follow-up [7]. Moreover, in patients with any known CTD, specific situations such as pregnancy require ENA profiling, as the presence of maternal anti-Ro/SSA is strongly associated with the development of neonatal cutaneous lupus and fetal complete heart block (CHB) [8]. Similarly, a recent multicentre study in women with MCTD further emphasized the clinical role of ENA profiling, including anti-U1RNP, when planning a pregnancy [9]. However, despite the fact that women affected by UCTD are common in clinical practice, therapeutic strategies and follow-up are mostly based on clinician expertise and little is known about the fetal/perinatal and maternal outcomes in women with UCTD.

Herein, we report pregnancy outcomes from a large multicentre cohort of women with UCTD and ANA positivity.

Methods

This multicentre retrospective study describes the fetal/perinatal and maternal outcomes of a cohort of patients ever-pregnant, who attended the following Health Institutions in a period lasting from 2010 to 2019: the S. Giovanni Bosco Hospital (Turin, Italy), the Sant’Anna University Hospital (Turin, Italy), the A.O.U. Mauriziano, Umberto I (Turin, Italy), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (São Paulo, Brazil), ASST Spedali Civili di Brescia

(Brescia, Italy) and A.O.U. Sant’Anna di Ferrara (Cona, Ferrara, Italy).

Data collection was performed retrospectively from clinical charts. Autoantibody detection (ANA, ENA, anti-dsDNA and aPL) and laboratory profile (full blood count, creatinine, liver enzymes, complement, serum protein electrophoresis, immunoglobulins, electrolytes, urinalysis) were measured before conception, according to local standard of care adopted by all centres involved in the study.

Cardiovascular risk factors (including hypertension, dyslipidaemia, diabetes, hormone replacement therapy and smoking) were assessed following the National Institute for Health and Care Excellence (NICE) guidelines [10].

The study was conducted under the principles set forth in the Helsinki Declaration of 1975, as revised in 2013. The study was conducted in line with the institutional review board policy for each centre involved in the study and informed consent was obtained from each patient.

Inclusion criteria were as follows: (i) women who had ever been pregnant with UCTD diagnosis [1–3, 11, 12]; (ii) confirmed ANA positivity; (iii) age at study inclusion <45 years; and (iv) pregnancies from 2010 to 2019.

ANA were tested by indirect immunofluorescence on HEp-2 cell substrate starting from 1:80 screening dilution of sera, up to 1:640 when appropriate. Fluoroscopic patterns were reported according to International Consensus on Antinuclear Antibody Patterns (ICAP) (www.anapatterns.org). ANA confirmed positivity was defined as ANA positivity \geq 1:160 tested on at least two different subsequent occasions 12 weeks apart.

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 considered statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

Results**Patients characteristics of our multicentre cohort**

The analysis included 133 consecutive women (mean age at conception 32.5 years, s.d. \pm 5.2; mean age at

data collection 38.3 years old, s.d. ± 6.8 ; mean disease duration at first conception 2.4 years, s.d. ± 10.1 ; mean follow-up after first conception 8.8 years, s.d. ± 11.7 ; mean disease duration at data collection 10.2 years, s.d. ± 5.1 ; mean follow-up at data collection 9.2 years, s.d. ± 4.7) who had a total of 224 pregnancies.

All patients were diagnosed with UCTD according to the established consensus [3, 5, 6]. Thirty-three patients (24.8%) tested persistently positive for aPL [6] [two patients (1.5%) had a confirmed triple positivity] and, of those, six patients also fulfilled the classification criteria for APS (two women had a previous history of thrombosis, three patients had a previous history of pregnancy morbidity and one patient had both clinical manifestations of APS [6]). Demographic and diagnostic characteristics of the patients included in the study are summarized in Table 1.

Joint involvement represented the most frequent clinical manifestation of the cohort (77 patients; 57.9%), followed by RP (55 patients; 41.3%), photosensitivity (43 patients; 32.3%) and haematological manifestations (36 patients; 27.1%).

All patients were positive for ANA and 48 patients (36.1%) were also found to be positive for anti-ENA, with anti-Ro/SSA positivity being the most common (45 patients; 33.8%), either alone or in combination with other anti-ENA antibody. In only three cases were anti-ENA detected without anti-Ro/SSA, namely three

TABLE 1 Demographic and diagnostic characteristics of the cohort

Patients characteristics	All (n = 133)	%
Age at conception, mean \pm s.d., years	32.5 \pm 5.2	
Age at data collection, mean \pm s.d., years	38.3 \pm 6.8	
Ethnicity		
Caucasians, n	114	85.7
Africans, n	14	10.5
Asians, n	1	0.75
Other, n	4	3
Diagnosis		
UCTD	133	100
Disease duration at data collection, mean \pm s.d., years	10.2 \pm 5.1	
Mean follow-up at data collection, mean \pm s.d., years	9.2 \pm 4.7	
UCTD and aPL	33	24.8
UCTD and APS	6	4.5
Disease evolution during follow-up		
Mean \pm s.d. years of follow-up for diagnosis evolution	5.3 \pm 2.8	
Patients achieving diagnosis of defined CTD at follow-up	16	12
SLE	7	5.3
MCTD	7	5.3
SSc	1	0.75
SS	1	0.75

patients tested positive for anti-RNP antibodies. Furthermore, 28 patients (21.1%) presented with low levels of C3, 19 patients (14.3%) presented with low levels of C4 and 30 patients (22.6%) presented with polyclonal hypergammaglobulinaemia. At the time of conception, however, no patients met the classification criteria for any definite CTD.

Clinical and laboratory characteristics of the patients included in the study are summarized in Table 2.

Sixty-three (47.4%) patients received low-dose aspirin and 19 (14.3%) cases were treated with low molecular weight heparin during pregnancy.

Thirty-eight patients (28.6%) received glucocorticosteroid treatment during pregnancy [medium daily prednisone-equivalent dosage 7.1 mg (± 3.1 mg)] and 58 patients (43.6%) were treated with HCQ. Immunosuppressant treatment with AZA was given in five (3.8%) women. Treatment received by the patients before, during and after pregnancy is outlined in Table 3.

Pregnancy outcomes

Of the 224 pregnancies analysed the fetal/perinatal outcomes were as follows: 177 (79%) resulted in live births, 45 (20.1%) in miscarriages (defined as pregnancy loss before 12 weeks gestation), 2 (0.9%) in stillbirths (pregnancy loss after 20 weeks' gestation) and 6 (2.7%) cases showed intrauterine growth restriction after 20 weeks' gestation. No pregnancy ended between 12 and 20 weeks' gestation. Maternal outcomes were as follows: 5 (2.2%) cases developed pre-eclampsia, 11 (4.9%) cases gestational hypertension and 12 (5.4%) cases were diagnosed with gestational diabetes.

When considering the live birth outcomes (177 live births), birth weight was ≤ 2500 g in 10.7% and ≤ 1500 g in 1.7%. In 11.9% of cases birth weight was below the 10th percentile (small for gestational age), while 9.1% cases had a birth weight between the 10th and 5th percentile, and 2.8% were under the 5th percentile. When considering gestational length in live births (total 177), 16.8% of all gestations lasted < 37 weeks, 12.4% between 37 and 34 weeks, and 4.4% lasted < 34 weeks.

Live birth pre-term (before 37 weeks of gestation) had a higher frequency of ENA positivity when compared with live births at term (57 vs 31%, $P < 0.05$, respectively).

The characteristics of fetal/perinatal and of maternal outcomes are summarized in Table 4.

Patients with first trimester miscarriages, were more likely to be diagnosed with obstetric APS (12.1 vs 0%; $P < 0.001$) when compared with those without, and were more frequently positive for aCL IgG/IgM (20 vs 9.8%; $P < 0.05$). In addition, patients with first trimester miscarriages were significantly more likely to have hyperlipidaemia (12.1 vs 2%; $P < 0.05$).

When considering patients who experienced more than one first trimester miscarriage, patients had significantly higher rates of aPL positivity (45.5 vs 22.6%; $P < 0.05$) when compared with those who did not, were

TABLE 2 Clinical and laboratory characteristics of the cohort

Clinical manifestations ^a	n (%)
Haematological	36 (27.1)
Leukopaenia	18 (13.5)
Thrombocytopaenia	10 (7.5)
Haemolytic anaemia	10 (7.5)
Skin	22 (16.5)
Malar rash	6 (4.5)
Telangiectasia	5 (3.8)
Alopecia	2 (1.5)
Livedo reticularis	2 (1.5)
Vitiligo	1 (0.75)
Morphea	1 (0.75)
Oral ulcers	5 (3.8)
Photosensitivity	43 (32.3)
Joints	77 (57.9)
Arthritis	32 (24.1)
Arthralgia	42 (31.6)
Tenosynovitis	3 (2.3)
Cardiac	6 (4.5)
Pericarditis	3 (2.25)
Valvulopathy	3 (2.3)
Renal	5 (3.8)
Urinary abnormalities	5 (3.8)
Muscular	13 (9.8)
Myalgia	9 (6.8)
Myositis	2 (1.5)
Enthesitis	2 (1.5)
RP	54 (40.6)
Pulmonary	7 (5.3)
Interstitial lung disease	4 (3)
Pleuritis	3 (2.3)
Xerophthalmia and xerostomia	20 (15)
Cardiovascular risk factors	
History of smoking	30 (22.6)
Arterial hypertension	11 (8.3)
Hyperlipidaemia	6 (4.5)
Diabetes mellitus (Type 2)	2 (1.5)
BMI, mean \pm s.d.	23.9 \pm 5.2
aGAPSS, mean \pm s.d.	1.92 \pm 3.3
Laboratory features	
ANA positive	133 (100)
Anti-ENA positive	48 (36.1)
Anti-Ro/SSA and anti-La/SSB	14 (10.5)
Anti-Ro/SSA	45 (33.8)
Anti-RNP	7 (5.3)
Anti-U1RNP	3 (2.3)
Anti-Sm	1 (0.75)
Anti-Jo1	1 (0.75)
Anti-Scl70	3 (2.3)
Anti-dsDNA positive	17 (12.8)
Low C3 levels	28 (21.1)
Low C4 levels	19 (14.3)
Hypergammaglobulinaemia	30 (22.6)
LA	15 (11.3)
aCL (IgG/IgM)	18 (13.5)
Anti- β 2GPI (IgG/IgM)	18 (13.5)

^aThe listed clinical manifestations of UCTD occurred at any time during disease course. Data are presented as *n* (%) unless otherwise indicated. Anti- β 2GPI: anti- β glycoprotein I; aGAPSS: adjusted Global AntiPhospholipid Score.

more likely to be diagnosed with obstetric APS (45.5 vs 0.8%; $P < 0.05$), had significantly more haematological manifestations (45.5 vs 25%; $P < 0.05$), in particular thrombocytopenia (18.2 vs 5.6%; $P < 0.05$), and had higher rates of positivity for LA (27.3 vs 9.6%; $P < 0.05$).

Of the two patients who experienced one episode of stillbirth, none was positive for aPL antibodies. Both patients were positive for anti-Ro/SSA and anti-La/SSB antibodies and fetuses had complete congenital heart block, identified by fetal echocardiography [8]. Of the two patients, one received low-dose aspirin and medium-high doses of steroids and IVIG plus plasmapheresis during pregnancy, while none received HCQ therapy. Notably, one of those patients presented with marked livedo reticularis at the lower limbs.

Disease evolution during follow-up

Patients had a mean follow-up at data collection of 9.2 years (s.d. ± 4.7). During the follow-up, 16 patients (12%) developed novel clinical and/or laboratory features, and their diagnosis was changed to definite CTD. Mean time of follow-up before the diagnosis of definite CTD was achieved was 5.3 years (s.d. ± 2.8). In more detail, seven patients (5.3%) were later classified according to ACR/EULAR classification criteria as SLE, seven patients (5.3%) as MCTD, one patient (0.75%) as SSc and one patient as SS. With a total follow-up after first pregnancy of 1417 patient-years, we observed an evolution to a defined CTD in one out every 88 patient-years.

When looking at pregnancy complications in patients who developed a definite CTD during follow-up, the patients that were later classified as having SLE had statistically higher frequencies of gestational hypertension (43 vs 7%; $P < 0.005$), pre-eclampsia (28 vs 2%; $P < 0.05$) and intrauterine growth restriction (28 vs 2%; $P < 0.05$).

Discussion

With regards to CTD conditions, a combination of clinical symptoms and laboratory findings are used to identify a distinct disease, or a definite CTD, according to the established classification criteria. Classification criteria are a set of characteristics (clinical or laboratory findings) that are used to group patients into well-defined homogeneous populations that share similar clinical features of disease. For autoimmune conditions, such criteria are often developed to select homogeneous cohorts of patients for clinical research and cannot be applied for diagnosis in a real-world setting [13]. Although the use of classification criteria to aid diagnosis is common in clinical practice, the suitability of their use in routine diagnosis is debated. In fact, classification criteria might fail to encompass all aspects of a disease. In the context of CTD, patients who do not fulfill criteria for a definite diagnosis are grouped under the term UCTD.

To date, the true prevalence and incidence of UCTD is unknown; however, some studies suggest that it

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

Therapy	Before pregnancy, N (%)	During pregnancy, N (%)	After pregnancy, N (%)
Immunosuppressants			
AZA	5 (3.8)	5 (3.8)	0
CSA	1 (0.75)	0	1 (0.75)
MMF	1 (0.75)	0	3 (2.3)
MTX	5 (3.8)	0	12 (9)
CYC	2 (1.5)	0	4 (3)
Rituximab	1 (0.75)	0	0
Glucocorticosteroids	47 (35.3)	38 (28.6)	48 (36.1)
Other			
Low-dose aspirin	20 (15)	63 (47.4)	18 (13.5)
Low molecular weight heparin	1 (0.75)	19 (14.3)	6 (4.5)
Vitamin K antagonists	0	0	1 (0.75)
HCQ	57 (42.9)	58 (43.6)	77 (57.9)
Statins	4 (3)	0	7 (5.3)
Anti-hypertensive drugs	3 (2.3)	0	18 (13.5)

should be considered one of the most frequent rheumatic diseases [14, 15]. Interestingly, a recent study in which 1210 first-trimester pregnant women were screened for rheumatic diseases showed that UCTD was the most frequently diagnosed systemic rheumatic disorder, with a prevalence as high as 2.5% [16]. While UCTD seems to be relatively common, the lack of definite classification criteria has some important implications, as to date there are no well-defined recommendations for UCTD patients. Consequently, there are no official recommendations on prevention and surveillance of maternal and fetal/perinatal complications during gestation for women with UCTD, who are followed-up according to their treating physician's judgement.

The findings of fetal outcomes in our cohort showed that the live birth rate was 79%, with 2.7% intrauterine growth restriction. Of the remaining pregnancies that ended in a pregnancy loss (21% of total pregnancies), the vast majority (95.5% of pregnancy loss) ended in a first trimester loss and only a small percentage (4.5% of pregnancy loss) ended in a stillbirth. Maternal outcomes showed that 2.2% of patients developed pre-eclampsia, 4.9% of the mothers developed gestational hypertension and 5.4% were diagnosed with gestational diabetes. Further, the rates of pre-term delivery (16.8%) and of Small gestational age (SGA) (11.9%) were rather high when compared with the general population [17, 18].

Our results are in line with previous experiences described in the literature, which report rates of any adverse pregnancy outcomes (including late pregnancy complications) in women with UCTD ranging from 25 to 30% [19–23], compared with an esteemed rate of early pregnancy loss in the general obstetric population from 10 to 20% [24–26].

It should be kept in mind that the results of our multi-centre study are influenced by the intensive surveillance conducted in the tertiary care centres participating in the study. All pregnancies are, in fact, prospectively

followed by a multidisciplinary team consisting of gynaecologists, obstetrics and rheumatologists specialized in the care of women during pregnancy with autoimmune conditions. In these regards, low-dose aspirin during pregnancy was given to 63 cases (47.4%), as a centre-specific indication for pregnancy treatment, independently from other concomitant factors such as maternal age or specific manifestations of underlying UCTD.

The rate of disease evolution of our cohort from a diagnosis of UCTD to a diagnosis of definite CTD was 12% with a mean follow-up of 9.2 years (s.d. ± 4.7), within a mean time of 5.3 years (s.d. ± 2.8). These results are in line with previous experiences reported in the current literature [5–7]. Importantly, we observed that the two patients who experienced one episode of stillbirth were both positive for anti-Ro/SSA and anti-La/SSB antibodies and their fetuses had complete CHB, supporting the need of specific counselling and surveillance when planning or during pregnancy in UCTD, as is routinely done in women with definite CTD. In a recent study by Fredi *et al.* [27], reporting data from the Italian Registry on Immune-Mediated Congenital Heart Block, the most frequent diagnosis was UCTD (24 out of 85 patients).

Interestingly, the mothers of the two fetuses who developed CHB were not treated with HCQ during pregnancy, the role of which in preventing cardiac neonatal lupus is supported by several retrospective studies [8, 28, 29]. In the same line, treatment during pregnancy in specific situations, such as anti-Ro/SSA positivity, might be advised through specific counselling. In this setting, considering that patients with UCTD might not have any clinical manifestations of the disease, pregnancy counselling is the most crucial, as patients might fear or fail to understand the importance of starting a therapy during such a critical time such as pregnancy. When considering study by Fredi *et al.* [27], the frequency of patients with isolated ENA positivity (anti-Ro/SSA and/or anti-La/SSB) and no clinical manifestations was as high as 45.8% of the entire Registry.

TABLE 4 Pregnancy outcomes

Pregnancy characteristics	All (n = 224) (%)
Age at conception, mean ± s.d.	32.5 ± 5.2
Mode of delivery	
Vaginal, n (%)	127 (71.8 ^a)
Vaginal spontaneous/induced, %	99/28
Cesarean section, n (%)	50 (28.2 ^a)
Outcomes	
Live births	177 (79)
Miscarriages	45 (20.1)
Stillbirths	2 (0.9)
Weight at birth, mean ± s.d., g	3192.4 ± 514
Gestation duration, mean ± s.d., weeks	36.2 ± 8.3
Birth at term (beyond 37 gestation weeks), n (%)	147 (83.1 ^a)
Mild pre-term birth (34–36 gestation weeks), n (%)	22 (12.4 ^a)
Moderate pre-term birth (28–33 gestation weeks), n (%)	7 (4 ^a)
Severe pre-term birth (prior to 28 gestation weeks), n (%)	1 (0.4 ^a)
Maternal and fetal complications	
IUGR	6 (2.7)
Pre-eclampsia	5 (2.2)
Eclampsia	0
Gestational hypertension	11 (4.9)
Gestational diabetes	12 (5.4)
Postpartum haemorrhage	2 (0.9)
Postpartum hypertensive crisis	1 (0.4)
Hypoxic-ischaemic syndrome	1 (0.4)
Neonatal complications	
Birthweight <10th percentile (small for gestational age), n	21 (11.9 ^a)
Birthweight 10th–5th percentile, n (%)	16 (9.1 ^a)
Birthweight <5th percentile, n (%)	5 (2.8 ^a)
Respiratory distress	1 (0.4)
Neonatal septicemia	2 (0.9)
Congenital heart block	2 (0.9)
Neonatal lupus	1 (0.4)
Placental thrombosis	1 (0.4)

^aPercentages are calculated considering viable babies (total = 177). IUGR: intrauterine growth restriction.

Our results also showed that a non-negligible number of UCTD patients have aPL positivity (14.7%). While only three patients (2.3%) fulfilled the diagnostic criteria for obstetric APS, nevertheless higher rates of aPL positivity were observed in those patients who presented with early miscarriages (less than 3), when compared with those without. These data support the concept that aPL testing should be routinely included in the laboratory assessment of UCTD patients, in order to identify those patients who are at higher risk for developing pregnancy morbidity.

This study has some limitations. First, its retrospective design might have influenced the reproducibility of the results and an intrinsic potential recall bias cannot be excluded. The high positivity of anti-Ro/SSA antibodies in the cohort (33.8%) could potentially be explained as

the reason for referral to the centres included in the study for a pregnancy follow-up. Second, previous medical history of UCTD patients was heterogeneous, including different organ involvement, and potentially affecting fetal/perinatal outcome. Third, as previously noted, since organ involvement was heterogeneous in this population, treatments before and during pregnancy were based on the treating physician's judgment and not according to a pre-defined standardized protocol.

The study has some strengths that need to be acknowledged as well. First, to the best of our knowledge, this is the largest and first multicentre cohort study to describe the overall fetal/perinatal and maternal outcomes in UCTD women with ANA positivity. Second, the inclusion criteria considered pregnancies from 2010 to 2019, in order to reflect current standard of care of pregnancy in women with UCTD and to improve the homogeneity of obstetric care in the cohort, which might help in reducing the intrinsic limitation of reproducibility of results and the potential recall bias. Nevertheless, some heterogeneity cannot be excluded, further supporting the need for updated classification criteria for UCTD, in order to identify homogeneous groups of patients at risk of developing diverse clinical manifestations, for both research and clinical settings.

In conclusion, this study has some important clinical messages. Women with UCTD should be referred to specialist follow-up when planning a pregnancy. Anti-ENA profiling and aPL testing should be mandatory, and further therapeutic approaches and management should be planned accordingly, as stated in the current EULAR recommendations [30] for pregnancy in women with SLE and APS.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

References

- 1 LeRoy EC, Maricq HR, Kahaleh MB. Undifferentiated connective tissue syndromes. *Arthritis Rheum* 1980;23: 341–3.
- 2 Alarcón GS, Williams GV, Singer JZ *et al.* Early undifferentiated connective tissue disease. I. Early clinical manifestation in a large cohort of patients with undifferentiated connective tissue diseases compared with cohorts of well established connective tissue disease. *J Rheumatol* 1991;18:1332–9.
- 3 Doria A, Mosca M, Gambari PF, Bombardieri S. Defining unclassifiable connective tissue diseases: incomplete, undifferentiated, or both? *J Rheumatol* 2005; 32:213–5.
- 4 Lunardi F, Balestro E, Nordio B *et al.* Undifferentiated connective tissue disease presenting with prevalent interstitial lung disease: case report and review of literature. *Diagn Pathol* 2011;6:50.

- 5 Mosca M, Tani C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): a new frontier for rheumatology. *Best Pract Res Clin Rheumatol* 2007;21:1011–23.
- 6 Mosca M, Tani C, Neri C, Baldini C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD). *Autoimmun Rev* 2006;6:1–4.
- 7 García-González M, Rodríguez-Lozano B, Bustabad S, Ferraz-Amaro I. Undifferentiated connective tissue disease: predictors of evolution into definite disease. *Clin Exp Rheumatol* 2017;35:739–45.
- 8 Brito-Zerón P, Izmirly PM, Ramos-Casals M, Buyon JP, Khamashta MA. The clinical spectrum of autoimmune congenital heart block. *Nat Rev Rheumatol* 2015;11:301–12.
- 9 Radin M, Schreiber K, Cuadrado MJ *et al.* Pregnancy outcomes in mixed connective tissue disease: a multicentre study. *Rheumatology (Oxford)* 2019;58:2000.
- 10 D'Agostino RB, Vasan RS, Pencina MJ *et al.* General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743–53.
- 11 Antunes M, Scirè CA, Talarico R *et al.* Undifferentiated connective tissue disease: state of the art on clinical practice guidelines. *RMD Open* 2018;4(Suppl 1):e000786.
- 12 Mosca M, Tani C, Vagnani S, Carli L, Bombardieri S. The diagnosis and classification of undifferentiated connective tissue diseases. *J Autoimmun* 2014;48–49:50–2.
- 13 Aggarwal R, Ringold S, Khanna D *et al.* Distinctions between diagnostic and classification criteria? *Arthritis Care Res (Hoboken)* 2015;67:891–7.
- 14 Bourn R, James JA. Preclinical lupus. *Curr Opin Rheumatol* 2015;27:433–9.
- 15 Elfving P, Marjoniemi O, Niinisalo H *et al.* Estimating the incidence of connective tissue diseases and vasculitides in a defined population in Northern Savo area in 2010. *Rheumatol Int* 2016;36:917–24.
- 16 Spinillo A, Beneventi F, Epis O *et al.* Prevalence of undiagnosed autoimmune rheumatic diseases in the first trimester of pregnancy. Results of a two-steps strategy using a self-administered questionnaire and autoantibody testing. *BJOG* 2007;115:51–7.
- 17 Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75–84.
- 18 Lesmes C, Gallo DM, Panaiotova J, Poon LC, Nicolaidis KH. Prediction of small-for-gestational-age neonates: screening by fetal biometry at 19–24 weeks. *Ultrasound Obstet Gynecol* 2015;46:198–207.
- 19 Spinillo A, Beneventi F, Locatelli E *et al.* The impact of unrecognized autoimmune rheumatic diseases on the incidence of preeclampsia and fetal growth restriction: a longitudinal cohort study. *BMC Pregnancy Childbirth* 2016;16:313.
- 20 Castellino G, Capucci R, Bernardi S *et al.* Pregnancy in patients with undifferentiated connective tissue disease: a prospective case-control study. *Lupus* 2011;20:1305–11.
- 21 Grava C, Ruffatti A, Milanese O *et al.* [Isolated congenital heart block in undifferentiated connective tissue disease and in primary Sjögren's syndrome: a clinical study of 81 pregnancies in 41 patients]. *Reumatismo* 2005;57:180–6.
- 22 Spinillo A, Beneventi F, Epis OM *et al.* The effect of newly diagnosed undifferentiated connective tissue disease on pregnancy outcome. *Am J Obstet Gynecol* 2008;199:632.e1–e6.
- 23 Mosca M, Neri R, Strigini F *et al.* Pregnancy outcome in patients with undifferentiated connective tissue disease: a preliminary study on 25 pregnancies. *Lupus* 2002;11:304–7.
- 24 Taraborelli M, Ramoni V, Brucato A *et al.* Brief report: successful pregnancies but a higher risk of preterm births in patients with systemic sclerosis: an Italian multicenter study. *Arthritis Rheum* 2012;64:1970–7.
- 25 Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *BMJ* 2000;320:1708–12.
- 26 Cohain JS, Buxbaum RE, Mankuta D. Spontaneous first trimester miscarriage rates per woman among parous women with 1 or more pregnancies of 24 weeks or more. *BMC Pregnancy Childbirth* 2017;17:437.
- 27 Fredi M, Andreoli L, Bacco B *et al.* First report of the Italian registry on immune-mediated congenital heart block (Lu.Ne Registry). *Front Cardiovasc Med* 2019;6:11.
- 28 Izmirly PM, Costedoat-Chalumeau N, Pisoni CN *et al.* Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. *Circulation* 2012;126:76–82.
- 29 Izmirly PM, Saxena A, Kim MY *et al.* Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. *Circulation* 2011;124:1927–35.
- 30 Andreoli L, Bertias GK, Agmon-Levin N *et al.* EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis* 2017;76:476–85.