Received: 20 May 2017 | Accepted: 22 August 2017

DOI: 10.1111/aji.12762

REVIEW ARTICLE

WILEY AJRI American Journal of Reproductive Immunology

Undifferentiated connective tissue diseases and adverse pregnancy outcomes. An undervalued association?

Arsenio Spinillo[1] | Fausta Beneventi[1] | Roberto Caporali[2] | Veronique Ramoni[2] | Carlomaurizio Montecucco[2]

[1]Division of Obstetrics and Gynecology, University of Pavia, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy

[2]Division of Rheumatology, University of Pavia, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy

Correspondence
Arsenio Spinillo, Department of Obstetrics and Gynecology. IRCCS Fondazione Policlinico San Matteo, Pavia, Italy.
Email: spinillo@smatteo.pv.it

Undifferentiated connective tissue diseases (UCTDs) are a heterogeneous group of disorders characterized by symptoms and signs suggestive of systemic autoimmune rheumatic disease (ARD), but which do not fulfill all the established criteria for definite diagnosis of a condition. Although a third of UCTDs can progress to a definite ARD within months or years, most UCTDs can remain stable for years with minimal disease activity. The annual incidence of UCTD in the general population ranges from 14 to 140 per 100 000 people. UCTDs are associated with the persistence of several circulating autoantibodies including antinuclear, antiphospholipid or antithyroid antibodies. Immunological evaluation of subjects with UCTDs suggests a proinflammatory state and dysregulation of the Th1/Th2 balance. Autoantibodies have well-known deleterious effects on placentation and have been associated with an increased risk of prematurity, fetal growth restriction (FGR), preeclampsia, and congenital atrioventricular heart block. Although epidemiological and biological data suggest a potential negative impact on reproductive outcomes, the relationship between UCTD and pregnancy outcomes has not been adequately studied. While awaiting definitive data from large studies, obstetricians should be aware that rheumatic disorders in their early, incomplete, or undifferentiated phases can adversely affect pregnancy outcomes, increasing the likelihood of pregnancy loss, FGR, preeclampsia, and prematurity.

KEYWORDS
autoimmune systemic diseases, fetal growth restriction, pregnancy, prematurity, rheumatic diseases, undifferentiated connective tissue diseases

1 | INTRODUCTION

The most common systemic autoimmune rheumatic diseases (ARDs) include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren syndrome (SS), polymyositis/dermatomyositis (PM/DM), systemic sclerosis (SSc), mixed connective tissue disease (MCTD), and antiphospholipid syndrome (APS), among others.[1] These disorders are characterized by the presence of autoantibodies and organ inflammation, including inflammation of the joints, muscles, blood vessels, skin, eyes, kidneys, lungs, gastrointestinal tract, and heart.[2,3] A well-established diagnosis of a rheumatic disease prior to pregnancy is associated with an increased risk of adverse pregnancy outcomes.[4] In particular, inflammatory arthritides are associated with increased rates of fetal growth restriction (FGR), small for gestational age (SGA) infants, preterm delivery, and cesarean section. Furthermore, APS and SLE are associated with increased risks of abortion, stillbirth, FGR, and preeclampsia.[5–7] Autoantibodies associated with APS or SLE are able to bind to trophoblasts, impairing angiogenesis and leading to defective placentation.[7,8] Extravillous trophoblast invasiveness could also be impaired by immune-mediated mechanisms involving the local production of cytokines.[9] Whatever the mechanism involved, compared to controls, pregnancies in women with rheumatic diseases are characterized by higher rates of defective placentation and increased resistance in maternal-fetal circulation, as demonstrated by Doppler

ultrasound studies.[10,11] Undifferentiated connective tissue diseases (UCTDs) are a heterogeneous group of systemic autoimmune rheumatic disorders characterized by clinical and serological findings that do not fulfill a definite diagnosis of rheumatic disease.[12–14] In almost a third of cases, these disorders precede a diagnosis of full-blown rheumatic disease by months or years but can also remain stable for years with minimal disease activity.[12–14] Biologically, UCTDs are accompanied by impaired regulatory T cells leading to an imbalance between pro- and anti-inflammatory cytokines, characterized by increased peripheral levels of IL-6, IL-1, IL-12, and IL-17, and simultaneous reduction in IL-10.[15]

Although there is epidemiological, clinical, and biological evidence suggesting a potential negative impact of UCTDs on reproduction, the role of these rheumatic disorders on pregnancy outcome remain poorly understood and are scarcely recognized in the literature.[1,4]

2 | EPIDEMIOLOGY AND DIAGNOSIS OF UNDIFFERENTIATED CONNECTIVE TISSUE DISEASES

Definite diagnosis of a systemic rheumatic disease, such as RA, SLE, SS, PM/DM, or APS, is usually made based on a combination of symptoms and laboratory findings, which can be used to identify a distinct disease according to the established classification criteria.[16] Sensitivity and specificity of the classification criteria are far from perfect, as most rheumatic disorders progress to a definite disease as the result of a dynamic process with spontaneous worsening or improvement of symptoms, which can last from months to years.[17] In this "preclinical" phase, rheumatic disorders usually lack criteria for classification as a distinct disease, and the definition of these disorders ranges from early, preclinical, unclassifiable, or undifferentiated.[18,19]

Undifferentiated connective tissue diseases are defined as a clinical entity characterized by the following: (i) signs and symptoms suggestive of a rheumatic disorder, but that do not fulfill the established criteria for a rheumatic disease; and (ii) the presence of antinuclear antibodies (ANA) at a titer ≥1:80[12–14]. According to longitudinal data, the duration of symptoms differentiates the two groups of UCTDs. The first group includes subjects with a stable disease for at least 3 years, with mild to moderate clinical manifestations that require only minimal therapeutic intervention[13,20]. The second group of UCTDs includes subjects with a recent onset of symptoms that are expected to evolve into a definite rheumatic disease within months to years. Therefore, a consistent diagnosis of UCTD, although retrospective in nature, is essential for standardizing the classification criteria in both clinical and research settings.

In Europe and North America, the annual incidence per 100 000 people for the most common major rheumatic diseases is 10-40 for adult RA, 2-7 for SLE, 13-30 for SSc, and 4-6 for SS.[21,22] In women, the lifetime risk of major rheumatic diseases such as RA, SLE, and SS, as evaluated by medical registries, is about 8%, corresponding to 1 in 12 women.[23] The main difficulty in evaluating the incidence of UCTD is related to the definition of the syndrome, both in terms of the characteristics of the disease and duration of symptoms. In a population with an RA incidence of 10 per 100 000 people, it was reported that more than 60% of the suspected cases of RA initially included in the study remained undetermined after 6 months of follow-up.[24] Other studies suggest that the annual incidence of undifferentiated arthritis ranges from 41 to 149 per 100 000 adults, with 21%-87% persistence in the undifferentiated state over time.[25] Similar to RA, in a cohort study of potential SLE subjects, more than 60% of subjects initially included in the study still had an undifferentiated form of connective tissue disease after 6 years of follow-up.[26] In a definite population from Finland, UCTD was the most common form of rheumatic disease with an annual incidence of 13.6 per 100 000 people.[27] In Italy, the annual incidence of early arthritis is higher (98 per 100 000 people) than that reported in Northern European countries, but similar to that reported for the USA.[28] Finally, in a screening study including first-trimester pregnant women, UCTD was the most frequently diagnosed systemic rheumatic disorder, with a prevalence of 2.5%.[29] Taken together, these data suggest that UCTDs are probably relatively common among women of reproductive age and can be frequently encountered by obstetricians both before and during pregnancy.

3 | UNDIFFERENTIATED CONNECTIVE TISSUE DISEASES AND PREGNANCY OUTCOMES

Full-blown ARDs have well-known deleterious effects on human fertility and pregnancy outcomes.[1,4] Reproductive failures are more common among women with SLE or APS than healthy controls.[1,2,6] Arthitides, including RA, are predominantly associated with increased rates of prematurity, SGA infants, and FGR.[1,5] Systemic lupus erythematosus and obstetric APS are associated with an increased risk of preeclampsia, FGR, and thrombosis, including the so-called catastrophic APS, a diffuse thrombotic microangiopathy causing multiple organ failure.[4,6]

Many epidemiological studies have suggested that increased rates of adverse pregnancy outcomes can precede a definite diagnosis of ARD by years, suggesting that autoimmune diseases in early, undifferentiated, or incomplete states can negatively affect the reproductive outcome.[30–35] A nationwide Danish cohort study on 1.9 million infants showed a reduction in birthweight and placental weight for infants born to women with preclinical AR, in addition to a 30% increased risk of preterm birth.[31] Increased rates of adverse pregnancy outcomes, such as a previous very low birthweight (<1500 g) infant, has been linked to a 4-time increase in the relative risk of a subsequent RA diagnosis.[32] In a study from the USA, rates of stillbirth, preeclampsia, prematurity, and FGR were significantly increased among women with preclinical SLE compared to healthy controls.[33] Similar results have been obtained by a recent population-based Swedish study.[34] In particular, compared to healthy controls, the rates of preterm delivery and preeclampsia were increased by 5-6 times among women that were subsequently diagnosed with SLE within 0-2 years, and by 2.5-3 times among those that were diagnosed within 3-5 years.[34] In a retrospective

multicenter matched case-controlled study, van Wyk et al found that the odds ratios of hypertensive complications of pregnancy and FGR were increased by 2.6 and 3.9 times, respectively, among women who later developed SSc.[35] Finally, evidence suggests that women with no criteria or incomplete APS had worse reproductive outcomes compared to controls, and these women benefited from standard treatment with low molecular weight heparin during pregnancy.[36] Although epidemiological data suggest that UCTDs, either as early or incomplete manifestations of a subsequent ARD or as a stable condition with minimal disease activity, are probably as common as other rheumatic disorders among women of reproductive age,[25–28] and the effect of these disorders on pregnancy outcomes are surprisingly poorly studied, scarcely acknowledged, and probably under evaluated.[1,4,7] Studies on the association between pregnancy and UCTD are limited and often focus on evaluation of the effect of pregnancy on UCTD outcome, rather than the reverse (Table 1). In 1996, Stephenson et al reported that UCTD was associated with an increased risk of habitual abortion[37]. Bowden et al performed a prospective case-controlled study of 133 pregnant subjects and showed that undifferentiated arthritis was associated with a lower birthweight compared to controls.[38] In prospective studies of women with stable UCTD, the prevalence of moderate to severe adverse pregnancy outcomes including spontaneous abortion, congenital fetal heart rate block, prematurity, or SGA ranged from 25% to 30%.[39–42] An increased risk of SGA infants and pregnancy complications were also found in a case-controlled study of 41 subjects with early UCTD that was diagnosed at the beginning of pregnancy.[41] Stable preexisting UCTDs are traditionally considered a low-risk condition with only a modest adverse effect on pregnancy outcome.[39,42] On the other hand, early, previously unrecognized UCTDs that are diagnosed during pregnancy appear to be associated with a more marked increase in the risk of adverse pregnancy outcomes.[41] In a recent cohort study, early UCTDs diagnosed during the first trimester of pregnancy were associated with a fourfold increase in the risk of either FGR or preeclampsia and were responsible for up to 19% of all cases of preeclampsia or FGR.[43] In epidemiological registries of neonatal lupus without heart block, UCTD is the most frequent rheumatic disease associated with this condition.[44] Undifferentiated rheumatic disorders are also the most frequent disorders that precede severe atrioventricular block in the fetus.[45] The bulk of these data suggest that preexisting UCTDs or those diagnosed during pregnancy negatively impact on pregnancy outcome. The impact is probably less severe than well-established rheumatic diseases; however, given their relative frequency, undifferentiated disorders may be responsible for a significant proportion of adverse reproductive outcomes.[25–28,43] As for the effect of pregnancy on the course of UCTD, a disease flare during gestation or puerperium requiring medical treatment, or progression to a definite rheumatic disease, has been reported in 25%-30% and 5%-10% of cases, respectively.[39–42]

4 | BIOLOGICAL BASIS OF ADVERSE PREGNANCY OUTCOMES

The adverse effects of ARDs on pregnancy outcomes are mediated by the negative interference of autoantibodies on the immune-mediated and uterine vascular modifications necessary for correct implantation and subsequent development of an adequate placental vascular bed.[1,4,6,7] Antiphospholipid antibodies (aPL) such as anticardiolipin (aCL), lupus anticoagulant (LAC), and anti-β2-glycoprotein-I (aβ2-GPI), which are typical but not exclusive of APS, can bind to phospholipid adhesion molecules causing trophoblast failure and intraplacental thrombosis, leading to functional impairment of the fetoplacental unit.[8] Antiphospholipid antibodies are also able to interfere with the endometrial angiogenesis and trophoblast invasiveness of maternal spiral arteries, increasing hemodynamic resistance in the uteroplacental system.[46] The consequences of early defective placentation include an increased risk of reproductive failure, FGR, preeclampsia, and prematurity typical of APS, SLE, or RA.[4,6,7] Other potential mechanisms causing poor placentation in ARDs include both humoral and cellular immunological consequences of

TABLE 1 Studies evaluating reproductive and pregnancy outcomes among subjects with undifferentiated connective tissue disease (UCTD)

Authors (year)	No. of patients	Type of study	Reproductive outcome
Bowden et al (2001)[38]	133 pregnant women with either RA or UCTD and 103 healthy pregnant controls	Cohort case-control RA or UCTD pregnancies vs matched healthy pregnancies	Infant born to women with RA or UCTD had lower birthweight than controls
Mosca et al (2002)[39]	25 pregnant women with stable UCTD	Cohort study. Observational	Spontaneous abortion and/or obstetric complications in 36% of subjects
Grava et al (2005)[40]	25 pregnant women with stable UCTD	Cohort study. Observational	One case (4%) of CHB and one case (4%) of transient neonatal heart conduction disturbances
Spinillo et al (2008)[41]	41 pregnant women with early UCTD and 82 healthy pregnant controls	Cohort case-control UCTD pregnancies vs healthy pregnancies	Increased odds of SGA and complications of pregnancy among UCTD
Castellino et al (2011)[42]	55 pregnant women with stable UCTD and 53 non-pregnant controls	Cohort case-control Pregnant vs non-pregnant UCTD	Complications of pregnancy in 21.8% of cohort
Spinillo et al (2016)[43]	199 pregnant women with ARDs or early UCTD and 597 healthy pregnant controls	Cohort case-control Pregnancies with ARDs or UCTD vs healthy pregnancies	Increased odds of SGA, FGR, preeclampsia, cesarean section among UCTD.

the proinflammatory state characteristic of systemic diseases.[1,4–7] It has been suggested that the high inflammatory environment associated with ARDs could influence the balance between blood levels of anti-angiogenic and angiogenic factors, such as soluble fms-like tyrosine-kinase 1 (s-Flt-1) and placental growth factor (PIGF), leading to an increased risk of preeclampsia.[47] It is also possible that modifications in the innate immune response associated with ARDs can influence the risk of pregnancy complications. Preeclampsia, for example, has been traditionally considered to result from an imbalance in the Th1 (inflammatory) and Th2 (tolerance) response of the immune system.[48] Recent data suggest that the innate immune system plays a significant role in the development of preeclampsia and FGR.[9] It has been suggested that upregulation of the Th17 lymphocyte subpopulations that sustain the Th1 response and downregulation of the T-reg subpopulations that impair immune tolerance are key factors in the pathogenesis of preeclampsia.[9,49] Interestingly, Th17 activity is consistently upregulated in RA, SLE, and Sjogren syndrome, whereas a reduction in the number and/or activity of Treg cells has been found to be associated with the occurrence and disease activity in RA and SLE.[50] Mesenchymal stem cells play a key role in the regulatory mechanism underlying the Th1/Th2/Th17 balance in both pregnancy and autoimmune diseases.[9,51] The tolerogenic action of these cells can be mediated by the secretion of HLA-G, which is typically upregulated by proinflammatory cytokines and during pregnancy.[9,52]

Some of the adverse effects of ARDs on pregnancy outcomes can be mediated by their association with thyroid autoimmunity. In particular, subjects with ARDs have an increased prevalence of antithyroid antibodies in both pregnant and non-pregnant states.[53,54] In addition, the detection of isolated antithyroid antibodies is a risk factor for the subsequent development of a rheumatic disorder.[54] Antithyroid antibodies, even in the presence of euthyroidism, have been associated with increased rates of pregnancy losses and preterm deliveries.[53,55]

The potential biological mechanisms underlying the association between UCTD and adverse pregnancy outcomes vary (Table 2). In the majority of cases, subjects with UCTD test positive for ANA, and up to 40% of cases show positivity for multiple autoantibodies including aPL and anti-Ro/SSA.[56] Indeed, aPL can exert a negative effect on placentation regardless of whether the patient shows rheumatic symptoms or has a well-defined rheumatic disease.[36,57] In both animal and human studies, ANA positivity is associated with increased pregnancy losses and pregnancy complications, suggesting that the presence of autoantibodies is an obvious risk factor for reproductive failure, even in the absence of a definite rheumatic disease.[2,7]

Markers of endothelial cell activation or damage and carotid intima-media thickness are increased among subjects with UCTD, whereas brachial artery flow-mediated vasodilatation is reduced, suggesting systemic endothelial dysfunction associated with autoimmune serological abnormalities.[61] The increased resistance of blood flow velocities of uterine arteries in the first and second trimesters of pregnancy, as measured by Doppler ultrasound, suggests that surrogate markers of adequate early placentation are impaired among pregnant subjects with UCTD compared to controls.[10]

Several studies have shown that the immunological abnormalities typical of major ARDs, such as an increased number of Th17 lymphocytes, elevated serum IL-17 concentration, and a corresponding reduction in the number or activity of Treg cells, can also be detected in UCTD and are further increased among subjects progressing from undifferentiated to definite ARDs.[64] Altered Th1/Th2 and Treg balance among pregnant UCTD subjects is further confirmed by the overexpression of maternal sHLA-G and by the direct correlation between maternal and cord blood sHLA-G concentration with maternal ANA titer.[52]

For the major ARDs, in addition to UCTD, it is possible that some of the pregnancy complications can be attributed to thyroid autoimmunity. Thyroid peroxidase and thyroglobulin autoantibodies can be detected in up to 60% of pregnant women with early UCTD, and conversely, rheumatic disorders are common among pregnant women with thyroid autoimmunity.[54] Cohort studies suggest that the negative effects of thyroid autoimmunity and rheumatic disorders on pregnancy outcomes are independent and additive.[54,67]

5 | SURVEILLANCE OF UCTD DURING PREGNANCY

Although UCTD is one of the most common rheumatic disorders among women of reproductive age, in the literature, there are no definite recommendations about prevention and surveillance of maternal and fetal complications during gestation. As for other rheumatic disorders, a disease in a quiescent status represents the ideal condition to start pregnancy. To identify a potential thrombophilic status, subjects with early or well-established UCTD should be tested in prenatal period and/or at the beginning of pregnancy for the presence of antiphospholipid antibodies (aCL, aβ2-GPI, and LAC). As UCTD is one of the most common rheumatic disorders preceding congenital fetal heart block (CHB), anti-extractable nuclear antigens (ENA) antibodies including anti-Ro/SSA and anti-La/SSA should be part of serological screening of UCTD subjects before and during pregnancy.[45,68] Antithyroperoxidase (anti-TPO) and antithyroglobulin (anti-TG) antibodies are rather common among UCTD subjects and have been associated with increased risk of pregnancy losses, CHB, and complications of pregnancy.[67,69] The rates of complications of pregnancy associated with UCTD are lower compared with well-defined rheumatic but higher than in healthy controls.[39–43] As for other ARDs, pregnant subjects with either early or established UCTD should be followed up during pregnancy by a multidisciplinary team including obstetricians and rheumatologists using a tailored approach taking into account the severity of signs and symptoms of rheumatic disorder. Guidelines for follow-up in pregnancy in subjects with SLE and/or APS have been recently published[70] and a similar approach modulated according to the autoantibody profile and clinical features can be used for UCTD subjects (Figure 1). To detect a disease flare or a complication of autoimmune disease, rheumatologic evaluations including clinical assessment and laboratory tests should be carried out every 4-8 weeks. Obstetric clinical evaluations should be performed

TABLE 2 Biological mechanisms potentially causing adverse pregnancy outcomes among women with undifferentiated connective tissue disease (UCTD)

Authors (year)	Type of study	Biological characteristics	Potential reproductive impact
Alarcon et al (1991)[12]	Cohort study. Stable UCTD	High prevalence (>50%) and persistence of ANA and other autoantibodies	ANA associated with poor reproductive outcome in IVF cycles. Increase thrombosis of placental vessels.[2,58]
Mosca et al (1999)[56]	Cohort study. Stable UCTD	High prevalence (>80%) of autoantibodies. High prevalence of anti-Ro-ssa (30%) and anti-RNP (28%)	Anti-Ro/SSA associated with defective placentation, increased risk of pregnancy loss, FGR prematurity, and CHB.[45,46,59]
Bortoluzzi et al (2016)[60]	Cohort study. Stable UCTD	10%-13% prevalence of aPL	aPL associated with defective trophoblast invasion and subsequent fetal loss, FGR, and preeclampsia.[2,8,57]
Laczik et al (2014)[61]	Cohort study. Stable UCTD	Increased plasma concentrations of markers of endothelial dysfunction (Endothelin-1, thrombomodulin) and increased arterial resistance to nitric oxide	Endothelin-1 regulate trophoblast invasion of spiral arteries. Upregulated in preeclampsia and FGR. Plasma thrombomodulin increased in preeclampsia as a marker of endothelial dysfunction.[62,63]
Szodoray et al (2013)[64]	Cohort study. Stable UCTD	Increase in plasma th17/Treg ratio Reduction in number and function of subsets of Treg cells	Upregulation of Th17 associated with defective placentation, pregnancy loss, and preeclampsia. Reduced number or function of Treg associated with preeclampsia.[49,65,66]

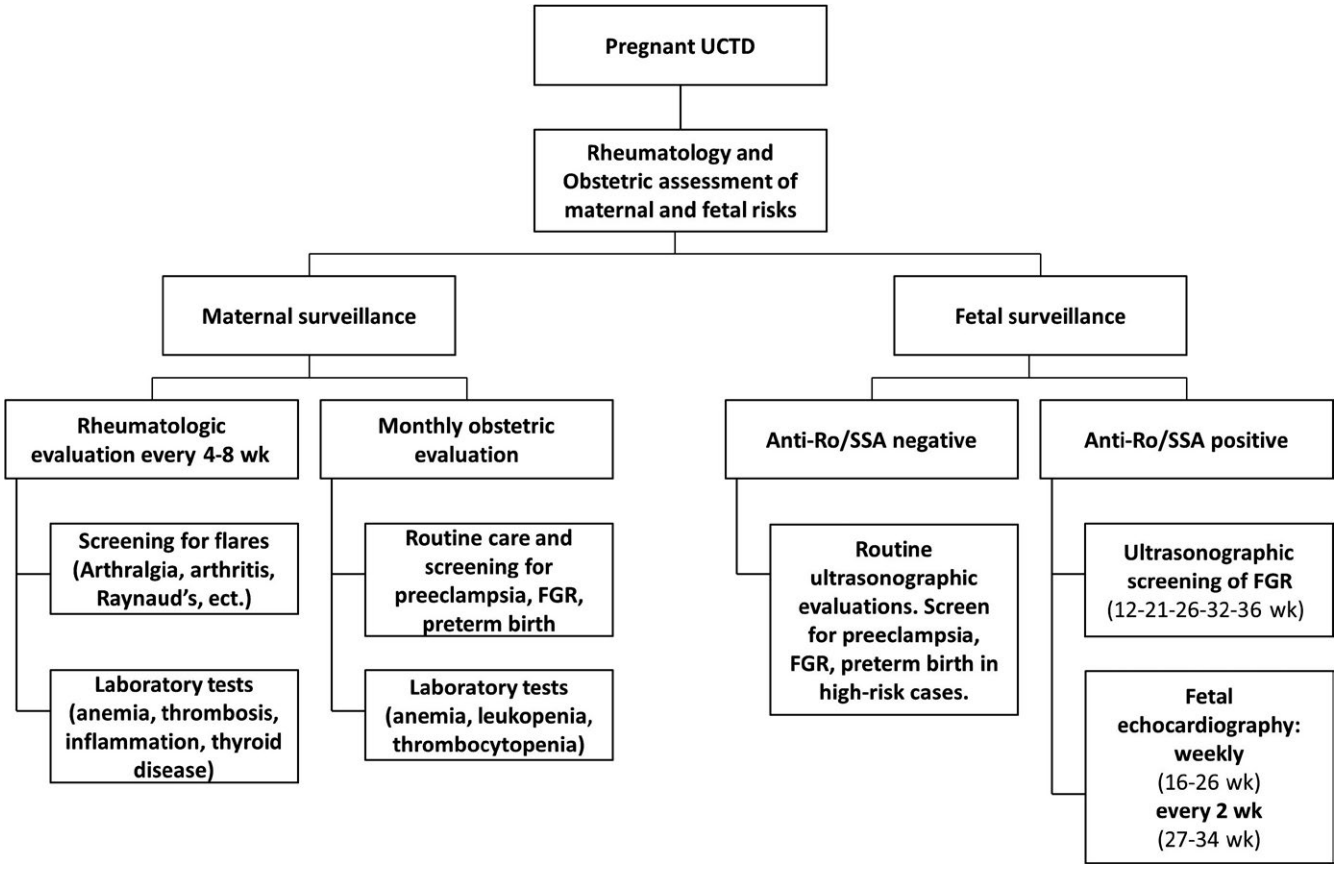

FIGURE 1 Surveillance of undifferentiated connective disease (UTCD) during pregnancy. FGR, Fetal growth restriction

monthly while the frequency of ultrasound scans with fetal biometry and Doppler sonography after first- and second-trimester routine ultrasonographic screenings should be scheduled according to the autoantibody picture, severity of disease, and 2nd trimester results of Doppler pulsatility index of uterine arteries. Third-trimester supplementary fetal surveillance with longitudinal ultrasound evaluations of fetal biometry and Doppler sonography of fetal district (umbilical artery, middle cerebral artery, and ductus venosus) can be reserved to subjects at risk for early and late fetal growth restriction.[70] Several studies[45,68] have found that UCTD is one of the most common rheumatic disorders antedating CHB, suggesting that UCTD subjects positive for Anti-Ro/SSA should be screened and followed for fetal atrioventricular block. In anti-Ro/SSA-positive subjects, fetal echocardiography should be performed weekly from 16 to 26 weeks

and then biweekly until 34 weeks, followed by an ECG and echocardiogram at birth.[71]

6 | TREATMENT OF UCTD AND ASSOCIATED PROBLEMS DURING PREGNANCY

Most UCTD subjects both before and during pregnancy present with mild clinical features including arthralgia, arthritis, Raynaud's phenomenon, or mild hematological alterations generally without severe organ involvement and not requiring a specific treatment.[12–14,20] Immunosuppressive treatment is rarely needed, while corticosteroids and hydroxychloroquine are generally used to control symptoms.[20] These drugs are safe and, if necessary, can be continued during pregnancy. About 25-30% of subjects with UCTD antedating pregnancy can have a disease flare requiring treatment during gestation including a 5%-10% of subjects who progress from UCTD to a definite rheumatic disease[39,41,42] (Figure 2). Although discontinuation of hydroxychloroquine during pregnancy increases the degree of activity and the rate of flares in lupus pregnant patients,[71] there are no data on the effect of antimalarial drugs on the rate of flares or progression to a definite ARD in pregnancy among women with stable UCTD. Results from case-control and cohort studies suggest that the use of hydroxychloroquine during pregnancy reduces the risk of congenital fetal heart block in subjects with SLE.[72,73] For this reason, among pregnant UCTD subjects with anti-Ro/SSA antibodies, anti-La/SSB antibodies with or without autoimmune hypothyroidism, antenatal hydroxychloroquine prophylaxis should be strongly considered.[72–74] In CHB cases, steroids and other treatments should be administered according to current standards.[75] Prophylactic anticoagulation with low molecular weight heparin and/or low-dose aspirin throughout pregnancy and 6-week postpartum is the accepted standard treatment to prevent fetal losses and complications of pregnancy among "high-risk" carriers of aPL (positivity in all the three aPL assays, the presence of a past thrombotic event).[70,76] However, current data suggest that anticoagulation may be appropriate to reduce fetal losses also for pregnant women with a single aPL positivity and without previous thrombotic events.[36,70,76]

7 | PERSPECTIVES

The overall prevalence of systemic autoimmune diseases in the general population range from 5% to 9%, with a steady annual increase of 6% in the incidence of rheumatic, intestinal, and endocrine disorders over the past 30 years.[21–24,77] At least part of this increase can be

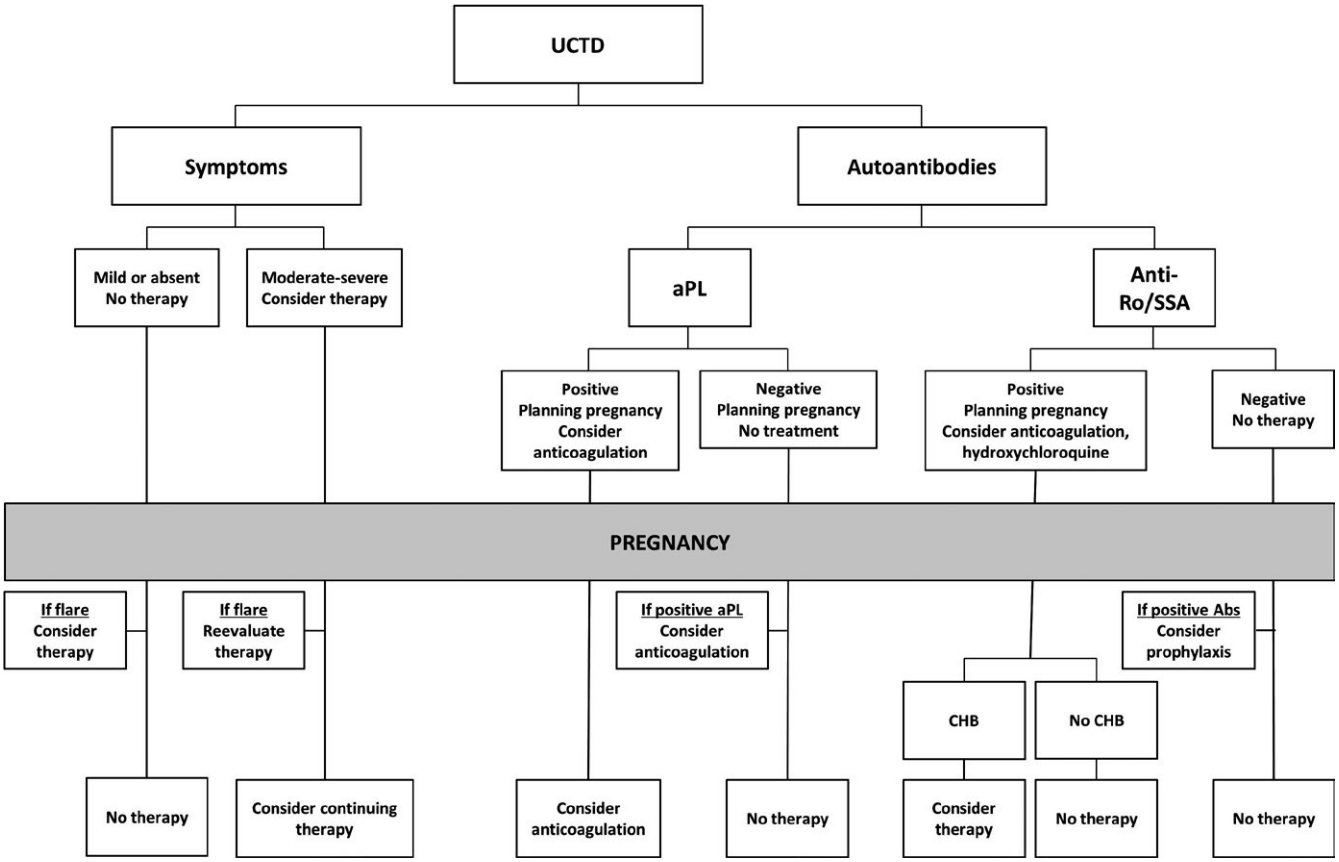

FIGURE 2 Treatment of undifferentiated connective tissue disease (UCTD) and associated problems during pregnancy. aPL, Antipholipid antibodies; CHB, Congential heart block

attributed to improved patient survival and increased physician awareness.[77] Among systemic autoimmune disorders, ARDs have a great impact on reproductive failure, disability, social, and healthcare costs and on quality of life.[1,4,6,7] The clinical course of ARDs is characterized by a long preclinical phase that lasts from months to years.[24–27] During this period, the clinical manifestations of rheumatic disorders are usually mild and often remittent; however, serum autoantibody levels and markers of immunological dysregulation such as cytokine imbalance are already detectable and can have a profound negative effect on reproduction, cardiovascular, and lung diseases.[30–35] The subsequent development of a definite ARD during this period is dependent on the interaction between hormonal, genetic, environmental, and microbiological factors, which are potentially modifiable, and therefore, the preclinical phase of ARDs is considered crucial for screening and prevention of disease progression.[18,19,25,26] Screening measures based on the detection of symptoms and/or markers of autoimmunity have been encouraged in the rheumatologic literature, but a precise screening strategy including identification of the population to be screened or the tests to be used has not yet been clearly defined.[78,79] Early evidence suggests that screening measures in pregnancy based on a two-step sequential approach, where the first step is the screening of symptoms and the second step is autoantibody detection among subjects with symptoms, can be useful for identifying early, incomplete, or undifferentiated rheumatic disorders.[29,43,80] Although data in non-pregnant subjects suggest that early identification and treatment of rheumatic disorders is associated with less severe organ damage and an increased likelihood of remission,[19,25,81] data on the effect of implementation of screening procedures for autoimmune diseases on pregnancy outcome are still lacking.

Early and stable UCTDs should be recognized as significant risk factors for poor reproductive outcomes, and similar to other rheumatic diseases, increased surveillance of the uterine artery during the first and second trimesters and umbilical artery Doppler velocities and fetal biometry during the third trimester should be taken into consideration. Additional tests and/or treatments such as fetal echocardiography, low-dose aspirin, or low molecular weight heparin should possibly be added based on patient autoantibody profile. Flares of rheumatic symptoms, which occur in 25% of subjects, should be promptly referred to rheumatologists for appropriate treatment. Only future studies can establish the potential beneficial impact of screening measures, increased surveillance, and early treatment of UCTDs on pregnancy outcomes. In the meantime, obstetricians should be aware that even in the absence of severe symptoms, rheumatic disorders in their early, incomplete, or undifferentiated phases can adversely affect pregnancy outcomes, increasing the likelihood of FGR, preeclampsia, and prematurity.

CONFLICT OF INTEREST

The authors report no conflict of interest.

ORCID

Arsenio Spinillo http://orcid.org/0000-0002-7755-1084

REFERENCES

1. Østensen M, Cetin I. Autoimmune connective tissue diseases. *Best Pract Res Clin Obstet Gynaecol*. 2015;29:658-670.
2. Scofield RH. Autoantibodies as predictors of disease. *Lancet*. 2004;362:1544-1546.
3. Satoh M, Vasqez-Del Mercado M. Clinical interpretation of antinuclear antibody tests in systemic rheumatic diseases. *Mod Rheumatol*. 2009;19:219-228.
4. Østensen M, Andreoli L, Brucato A, et al. State of the art: reproduction and pregnancy in rheumatic diseases. *Autoimmun Rev*. 2015;14:376-386.
5. Ince-Askan H, Dolhain RJ. Pregnancy and rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2015;29:580-596.
6. Østensen M, Clowse M. Pathogenesis of pregnancy complications in systemic lupus erythematosus. *Curr Opin Rheumatol*. 2013;25:591-596.
7. Carp HJ, Selmi C, Shoenfeld Y. The autoimmune bases of infertility and pregnancy loss. *J Autoimmun*. 2012;38:J266-J274.
8. Di Simone N, Meroni PL, de Papa N, et al. Antiphospholipid antibodies affect trophoblast gonadotropin secretion and invasiveness by binding directly and through adhered beta2-glycoprotein I. *Arthritis Rheum* 2000;43:140e50.
9. Perez-Sepulveda A, Torres MJ, Khoury M, Illanes SE. Innate immune system and preeclampsia. *Front Immunol*. 2014;5:244.
10. Beneventi F, Locatelli E, Ramoni V, et al. Uterine artery Doppler velocimetry and obstetric outcomes in connective tissue diseases diagnosed during the first trimester of pregnancy. *Prenat Diagn*. 2012;32:1094-1101.
11. Le Thi Huong D, Wechsler B, Vauthier-Brouzes D, et al. The second trimester Doppler ultrasound examination is the best predictor of late pregnancy outcome in systemic lupus erythematosus and/or the antiphospholipid syndrome. *Rheumatology (Oxford)*. 2006;45:332-338.
12. Alarcón GS, Williams GV, Singer JZ, et al. Early undifferentiated connective tissue disease.I. Early clinical manifestations in a large cohort of patients with undifferentiated connective tissue diseases compared with cohorts of well established connective tissue disease. *J Rheumatol*. 1991;18:1332-1339.
13. Mosca M, Tani C, Vagnani S, Carli L, Bombardieri S. The diagnosis and classification of undifferentiated connective tissue diseases. *J Autoimmun* 2014;48:50-52.
14. Doria A, Mosca M, Gambari PF, Bombardieri S. Defining unclassifiable connective tissue diseases: incomplete, undifferentiated or both? *J Rheumatol*. 2005;32:213-215.
15. Nakken B, Bodolay E, Szodoray P. Cytokine milieu in undifferentiated connective tissue disease: a comprehensive review. *Clin Rev Allergy Immunol*. 2015;49:152-162.
16. Johnson SR, Goek ON, Singh-Grewal D, et al. Classification criteria in rheumatic diseases: a review of methodologic properties. *Arthritis Rheum*. 2007;57:1119-1133.
17. June RR, Aggarwal R. The use and abuse of diagnostic/classification criteria. *Best Pract Res Clin Rheumatol*. 2014;28:921-934.
18. Raza K, Gerlag DM. Preclinical inflammatory rheumatic diseases: an overview and relevant nomenclature. *Rheum Dis Clin North Am*. 2014;40:569-580.
19. Deane K, Norris JM, Holers VM. Pre-clinical rheumatoid arthritis: identification, evaluation and future directions for investigations. *Rheum Dis Clin North Am*. 2010;36:213-241.
20. Vaz CC, Couto M, Medeiros D, et al. Undifferentiated connective tissue disease: a seven-center cross-sectional study of 184 patients. *Clin Rheumatol*. 2009;28:915-921.
21. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality and comorbidity of rheumatic diseases. *Arthritis Res Ther*. 2009;11:229-245.

22. Shapira Y, Agmon-Levin N, Shoenfeld Y. Geoepidemiology of autoimmune rheumatic diseases. *Nat Rev Rheumatol*. 2010;6:468-476.
23. Crowson CS, Matteson EL, Myasoedova E, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis Rheum*. 2011;63:633-639.
24. Hazes JM, Luime JJ. The epidemiology of early inflammatory arthritis. *Nat Rev Rheumatol*. 2011;14:381-390.
25. Deane KD, El-Gabalawy H. Pathogenesis and prevention of rheumatic disease: focus on preclinical RA and SLE. *Nat Rev Rheumatol*. 2014;10:212-228.
26. Bourn R, James J. Preclinical lupus. *Curr Opin Rheumatol*. 2015;27:433-439.
27. 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;36:917-924.
28. Benucci M, Cammelli M, Manfredi M, Saviola G, Baiardi P, Mannoni A. Early rheumatoid arthritis in Italy: study of incidence based on two-level strategy in a sub area of Florence (Scandicci-Le Signe). *Rheumatol Int*. 2008;28:777-781.
29. Spinillo A, Beneventi F, Epis OM, 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*. 2008;115:51-57.
30. Gleicher N. Reproductive failure prior to the onset of clinical autoimmune diseases. *Rheumatology*. 1999;38:485-487.
31. Rom AL, Wu CS, Olsen J, et al. Fetal growth and preterm birth in children exposed to maternal or paternal rheumatoid arthritis: a nationwide cohort study. *Arthritis Rheumatol*. 2014;66:3265-3273.
32. Ma KK, Nelson JL, Guthrie KA, Dugowson CE, Gammill HJS. Adverse pregnancy outcomes and risk of subsequent rheumatoid arthritis. *Arthritis Rheum*. 2014;66:508-512.
33. Dhar JP, Essenmacher LM, Ager JW, Sokol RJ. Pregnancy outcomes before and after a diagnosis of systemic lupus erythematosus. *Am J Obstet Gynecol*. 2005;193:1444-1455.
34. Arkema EV, Palmsten K, Sjowall C, Svenungsson E, Salmon JE, Simard JF. What to expect when expecting with systemic lupus erythematosus (SLE): a population-based study of maternal and fetal outcomes in SLE and pre-SLE. *Arthritis Care Res (Hoboken)*. 2016;68:988-994.
35. Van Wyk L, van der Marel J, Schuerwegh AJ, et al. Increased incidence of pregnancy complications in women who later develop scleroderma: a case-control study. *Arthritis Res Ther*. 2011;13:R183.
36. Arachchillage DR, Machin SJ, Mackie IJ, Cohen H. Diagnosis and management of non-criteria obstetric antiphospholipid syndrome. *Thromb Haemost*. 2015;113:13-19.
37. Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. *Fertil Steril*. 1996;66:24-29.
38. Bowden AP, Barrett JH, Fallow W, Silman AJ. Women with inflammatory polyarthritis have babies of lower birth weight. *J Rheumatol*. 2001;28:355-359.
39. 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;11:304-307.
40. Grava C, Ruffatti A, Milanesi 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;57:180-186.
41. 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;199:632-636.
42. Castellino G, Capucci R, Bernardi S, et al. Pregnancy in patients with undifferentiated connective tissue disease: a prospective case-control study. *Lupus*. 2011;20:1305-1311.
43. 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;16:313-320.
44. Neiman AR, Lee LA, Weston WL, Buyon JP. Cutaneous manifestations of neonatal lupus without heart block: characteristics of mothers and children enrolled in a national registry. *J Pediatr*. 2000;137:674-680.
45. Eliasson H, Sonesson SE, Sharland G, et al. Fetal Working Group of the European Association of Pediatric CardiologyIsolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. *Circulation*. 2011;124:1919-1926.
46. Abou-Nassar K, Carrier M, Ramsay T, Rodger MA. The association between antiphospholipid antibodies and placenta mediated complications: a systematic review and meta-analysis. *Thromb Res*. 2011;128:77-85.
47. Qazi U, Lam C, Karumanchi SA, Petri M. Soluble Fms-like tyrosine kinase associated with preeclampsia in pregnancy in systemic lupus erythematosus. J Rheumatol. 2008;35:631-4. Erratum. *J Rheumatol*. 2008;35:729.
48. de Groot CJ, vander Mast BJ, Visser W, DeKuiper P, Weimar W, VanBesouw NM. Preeclampsia is associated with increased cytotoxic T-cell capacity to paternal antigens. *Am J Obstet Gynecol* 2010;203:491-496.
49. Darmochwal-Kolarz D, Kludka-Sternik M, Tabarkiewicz J, et al. The predominance of Th17 lymphocytes and decreased number and function of Treg cells in preeclampsia. *J Reprod Immunol*. 2012;93:75-81.
50. Dejaco C, Duftner C, Grubeck-Loebenstein B, Schirmer M. Imbalance of regulatory T cells in human autoimmune diseases. *Immunology*. 2006;117:289-300.
51. Sun Y, Deng W, Geng L, et al. Mesenchymal stem cells from patients with rheumatoid arthritis display impaired function in inhibiting Th17 cells. *J Immunol Res*. 2015;2015:284215.
52. Beneventi F, Badulli C, Locatelli E, et al. Soluble HLA-G in pregnancies complicated by autoimmune rheumatic diseases. *J Reprod Immunol*. 2015;110:67-73.
53. Elnady BM, Kamal NM, Shaker RH, et al. Prevalence and clinical significance of nonorgan specific antibodies in patients with autoimmune thyroiditis as predictor markers for rheumatic diseases. *Medicine (Baltimore)*. 2016;95:e4336.
54. Beneventi F, Locatelli E, Caporali R, et al. Connective tissue diseases and autoimmune thyroid disorders in the first trimester of pregnancy. *J Reprod Immunol*. 2016;114:32-37.
55. Kumru P, Erdogdu E, Arisoy R, et al. Effect of thyroid dysfunction and autoimmunity on pregnancy outcomes in low risk population. *Arch Gynecol Obstet*. 2015;291:1047-1054.
56. Mosca M, Neri R, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. *Clin Exp Rheumatol*. 1999;17:615-620.
57. Taraborelli M, Andreoli L, Tincani A. Much more than thrombosis and pregnancy loss: the antiphospholipid syndrome as a 'systemic disease'. *Best Pract Res Clin Rheumatol*. 2012;26:79-90.
58. Veglia M, D'Ippolito S, Marana R, et al. Human IgG Antinuclear Antibodies Induce Pregnancy Loss in Mice by Increasing Immune Complex Deposition in Placental Tissue. In Vivo Study. *Am J Reprod Immunol*. 2015;74:542-552.
59. Luo Y, Zhang L, Fei Y, et al. Pregnancy outcome of 126 anti-SSA/Ro-positive patients during the past 24 years–a retrospective cohort study. *Clin Rheumatol*. 2015;34:1721-1728.
60. Bortoluzzi A, Furini F, Campanaro F, Govoni M. Application of SLICC classification criteria in undifferentiated connective tissue disease and evolution in systemic lupus erythematosus: analysis of a large monocentric cohort with a long-term follow-up. *Lupus*. 2017;26:616-622.
61. Laczik R, Soltesz P, Szodoray P, et al. Impaired endothelial function in patients with undifferentiated connective tissue disease: a follow-up study. *Rheumatology (Oxford)*. 2014;53:2035-2043.

62. Majali-Martinez A, Velicky P, Pollheimer J, et al. Endothelin-1 downregulates matrix metalloproteinase 14 and 15 expression in human first trimester trophoblasts via endothelin receptor type B. *Hum Reprod*. 2017;32:46-54.
63. Dusse L, Godoi L, Kazmi RS, et al. Sources of thrombomodulin in preeclampsia: renal dysfunction or endothelial damage? *Semin Thromb Hemost* 2011;37:153-157.
64. Szodoray P, Nakken B, Barath S, et al. Altered Th17 cells and Th17/regulatory T-cell ratios indicate the subsequent conversion from undifferentiated connective tissue disease to definitive systemic autoimmune disorders. *Hum Immunol*. 2013;74:1510-1518.
65. Cornelius DC, Amaral LM, Wallace K, et al. Reduced uterine perfusion pressure T-helper 17 cells cause pathophysiology associated with preeclampsia during pregnancy. *Am J Physiol Regul Integr Comp Physiol*. 2016;311:R1192-R1199.
66. Vargas-Rojas MI, Solleiro-Villavicencio H, Soto-Vega E. Th1, Th2, Th17 and Treg levels in umbilical cord blood in preeclampsia. *J Matern Fetal Neonatal Med*. 2016;29:1642-1645.
67. Beneventi F, Locatelli E, Alpini C, et al. Association between previously unknown connective tissue disease and subclinical hypothyroidism diagnosed during first trimester of pregnancy. *Fertil Steril*. 2015;104:1195-1201.
68. Brucato A, Frassi M, Franceschini F, et al. Risk of congenital complete heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmunoelectrophoresis: a prospective study of 100 women. *Arthritis Rheum*. 2001;44:1832-1835.
69. Spence D, Hornberger L, Hamilton R, Silverman ED. Increased risk of complete congenital heart block in infants born to women with hypothyroidism and anti-Ro and/or anti-La antibodies. *J Rheumatol*. 2006;33:167-170.
70. Andreoli L, Bertsias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N. 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;76:476-485.
71. Friedman DM, Kim MY, Copel JA, et al. Utility of cardiac monitoring in fetuses at risk for congenital heart block: the PR Interval and Dexamethasone Evaluation (PRIDE) prospective study. *Circulation*. 2008;117:485-493.
72. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum*. 2006;54:3640-3647.
73. Izmirly PM, Kim MY, Llanos C, et al. Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. *Ann Rheum Dis*. 2010;69:1827-1830.
74. Espinosa G, Cervera R. Current treatment of antiphospholipid syndrome: lights and shadows. *Nat Rev Rheumatol*. 2015;11:586-596.
75. Baruteau AE, Pass RH, Thambo JB, et al. Congenital and childhood atrioventricular blocks: pathophysiology and contemporary management. *Eur J Pediatr*. 2016;175:1235-1248.
76. Committee on Practice Bulletins—Obstetrics, American College of Obstetricians and Gynecologists. Practice Bulletin No. 132: Antiphospholipid syndrome. *Obstet Gynecol*. 2012;120:1514-1521.
77. Lerner A, Jeremias P, Matthias T. The world incidence and prevalence of autoimmune diseases is increasing. *Int J Celiac Dis*. 2015;4:151-155.
78. Calonge N. Developing evidence-based screening recommendations, with consideration for rheumatology. *Rheum Dis Clin North Am*. 2014;40:787-795.
79. Bizzaro N, Tozzoli R, Schoenfled Y. Are we at a stage to predict autoimmune rheumatic diseases? *Arthritis Rheum*. 2007;56:1736-1744.
80. Spinillo A, Beneventi F, Locatelli E, et al. Early, Incomplete, or Preclinical Autoimmune Systemic Rheumatic Diseases and Pregnancy Outcome. *Arthritis Rheumatol*. 2016;68:2555-2562.
81. Ledingham JM. British Society for Rheumatology National Audit, Project Working Group and Steering Committee. Importance of early detection and referral of rheumatoid arthritis. *BMJ*. 2016;353:i2172.

How to cite this article: Spinillo A, Beneventi F, Caporali R, Ramoni V, Montecucco C. Undifferentiated connective tissue diseases and adverse pregnancy outcomes. An undervalued association?. *Am J Reprod Immunol*. 2017;78:e12762. https://doi.org/10.1111/aji.12762