Comparing pregnancy outcomes in patients with Systemic Lupus Erythematosus and Undifferentiated Connective Tissue Disease: a descriptive cohort study.

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Abstract

Introduction

Systemic Lupus Erythematosus (SLE) and Undifferentiated Connective Tissue Disease (UCTD) affect women of childbearing age. Despite a well-established association with Adverse Pregnancy Outcomes (APO) in SLE, there is conflicting evidence as to whether this association exists in patients with UCTD. Therefore, we carried out a descriptive study in people with SLE and UCTD to determine whether pregnancy outcomes between those groups are comparable.

Methods

A retrospective cohort analysis of people with SLE (n=51) and UCTD (n=20) reviewed at University College London Hospital from 2006-2019. All people with SLE fulfilled *American College of Rheumatology* and Systemic Lupus Collaborating Clinics criteria. People with UCTD were defined with symptoms and persistent positivity of antinuclear antibodies on two separate occasions for at least three years, that does not meet classification criteria for any specific autoimmune rheumatic disease.

Results

Subjects were predominantly white pregnant females (47% of SLE and 80% of UCTD cohort). The SLE group included more patients compared with the UCTD group (72% vs 28%). In the SLE group, the most common features observed included mucocutaneous and/or articular involvement (77%) followed by lupus nephritis (33%). In the UCTD group, arthralgia (70%), rash (35%) and Raynaud's (25%) were the main features.

The majority of SLE and UCTD pregnancies were planned (81% vs 77%, respectively) and the patients had inactive disease at conception (96% vs 89%). Most people with SLE were on hydroxychloroquine treatment at conception (86%) compared with 36% of UCTD at conception.

Both SLE and UCTD groups had a similar number of disease flares during pregnancy and/or puerperium (14% vs 10%). There was no significant difference identified for APO in SLE compared to UCTD pregnancies.

Conclusions

We found a similar prevalence of APO between SLE and UCTD pregnancies. The low prevalence of APO in our SLE group was most likely due to a high percentage of planned pregnancies with low disease activity and hydroxychloroquine usage during their pregnancies. Our findings highlight the importance of pregnancy planning and maintenance of treatment during pregnancy to ensure low disease activity in SLE and UCTD pregnancies.

Keywords: Adverse Pregnancy Outcomes, Undifferentiated Connective Tissue Disease, Systemic Lupus Erythematosus.

Introduction

Autoimmune rheumatic diseases (ARD) are characterised by immune dysfunction, complement dysregulation and pathogenic autoantibody formation (1-2). They have a female predominance with onset typically during reproductive years (3) and association with an increased risk of Adverse Pregnancy Outcomes (APO) (1-2). Systemic lupus erythematosus (SLE) is one of the most studied ARD in pregnancy. It is well-known that females with SLE who are pregnant have an increased risk of APO including pregnancy loss, preeclampsia, preterm birth, intra-uterine growth restriction (IUGR) or small for gestational age (SGA) when compared to the general population (4-9).

Undifferentiated Connective Tissue Disease (UCTD) is the term used to describe people with symptoms suggestive of an ARD lasting for at least three years and persistent positive antinuclear antibodies that does not meet established criteria for any ARD (10). In contrast, UCTD pregnancies, are less well characterised with conflicting findings. While some studies suggested an increased risk of preterm birth, pre-eclampsia, stillbirth and SGA (11-12); others found a similar rate of APO compared with non-ARD and/or population pregnancy controls (13-14). A recent systematic review concluded that people with UCTD or other non-criteria CTD have an increased risk of APO compared to non-ARD and/or population pregnancy controls (15).

Despite a well-recognised association with APO in people with SLE, there is conflicting evidence as to whether this association also exists in people with UCTD. Only one recent study has compared outcomes between SLE and UCTD pregnancies (14). Therefore, we carried out a retrospective cohort study of SLE and UCTD pregnancies at University

College London Hospital (UCLH) to identify whether pregnancy outcomes are comparable between people with SLE and UCTD.

Methods

A retrospective analysis of all SLE and UCTD pregnancies reviewed at UCLH from 2006 to 2019. All people with SLE fulfilled ACR and SLICC criteria (16-17). People with UCTD had symptoms and persistent positivity of antinuclear antibodies on two separate occasions for at least three years and did not meet criteria for any other specific ARD (10). All relevant definitions/abbreviations are shown in Table 1. This is an observational retrospective study of medical records collected over a period of over 30 years. All data were derived from normal clinical management and no patients underwent extra questionnaires or research procedures. No individualized or identifiable data are presented in this study. Therefore, ethical approval and informed consent were not required.

Eligibility criteria

All people reviewed at UCLH with complete records of pregnancy outcomes to at least four weeks postpartum, including females who gave birth elsewhere were included. People with SLE and a concomitant secondary ARD and patients with UCTD and an organ-specific autoimmune disorder (e. g. Hashimoto´s or Addison´s disease) or APS with symptoms and autoimmune profile not fully explained by APS were included. People with incomplete information on pregnancy, other ARD diagnoses and multiple pregnancies were not included in the final analysis. We also excluded people with incomplete follow-up data.

Data collection

Collected data included demographics; smoking, body mass index, fertility and whether those pregnancies were planned; disease duration; co-morbidities including hypertension, diabetes, thyroid disorders or other autoimmune disorders; previous and/or current APO [miscarriage, stillbirth, terminations, preterm birth, intrauterine growth restriction (IUGR), pre-eclampsia/eclampsia/HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, abruptio placentae, cardiac heart block (CHB) and other cardiac abnormalities], number of terminations and autoantibody profile. People with SLE were divided in 4 subgroups: mucocutaneous and/or articular; renal; neurological; and haematological. We have also analysed information about their last pregnancy including, activity at conception [BILAG index for SLE patients and physician global assessment (PGA) for UCTD], therapeutic regime during pregnancy, disease flare during pregnancy [PGA 0= no-low activity, PGA 1= moderate/severe activity] and mode of delivery [vaginal or caesarean section (CS)]. Disease flare was defined as a change in activity scores.

Data analysis

Demographics, disease characteristics and outcomes were compared in SLE and UCTD groups using Pearson’s Chi-Square or Fisher’s exact test for categorical variables and either Student's-T test or Mann-Whitney test for numerical variables, according to the variable's distribution. Statistical analysis was performed with IBM® SPSS® statistics version 22.

Results

Information related with their latest pregnancy.

Demographics and disease characteristics

More than 150 people with SLE or UCTD were reviewed, after exclusions, a total of 71 (51 SLE and 20 UCTD) people were included for study analysis. There were significant differences identified in the ethnicity composition between groups. The cohort consisted of predominantly white [SLE (47 %); UCTD (80%)], Asian in the SLE (28%) only, with no difference in Black (12% vs 10%) and other background (14% vs 10%) in SLE and UCTD, respectively.

Maternal age at conception, disease duration, history of infertility and body mass index at their last pregnancy were not significantly different in the SLE compared with the UCTD pregnant groups. Smoking status data was recorded in 66 out of 71 patients and all were reported as being non- smokers.

In the SLE group, mucocutaneous and/or articular involvement were most common (77%), followed by lupus nephritis (33%). Neurological and haematological involvement were less frequent (6% each subgroup). No cardiac, pulmonary or other potential SLE involvements were found (table 2).

In the UCTD group, arthralgia (70%), skin rash (35%) and Raynaud´s (25%) were the main features identified, followed by myalgia (10%) and mouth ulcers (10%).

Autoimmune profile at conception

Anti-dsDNA and anti-Ro antibodies were significantly higher in SLE group when compared with UCTD group (anti-dsDNA 25% vs 0%; p=0.014 / anti-Ro 62% vs 25%; p=0.005). Antinuclear antibodies (ANA), low C3 +/- C4, anti-La and anti-RNP antibodies showed similar prevalence between groups. Interestingly, both SLE and UCTD also presented comparable positive results for antiphospholipid antibodies (aPL) including, lupus anticoagulant, anti-beta 2 glycoprotein-I and anti-cardiolipin antibodies (table 2).

Co-morbidities

Various co-morbidities were reported including hypertension, diabetes mellitus, thyroid disorders, antiphospholipid syndrome (APS) and other organ-specific autoimmune diseases. A significantly higher prevalence of thyroid disorders was observed in the UCTD group in comparison to SLE (20% vs 4%; p=0.049) pregnancies. However, no differences were identified in the frequency of other co-morbidities (Table 2).

Medication during pregnancy

Hydroxychloroquine (HCQ) at a dose between 100-400 mg/day (p<0.001), low-dose (< 7.5 mg/day) and high-dose (>7.5 mg/day) steroids (p=0.001) and low-dose aspirin (LDA) at 75 mg/day (p=0.026) were more frequently prescribed in SLE compared to UCTD pregnancies (Table 2). In contrast, there was no difference in usage of azathioprine (p=0.063), calcineurin inhibitors (p=0.554) and low-molecular weight heparin (p=0.204) between groups (Table 2).

Pregnancy planning, disease activity at conception and flare during/post-partum period during pregnancy

The majority of both SLE and UCTD pregnancies were planned (81% vs 77%, p=0.732) and had inactive disease (96% vs 89%, p=0.296) at conception (table 2). There was a similar percentage of disease flares during pregnancy and/or puerperium (14% vs 10%, p=1.000) in SLE and UCTD pregnancies (table 2).

Pregnancy outcomes

The majority of pregnancies resulted in live birth with 96% in the SLE and 100% in the UCTD group with no significant differences between groups (p=1.000). There were no significant differences in APO between SLE and UCTD pregnancies (16% vs 5%; p=0.429) (table 2).

Delivery methods

The most frequent modes of delivery were CS and vaginal delivery, in SLE and UCTD pregnancies, with no significant differences between groups (table 2).

History of number of pregnancies and adverse pregnancy outcomes in SLE and UCTD patients

Obstetric histories were found to be similar between SLE and UCTD pregnancies, with no differences in the number of previous pregnancies, miscarriage, stillbirth, terminations, preterm birth, IUGR, pre-eclampsia/eclampsia/HELLP syndrome, abruptio placentae and CHB or other cardiac abnormalities (Table 3).

A sub-analysis conducted for patients who were positive for anti-Ro antibodies (table 4) did not identify any significant differences in terms of CHB and other cardiac abnormalities when UCTD and SLE pregnancies were compared (40% vs 9.7%; p=0.132).

Discussion

We found a comparable prevalence of APO between SLE and UCTD pregnancies. Few studies examining APO in SLE (6-8) or UCTD (11-13) pregnancies have been published and only one study comparing gestational outcomes in SLE and UCTD pregnancy is currently available (14).

It is well-known that ethnicity plays a key role in the pathogenesis of SLE with people of Black and Asian ethnicities were found to have more severe disease (18-19). Our cohort consisted of predominantly white pregnant women in both SLE and UCTD patients. Although a significantly higher prevalence of people of Asian ethnicity was found in SLE compared with UCTD pregnancies, no differences were observed in APO.

To evaluate risk of developing obstetric complications, people with SLE and other ARD are routinely tested for different antibodies and other immunological molecules. Low complement levels, positivity for anti-dsDNA, aPL and/or anti-ENA antibodies have been associated with a higher rate of pregnancy complications in SLE (4, 20-21) and UCTD (13,22). Our cohort had significantly higher levels of anti-dsDNA and positive anti-Ro antibodies occurring in the SLE group when compared with UCTD pregnancies. However, this imbalance between the two groups did not lead to a difference in APO.

We also found that 5/71 people had delivered babies with CHB. People with positive anti-Ro antibodies can develop poor pregnancy outcomes including neonatal lupus or CHB in the baby. The prevalence of CHB is estimated at around 1-2% which increases to 18% in subsequent pregnancies in those who previously had a baby with CHB (23-24). In addition, some studies have shown that people with UCTD who were positive for anti-Ro antibodies were more likely to have pregnancies complicated by CHB than people with SLE and anti-Ro antibodies (23,25). These differences, however, may be due to the clinical heterogeneity of the patients recruited in these studies (25). Therefore, we carried out a sub-analysis of people with anti-Ro antibody positivity in UCTD and SLE pregnancies (table 4). We found that although anti-Ro antibodies were more prevalent in SLE compared with UCTD pregnancies (62% vs 25%, p=0.005), there was no significant difference in CHB between both groups (40% vs 9.7%, p =0.132). This finding may be explained by the increased use of HCQ in SLE pregnancies as this drug which is well-known to prevent subsequent CHB in anti-Ro positive mothers with previously affected pregnancies (26). Other potential explanations include the small sample size in the UCTD group and different prevalence of anti-Ro subtypes that we were unable to test for in this study (27).

Other autoantibodies that cause APO are aPL that are found in APS and other ARD, mainly SLE with an estimated prevalence of 30-40% (28-29). These antibodies confer greater risk of gestational complications including preterm birth, preeclampsia or miscarriages (4, 30-31). Intriguingly, the prevalence of aPL antibodies in our cohort was low and similar between both groups. These numbers are comparable to the article by

Kaufman et al in SLE and UCTD pregnancies (14). The low levels of aPL positivity found in our cohort may have contributed towards the lower rates of APO identified.

A similar percentage of disease flares occurring during pregnancy and/or puerperium in SLE and UCTD pregnancies was observed. The differences in medication usage could explain this fact. HCQ is frequently used to treat ARD that has been extensively studied in pregnancy to reduce risk of disease flares in SLE pregnancies (32-33). Furthermore, HCQ has been also shown in anti-Ro positive pregnancies to reduce recurrence of CHB in subsequent pregnancies (26). We found an increased use of HCQ occurred in SLE compared to UCTD pregnancies, which may have contributed to the low levels of disease activity and rates of APO in SLE pregnancies.

Differences in treatment regimens between groups may have contributed to similar rates of APO. Corticosteroids are the drug of choice to suppress SLE disease flares during pregnancies (34-35). We also reported a significantly higher administration in SLE compared with UCTD. Low-dose aspirin (LDA) is an antiaggregant which is preferably given before 16 weeks and prescribed in high risk SLE people, high risk aPL profile and APS patients to reduce the chances of APO such as preterm birth and severe pre-eclampsia (36). Our SLE group were observed to have also been prescribed with LDA more significantly when compared to UCTD patients. We did not find any differences between groups with other treatments deemed safe to use in pregnancy such as azathioprine, calcineurin inhibitors or low molecular weight heparin. The reason for this may be related to the limited number of patients analysed.

In summary, our SLE patients were found to significantly be treated with more HCQ, steroids and LDA in comparison to the UCTD patients which could potentially be the main reason why our SLE patients were observed to have fewer incidences of APO than previously reported cases in the literature and similar to UCTD patients.

Cardiovascular factors can also influence the course of pregnancies in ARD patients (37). We did not note any differences between both groups in terms of pre-existing hypertension or diabetes. However, we found that thyroid disorders were significantly more frequently occurring in UCTD patients when compared with SLE pregnancies (20% vs 4%, $p < 0.049$). Thyroid disorders have been previously found in our SLE cohort at UCLH, with 5.2% having hypothyroidism and 1.4% hyperthyroidism (38). Danieli et al (39) also found similar rates of thyroid disorders in UCTD patients of 6.6%. Despite some papers describing thyroid autoimmune profile in UCTD pregnant women (40), we did not find articles describing this increased prevalence in UCTD pregnant women which requires further investigation.

Our finding noting that SLE and UCTD pregnancies had similar rates of APO during their last pregnancy agrees with the findings reported by Kaufman et al (14). However, they reported that the percentage of APO was significantly higher in SLE pregnancies with active disease. Therefore, the likely explanation as to why we did not find similar differences between both groups is that the majority of our SLE pregnancies were pre-planned where disease activity was noted to be quiescent/stable at conception, where the main SLE symptoms presented included with mucocutaneous and articular joint involvement which had been HCQ+/- LDA +/- steroids.

Limitations of the study

Data for this study was collected retrospectively from clinical assessments obtained during routine appointments. Information on other autoantibodies such as anti-Ro subtypes is lacking and may be relevant for identifying associations with APO. Our findings are also limited by the overall small sample size specially in the number of UCTD patients, as well as the lack of healthy pregnancy control group.

Conclusions

We found a similar prevalence of APO between SLE and UCTD pregnancies. The low prevalence of pregnancy complications occurring in our SLE group in comparison to other published studies is likely to be explained by the fact that most of our SLE pregnancies were planned, patient had stable disease activity at conception and patients were also appropriately treated with safe treatments including HCQ +/- LDA +/- steroids during their pregnancies. Thus, highlighting the importance and need to continue with the use of safe medications during pregnancies to enhance the chances for patients to conceive and deliver healthy babies. We identified similar rates of CHB despite a lower prevalence of anti-Ro antibodies in UCTD pregnancies, thus highlights the importance for routine testing of these particular antibodies during pre-pregnancy counselling of people with UCTD.

Declaration of competing interest

The authors do not report any conflicts of interest.

Funding

CM received support from Foundation for the Development of Internal Medicine in Europe (FDIME) Research Grant.
CM received support from Alfonso Martin Escudero Foundation, Spain.
CM received support from Lupus UK, United Kingdom.

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Table 1. Definitions and abbreviations.

Term	***Definition***
SLE	Patients who fulfil *American College of Rheumatology* and Systemic Lupus Collaborating Clinics classification criteria.
UARD	Patients with signs and symptoms suggestive of an autoimmune rheumatic disease (ARD) but not fulfilling criteria for a defined ARD, lasting for at least three years and persistent positivity of antinuclear antibodies on two separate occasions.
APO	Adverse Pregnancy Outcomes included were: pre-eclampsia (new onset hypertension after 20 weeks gestation and proteinuria); eclampsia (generalized convulsions in a patient with preeclampsia; HELLP syndrome(haemolysis elevated liver enzymes and low platelet count); preterm birth (<37 weeks) of gestation; termination (interruption of the pregnancy); miscarriage(<13 weeks gestation); pregnancy loss (13-20 weeks); stillbirth (>20 weeks gestation); intrauterine growth restriction (IUGR), Small for Gestational Age (SGA) as those infants whose weight < 10 percentile for gestational age, abruptio placentae (premature separation of the placenta from the uterus), cardiac heart block (slowing down or interruption of the electrical signal from the upper chambers of the heart (the atria) to the lower chambers (the ventricles).

Table 2: Disease characteristics, baseline variables and pregnancy outcomes (*at the time of the latest pregnancy*) in patients with SLE and UCTD

		SLE N=51	UCTD N=20	P
Ethnicity	**White**, N (%)	24 (47)	16 (80)	**0.037**
	Black, N (%)	6 (12)	2 (10)	
	Asian, N (%)	14 (28)	0 (0)	
	Other, N (%)	7 (14)	2 (10)	
Age at pregnancy (y), median (IQR)		35 (7.0)	35 (6.8)	0.349
Disease duration (y), median (IQR)		10.5 (11.0)	5.0 (11.0)	0.060
Body mass index, median (IQR)		22.8 (4.9)	21.6 (1.8)	0.162
Current smoker, N (%)		0 (0)	0 (0)	NA
SLE organ involvement, N (%)				
Mucocutaneous and/or articular		39 (77)	NA	
Renal		17 (33)	NA	
Neurologic		3 (6)	NA	
Haematological (AIHA)		3 (6)	NA	
UCTD features				
Arthralgia		NA	14 (70)	
Skin rash		NA	7 (35)	
Raynaud		NA	7 (35)	
Myalgia		NA	2 (10)	
Mouth ulcers		NA	2 (10)	
Serology at conception, N (%)				
ANA		47 (97)	20 (100)	1.000
Low C3 and/or C4		5 (10)	1 (6)	1.000
Anti-dsDNA		12 (25)	0 (0)	**0.014**
Anti-Ro		31 (62)	5 (25)	**0.005**
Anti-La		3 (6)	2 (10)	0.619
Anti-RNP		8 (16)	5 (25)	0.496
Lupus anticoagulant		3 (6)	0 (0)	0.552
Anti-cardiolipin		4 (8)	2 (10)	1.000
Anti-Beta 2 Glycoprotein I		5 (10)	2 (10)	1.000
Antiphospholipid Syndrome, N (%)		3 (6)	1 (5)	1.000
Other autoimmune disease, N (%)		11 (22)	5 (25)	0.760
Hypertension, N (%)		5 (10)	0 (0)	0.312
Diabetes, N (%)		2 (4)	0 (0)	1.000
Thyroid disorders, N (%)		2 (4)	4 (20)	**0.049**
Treatment during pregnancy, N (%)				
Hydroxychloroquine		44 (86)	7 (35)	**<0.001**
Steroids		25 (49)	1 (5)	**0.001**
≤ 7.5 mg prednisolone		17 (33)	1 (5)	
> 7.5 mg prednisolone		8 (16)	0 (0)	
Azathioprine		16 (31)	2 (10)	0.063
Calcineurin inhibitors		3 (6)	0 (0)	0.554
Low-dose aspirin		25 (69)	8 (40)	**0.026**
Low-molecular weight heparin		13 (26)	2 (10)	0.204
Active disease at conception, N (%)		2 (4)	2 (11)	0.296
Planned pregnancy, N (%)		38 (81)	13 (77)	0.732
History of infertility, N (%)		15 (30)	2 (12)	0.200
Disease flare during latest pregnancy, N (%)		7 (14)	2 (10)	1.000
During pregnancy, N (%)		3 (6)	2 (10)	0.623
Postpartum, N (%)		4 (8)	0 (0)	0.315
Vaginal delivery, N (%)		20 (41)	12 (60)	0.147

Live birth, N (%)	49 (96)	20 (100)	1.000
Adverse pregnancy outcome, N (%)	8 (16)	1 (5)	0.429
Preterm birth, N (%)	3 (6)	0 (0)	
Intrauterine growth restriction, N (%)	2 (4)	0 (0)	
Pre-eclampsia, N (%)	1 (2)	1 (5)	
Miscarriage, N (%)	2 (4)	0 (0)	

SLE: Systemic Lupus Erythematosus; UCTD: undifferentiated connective tissue disease

Table 3: Past obstetric outcomes in patients with SLE and UCTD

	SLE N=51	UCTD N=20	p
No. pregnancies, N (%)			
1	12 (24)	3 (15)	
2	23 (45)	7 (35)	0.332
≥ 3	16 (31)	10 (50)	
History of adverse pregnancy outcome, N (%) [a]	31 (61)	12 (60)	0.951
Miscarriage, N (%)	15 (29)	7 (35)	0.647
Stillbirth, N (%)	4 (8)	1 (5)	1.000
Termination, N (%)	8 (16)	1 (5)	0.429
Preterm birth, N (%)	8 (16)	2 (10)	0.714
Pre-eclampsia, N (%)	5 (10)	1 (5)	0.668
Eclampsia, N (%)	0 (0)	1 (5)	0.282
HELLP syndrome, N (%)	1 (2)	0 (0)	1.000
Intrauterine growth restriction, N (%)	4 (8)	1 (5)	1.000
Abruptio placentae, N (%)	0 (0)	1 (5)	0.282
CHB or other cardiac abnormalities, N (%)	3 (6)	2 (10)	0.616

SLE: Systemic Lupus Erythematosus; UCTD: undifferentiated connective tissue disease; CHB: congenital heart block
[a] Including all pregnancies. N refers to number of patients having the outcome and not number of pregnancies with that outcome.

Tabla 4. **CHB or other cardiac abnormalities (including only patients with positive anti-Ro)**

			group		
			UCTD	SLE	Total
CHB or other cardiac abnormalities	NO	Count	n = 3	n = 28	n = 31
		%	60,0%	90,3%	86,1%
	YES	Count	n = 2	n = 3	n = 5
		%	40,0%	9,7%	13,9%
Total		Count	n = 5	n = 31	n = 36
		%	100,0%	100,0%	100,0%

CHB: Congenital Heart block; Systemic Lupus Erythematosus; UCTD: undifferentiated connective tissue disease.