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Title: Patient care pathways for pregnancy in rare and complex rheumatic diseases: results from an international survey

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Statement of ethics and consent: an ethics committee approval was not needed since the survey was completely anonymous and completed by clinicians, and patients were not recruited.

ABSTRACT

Objectives: To map existing organizational care pathways in clinical centers of expertise that care for pregnant women affected by rare and complex connective tissue diseases (rcCTDs).

Methods: An international working group composed of experts in the field of pregnancy in rcCTDs co-designed a survey focused on organizational aspects related to the patient's pathway before, during and after pregnancy. The survey was deployed to subject experts via referral sampling.

Results: Answers were collected from 69 centers in 21 countries. Patients with systemic lupus erythematosus and/or antiphospholipid syndrome were followed by more than 90% of centers, while diseases such as IgG4-related diseases were rarely covered.

In the majority of centers, a multidisciplinary team was involved, including an obstetrician/gynaecologist in 91.3% of cases and other healthcare professionals less frequently. Respondents indicated that 96.0% of the centers provided routine pre-pregnancy care, while the number of patient visits during pregnancy varied across centers. A formalized care-pathway was described in 49.2% of centers, and 20.3% of centers had a pre-defined protocol for the monitoring of pregnant patients. Access to therapies during pregnancy also was heterogeneous among different centers.

Conclusions: In international referral centers, a high level of care is provided to patients with rcCTDs before, during and after pregnancy. No significant discrepancies were found between European and non-European countries. However, this work highlights a potential benefit to streamline the care approaches across countries in order to optimize pregnancy and perinatal outcomes among patients with rcCTDs.

INTRODUCTION

As rare and complex connective tissue diseases (rcCTDs) frequently affect women of childbearing age, pregnancy and family planning are important facets of rheumatology and interdisciplinary care.

rcCTDs may worsen in the context of pregnancy, leading to severe maternal morbidity and mortality or to fetal loss. Moreover, many people with childbearing capacity are routinely prescribed teratogenic anti-rheumatic drugs, increasing the risk of fetal death, congenital anomalies, or neurodevelopmental sequelae.

For decades, women with rcCTDs were advised not to become pregnant in order to avoid adverse pregnancy and perinatal outcomes. However, with advancements in diagnosis and treatment of rcCTDs, as well as in obstetric and neonatal care, people with rcCTDs are increasingly having safe and healthy pregnancies, particularly if their diseases are well-controlled prior to and during pregnancy with pregnancy-compatible medications. Studies indicate that a rising number of women with rcCTDs are becoming pregnant, underscoring the need to develop clear guidelines and clinical pathways to address the potential health risks and challenges of these pregnancies. (1-4).

Several international rheumatology societies have developed recommendations for the management of pregnancy, family planning and other aspects of reproductive health in patients with rheumatic diseases (5, 6). However, at sites where clinical rheumatology care is delivered, uniformly accepted and validated protocols for women affected by rcCTDs are rarely available and yet unknown is how to implement evidence-based recommendations around reproductive health effectively in clinical practice. Moreover, evidence-based data on pregnancy management ofthe rarer rheumatologic conditions, such as inflammatory myopathy and systemic sclerosis, are scarce and often based on case series or small observational studies.

As a consequence, in the real-life setting, the physician's experience and judgment often guides guide the management of pregnancy care, leading to significant heterogeneity and potentially fragmentation in the patient's pregnancy care across different clinical disciplines.

During the 11th International Conference on Reproduction Pregnancy and Rheumatic Diseases (RheumaPreg2021) (7), a Steering Committee (SC) composed by MM, YS, AB, MK and CT proposed a project aimed at creating a consensus-based, clear and well-defined care pathway model for pregnancy and reproductive issues in patients with rcCTDs in order to improve the quality of pregnancy-related health care, clinical outcomes, and patients' experiences.

In the project described herein, we sought to describe existing organizational care delivery models offered to pregnant patients with rcCTDs across different clinical settings and countries in order to highlight to strengths and areas for future improvement.

METHODS

The working group (WG) was composed by the SC members and by a multidisciplinary international panel of experts in the field of pregnancy in rheumatic diseases. The University of Pisa coordinated the project.

Means and methods of this study have been inspired by the RarERN Path (8, 9), a methodology specifically designed for the development of common and shared organisational reference patients' pathway model for rcCTDs.

Framed by the RarERN methodology, the WG designed a survey that focused on specific organizational aspects related to the health care delivery pathways of people with rcCTDs immediately prior to, during and after pregnancy.

The WG decided to prioritize rare and complex rcCTDs that are either associated with adverse pregnancy outcomes or for which an evidence basis for pregnancy management is limited: antiphospholipid syndrome and aPL carriers (APS), Behcet's disease (BD), idiopathic inflammatory

myopathies (IIM), IgG4-related diseases (IgG4), large vessel vasculitides (LVV), mixed connective tissue disease (MCTD), relapsing polychondritis (RP), Sjögren syndrome (SS), small vessel vasculitides (SVV), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and undifferentiated connective tissue disease (UCTD).

We decided to include rare and complex diseases and no other categories such as inflammatory arthritis since these diseases share common management aspects, and should be taken care of by a multidisciplinary team.

The survey assessed three different phases of the patients' care pathway: pre-pregnancy counselling, monitoring/follow up of the pregnancy and post-partum care.

The survey was launched through the EU platform EU-survey (https://ec.europa.eu/eusurvey/runner/rheumapregRarERNPath) and was active from June 20th to July 20th, 2021.

Referral sampling was used to identify clinicians involved in the management of pregnancy-related issues in rcCTDs; these individuals were invited to participate via e-mail. In addition, authors circulated the invitation to their networks of colleagues. Only one questionnaire was completed per center.

The answers were evaluated using descriptive statistics.

An ethics committee approval was not deemed necessary as the survey was anonymous, as reported in supplementary file.

We obtained the participant's written informed consent to publish the material.

RESULTS

A total of 69 responses were collected from centers in 21 countries (Argentina, Austria, Brazil, Canada, China, France, Germany, India, Italy, Netherlands, Norway, Peru, Poland, Portugal, Qatar, Romania, Spain, Switzerland, United Kingdom, Ukraine, USA); 54 were European centers, 27 of which from Italy.

Clinicians from more than 80% of the centers reported that they cared for patients with SLE, APS, SS, UCTD, MCTD and SSc during pregnancy. In contrast, pregnant patients with RP, IgG4 disease, IIM and BD were followed in less than 63% of centers (Figure 1).

In the majority of the centers (88.1% in Italy, 80.3% outside Italy, 73.2% outside the EU), the pregnancy clinic involved multidisciplinary providers, including gynaecologist/obstetrician in 91.3% of centers and less frequently other healthcare professionals, as detailed in Table 1. However, the disciplines included in the multidisciplinary teams were formalized in only 30.4% of the cases.

Regular pre-pregnancy care was performed in 96.0% of cases (96.2% in Italy, 95.2% outside Italy, 93.4% outside the EU), and the most frequent referrals for pre-pregnancy care were to a gynaecologist/obstetrician working in the same hospital (76.8%) and/or other rheumatologist working outside or inside the team (71.0% and 69.5%, respectively). In 63.7% of centers, patients were referred to general practitioners for pre-pregnancy care.

Joint consultations with a rheumatologist and obstetrician/gynaecologist were regularly conducted in 43.3% of centers (48.4% Italy, 40.1% outside Italy, 33.3% outside the EU). The time of the patient's first appointment to a multidisciplinary pregnancy clinic was variable: 47.8% at the time of positive pregnancy test, within first 8 weeks of gestation in 33.3%, and within first 12 weeks of gestation in 18.8%. The frequency of monitoring/follow up visits and post-partum visit was also variable between centers, as detailed in Table 2. A formalized pregnancy care pathway for people with rcCTDs was present in 49.2%, and a pre-defined protocol/checklist for the monitoring of the patients during pregnancy was used in 20.3% of centers, and in the postpartum period in 18.8% of centers.

Access to pregnancy-compatible rcCTD treatments during pregnancy seemed to be heterogeneous among different centers, especially with respect to cyclosporine, tacrolimus, biologics (e.g., TNF alpha inhibitors) and intravenous immunoglobulins. Available treatments at the various centers are summarized in Table 1.

DISCUSSION

This study sought to describe the existing patient's care pathways that are currently in place in international centers of expertise that provide care for pregnant women affected by rcCTDs.

From the survey, appeared that most centers provided care for patients with with rcCTDs before, during and after pregnancy. No significant discrepancies were found between Italy, other European countries, and non-European Countries. However, a certain degree of fragmentation in health care practices emerged among different centers, underscoring the potential benefits of streamlining resources to improve patient care and outcomes.

First, while rheumatologists/immunologists/internal medicine subspecialists and obstetrician/ gynecologists were always represented in the multidisciplinary teams, few other healthcare professionals were involved in the pregnancy clinics. rcCTDs are often systemic diseases that affect end organs, which provides a rationale to include subspecialists from other disciplines (e.g., gastroenterology, nephrology, cardiology). This is not surprising and is similar to other more common medical conditions in pregnancy for which multidisciplinary team management is recommended to reduce the occurrence of adverse maternal and fetal outcomes (10). We also noted that about half of centers did not facilitate joint consultations with the rheumatologist and the obstetrician/gynaecologist; however, joint consultations might facilitate close communication about patient care, ensure that patients receive consistent medical advice and recommendations, and provide convenience for patients. Because this survey was conducted among experts in reproductive rheumatology who care for patients at specialized centers, it is reasonable to imagine that in non-

referral centers the frequency of joint rheumatology-obstetricians/gynecology consultations would be even lower.

Many centers also did not have a formalized care pathway or defined protocols for pre-pregnancy planning that might lead to better pregnancy and fetal outcomes, including supplementation with folic acid, smoking cessation, switching from teratogenic medications to pregnancy-compatible anti-rheumatic drugs. Many centers also lacked protocols and checklists for standard pregnancy care, to ensure monitoring of disease activity and/or potential complications specific to rcCTDs such as congenital heart block from SSA/Ro-antibodies. Some of the heterogeneity in pregnancy-related and fetal outcomes that have been observed in the literature may arise from the variation in pre-pregnancy and pregnancy care pathways. The availability of structured clinical pathways to guide patient care is also an important strategy to ensure an effective knowledge transfer and sharing among clinicians and to promote standardised evidence-based practices that are critical to facilitate better pregnancy outcomes among people with rcCTDs. For example, Wind M et al (11) recently demonstrated a significant reduction in maternal complications in patients with SLE/APS that were managed within a structured multidisciplinary clinical pathway compared to a cohort of patients that was not managed in a clinical pathway.

Formalised clinical pathways might also help promote the delivery of high quality, accessible and cost-effective healthcare for all patients with rcCTDs. The RarERN Path methodology could provide a robust methodological framework for this project as it integrates the perspectives of large communities of patients, expert clinicians, health economists and healthcare providers from different EU countries.

Lastly, it is important to note that the questionnaire was mainly filled in by physicians from High-Income countries. Many countries around the world lack rheumatologists or sufficient clinicians to diagnose and care for people with rcCTDs, let alone to care for these patients during pregnancy. Furthermore, many centers across the world lack have the ability and/or experience to prescribe

biologics, intravenous immunoglobulin and some traditional immunosuppressants during pregnancy. The results confirm significant disparities in access to care and medications among different centers and underscore that access to high-quality care is a challenge for many patients with rcCTDs (12, 13).

This study has several limitations. The survey did not elicit information on the clinical background and expertise of the respondents. As the RheumaPreg scientific network was the main source of survey respondents, one of the most significant limitations of our survey might be the potential for sampling bias. Most of the people who responded to the survey were experts in reproductive rheumatology, which suggests that they are practicing at clinical centers that support their expertise. These respondents may be more likely than other rheumatologists to practice in health care systems that have established models of care for the reproductive health needs of patients with rcCTDs.

Thus, these results are not generalizable as they may not accurately reflect clinical practices in non-referral centers.

Another limitation of our study was that the more centers in Italy were represented among the survey respondents than any other country in the study centers. However, we did not find significant differences in answers from Italy with respect to European and non-European Countries.

In conclusion, our study represents the first evaluation of reproductive health care models of care in Europe and outside of Europe. Our findings highlight the need to streamline the reproductive health care provided among different countries, in order to ensure that all patients with rcCTDs receive consistent and high-quality reproductive health care. A shared organizational model may also create a more efficient use of resources, allowing clinicians from around the world to determine what models of care are most effective at caring for patients with rcCTDs.

Indeed, organization always matters in health systems, especially when approaching rare and complex diseases and in specific health contexts such as pregnancy.

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FIGURES LEGENDS

Figure 1: Diseases followed in pregnancy clinics

SLE: systemic lupus erythematosus, APS: antiphospholipid syndrome and aPL carriers, UCTD: undifferentiated connective tissue disease, SS: Sjögren syndrome, MCTD: mixed connective tissue disease, SSc: systemic sclerosis, SVV: small vessel vasculitides, LVV: large vessel vasculitides, BD: Behçet's disease, IMM: idiopathic inflammatory myopathies, RP: relapsing polychondritis, IgG4: IgG4-related diseases

Table 1: Healthcare professionals involved in the multidisciplinary team and treatments prescribed in pregnancy clinics

Healthcare professionals involved in the multidisciplinary team	%
Gynaecologist/Obstetrician	91.3
Nephrologist	49.2
Midwife	18.8
Psychologist	15.9
Nutritionist	7.2
Other dedicated healthcare professionals (nurse, social worker, etc)	24.6
Other	31.8
Centers with ability to prescribe treatments during pregnancy	%
Low dose aspirin	100
Glucocorticoids	98.5
Low molecular weight heparin	95.6
Antimalarials	94.2

Azathioprine	92.7
Biological drugs	79.7
Intravenous immunoglobulins	78.2
Cyclosporine	75.3
Tacrolimus	62.3
Other treatments	11.5

Table 2: Frequency of rheumatologist visits in pregnancy clinics

Frequency of monitoring/follow up rheumatologist visits during pregnancy	%
Every month	31.8
It is variable depending on the clinical picture but not less than every 2 months	28.9
It is variable depending on the clinical picture but not less than 3 months	18.8
One visit per trimester	10.1
Every 3 months	4.3
Every 2 months	2.8
With same frequency as outside pregnancy (i.e. every 6 months)	0.0
When does the post-partum visit occur?	%
Within 4 weeks of delivery	36.2
Within 8 weeks of delivery	33.3
Within 12 weeks of delivery	14.5
No Answer	7.2
Within 2 weeks of delivery	5.8

Within 6 months of delivery	2.9

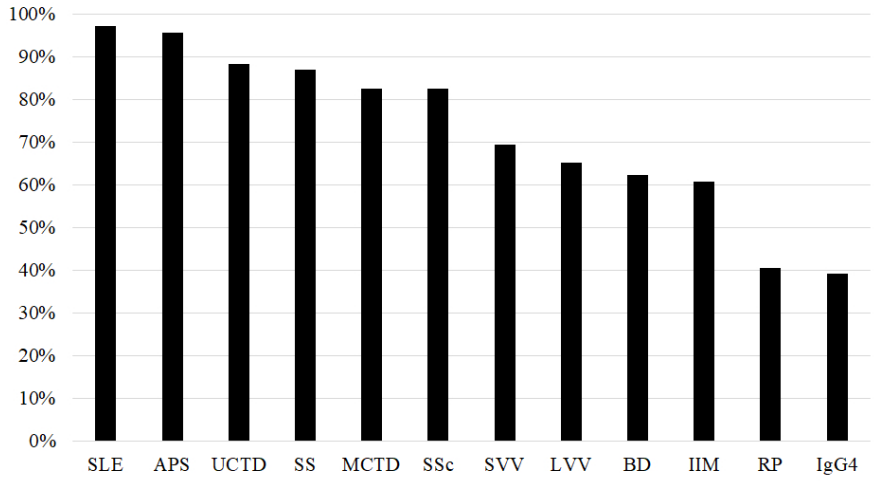

Figure 1

186x113mm (144 x 144 DPI)