Immunology of pregnancy and reproductive health in autoimmune rheumatic diseases.

Update from the 11th International Conference on Reproduction, Pregnancy and Rheumatic Diseases.

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ABSTRACT

Autoimmune rheumatic diseases (ARD) can affect women and men during fertile age, therefore reproductive health is a priority issue in rheumatology. Many topics benefit from preconception counselling: fertility, the impact of disease-related factors on pregnancy outcomes, the influence of pregnancy on disease activity, the compatibility of medications with pregnancy and breastfeeding. Risk stratification and individualized treatment approach elaborated by a multidisciplinary team minimize the risk of adverse pregnancy outcomes (APO). Research has been focused on identifying biomarkers that can be predictive of APO. Particularly, preeclampsia and hypertensive disorders of pregnancy tend to develop more frequently in women with ARD. Placental insufficiency can lead to intrauterine growth restriction and small-for-gestational age newborns. Such APO have been shown to be associated with maternal disease activity in different ARD. Therefore, a key message to be addressed to the woman wishing for a pregnancy and to her family is that treatment with compatible drugs is the best way to ensure maternal and fetal wellbeing. An increasing number of medications have entered the management of ARD, but data about their use in pregnancy and lactation are scarce. More information is needed for most biologic drugs and their biosimilars, and for the so-called small molecules, while there is sufficient evidence to recommend the use of TNF inhibitors if needed for keeping maternal disease under control.

Other issues related to the reproductive journey have emerged as "unmet needs", such as sexual dysfunction, contraception, medically assisted reproduction techniques, long-term outcome of children, and they will be addressed in this review paper.

Collaborative research has been instrumental to reach current knowledge and the future will bring novel insights thanks to pregnancy registries and prospective studies that have been established in several Countries and to their joint efforts in merging data.

ABBREVIATIONS:

ACE-2: Angiotensin-converting enzyme 2
ACR: American College of Rheumatology
AMH: anti-Müllerian hormone
ANCA: Anti-neutrophil cytoplasmic antibody
aPL: antiphospholipid antibodies
APO: adverse pregnancy outcomes
APS: antiphospholipid syndrome
Anti-PS/PT: anti-phosphatidylserine-prothrombin antibodies
Anti-TPO: anti-thyroperoxidase antibodies
ARD: Autoimmune Rheumatic Diseases
ARTs: assisted reproductive techniques
axSpA: axial spondyloarthritis
ß2GPI: ß2glycoprotein I
bDMARDs: Biologic Disease-Modifying Anti-Rheumatic Drugs
BAFF: B-cell Activating Factor
BD: Behçet's Disease
BSR: British Society for Rheumatology
CHB: congenital heart block
CRP: C-reactive protein
CTDs: connective tissue disorders
CYC: cyclophosphamide
DMARDs: disease modifying anti-rheumatic drugs
EC: endothelial cells
EULAR: European Alliance of Associations for Rheumatology
Foxp3: Forkhead Box P3
GCA: Giant Cell Arteritis
GnRH: Gonadotropin Releasing Hormone
HELLP Syndrome: Hemolysis, Elevated Liver Enzymes and Low Platelets Syndrome
IA: inflammatory arthritis
IL: interleukin
ILD: Interstitial Lung Disease
IMM: Idiopathic inflammatory myopathy
IUGR: Intrauterine Growth Restriction
IVF: *in vitro* fertilization
JIA: Juvenile Idiopathic Arthritis
LAC: Lupus Anticoagulant
LDASA: low dose acetylsalicylic acid
LMWH: low molecular weight heparin
MCTD: mixed connective tissue disease
Mo: monocytes
NLS: neonatal lupus syndrome
NSAIDs: non-steroidal anti-inflammatory drugs
NYHA: New York Hear Association
OR: Odd Ratio
oxLDL: oxidized low density lipoproteins
PAH: Pulmonary Arterial Hypertension
PE: Preeclampsia
PGA: Physician's Global Assessment
PlGF: Placental Like Growth Factor
PM: pregnancy morbidity
PP: platelets
PsA: psoriatic arthritis
TNF: tumour necrosis factor
TNFi: TNF inhibitors
TORCH: Toxoplasmosis, Others (Syphilis, Parvovirus B19, Hepatitis, HIV), Rubella, Cytomegalovirus, Herpes simplex
RA: rheumatoid arthritis
sDMARDs: Synthetic Disease-Modifying Anti-Rheumatic Drugs

sFlt-1: Soluble fms-like Tyrosine Kinase-1
SGA: small for gestational age
SLE: Systemic Lupus Erythematosus
SLR: Systematic Literature Review
SpA: spondyloarthritis
SRC: Scleroderma Renal Crisis
SSc: Systemic Sclerosis
TAK: Takayasu Arteritis
TGFß: Transforming Growth Factor-Beta
TTP: time-to-pregnancy
UCTD: Undifferentiated connective tissue disease
WHO: World Health Organization

1. Introduction

It is essential to provide adequate awareness of the implications of rheumatic diseases on reproductive health. For that purpose, the "11th International conference on Reproduction Pregnancy and Rheumatic Diseases" took place in August 2022 as an online event, due to the COVID-19 regulations. Hundreds of virtual delegates participated and interacted remotely with experts and presenters, making the conference a successful educational event.

In this introduction, two main points related to COVID-19 and autoantibodies associated with infertility are addressed.

COVID-19, auto-antibodies, and fertility:

Firstly, although much is still unknown about SARS-CoV-2 and COVID-19, it is well understood that the virus can trigger a hyperstimulated immune response and lead to broadly diverse autoimmune manifestations, more commonly in severely ill COVID-19 patients [1]. The disruption of the physiological immune response is key to severe COVID-19 and mortality. Thus, many immunoregulatory therapies have been investigated as therapeutic options for COVID-19 patients [2]. Angiotensin-converting enzyme 2 (ACE-2) is widely distributed in numerous cells types of the human body and acts as a port of entry to cells for SAR-CoV-2. ACE-2 is found in both the reproductive organs of males and females, which may lead to direct injury by the virus followed by a hyperinflammation immune response against it. One of the highest ACE-2 expressing cells are those located in the testis; thus, SARS-CoV-2 may cause significant inflammation and possibly spermatogenic impairment. Accordingly, there is evidence of reproductive damage in male individuals alongside impairment of sperm quality in COVID-19 patients compared to other long-term infection, such as some influenza viruses [3]. Furthermore, molecular resemblance was found between viral peptides of SARS-CoV-2 and proteins necessary for female reproduction, which may lead to cross-activation of immune components [4].

Secondly, since the SARS-CoV-2 pandemic outbreak, a great deal of resources and effort have been aimed to improve the therapeutic options for the acute manifestations of COVID-19. Currently, many are beginning to comprehend the drastic long-term implication of COVID-19, referred to as 'post-COVID19 syndrome', and the necessity of a sufficient coping strategy [5]. A significant compound of the long-term effects of COVID-19 is autoantibodies production [1,5]. Notably, a wide variety of autoantibodies are present in COVID-19 patients; some are well known to be associated with infertility, such as anti-cardiolipin and anti-thyroid peroxidase (anti-TPO) [1]. In addition, antiphospholipid autoantibodies, which are present in many severe COVID-19 patients, can lead to pregnancy complications and miscarriage [1].

Today, it is still difficult to estimate the long-term effects of SARS-CoV-2 infection on fertility, yet investigating this field should not be neglected [6]. Alongside numerous manifestations, COVID-19 may trigger long-term reproductive dysfunction that SARS-CoV-2 may cause, highlighting the importance of illness prevention. Furthermore, sufficient treatment that reduces both viral load and hyperinflammation should not be neglected, for it could assist in minimizing the risk of developing long-term complications [2].

2. The interplay between sex hormones and the immune system in rheumatic diseases

2.1. Gender bias in rheumatic diseases: the role of sex hormones and beyond

Women and men differ in three major biological points: the number of X chromosomes per cell, the type and quantities of sex hormones present and the ability to be pregnant, all of which have immunological consequences [7]. The term "neuroendocrine immunology" stands for a complex network that includes the interplay between gonadal hormones and immune cells, suggesting that biological sex is one of the drivers of chronic inflammation and autoimmunity [8]. Estrogens can stimulate certain immune responses (particularly on innate immunity, by enhancing antigen presentation and loss of tolerance towards self, and B cells, with boosting effect on antibody production), but can also have dose-related anti-inflammatory effects on T cells, macrophages and other immune cells. These observations can help explaining why hormonal compounds (such as combined contraceptives and hormone replacement treatment for menopause) and pregnancy itself can enhance or decrease the activity of ARD at a genetic or epigenetic level. By studying SLE flares, it was possible to show that environmental agents that inhibit DNA methylation can combine in a dose-dependent fashion with SLE genes and estrogens to induce disease exacerbations [9].

Conversely, androgens have predominantly immunosuppressive and anti-inflammatory effects. Testosterone was shown to be an endogenous regulator of BAFF. Male mice lacking the androgen receptor have increased splenic B cell numbers and serum BAFF levels. Among healthy men, serum BAFF levels are higher in men with low testosterone [10].

There are also non-endocrine mechanisms to explain sex bias in ARD, including X chromosome inactivation, sex chromosome aneuploidy and microchimerism. From birth, our epigenome and microchiome are shaped and undergo transformations according to our sex, type of birth, childhood and pregnancy history (for women), which have long-term consequences on health and response to treatments [7].

In addition, it is becoming evident that the gut microbiota differs between the sexes (the sexually dimorphic microbiome has been called "microgenderome") and leads to sex-dependent genetic and epigenetic changes in gastrointestinal inflammation, systemic immunity and, potentially, susceptibility to autoimmune or inflammatory rheumatic diseases [11]. The gut microbiota activates estrogens by secreting ß-glucoronidase and facilitates their translocation into the bloodstream for reaching distal sites. The alteration of such fine-tuned regulation can contribute to chronic inflammation and the onset of autoimmunity [12].

2.2. Interaction between pregnancy and the immune system

During human pregnancy, the semiallogenic fetus that grows within the maternal uterus is not rejected by the maternal immune system [13]. To enable both tolerance towards the fetus and defense against pathogens, multiple modifications of the maternal immune system occur during gestation and are most pronounced at the feto-maternal interface [13]. The players involved in this process are fetal antigens and pregnancy hormones, such as estrogen, progesterone and human chorionic gonadotropin. They act in concert to induce tolerogenic dendritic cells, expand Foxp3-expressing regulatory T cells, tune the rapidly increasing number of natural killer cells and downregulate T effector cells at the feto-maternal interface [13].

As a result, pregnancy enters a state of tolerance, reflected by the increase of IL-10, TGFß and other anti-inflammatory cytokines as well as regulatory proteins such as glycosylated immunoglobulins

[13]. Some of these immunological adaptations are detectable in the peripheral blood of pregnant women, indicating that immune tolerance during pregnancy has a systemic effect. Transcriptome analysis of circulating immune cells in pregnant healthy women show that the gene expression pattern of monocytes is activated whereas that of lymphocytes is suppressed [14].

2.3. Immunology of APS pregnancy

Obstetric APS is a specific subset within APS without maternal thrombosis. There is a general agreement that ß2glycoprotein I (ß2GPI)-dependent antiphospholipid antibodies (aPL) are the main pathogenic aPL for both the vascular and the obstetric APS. In fact, these antibodies interact with soluble coagulation factors and recognize ß2GPI not only on the surface of several cells involved in the coagulation process (e.g. endothelial cell-EC, monocytes-Mo, platelets-PP, and neutrophils) but also on trophoblast and decidual cells [15].

We still do not know the true physiological role of ß2GPI, which is a pleiotropic protein involved in several biological pathways, present in large amounts in the plasma, and highly conserved across the animal kingdom. Initially, ß2GPI was reported as a natural anticoagulant and anti-ß2GPI autoantibodies were thought to switch the hemostatic balance towards a pro-coagulant state. However, additional studies showed that the molecule may exert both anticoagulant and procoagulant effects making it complex to draw definitive conclusions on its impact on coagulation [16].

There is evidence that ß2GPI exerts a scavenging role towards several dangerous molecules such as LPS, viruses, and bacteria [16]. ß2GPI binds apoptotic material and favors its uptake by phagocytes [16]; it forms complexes with oxidized Low Density Lipoproteins (OxLDL), and favors their clearance mitigating the OxLDL toxicity [17]. There is evidence that ß2GPI plays also a role as a complement regulator [16]. The redox switch at the level of the domain V of the molecule is crucial for its anti-oxidant activity [16]. Conditions characterized by important oxidative stress such as ischemia/reperfusion injury or hypoxic state may affect ß2GPI levels. The involvement of ß2GPI in inflammation, coagulation, and oxidative stress regulation suggests a role of the molecule in the implantation and normal placentation reinforcing the concept that ß2GPI is more than the aPL autoantigen in APS. In particular, the reduction of ß2GPI plasma levels in women with early-onset preeclampsia and the variations in the placental oxygenation during pregnancy support a key anti-oxidant function in normal placentation [18]. Consistent with its role in placentation, ß2GPI is present in large amounts on trophoblasts and decidual cells in the normal human placenta [15]. Although ß2GPI null mice are fertile and carry viable fetuses to term, defective placentation was reported in these animals [19].

Whatever is the physiological role of ß2GPI in pregnancy, its binding with specific autoantibodies may trigger local inflammation mainly mediated by complement activation and intracellular signaling that ends in defective trophoblast proliferation/maturation and abnormal spiral artery development resulting in defective placentation [15]. The local inflammation is thought to be responsible mainly for early miscarriages while the defective placentation plays a major role for late pregnancy complications.

ß2GPI is present on the cells of the coagulation cascade (i.e. EC, Mo, PP) only after inactivation, while the plasma circulating molecule (closed form) is not well recognized by ß2GPI-dependent aPL. In contrast, the open conformation of the molecule is present on trophoblast and decidual cells being available for maternal ß2GPI-dependent aPL. This different tissue distribution was suggested to

explain the prognostic value of persistent low aPL titers in APS-associated miscarriages, while this is not the case for vascular manifestations [15,20].

3. Reproductive Health and Family Planning

3.1. Preconception Counselling and Risk Stratification

Individual risk stratification is the main objective of preconception counselling and should include both disease-specific and general risk factors (Figure 1), often assessed by different specialists. Rheumatologists will assess disease activity and modify the treatment if necessary for reaching stable disease remission prior to conception (ideally 6-12 months), using drugs that are compatible with pregnancy. In addition, autoantibodies with a potential negative impact such as aPL and anti-Ro/SSA ± anti-La/SSB should be tested if not available in the history of the patient. Although the frequency of positivity for these autoantibodies is variable in different ARD (more common in patients with connective tissue disorders as compared to women with chronic arthritis), it may be considered to check any women with ARD prior to pregnancy in order to broad the spectrum of risk stratification. Regarding aPL, the 3 "criteria" tests (Lupus Anticoagulant, anti-cardiolipin antibodies, anti-beta2glycoprotein I antibodies) best define the so called "aPL profile". It is accepted by consensus that a "high risk" aPL profile (risk of thrombosis and pregnancy morbidity) is identified as the presence of: 1) positive Lupus Anticoagulant; 2) triple aPL positivity (all 3 positive tests); 3) the presence of medium-high titres of IgG anti-cardiolipin and anti-beta2glycoprotein I; 4) persistence of positive aPL overtime (transient aPL are more likely to be non-autoimmune, non-pathogenic aPL)[21].

Gynaecologists/obstetricians typically focus on maternal comorbidities (e.g. arterial hypertension, obesity, etc.), harmful lifestyle habits (e.g. cigarette smoking), and previous pregnancy complications. The joined assessment of disease-specific and general obstetric risk factors will yield an individual risk profile for tailoring a treatment plan.

The multidisciplinary team has also the task to explain contraindications to pregnancy, either permanent or temporary. It can be wise to suggest to postpone pregnancy in patients with either new-onset ARDs, or active disease (especially if renal involvement) or recent arterial thrombosis (stroke, myocardial infarction). Because of the risk to maternal survival in pregnancy, patients with ARD should be discouraged from pregnancy in the case of severe organ involvement (e.g.: pulmonary hypertension, cardiomyopathy), previous pre-eclampsia with HELLP syndrome while on treatment [22].

3.2. Sexuality in patients with rheumatic diseases

Sexual health is defined by WHO as a state of physical, emotional, mental and social well-being in relation to sexuality. The sexual life of patients represents an important sphere of their lives and it contributes to quality of life. Therefore, it should be part of the evaluation also in patients with rheumatic diseases, an issue often ignored by health professionals. Indeed, in a recent survey among rheumatologists, it emerged that only 12% of patients seen in clinical practice where questioned about sexual activity. Rheumatologists attributed their reluctance to discuss issues related to sexuality with patients to time constraints, the lack of confidence with the topic and the concept that sexuality does not fall within rheumatological expertise [23]. On the other hand, 2/3 of patients felt embarrassed to discuss the problem with a health professional. Pain, fatigue and decreased joint mobility caused by rheumatic diseases often decrease sexual health in these patients. Absence of desire, vaginal dryness, erectile dysfunction related to vasculopathic and fibrotic changes, dyspareunia and the distribution pattern of psoriasis can be additional barriers to intimate relationship [24]. These symptoms might result in feelings of guilt or frustration and tensions in the relationship with the partner, which in turn further worsen sexual health. Therefore, it is important to give support to the patients and suggest ways of overcoming the most common difficulties [22].

Useful instructions for patients include favouring communication with the partner -which is the key to resolve any difficulty-, feeling fit and active, take pain medication, avoid cold temperatures, relax joints and muscle before sex, experiment different sexual positions.

3.3. Male fertility

To date, evidence on the safety of disease modifying anti-rheumatic drugs (DMARDs) in men with inflammatory rheumatic disease wishing to conceive remains limited, but reassuring about their general safety. The 2016 British Society of Rheumatology (BSR) guidelines on prescribing DMARDs in pregnancy noted that data relating to the impact of paternal exposure to these drugs (both fertility and male-mediated teratogenicity) are particularly limited, and further research in these areas is urgently required [25]. The more recent American College of Rheumatology (ACR) 2020 guidelines on reproductive health in rheumatic disease make similar observations on the limited evidence on paternal exposure in males with rheumatic disease [26].

During drug development and clinical trials, pregnancy following male or female exposure is contraindicated and relevant data slowly accumulates through reporting of accidental pregnancy exposure, post-marketing surveillance and registry data recording pregnancy exposure. Clinicians often ask female patients about pregnancy planning, but this questioning is less routine with male patients, compounding the lack of understanding and guidance. In women, effective disease control improves pregnancy outcomes; however, this relationship between disease activity and fertility is less studied in men. A recent multicentre cross-sectional study in men with IA, the iFAME (Inflammunity and Fertility in Men)-Fertility study, found that men diagnosed with IA before and during the peak of reproductive age had a lower fertility rate, higher childlessness rate and more fertility problems [27]. Further analysis of this cohort found that pregnancies conceived after the diagnosis of IA had higher rate of miscarriage (12.27 vs 7.53%, p = <0.05), after adjusting for confounders (OR 2.03, 95% CI 1.12-3.69, p= 0.015), although the overall rate of miscarriage was comparable to population estimates [27].

In addition to BSR and ACR guidance, recent systematic reviews of all peer-reviewed published human data have found largely reassuring evidence for paternal exposure to various DMARDs [28]. In fact, there is no consistent evidence that any paternal exposure induces adverse fetal development or pregnancy outcomes. Further research in this area is required to provide men wishing to conceive with more information on outcomes following paternal exposure. Unbiased prospective reporting of any maternal or paternal exposures to DMARDs, followed by reporting of the pregnancy outcome when available would help to achieve this goal. For now, it is important to provide reassurance when counselling men about the low risks of anti-rheumatic drugs to fertility and pregnancies and following accidental conception.

Sulfasalazine is associated with worsening seminal parameters, there are also numerous reports of conception whilst on sulfasalazine, and seminal parameters resolve within 3 months. In counselling men taking these medications, it is important to consider the potential adverse impact of stopping medications such as sulfasalazine, that are controlling rheumatic disease activity, as this may do more harm than good and stopping sulfasalazine pre-paternal conception is not recommended unless conception is delayed.

Cyclophosphamide, on the other hand, is associated with permanent azoospermia in some men. Sperm cryopreservation should be considered prior to cyclophosphamide dosing. Limiting the dose and duration of cyclophosphamide therapy may also limit the severity and duration of azoospermia.

Due to chromosomal changes that occur in the sperm created during cyclophosphamide treatment, men should avoid conception for at least 3 months after dosing.

3.4. Female fertility

Fertility is defined as the ability to have a clinical pregnancy, whereas fecundity is clinically defined as the capacity to have a live birth, including gamete production, fertilization and carrying a pregnancy to term. In the literature, fertility is often considered as the ability to get pregnant, which is best reflected by time to pregnancy (TTP). Fertility rate is defined as the average number of children per woman in a lifetime. The fertility rate is determined by time to pregnancy, pregnancy outcome (e.g. miscarriages) and personal choice. In women with rheumatoid arthritis (RA) a decreased fertility rate has been described long ago [29]; such decreased fertility may be ascribed, among other factors, to a prolonged TTP [30,31]. For women with inflammatory arthritis (IA) other than RA, conflicting results have been reported [32,33].

In clinical practice, the decreased fertility observed in women with RA is a concern. In past times, when treatment options during pregnancy and during the preconception period were limited, TTP exceeded more than one year in roughly 40% of women with RA. This was associated with active disease, the use of prednisone in a daily dose exceeding 7,5 mg and the use of non-steroidal anti-inflammatory drugs (NSAIDs) [30]. How active disease may contribute to an increased TTP remains an unanswered question. A reduced ovarian reserve was described in patients with RA and spondyloarthritis (SpA) [34], whereas an inverse correlation between disease activity markers and anti-Müllerian hormone (AMH) levels, suggesting that disease activity can play a role [35]. Circulating interleukin (IL)-6 levels have been shown to correlate with time to pregnancy, even after correction for disease activity, suggesting that systemic inflammation may play a role [36]. Interestingly, in a small study, treatment with tumour necrosis factor (TNF)-inhibitors was associated with a shorter TTP. However, this study was too small to correct for relevant confounders [37]. A decreased intercourse frequency in women with (active) RA has been suggested as an explanation for the lower fertility rate. Although sexual dysfunction is highly prevalent in women with RA, this has mainly been studied in postmenopausal women in long term relationships [38] while data in young RA patients with a wish to conceive are lacking. Lastly, it has been shown that women with RA may enter menopause at an earlier age compared to healthy controls, thereby reducing their reproductive lifespan [29]. This observation was made in times when strict control of disease activity was not common in RA patients; thus it could be envisaged that it provided an extra-articular feature of RA related to chronic elevated disease activity. It is not known whether such observation can be translated to women that have always been treated according to a treat-to-target approach aimed at remission.

In women with systemic lupus erythematosus (SLE), primary infertility does not seem to be different from the general population, while there are several factors that may contribute do secondary infertility: menstrual irregularity or amenorrhea due to severe flares, renal insufficiency-related hypofertility, menstrual disorders (e.g. due to endometriosis) and premature ovarian failure (POF). POF is due to accelerated reduction of ovarian reserve due to either direct autoimmune oophoritis or to the use of cytotoxic drugs [39]. Cyclophosphamide (CYC) exposure is one of the causes of premature ovarian failure described in SLE women; it is associated with lower levels of AMH which are directly related to cumulative doses and women's age at the beginning of treatment [40,41]. It is recommended to offer fertility preservation methods, especially GnRH analogues, to all menstruating women with SLE who are going to receive alkylating agents [42].

Despite all these factors, TTP in women with SLE was found to be normal (except for those women that have been treated with CYC) [43]. Instead, women with SLE have decreased fecundity as a result of a higher rate of miscarriage, a lower rate of live birth and due to personal choices [44].

3.5. Contraception

The use of reversible contraceptive methods is a relevant issue for women with ARD because preventing pregnancy during disease flares or during treatment with teratogenic drugs avoids adverse pregnancy outcomes. Despite their unique medical situations, patients with ARD may want to have a family just like their peers.

There are a wide range of effective contraceptive methods: estrogen-containing methods, which contain both estrogens and progesterone, such as combined oral contraception (COC), vaginal ring, and transdermal patch; progestin-only compounds, like the progestin-only pill (POP) or the subdermal implant; intra-uterine devices (IUD) which can be either copper-IUD (without any hormones) or progestin-releasing IUD. Regarding the degree of efficacy, the implant and IUD are considered to be highly effective, with a 1-year failure rate (pregnancy rate) of less than 1%, while and COC or POP are considered effective with optimal and frequent use (1-year failure rate between 5 and 8%) (World Health Organization, Medical Eligibility Criteria). Several medical conditions may impact the safety of some contraceptive options and imply a tailored choice for the individual patient. This is mostly due to safety concerns related to the risk of thrombotic events and disease flares upon the use of estrogen-containing contraceptive methods [45,46]. General risk factors (hypertension, obesity, tobacco use, family history of hormonal-dependent cancers) and patient's preference should be also addressed during contraception counselling.

The ACR proposed an algorithm for navigating physicians in the choice of contraceptive measures for women with ARD [26]. Clinicians should start to look for the presence of aPL antibodies and stratify the patients accordingly. Then, the type of ARD (SLE or non-SLE ARD) and disease activity must be addressed. Generally, IUD is the preferred choice, followed by POP (less effective than IUD). Estrogen-containing compounds are contraindicated in aPL positive patients, due to their increased risk for thrombosis, and in SLE patients with moderate to severe disease activity. The use of transdermal patch should be discouraged in women with SLE due to the release of higher concentrations of estrogens.

IUD can be offered to all patients unless there is a gynaecological contraindication. Either the copper or the hormonal IUD can be used in any patient with ARD. The levonorgestrel-containing IUD is not contraindicated in patients with APS, although the individual risk profile should be assessed [42]. Compounds containing progestin only (pill, subcutaneous depot injections) are suitable for these women, although their use should be weighed against the risk of thrombosis. Progestin-only emergency contraception is not contraindicated in patients with ARD and can be recommended also to women with SLE and/or APS, as the benefit of avoiding unintended pregnancy is likely to overweight the risk of adverse events.

The choice of a contraceptive method should be a shared decision between the multidisciplinary team and the patient. The Rheumatologist and the Gynaecologist should highlight "pros" and "cons" and offer the best method, taking into account the patient's preferences.

3.6. Assisted Reproduction Techniques

As fertility can be temporarily or permanently affected by rheumatic diseases and/or their treatment, the approach to assisted reproductive techniques (ARTs) is a relevant topic for some women [26,42]. ARTs include ovulation induction treatment, intrauterine insemination, and in vitro fertilization (IVF) requiring ovarian stimulation for the induction of multiple follicular growth. The administration of

hormonal preparations, particularly estrogens, can elicit activity of some diseases (particularly SLE and APS), increase the risk of thrombotic events (especially in patients with positive aPL) and of ovarian hyperstimulation syndrome, a life-threatening condition that could be prevented by the use of "friendly" ovarian stimulation protocols. Therefore, it is of fundamental importance to individualize the approach toward ARTs by thoroughly discussing risks and preventative measures.

In RA, there are generally no implications for maternal disease during ARTs. It was shown that the chance of a live birth after ART was significantly reduced as compared to women without RA [47]. A Danish nation-wide study found better results in the case of transfer at the blastocyst stage and in presence of treatment with glucocorticoids before embryo transfer. On the contrary, intracytoplasmic sperm injection was associated with a small reduced chance of a live birth as compared to IVF. Type of hormone treatment protocols and anti-inflammatory or immunosuppressive therapies within 6 months before embryo transfer did not have significant impact on the chance of live birth [48].

Among connective tissue diseases (CTDs), SLE and APS are the most relevant during childbearing age. Observational nationwide studies conducted in France [49] and Italy [50] showed that ARTs, especially IVF, can be safely and successfully performed in women with SLE and/or APS who become pregnant during a period of disease remission and carefully adhere to medications for the prevention of SLE flares and thrombotic events. Active SLE, poorly controlled arterial hypertension, advanced renal disease, and major previous thrombotic events are situations in which ARTs should be considered with caution, due not only to the risks linked to ARTs but also to the subsequent pregnancy. As for spontaneous pregnancies, risk stratification and correct timing (at least 6 months of stable inactive disease on compatible medications) are key points for the prevention of maternal and obstetrical complications [51].

Although the prophylactic treatment during ARTs should be tailored for each patient, some general measures can be suggested. The type and dosage of anti-thrombotic treatment should be recommended as during pregnancy according to the individual risk profile. Low dose acetylsalicylic acid should be stopped three days before egg retrieval and resumed the following day, while heparin should be stopped 12 hours prior to the procedure and resumed the very same day as long as there is no bleeding [42].

4. Disease course and predictors of adverse pregnancy outcomes in rheumatic diseases

4.1. Predictors of preeclampsia and obstetric complications in patients with rheumatic diseases

Taking care of pregnant women with underlying medical complications and in particular with rheumatic diseases is a challenge. A careful preconception assessment and timing pregnancy during the quiescent phase of a disease, can have the potential to substantially reduce the risk of adverse outcomes. During pregnancy, a close collaboration between rheumatologists and obstetricians is necessary. The immune state related to pregnancy, the associated organ alterations, circulating autoantibodies and certain drugs may mimic or increase the risk of typical obstetric complications such as preeclampsia, miscarriage and preterm delivery. Fetal complications, such as cardiac arrhythmia due to transplacental migration of cardiotoxic antibodies or growth restriction due to placental failure, are other important complications which can be encountered in this particular setting.

The placenta seems to be the target of many rheumatic diseases leading to altered morphologic and functional development primarily of the intervillous space. This particular environment, where the placental villi are surrounded by maternal blood and where a limited cell barrier allows for maternal-fetal delivery of oxygen and nutrients, develops in the first 16 weeks of gestation initially under hypoxic conditions. After the remodelling of spiral arteries, the oxygen content in the intervillous space increases dramatically [52]. Hypoxia and hyperoxia are important regulating stimuli for the development of the villous arteries and of the human hemochorial placenta. Therefore, an altered angiogenesis - mainly driven by a persistent intervillous hypoxia with reduced blood flow - induces an anti-angiogenic state with poor placental development [52].

Angiogenic biomarkers such as placental like growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) and others, are laboratory methods to monitor high risk pregnancies or to screen for preterm preeclampsia as soon as in the first trimester [53–58].

Of importance, angiogenic biomarkers and in particular the sFlt-1/PlGF ratio are also helpful to differentiate preeclampsia or superimposed preeclampsia from mimickers and from the worsening of an underlying medical condition, particularly rheumatic disease [59–61].

Moreover, by combining the angiogenic information provided by the sFlt-1/PlGF ratio with baseline characteristics such as lupus anticoagulant, the predictive capability for adverse pregnancy outcome can be significantly increased [62].

In conclusion, the implementation of angiogenic biomarkers during the monitoring of pregnant women with underlying rheumatic disease may have the potential to decrease the incidence of adverse outcomes. Moreover, the information provided by these markers may be used as "common" language between obstetricians and rheumatologists caring for such pregnancies.

4.2. Pregnancy in patients with rheumatoid arthritis and spondyloarthritis

The immunological modifications that occur during pregnancy, are able to bring about a natural improvement of rheumatoid arthritis (RA), a phenomenon that was first described by Philip Hench in 1938 [13,63]. In the decades before 2000, in which women with RA entered pregnancy with more active disease, a change towards a disease amelioration was noted by about 90% of the patients; however, only 16% achieved remission [13,64]. In the last decades, more effective treatment options for RA patients planning a pregnancy have emerged. Thus, the percentage of patients experiencing a change of their disease activity towards improvement is now lower (48-65%), yet the proportion of pregnant RA patients being in low disease activity or remission increased to 90% [13,65]. After delivery, the immunomodulatory effects mediated by fetal antigens and pregnancy hormones vanish,

giving rise to lymphocyte activity together with persistent monocyte gene activity which might trigger a disease flare [14].

SpA is a large and heterogeneous group of diseases which includes axSpA and PsA. Regarding disease activity during pregnancy, axSpA has the tendency to remain unchanged or get worse, while PsA may remain stable or improve. Both diseases display a high frequency of flare in the post-partum period [66]. In terms of obstetric complications, SpA as a group of diseases seems to be associated with an increased risk of preterm birth, small for gestational age, preeclampsia, and caesarean section [66].

By analysing PsA pregnancies only, no risk elevation for gestational diabetes, small for gestational age and low birth weight was noted, while a higher risk for pre-eclampsia, elective caesarean section and preterm birth in PsA pregnancies cannot be ruled out due to methodological heterogeneity across studies [67]. Conversely, studies about pregnancy in axSpA showed an increased prevalence of cesarean sections compared to the general population and a trend towards increased frequency of preeclampsia, IUGR, SGA babies and neonatal admission to NICU [68].

Data from EuNeP showed a very good outcome of pregnancies in axSpA, with a live birth rate of 98.8%. TNFi treatment was received by 53%, 27.5%, and 21.4% of women before pregnancy, during the first and the third trimester, respectively. An individualized approached since the preconception period is likely to explain that pooled rates of most outcomes were better than what had been reported in the literature and within expected rates of those reported for the general population [69].

4.3. Pregnancy in juvenile idiopathic arthritis

In reproductive rheumatology, juvenile idiopathic arthritis (JIA) provides a unique scenario as women usually embark on pregnancy with longstanding disease duration, prolonged exposure to csDMARDs and bDMARDs and irreversible articular damage. The research interest about reproductive issues in women with JIA has flourished only over the recent years, explaining why available data regarding obstetric and neonatal outcomes in JIA are still scanty and not consistent. Discrepancies concern the fluctuation of JIA disease activity during pregnancy: earlier studies suggested improvement of disease activity during gestation [13,22,70], while more recent investigations have reported a high rate of flares during gestation [71–75]. In particular, the letters have shown that disease activity remains substantially stable in the first trimester to significantly increase in the second trimester. Current concept implies that the optimal pre-conceptional disease control obtained in modern era reduces the impact of pregnancy-induced amelioration of disease activity. Nevertheless, pre-conceptional disease severity and disease activity provide the main determinants of disease activity during pregnancy, an observation that highlights the pivotal importance of a careful family planning even in the setting of JIA. Unfortunately, any conclusion about a potentially different behaviour of JIA categories during pregnancy and in the post-partum is prevented by the paucity of evidence. Indeed, most data come from population-based studies analysing administrative health databases or hospital discharge records, which do not allow to adequately account for potential confounders, including JIA category. According to available reports, disease activity tends to peak again in the post-partum [22,70,73–75]; it is important to note that the sooner bDMARDs are reintroduced after delivery, the sooner disease control is obtained [74].

There is a substantial consensus in literature in reporting preterm delivery and low neonatal birth weight as the main obstetric complications among JIA women [74,76–81], while data about the risk of pre-eclampsia in JIA pregnancies are conflicting [70,74,80,82,83]. Interestingly, in a very recent Italian monocentric study, the duration of biological treatment during gestation and the number of

pre-conception bDMARDs were identified as significant predictors of pregnancy complications. [74]. Caesarean section is very commonly pursued among women with JIA, possibly due to obstetrical concerns about parturition stress on hip prosthesis.

Following an alarming report of a 9% rate of congenital malformations (mainly heart and neural tube defects) in neonates born to mothers with JIA, reassuring data have been raised, all concordant in denying an increase of such risk [72,74,76,77,83].

Rheumatologists are gaining confidence in the management of JIA women during gestation, and counselling about family planning should be incorporated in the routine assessment of young women with JIA, which are very keen to receive information about reproductive issues as emerged in a recent survey.

4.4. Pregnancy in patients with systemic lupus erythematosus

4.4.1. Pregnancy outcomes in SLE

As SLE is a disease that targets predominantly young women in the reproductive years, pregnancy is frequently observed. This represent a big change form 1970's, when most women with lupus were counselled not to become pregnant. Key changes include improvement in outcomes (Mehta B et al Ann Intern Med. 2019); better understanding of pathogenesis of pregnancy complications in APS and SLE [59], improvement in risk stratification of patients [84,85], and identification of potential targets for treatment [86].

Retrospective data show that maternal mortality in SLE patients has decreased, approaching that of women without SLE over the past 20 years in the United States, and fetal mortality has also decreased. The frequency of preeclampsia (PE), however, has not improved and occurs in up to 10% of SLE pregnancies [87]. The PROMISSE Study (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus; ClinicalTrials.gov Identifier: NCT00198068), a prospective, multi-center, multi-ethnic study enrolled 385 SLE patients with quiescent or mild disease with the goal of identifying predictors of adverse pregnancy outcomes (APO): fetal/neonatal death; birth <36 weeks due to placental insufficiency, hypertension, or preeclampsia and small for gestational age (<5%). APOs occurred in 19% of patients. Baseline predictors of APO included lupus anticoagulant positive (LAC), antihypertensive use, PGA >1; non-Hispanic White ethnicity was protective. Among women with no risk factors at baseline, the APO rate was 7.8%, whereas in those women either LAC positive, or LAC negative but non-White or Hispanic and treated with anti-hypertensives, APO rate was 58% and fetal/neonatal mortality 22% due to complications of prematurity [59]. History of thrombosis also increased risk. Early evidence of complement activation was associated with subsequent APOs.

Pathogenesis and potential therapy for APS in Pregnancy:
Some APOs in APS may be due to a failure of adequate vascularization of the developing placenta, resulting in under-perfusion of the intervillous space by oxygenated maternal blood and subsequent placental hypoxia. Different animal studies show that poor placental vascularization is due primarily to inflammation. In a murine model of aPL-induced pregnancy complications, aPL target placental tissue and activate complement via the classical pathway, leading to the generation of potent anaphylatoxins, recruitment of neutrophils, release of proinflammatory mediators (TNF-α), and anti-angiogenic factors, ultimately causing abnormal placentation and fetal death. Notably, in an aPL-induced mouse model of pregnancy complications and in antibody-independent models of PE, it was found that complement activation and TNF-α were critical effectors of placental dysfunction and fetal damage and that blockade of complement or TNF-α restored angiogenic balance and spiral artery

remodelling and rescued pregnancy [86,88]. These findings identify new targets to prevent placental dysfunction in APS and SLE.

Based on the observations in PROMISSE and the favourable results of TNF-α blockade in mouse models, it was hypothesized that TNF-α blockade, added to a regimen of heparin and low dose aspirin, will significantly decrease the rate of fetal death and/or preterm delivery due to preeclampsia or placental insufficiency in women with clinical APS (with or without SLE) and LAC. The IMPACT Study (IMProve Pregnancy in APS with Certolizumab Therapy), an open label single-stage Phase II trial of certolizumab, a TNF-α inhibitor that does not cross the placenta (ClinicalTrials.gov Identifier: NCT00198068) is the first interventional study of a biologic therapy to prevent placental insufficiency and the resultant maternal and fetal morbidity and mortality.

4.4.2. Biomarkers in SLE pregnancy: are there any predictors of APO?
The holy grail about biomarkers is that they will fulfil the following promises in their application to pregnancies in patients with SLE: aid the clinician in managing the patient, sort out phenotypic heterogeneity, inform about pathogenesis and provide targets for therapy to achieve "biomarker coverage" [89]. However, in thinking about biomarkers, might we really also be referring to risk factors? Disease risk factors can be defined as measurable biological characteristics of an individual that precede a defined disease outcome such as fetal death, congenital heart block and or a lupus flare, predict that outcome, and are directly in the biological causal path such as high titer anti-Ro/SSA antibodies, complement activation products, and or anti-phospholipid antibodies. Biomarkers are biological indicators for processes involved in developing a disease that may or may not be causal, e.g. N-terminal pro-B-type natriuretic peptide (NT-proBNP). The difference between a risk factor and biomarker is subtle. A biomarker can be a risk factor when it is causal, but this is not a necessary characteristic for a biomarker. When a biomarker is not predictive or causal to a disease, it is not considered a risk factor, but can still inform processes involved in the development of a disease. One of the pitfalls in considering biomarkers during pregnancy is that acute phase reactants may increase during normal pregnancy with examples being ESR, CRP, and C3 and C4. With these concepts in mind various biomarkers were considered as they assess different components of pregnancy including maternal, placental, and fetal.

The PROMISSE study was reviewed and five factors at baseline associated with adverse pregnancy outcomes, race/ethnicity other than non-Hispanic white, prescribed anti-hypertensive medications, low platelet counts, the presence of a lupus anticoagulant and active lupus [59,90]. Further data showed that alternative and terminal pathway activation complement products as early as 12 weeks predicted adverse pregnancy outcomes [84]. Likewise, an elevated sFlt1/PlGF ratio by 15 weeks of gestation associated with poor pregnancy outcomes. Applying a logistic regression model, baseline variables predictive of lupus flares during pregnancy included younger age, lower C4 and higher physician global assessment. There were no predictors of postpartum flares. The baseline proteinuria, serum creatinine, and/or blood pressure did not predict renal flares. However for those patients with previous kidney disease, those in complete remission had fewer renal flares (7/89 = 7.9 %) than those in partial remission (6/29 = 20.7%), (P = 0.08).

Antibodies to dsDNA alone should not raise concern, even in patients with past kidney disease, if in remission.

Neonatal Lupus:
Turning to the fetal component, the focus was on cardiac manifestations of neonatal lupus [91]. With regard to the severity of cardiac manifestations, higher cord blood levels of CRP, NT-pro-B-type

natriuretic peptide (NT-proBNP), troponin I; matrix metalloproteinase (MMP)-2, urokinase plasminogen activator (uPA), and urokinase plasminogen activator receptor (uPAR) associated with more severe cardiac disease. Several of these markers associate with activation of TGFbeta, which promotes fibrosis. Maternal total 25(OH) vitamin D levels overall and during the second trimester did not associate with the risk of cardiac disease in anti-SSA/Ro positive mothers. Higher than average levels of maternal vitamin D during pregnancy were associated with later age of pacemaker placement in multivariate analysis. With regard to antibody specificities and the development of cardiac manifestations of neonatal lupus (cardiac-NL), several points are of note. Reactivity to native Ro60 is the most sensitive test for cardiac -NL. Reactivity to p200 does not confer added risk over measuring full length Ro52 antibodies. For a mother with a cardiac-NL child, the frequency and titer of anti-Ro52 and p200 antibodies are not informative with regard to risk of recurrence. Although antibodies to Ro60, Ro52, and p200 are < 50% specific for cardiac-NL, reactivity to p200 is the least likely to be false positive in mothers who have never had an affected child. Mothers with low titer anti-Ro60 and Ro52 may require less stringent echocardiographic monitoring [91]. A new NIH supported study is enrolling anti-SSA/Ro positive mothers across nearly 20 sites to evaluate ambulatory fetal heart rate and rhythm monitoring [92] done by the mother thrice per day and the efficacy of dexamethasone and IVIG to restore normal sinus rhythm if second degree block is identified by the maternal home monitoring and confirmed by echocardiogram within 12 hours.

4.5. Pregnancy in patients with antiphospholipid antibodies

The presence of antiphospholipid antibodies (aPL) has been consistently linked with adverse pregnancy outcomes, including recurrent early miscarriage, fetal death, IUGR, preeclampsia, prematurity, and maternal thrombosis [93]. Women positive for LAC and, particularly, those triple-positive are at the highest risk. Approximately 10%-15% of women with recurrent miscarriage are diagnosed as having antiphospholipid syndrome (APS). Pregnancy loss can occur at any stage of gestation, particularly during the second and third trimesters (about 50% of cases). This differs from the pattern of pregnancy loss in the normal population, in which pregnancy loss usually occurs during the first trimester and is most often caused by morphologic or chromosomal abnormalities. It is important to note that the current classification criteria for APS have been amended to highlight the fact that not only foetal loss but also premature birth before 34 weeks as a result of preeclampsia, placental abruption, or IUGR, and positive aPL or LAC, may allow the patient to be labelled as having APS [94].

The use of LDA and LMWH has greatly improved the prognosis of pregnancies in women with aPL. There are some debates regarding the dose of LMWH and the optimal combination in different clinical scenarios. Preconception LDA therapy is desirable due to its possible beneficial effects on early stages of implantation. Despite recent expert guidelines recommend the combination of LDA with LMWH, many observational studies have reported 80%-100% pregnancy success rate with LDA alone in APS patients with history of recurrent early miscarriages [21]. Because foetal loss is a more severe and specific manifestation of APS, combination therapy with LDA and prophylactic-dose LMWH is generally recommended. For pregnant women with APS who have had prior thrombotic event, LDA and therapeutic-dose LMWH anticoagulation are recommended. Vitamin K antagonists are teratogenic and should be avoided between 6- and 9-weeks' gestation. Due to the risk of foetal bleeding thereafter, warfarin should be used after 9 weeks' gestation only in exceptional circumstances.

Alternative therapies for refractory and difficult cases include increase of heparin to therapeutic-dose, addition of hydroxychloroquine, or addition of low-dose prednisolone in the first trimester. In refractory obstetric APS, pravastatin has improved pregnancy outcomes at the time of onset of preeclampsia or severe IUGR [95]. Several studies have demonstrated statins not to be teratogenic.

There is increasing number of publications of successful use of eculizumab for off-label indications, including pregnant women with aPL, APS-related thrombotic microangiopathy or catastrophic APS. Eculizumab crosses the placenta only minimally and does not affect the foetus.

With proper management, more than 70% of pregnant women with APS deliver a viable, healthy infant. Preconception counselling is essential to estimate the chance of both foetal and maternal problems. Despite the good prognosis achievable with correct management, patients must be aware that there is an increased risk of serious complications, including miscarriage, foetal death, prematurity, preeclampsia, and thrombosis [96]. All pregnant women with APS should be cared for by high-risk medical-obstetrical clinics. Uterine and umbilical artery Doppler evaluations are widely used to assess the risk of preeclampsia, placental insufficiency, and IUGR, with normal examination findings having high negative predictive value.

4.6. Pregnancy in patients with Systemic Sclerosis

Like in others autoimmune diseases, pregnancy in women with SSc can be a challenge, though many women can have successful pregnancies. Despite the historical belief of SSc as a contraindication to pregnancy, studies in the last decades have reported generally good outcomes [97–99].

Overall, studies on SSc pregnancies have shown a slightly increased risk of miscarriages (Odd Ratio OR of about 1.6), and a higher prevalence of gestational hypertension (OR=2.8), growth restriction (OR=3.2), preterm delivery (OR=2.4) and caesarean delivery (OR=2.3) [97]. The IMPRESS-2 (International Multicentre prospective study on PREgnancy in Systemic Sclerosis) study has also shown a high risk of pre-eclampsia, suggesting to consider prophylactic low-dose aspirin for SSc pregnancies. Children of SSc mothers are more frequently low weighted at birth (OR=3.8) and small for gestational age, frequently requiring neonatal intensive care [97,98,100]. A proposed mechanism underlying these events is placental insufficiency, which might be part of SSc-related vasculopathy.

The limited available data suggest that most women with SSc have relatively stable disease through pregnancy. Most of SSc mother report stability in the majority of disease domains. About 15% of these mothers complains of worsening gastrointestinal symptoms during pregnancy, which might be potentially related to gestational nausea. On the other hand, about 35% of mothers reports improvement of Raynaud's and digital ulcers during pregnancy [97], which is believed to reflect pregnancy-associated hyperdynamic circulation with decreased peripheral vascular tone and increased cardiac output.

In general, difficulties that have to be faced during pregnancies of women with SSc are not only limited to obstetric complications, but include also severe baseline organ involvement, the occurrence of severe disease flares, and the limitations in therapeutic armamentarium [101]. Pregnancy planning for women with SSC women should take into consideration several high-risk situations, which include I) potentially teratogenic medications such as bosentan, immunosuppressive agents such as methotrexate or mycophenolate mofetil, and anti-fibrotic therapy with nintedanib, II) early diffuse cutaneous disease or rapidly progressive disease - due to the risk of severe heart or lung involvement and scleroderma renal crisis (SRC), III) pulmonary arterial hypertension, IV) heart failure (NYHA class III-IV or left ventricular ejection fraction below 40%), and V) severe interstitial-lung disease.

Pregnancy does not appear to represent a frequent triggering factor for scleroderma renal crisis (SRC). SRC can be difficult to differentiate from pre-eclampsia and HELLP syndrome during late pregnancy. Occurrence or worsening of arterial hypertension, renal failure or thrombocytopenia in pregnant women with SSc require considering SRC, pre-eclampsia and other thrombotic microangiopathies. Weighting respective risk factors and dosing blood renin levels might be of help. Whenever SRC is suspected during pregnancy, an intensive monitoring is required and high-dose ACE-inhibitors should be started, weighing the risk of these medications on fetal renal development with the overall health and life of the mother and fetus.

Delivery of SSc women should consider avoiding general anesthesia whenever possible, due to potential difficulties in intubation and risk of aspiration pneumonia, and a special warming of the delivery room, the mother and intravenous fluids.
Post-partum follow-up require progressive re-introduction of preconception medications considering the breastfeeding status, monitoring for SRC in women at high risk and considering difficulties in childcare due to disease-related fatigue or skin/organ involvement.

4.8. Pregnancy in patients with others connective tissue diseases

4.8.1. Undifferentiated Connective Tissue Diseases
Disease flares during pregnancy or puerperium in Undifferentiated Connective Tissue Diseases (UCTDs) were reported in 25%-30% of pregnancies in a monocentric study on 100 patients. Usually flares are mild, risk factors for flares have been reported and include active disease at conception and anti-dsDNA antibodies [102]. The rate of disease evolution from a diagnosis of UCTD to a diagnosis of definite CTD was 12% within a mean time of 5.3 ± 2.8 years in a multicentre study [103]. The live birth rate was 89% and 79% in these two studies, respectively [102,103]. The overall risk of obstetric complications seems to be low in followed-up pregnancies, but in women with mild preclinical or incomplete rheumatic diseases detected during the first trimester, the rates of adverse obstetric events are significantly higher than in controls [104]. Anyway, pregnancies in women with UCTD managed by a rheumatologist have a high rate of pregnancy success and fewer risks than those in women with SLE [105].

4.8.2. Mixed Connective Tissue Disease
Mixed Connective Tissue Diseases (MCTDs) may be associated with an increased risk of APO [106]. Active disease during pregnancy was associated to an increased risk of premature birth and perinatal mortality. Maternal deaths associated with PAH were historically reported, therefore patients should be screened for PAH before conception.
In a more recent multicentre study on 203 pregnancies in MCTD, live birth rate was 72%. Women with MCTD and aPL and pulmonary or muscular involvement had worse foetal outcomes as compared with those without [107].
Cases of neonatal lupus have been reported in pregnant women with MCTD in absence of anti-Ro/SSA antibodies [106,107].

4.8.3. Idiopathic inflammatory myopathies (IIM)
Pregnant patients with IIM appear at increased risk higher risks of miscarriage [108], caesarean section, preterm birth and low birth weight [109]. High pregnancy risk is associated with joint involvement and anti-Jo1 positivity [110], and a good control of disease activity has crucial importance for favourable pregnancy outcome [111].

4.8.4. Interstitial Lung Disease (ILD)

A retrospective study of 86 pregnancies in 60 women with ILD showed surprisingly favourable pregnancy outcomes for all but the most severely-ill women [112]. None of the women died during or following pregnancy; only one was delivered preterm due to worsening lung disease, and only one was intubated (for asthma, not worsening ILD). Excluding the 7 women with very severe ILD (pulmonary function tests <40% of predicted), 17% suffered severe adverse pregnancy outcomes. This data suggests that women with ILD are often able to have successful pregnancies.

4.9. Pregnancy in patients with Takayasu Arteritis

As we have seen in others rheumatic disease, knowledge about pregnancy in patients with vasculitides is increasing. Belonging to the large vessel vasculitides, Takayasu Arteritis (TAK) may be considered the little sister of giant cell arteritis (GCA). In contrast to GCA which is most prevalent in old age, TAK begins in childhood or adolescence and predominantly affects females. Diagnoses is often delayed by years and is made based on established structural damage. In a recent French multicenter study 4/33 patients were diagnosed during pregnancy [113]. In a recent study made by Gloor et al., the cohort encompasses 35 patients resulting in a prevalence of the disease in Switzerland of 14.5/Million inhabitants [114]. Female were 97% of cases, the median age at onset was 27 years, the median diagnostic delay 6 years. The key symptoms were (I) asthenia/fatigue/feeling sick, (II) claudication of upper limbs and (III) carotidynia/sore throat. The affected blood vessels were the aortic arch (74%), the abdominal aorta (48%), the subclavian arteries (right 58%, left 77%) and the carotid arteries (right 58%, left 68%). In many cases the stenosis of the carotids, the subclavian arteries and/or the abdominal aorta was advanced and remained unchanged upon treatment, indicating a long preexisting subclinical disease process. Accordingly, classification criteria of TAK are primarily based on disease damage and not on disease activity [115].

Treatment of TAK has changed over the last decade. Although the EULAR criteria about management of large vessel vasculitides [116] still propose glucocorticoids as a first line agent, biologics such as TNF-inhibitors (infliximab and adalimumab) as well as the IL-6R targeting tocilizumab now plays key roles. In the study of Gloor et al., biologics were prescribed in 20/31 patients (anti-TNF: 5; anti-IL-6: 15 patients). Prior to conception tocilizumab was switched to anti-TNF. In all patients, a total of 23 successful pregnancies were achieved. In addition, the following complications were registered: new hypertension, new postprandial abdominal pain, IUGR and preeclampsia.

The main risk of pregnancy in established TAK is a compromised in aortic function. Due to the vessel wall fibrosis, the compliance, i.e. the ability of the aorta to distend and increase volume with increasing transmural pressure, decreases. A simple measure to estimate the compliance is the pulse pressure (the difference between the systolic and diastolic blood pressure, measured in millimeters of mercury). In young females the pulse pressure should stay below 50 mmHg. Thus, it is plausible that arterial hypertension is the most important and most frequent complication of TAK [113]. And, following these arguments, an increased heart rate, stroke volume and cardiac output toward the end of pregnancy bears the risk of aortic rupture and of heart failure [117]. However, the effect of pregnancy on disease activity and disease activity on pregnancy outcome remains debated.

4.10. Pregnancy in patients with Behçet's disease (BD)

A SLR published in 2020 described controversial observations about the course of BD during pregnancy: some found that symptoms may get worse, while others showed that disease activity may improve [118]. Recent studies reported contrasting results [119–121], suggesting that BD may be a heterogeneous disease during pregnancy, possibly based on different disease manifestations

and different ethnicities. There is general agreement on thromboembolic events being the most severe maternal complication, either in pregnancy or in puerperium; therefore, anti-thrombotic prophylaxis during pregnancy should be considered case by case. Regarding obstetric complications, it seems that miscarriage, IUGR and caesarean section occurred more frequently in BD patients as compared to the general obstetric population [118]. Few case reports described transient neonatal BD mostly consisting of oral or genital ulcerations and skin findings, that resolve within 8 weeks after birth [122]. The neonatal disease has been hypothesized to be mediated by transplacental transfer of maternal pro-inflammatory factors.

4.11. Pregnancy in patients with ANCA-associated vasculitis

ANCA-associated vasculitis are rare diseases that do not typically occur during childbearing age. However, due to the possibly severe organ involvement, it is necessary to counsel women of childbearing age about the risks during pregnancy and measures to minimize these risks [123]. In a SLR between 1970 and 2017, 87 pregnancies in 72 women with Granulomatosis with Polyangiitis were analysed [124]. A disease flare was reported in 39% of cases; preeclampsia occurred in 14% of cases, mostly women on treatment with corticosteroids. Pregnancy outcomes were linked to the status of the disease at conception and the timing of flares, with premature birth being the most common complication.

5. Management and treatment during pregnancy

5.1 Keeping maternal disease under control with anti-rheumatic drugs before, during and after pregnancy: from conventional drugs to biologics, biosimilars and small molecules.

While counselling women with ARDs, it should be stressed that maternal active disease during pregnancy can negatively impact fetal development and pregnancy outcome [125]. Active disease is deleterious; therefore, it is preferred to keep the disease under control by using drugs that are not harmful to the fetus.

The large majority of csDMARDs can be used during pregnancy and lactation (Table 1) [25,26,126].
Teratogens:
Very few are known teratogens (methotrexate, cyclophosphamide, mycophenolate mofetil) and need to be withdrawn prior to conceptions (allowing a period of wash-out, 6 weeks for mycophenolate, 3 months for methotrexate, and 6 months for cyclophosphamide). In some clinical situations, it may be prudent to wait for longer periods after the withdrawal of these drugs (and switch to other ones compatible with pregnancy) to ascertain that the disease is well controlled.

Pregnancy-Compatible Medications:
Among compatible medications, particular attention should be given to hydroxychloroquine (HCQ). Older and recent studies have shown multiple beneficial properties of HCQ in SLE pregnancy [127]: i) it may prevent SLE flare during pregnancy, particularly as HCQ discontinuation at positive pregnancy test is associated with increased risk for flares; ii) it may able to reduce by 85% the rate of SGA neonates in women with lupus nephritis; iii) it can help reducing the risk of recurrence of AVB in anti-Ro positive women who already had a baby with AVB, and reducing the risk for skin manifestations of neonatal lupus in anti-Ro positive women; iv) it may help improve pregnancy outcome in women with primary obstetric APS refractory to conventional treatment. More recent studies keep confirming the safety and utility of HCQ during pregnancy. It was confirmed in the OTIS study that *in utero* exposure to HCQ was not associated with an increased risk of birth defects or other APO [128]. HCQ use was associated less SLE activity during pregnancy in an individual patient meta-analysis on 938 pregnancies and, in those women with quiet SLE in the first trimester, HCQ was associated with fewer preterm births. In this large meta-analysis, however, HCQ had no impact on fetal loss or preeclampsia [129]. Adherence to treatment was also shown to be important as lower HCQ circulating levels were associated with poorer pregnancy outcomes [130]. Altogether these findings highlight the importance of maintaining HCQ throughout pregnancy, if already on treatment, or to consider to start it when pregnancy is planned.

In the past two decades, an increasing number of bDMARDs and tsDMARDs have been successfully introduced in the management of ARD, posing the question about their compatibility with pregnancy and lactation.
For TNF inhibitors, it has been shown that more harm results from stopping these drugs before conception or in the first two trimesters of pregnancy than from continuing the drugs to ensure continued disease remission. Therefore, guidelines suggest their use when needed to control active maternal disease [25,26,126].

Medications with limited information:

Some drugs are currently not recommended during pregnancy and lactation not because of proof of harm, rather because there is lack of data. In the case the drug is the only available choice, the benefit-risk ratio of the potential risk for the medication vs active disease should be discussed with the patient. It is important to share with the patient what it is known and what is not about the use of a drug during pregnancy and lactation, so that she can make an informed decision.

A recent international survey has actually captured a shift towards a more liberal use of bDMARDs during pregnancy after 5 years from the publication of guidelines [131].
There are fewer data for the newer biologics used in ARD. However, the same principles apply when counselling women before pregnancy about use of these newer drugs and especially the EULAR overarching principle that 'the risk of drug therapy for the child should be weighed against the risk that untreated maternal disease represents for the patient and the fetus or child'.

When deciding how to counsel women regarding use of the newer biologics in pregnancy the clinician must consider:
1. The available literature regarding use of the particular drug in pregnancy
2. The pharmacokinetics of the particular drug
3. The likelihood of disease flare if the drug is discontinued
4. The options for alternative therapy
5. The views and attitudes of the patient

There is a risk that stopping biologic therapy will result in disease flare, significant morbidity for the mother and necessitate the use of corticosteroids, which may in turn cause morbidity including gestational diabetes, infection [132] and preterm premature rupture of the membranes with higher doses.

Belimumab, a B cell activating factor (BAFF) inhibitor used for the treatment of SLE, has been studied by Jui-Hung Kao and colleagues [133] who reported 13 pregnancies and no fetus had anomalies, leukopenia, lymphopenia, neutropenia, or thrombocytopenia after birth. This paper adds to the reassuring data from 66 pregnancies in the pharmaceutical registry regarding mainly first trimester exposure.

Youngstein has reported 31 IL-1 inhibitor maternal-exposed pregnancies from 7 countries using the International Society for Systemic Autoinflammatory diseases [134]. There were 23 anakinra-exposed pregnancies leading to 21 healthy infants, 1 baby with unilateral renal agenesis and ectopic neurohypophysis. There were 8 canakinumab-exposed pregnancies resulting in 7 healthy infants of normal gestational age and birthweight and 2 first trimester miscarriages affecting a mother with active disease. There were no serious neonatal infections and 14 infants were breast fed with no complications. There were no reports of developmental delay during follow-up of up to 10 years (median 18 months).

Increasing data are now available regarding anti IL6 inhibitors, particularly tocilizumab because of its use for COVID-19. Jorgensen and Lapinsky have reviewed the use of tocilizumab in 610 cases (n = 20 with COVID-19) together with seven mother-infant breastfeeding pairs [135]. Although higher rates of spontaneous miscarriage and premature birth have been reported compared with the general population multiple confounding variables limit interpretation. There remain few data on tocilizumab exposure in the second and third trimesters when transplacental transport is highest, however use for COVID-19 should increase this data set. Neonatal follow up was limited. Tocilizumab appears to be compatible with breastfeeding.

A study examining pregnancy outcome following abatacept exposure by Kumar and colleagues illustrates the problem with many studies in this field [136]. There were 161 pregnancies with known outcomes and although seven of 86 (8.1%) live births following maternal exposure had congenital anomalies, there was no pattern, and many of these pregnancies had other risk factors for congenital malformations including exposure to mycophenolate and type 1 diabetes. The authors concluded that abatacept should be used in pregnancy if the potential benefit to the mother justifies the potential risk to the fetus.

Although many clinicians continue TNFi biosimilars in pregnancy, assuming they will behave the same as the parent drug, there are few studies examining this. Scott et al have reported a series of 18 women exposed to a TNFi biosimilar drug preconception and in pregnancy [137]. Seven women continued their biosimilar throughout pregnancy, 11 stopped their biosimilar therapy in pregnancy (2 in 1st trimester, 8 in 2nd trimester and 1 in 3rd trimester). Flare rates were higher in those who stopped their biosimilar (7 out of 11 versus 2 out of 7). All women had live births, mean gestation 39^{+0} week's (36^{+6} -41^{+1}), birthweights were normal. No infants required admission to the neonatal unit, there were no congenital abnormalities. 16 women were breast feeding on discharge from hospital.

In contrast to the biologic drugs and biosimilars, data for the small molecules such as tofacitinib continue to raise concern [138]. In animal studies it is feticidal and teratogenic in rats and rabbits (although these studies use much higher doses than the standard human dose). Reported outcomes of pregnancy cases identified from tofacitinib randomised controlled trials, post-approval and non-interventional studies, and spontaneous adverse-event reporting appear similar to those observed in the general population. Nevertheless, at present, the use of tofacitinib during pregnancy should be avoided. No human studies have reported outcomes of breastfeeding with small molecules such as tofacitinib, this drug is present in lactating rat milk so, at present, breastfeeding should be avoided.

5.2. The importance of adjunct treatments

In addition to disease related specific therapies, patients suffering with rheumatic disease can take advantage to adjunct therapies that have been demonstrated to be effective for the reduction of the risk of adverse pregnancy outcome in the general population.

Low-dose Aspirin: Among them, LDASA is one of the most investigated drug and has been shown to reduce the risk of pre-eclampsia [57]. Treatment with LDASA 150 mg/day was shown to be associated with a lower risk of preterm preeclampsia in high risk women identified by the screening algorithm proposed by the Fetal Medicine Foundation. Effectiveness was more evident for early events (before 34 gestational weeks) [57].Similarly, a systematic review and metaanalysis performed by Roberge et al. showed that aspirin reduces the risk of preterm preeclampsia, but not term preeclampsia, and only when it is initiated at ≤16 weeks of gestation and at a daily dose of ≥100 mg. The dose of aspirin used in pregnancy varies between countries (i.e. 81mg in the US, etc.….); a meta-analysis suggests that the higher the dose, with a maximum assessed of 150mg, the more effective the aspirin decreased preeclampsia.

Vitamin D: The importance of vitamin D supplementation in rheumatic pregnant patients has been underlined in the 2017 EULAR recommendations [42]. On one hand, low vitamin D levels were frequently detected in pregnant women and this deficiency has been associated to a higher risk of APO in the general population. On the other hand, several authors have suggested that this compound can modulate the immune response and CD4+ T cells activation, resulting in a more

balanced Th1/Th2 response, that can potentially reduce the risk of maternal disease flare during pregnancy [139]. Calcium deficiency has been also associated with a higher risk of PE and gestational hypertension so that calcium supplementation is recommended for pregnant women by the WHO. It is also of utmost importance to remind folic acid supplementation to all women who are planning a pregnancy as an evidence-based preventative measure against spina bifida.

5.3. Maternal infections and vaccinations in pregnant patients with rheumatic diseases

The TORCH panel is a group of tests generally used to screen pregnant women infections that can cause birth defects and fetal infections. It must be taken into account that APS, SLE, and other autoimmune diseases are often associated with false-positive serological tests for Syphilis and for other infections (CMV, Rubella, and Toxoplasmosis). This may reflect a non-specific activation of B-lymphocytes. The obstetrical outcome in pregnancies with false-positivity for TORCH was shown to be partially impaired in comparison to that of pregnancies not having this false-positivity, in terms of lower birth weight, lower birth weight percentile, and lower week of delivery [140]. On the other hand, a result of false-positivity TORCH could be used as indicator for the research of antiphospholipid antibodies in otherwise healthy women [141].

Vaccination: Some vaccines are routinely recommended in pregnancy.
Firstly, pertussis vaccine (dTpa) that is provided to all pregnancies in every pregnancy (even close) between 28-34 weeks of gestation in order to facilitate the transplacental passage of IgG and avoid a primary infection in the first months of life in infants. Flu vaccine is also offered to all pregnancies during the winter season, keeping in mind the general contraindications to vaccines. The safety of these vaccines is supported by high quality evidence. DTpa and flu vaccines can be recommended also for pregnant women affected by ARD.
Secondly, vaccination against COVID-19, except for the first trimester of pregnancy, is actually recommended in healthy pregnant women and lactation, because the benefits outweigh the risks. However, pregnant women continue to be excluded from most clinical trials of COVID-19 vaccines and medication [142]. Compounded by their exclusion, there is considerable vaccine hesitancy amongst pregnant women. Such hesitancy persists, even though at present adverse outcomes of COVID-19 infection are increasing among pregnant and postpartum women in many countries, while these are improving in most other groups. By preventing maternal disease, vaccination may prevent obstetrical complications as intrauterine fetal death, preterm delivery and associated neonatal complications. Simultaneously, it has become clear that pregnant and postpartum healthy women are at higher risk of serious illness compared to their non-pregnant contemporaries [143]. Recent findings emphasize the message to unvaccinated pregnant women, their partners, and health professionals caring for pregnant women, decision makers and politicians that vaccination protects against severe disease [144]. The benefit of COVID-19 vaccination outweighs the potential risks for a flare or new-onset autoimmune disease; however, the rheumatology health care provider is responsible for engaging in a shared decision-making process to discuss receiving the COVID-19 vaccine.

6. When the baby is born

6.1. Mutual gaze and early mother-infant interactions

Women affected by rheumatic diseases have to face pain, physical disability and emotional distress that provide a challenging context for motherhood. Worries for fetal health, impact of the disease on the ability to be a mother and interactions with healthcare providers are few examples of barriers to experiencing pregnancy among women with autoimmune disorders [145]. Children from mothers with rheumatic disorders usually do not develop their mothers' disease, but some adverse effects such as prematurity, low birth weight and minor developmental problems may occur [145]. Thus, counselling regarding pregnancy and childbirth is mandatory for a good outcome in the relationship with the newborn, for example helping women to find value in motherhood as a source of purpose and motivation and creating a self-identity as mothers beyond their disease.

Mother-infant bonding is a process that includes the emotional tie of a mother to her infant, an "affective state" of the parent, occurring during pregnancy or immediately after birth and developing over the first months of the infant's life. Touch, breastfeeding, physical care and, most notably, gaze, represent the principal behavioural manifestations of this kind of relationship.

Eye-to-eye contact starts to appear already at birth and constitutes the earliest intentional behaviour of newborns, being attracted by human faces that make eye contact with them [146]. In this context, mutual gaze is a strong bonding experience, assumed to indicate social engagement and to absolve crucial communicative and affiliative functions [147]. Thus, eye contact is considered a precursor for joint attention and intersubjectivity: in their dyads, infants and mothers share experiences, during the first months of the newborn's life, paying attention to each other and, when the ability to follow gaze emerges, by sharing attention toward a common referent object [148].

Recognizing mutual gaze as a powerful activator of plasticity is of pivotal importance: in the mother, the early exposition to visual stimuli derived from the mother-own infant interactions activates specific brain networks implicated in reward, attention, emotion processing and related to maternal responsiveness [149], while in infants it promotes neurodevelopmental competencies, adaptive functions and the emergence of higher-level socio-cognitive skills, such as learning, empathy and the ability to infer other's mental states, as well as the emotional regulation later in childhood [148]. Therefore, promoting mutual gaze through early intervention is a crucial tool for contributing to the quality of mother-infant interaction and a favourable context for the emergent skills.

6.2. The management of puerperium

Approximately half of all maternal deaths occur in the puerperium, i.e. the 6 weeks after birth. The most common complications include infection, haemorrhage, and thromboembolism. In addition, hypertensive diseases (PE, HELLP syndrome) can still manifest after delivery, usually during the first 7-10 days. Most studies examining risk factors for these complications do not separate pregnancy from the postpartum period. Despite this lack of specific data, an increased risk can be assumed for women with SLE or APS regarding thromboembolic events and hypertensive disorders in the puerperium. In this regard, delicate tailoring of low dose aspirin and heparin around delivery is best addressed in an interdisciplinary manner. A multicentre study has found a combined antithrombotic therapy in women with APS to be safe even with short interval between heparin or low dose aspirin and delivery (<24 hours and <5 days, respectively) [150].

Post-partum flares: In rheumatoid arthritis, the postpartum relapse is a long-known phenomenon, and according to a recent meta-analysis, about half of the patients are affected [151]. For axial Spondyloarthritis, the data is less conclusive, yet most studies also indicate an increased flare risk in the puerperium. In psoriatic arthritis, a systematic literature review found a deterioration compared to pregnancy in both skin involvement (33-50% of cases) and arthritis (27-34%) across studies [67]. Women with SLE also face an increased risk of relapse during the first months after birth. Within the PROMISSE cohort, only 27.7% of patients experienced a mild/moderate flare, which rarely required treatment, while 1.7% suffered from a severe flare according to SELENA-SLEDAI Flair Index (SFI) [152]. Stable low disease activity at conception and continuation (or re-initiation) of appropriate medication act as protective factors. TNF inhibitors (TNFi) are increasingly used during pregnancy. To prevent relevant placental transport, there are recommendations to discontinue the various TNFi at different gestational ages [126]. In an analysis with 111 patients from the PreCARA study, stopping TNFi around the gestational ages advised by EULAR resulted in absence or low levels of TNFi in the newborn [153]. One concern regarding the infant's exposure to TNFi is a higher rate of infections. A large population-based cohort study analysed the Incidence Rate Ratio (IRR) of different outcomes for TNF-exposed children vs. children of the general population. During the first year of life, they found an IRR of 1.29 (95% CI 1.11-1.50) for hospital admissions for infection, whereas the IRR for first year antibiotic prescriptions was 1.06 (95% 0.96-1.16). The IRRs were comparable whether women were treated before 3rd trimester only or throughout pregnancy [154]. Taking these results together, the higher IRR for hospital admissions might reflect an unadjusted confounding by healthcare-seeking behaviour.

6.3. Breastfeeding: yes or not?

Breast milk contains all the nutrients the infant needs and has many benefits. For the mother, breastfeeding reduces the risk of breast cancer and ovarian cancer, and in the infant, breastmilk helps the neonate fight infections and decreases the later rates of obesity, cardiovascular disease and diabetes [155]. Professional organizations such as the American Academy of Pediatrics recommend exclusive breast-feeding for the first six months of life with continued breast-feeding until year one. For women with rheumatic diseases, the benefits of breast-feeding should be weighed against any potential risk of medications that transfer into breast milk. Fortunately, most of the medications used to treat rheumatic diseases are compatible with nursing. Lactogenesis begins during the second half of pregnancy when the pituitary gland releases prolactin to stimulate milk production in the breast. Prolactin causes increased TNF expression that could potentially increase rheumatoid arthritis disease activity, and prolactin levels are associated with SLE disease activity. However, other hormonal and immunologic changes in the post-partum period also contribute to disease flares.

Maternal medications are transferred into breast milk by diffusion of unbound drug. In general, large molecules and protein bound molecules cross minimally into breast milk whereas lipid soluble, low molecular weight, non-protein bound medications will cross easily into breast milk. Breast milk levels of less than 10% the infant therapeutic dose or maternal weight-adjusted dose are considered safe. Most anti-rheumatic medications are compatible with lactation (Table 1). Glucocorticoids, NSAIDs, LDASA, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine and tacrolimus, colchicine, TNFi are all safe in breastfeeding patients. Some professional organizations recommend avoiding breast-feeding for four hours if the woman is on doses of greater than 20mg prednisone equivalent a day [26]. While clear data does not exist on all biologics lactation compatibility, their large size (> 150 KD) suggest that miniscule amounts transfer into to breast milk. In contrast, small molecules such as the JAK inhibitors will readily transfer into breast milk and should be avoided.

Mycophenolate mofetil, leflunomide, methotrexate, thalidomide and CYC are contraindicated in nursing women [25]. In the absence of clear data, providers can engage in shared decision making with their patients discussing the benefits of breast-feeding and the potential low risk of biologics in general in lactating women. Breastfeeding provides health benefits to both the mother and the infant. However, we must always be mindful that our role is to inform and support and not judge our patients' decisions, whether they choose to breastfeed or not.

6.4. The long-term outcome of children born to mothers with rheumatic diseases

Patients with autoimmune rheumatic diseases have a reduced family size and, according to a recent Italian survey, about 30% of the affected women have no children at all. One of the main reasons of this phenomenon is the concern about children's health, especially in the long-term. The possibility to transmit their disease to the baby is a common fear. According to the results of large register-based studies, children of mothers with systemic lupus erythematosus do not have a higher risk of autoimmune rheumatic diseases, but they have an increased risk of autoimmune non-rheumatic disease, allergy and asthma, while children of mothers and fathers with rheumatoid arthritis have a slightly increased risk of juvenile idiopathic arthritis, dermatomyositis, and asthma [156]. In our experience, based on 299 children born to women with different rheumatic diseases, the frequency of celiac disease was higher as compared to that of the pediatric Italian population [157]. Children of patients with anti-Ro/SS-A antibodies, independently from maternal diagnosis, can develop congenital heart block, which is another reason of fear. This rare event occurring in nearly 1-2% of anti-Ro/SSA pregnant carriers, often requires the early implant of a pacemaker and seems to be associated to an increased risk of autoimmune diseases, cardiovascular disease (including heart failure and cardiomyopathy), and cerebral infarction in the long-term. In the Italian experience, children born with CHB were investigated for the presence of neurodevelopment disorders (learning disabilities and stress disorders), however the same problems were found with a similar rate also in non-affected children born to mothers with anti-Ro/SS-A antibodies [158]. This is another important issue to consider, as neurodevelopmental disorders have been reported since the 80s in children of patients with autoimmune rheumatic diseases, particularly SLE. It is still not clear whether these alterations are linked to genetic factors, inflammatory disease activity, maternal medications, autoantibodies etc. Focusing on the children of patients with antiphospholipid antibodies, we observed the presence of several minor neurodevelopmental problems, such as learning disabilities, anxiety, sleep disorders together with an increased rate of epilepsy compared to that of the general pediatric population. In children of patients with inflammatory arthritis, some reports underline a possible increased risk of autism disorders, while a large register-based study underline a slight decrease of mathematics skills. These children, according to our observations, can show an adult behaviour, characterized by very good performance at school but poor in sports and playing activities, as they had physical limitations resembling those of their mothers [159–161]. Although not conclusive, these data suggest the chance for neurodevelopmental problems in children born to women with rheumatic disease. The risk might be increased as compared to the general population, but the absolute numbers are generally low. The reassuring message should be that most of the described disturbance can be early diagnosed by means of school surveillance and specialist evaluations and managed successfully.

7. The great debates

7.1. Pregnant patients with anti-Ro/SSA: intensive surveillance or not?

This was presented as a debate and therefore does not represent the opinion of all the authors on this manuscript. Congenital heart block (CHB), the main feature of neonatal lupus syndrome (NLS), may complicate around 1% of pregnancies in patients with connective tissue diseases and anti-SSA/SSB antibodies. This incidence is much higher when the mother has previously had a fetus with CHB, with a risk of recurrence around 12-18% [162]. CHB is associated with significant mortality (16 to 28% including in utero and post-natal deaths) and morbidity (70 to 75% require pacing at 10 years). To detect CHB, it is widely recommended to perform echocardiographic screening every other week (or even every week), from 16 to 25 weeks of gestation (or even 28) in pregnant women with anti-SSA antibodies [42]. Such screening is routinely performed in many centres around the world, meaning that at least 500 ultrasounds are performed to find one CHB (5 additional ultrasounds per pregnancy and a risk of 1%) [163]. When CHB is discovered by echocardiography, usually around 22 weeks, the usefulness of treatment with fluorinated steroids (dexamethasone or betamethasone) remains unproven and highly controversial, whereas their side effects are well known [164]. Accordingly, administration of fluorinated steroids is not routinely recommended, except in clinical trials. Finally, such screening misses most CHB cases since many women with fetal CHB are not known to have anti-SSA antibodies prior to the event. In the debate, full agreement was met about several issues. First, the current literature remains very limited with mainly retrospective and/or observational data on a rare condition [165–167]. The corollary of this is that research is much needed, especially i) to develop new techniques to detect CHB earlier, when the treatment might be more effective, ii) to develop better predictors of the occurrence of CHB than the simple presence of maternal auto-antibodies, and iii) to discover more effective treatments. Teams around the world are working on all these aspects, including on daily maternal home monitoring of fetal heart rate by handheld Doppler, a device that costs around 30-50 euros [92]. In the meantime, and due to the current absence of proven efficient treatment, the routine screening in primary care and non-expert centres may be called into question since the 5 or more additional echocardiograms per pregnancy performed in anti-SSA women very rarely identify cases of high-degree CHB, for which no treatment has proven its efficacy. In practice, we again agreed on the importance to discuss the screening and treatment plan with the women and their partners and to offer, whenever possible, the possibility of participating in research protocols. In primary care, auscultation of the fetal heart can easily be performed at each monthly routine antenatal visit to screen for dysrhythmia/bradycardia, and routine fetal ultrasound is already performed at 22 weeks in most countries. A single additional echocardiogram at 26-28 weeks seems acceptable. In conclusion, while routine screening for CHB could be abandoned (until of course a curative treatment of CHB has proven beneficial), we advocate for more research in this field.

7.2. Non-criteria obstetric APS: to treat or not treat?

Outside the frame of the current set of classification criteria for APS, areas of uncertainty relate to some clinical conditions that might be associated with aPL positivity, and thus deserve treatment. In this grey zone lays "seronegative APS", a term designating patients with APS-related manifestations, such as pregnancy morbidity (PM) with negative criteria aPL and positivity in assays not included in the classification criteria. The most promising of these are anti-phosphatidylserine-prothrombin antibodies (anti-PS/PT), found in between 5 and 48% of women with seronegative obstetric APS. In the 3 available studies, LDASA alone did not protect against PM explaining why it is not currently recommended to treat pregnant women with isolated anti-PS/PT and previous PM [168–171]. In

literature, there is growing support to the association between low-titer aPL and PM, although to a lower extent than what observed for medium-high titer. Most importantly, if LDASA alone is not effective in all women with low titer, combining LDASA + LMWH significantly reduces PM [169,172]. In the same grey zone, we might find aPL-positive women with complications suggestive of APS but not fulfilling classification criteria, such as those with one or two early losses, premature birth due to placental insufficiency before 34 weeks and asymptomatic aPL carriers (women without a history of PM occasionally found to have persistent aPL positivity). These women have more PM than controls, but lower than full-blown APS patients; no improvement of obstetric outcome results with LDASA monotherapy, whereas LDASA+LMWH combination is effective [169,172]. Even in these clinical settings, the aPL profile emerges as the main determinant of obstetric outcome and of the response to treatment. Surely, not an unexpected finding: aPL are well-characterized pathogenic effectors of PM exerting their detrimental role on decidual and trophoblastic cells, irrespectively of the previous obstetric history. Many experts judge as inconclusive the available evidence on treating women with low titer aPL or non-criteria obstetric APS, due to the many limitations affecting the reliability of results: small sample size, heterogeneously defined outcomes, lack of controls and differential diagnosis of early pregnancy loss not adequately pursued. However, to optimize clinical care, we should come to term with such poor quality of literature, difficult to overcome due to the rarity of the syndrome and the peculiarity of obstetric outcome. In the vibrant debate of clinicians supporting treatment of women with non-criteria obstetric APS opposed to those in the front of "No, don't treat!", the optimal approach lays between: the obstetric risk of each woman should be carefully weighted, opting for treatment in case of high-risk aPL risk profile or advanced maternal age, as suggested by international recommendations.

8. The experience of Pregnancy Registries in Rheumatology

In the last decade, several pregnancy registries have been established worldwide to prospectively collect and analyse data on pregnant women with ARD. Most of these national registries have been set up in Europe, while patients from the USA and Canada have been enrolled in the MotherToBaby/OTIS Pregnancy Studies or several single-center registries. The features of each registry are summarized in Table 2.

Joint analysis of data from different sources is desirable, especially for rare diseases and rare exposures to medications, but this task requires a certain degree of homogeneity among the collected data. The EULAR has supported initiatives to foster collaborative research in this area. In 2017, the European Network of Pregnancy Registers in Rheumatology (EuNeP) was started and included four registers: EGR2 (France), RePreg (Switzerland), RevNatus (Norway), and Rhekiss (Germany). The first exercise within this network was to survey similarities and differences in data collection [173]; for instance, major discrepancies were found in the instruments used to measure disease activity during pregnancy. In order to facilitate harmonization and standardization of items and measurements, a EULAR Task Force was convened to define a core data set for registries and observational studies that prospectively collect information about pregnant women with ARD, including the neonatal phase (up to 4 weeks after delivery) [174]. As the design of registries may vary considerably between countries and might be influenced by the different health care systems, the core data set was deliberately kept short and simple, concentrating on a minimum of standardised items to be collected in order to allow multinational joint data analysis.

9. Conclusions

The 11th International Conference on Reproduction, Pregnancy, and Rheumatic diseases gathered health care professionals (physicians from different specialties, midwifes, nurses) with a common interest in research about reproductive health in Rheumatology. This is not an easy field in which to perform research, as the reproductive sphere, especially pregnancy, is considered sensitivity. For instance, it is highly challenging to perform randomized clinical trials in pregnant women, particularly for complex and rare diseases that struggle to get dedicated funding for such studies and require a multicentre international approach in order to reach sufficient numbers. As a consequence, there is lack of unbiased, rigorous data that can drive clinical decisions. Prospective studies and registries have been helpful in filling the gap, but there is need for more robust, evidence-based data.
The international scientific community of "Reproductive Rheumatology" acknowledges the multiple unmet needs of patients and strongly believes that collaborative research in this rapidly evolving field can support their reproductive journey, as well as advocates for regulatory and financial resources to foster and facilitate this patient-centred research.

DECLARATION OF COMPETING INTEREST

None declared.

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Figure 1. Checklist for preconception risk assessment in women with autoimmune rheumatic diseases.
Abbreviations: aPL, antiphospholipid antibodies; aPL profile: Lupus Anticoagulant, anti-cardiolipin antibodies, anti-beta2glycoprotein I antibodies; HELLP Syndrome: Hemolysis, Elevated Liver enzyme levels, Low Platelet count Syndrome; IUGR, intrauterine growth restriction; SGA, small-for-gestational-age; SLE: Systemic Lupus Erythematosus.
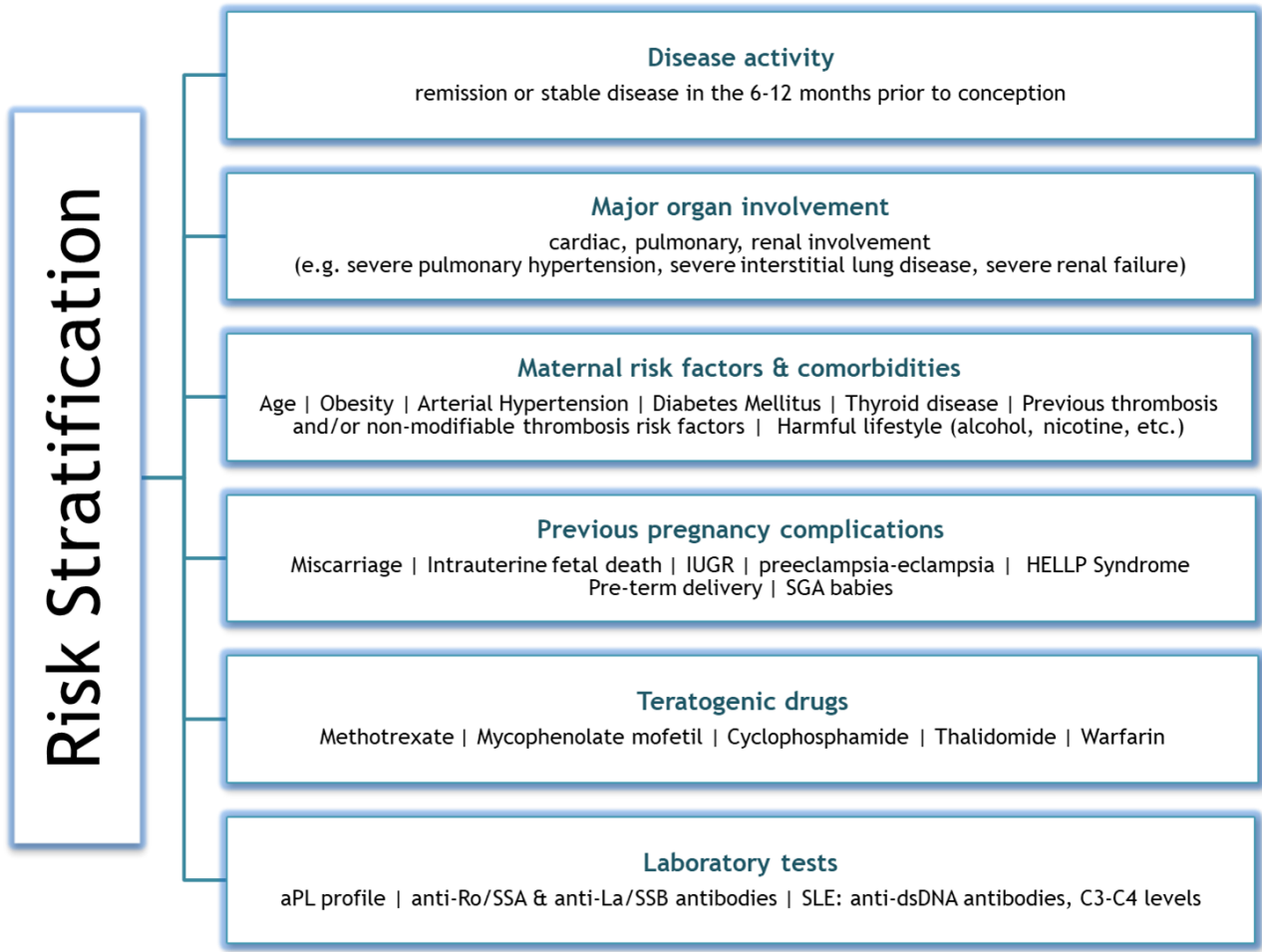
Table 1. Compatibility of use of anti-rheumatic drugs during pregnancy and lactation. Adapted from the 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases [26]. Abbreviations: csDMARDs: conventional synthetic DMARDs; bDMARDs: biotechnological DMARDs; tsDMARDs: targeted synthetic DMARDs.
conditionally recommend non-selective NSAIDs over Cox2-specific inhibitors in the first two trimesters due to lack of data for Cox2-specific inhibitors.
° small molecular size suggests transfer across the placenta and into breast milk.
* limited safety data; minimal to no transfer in early pregnancy but high transfer during the second half of pregnancy.
§ Expected minimal to no transfer due to large molecular size.

MEDICATIONS	USE DURING PREGNANCY	USE DURING LACTATION
Prednisone, 6-methylprednisolone	Yes	Yes
Colchicine	Yes	Yes
Hydroxychloroquine	Yes	Yes
Chloroquine	Yes	Yes
NSAIDS (COX2 inhibitors not preferred) #	Yes, discontinue in third trimester	Yes (Ibuprofene preferable for short half-life)
Mepacrine	Not recommended (lack of data)	Not recommended (lack of data)
csDMARDs		
Azathioprine	Yes	Yes
Cyclosporine -A	Yes	Yes
Tacrolimus	Yes	Yes
Intravenous immunoglobulins	Yes	Yes
Sulfasalazine	Yes	Yes
Cyclophosphamide	Conditionally recommend (for life / organ threatening disease in the 2nd & 3rd trimesters)	Strongly recommend against
Leflunomide	Strongly recommend against (cholestyramine wash–out is suggested)	Strongly recommend against
Methotrexate	Strongly recommend against (3 months wash-out and folic acid supplementation)	Conditionally recommend against (Limited data suggest low transfer)
Mycofenolate mofetil	Strongly recommend against (6 weeks wash-out)	Strongly recommend against
Thalidomide	Strongly recommend against (Stop 1-3 months prior to conception)	Strongly recommend against
tsDMARDs		
Tofacitinib °	Not recommended (lack of data)	Not recommended (lack of data)
Apremilast °	Not recommended (lack of data)	Not recommended (lack of data)
Baricitinib °	Not recommended (lack of data)	Not recommended (lack of data)
Upadacitinib °	Not recommended (lack of data)	Not recommended (lack of data)
Filgotinib°	Not recommended (lack of data)	Not recommended (lack of data)
bDMARDs		
Certolizumab pegol	Yes	Yes
Etanercept	Yes (Continue in 1st & 2nd trimesters; discontinue in 3rd trimester)	Yes
Infliximab	Yes (Continue in 1st & 2nd trimesters; discontinue in 3rd trimester)	Yes
Adalimumab	Yes (Continue in 1st & 2nd trimesters; discontinue in 3rd trimester)	Yes
Golimumab	Yes (Continue in 1st & 2nd trimesters; discontinue in 3rd trimester)	Yes
Rituximab	Only if necessary for severe and/or life-threatening disease (discontinue at conception)	Yes
Anakinra*	Not recommended (discontinue at conception)	Conditionally recommend, but no available data§
Abatacept*	Not recommended (discontinue at conception)	Conditionally recommend, but no available data§
Tocilizumab*	Not recommended (discontinue at conception)	Conditionally recommend, but no available data§
Secukinumab*	Not recommended (discontinue at conception)	Conditionally recommend, but no available data§
Ustekinumab*	Not recommended (discontinue at conception)	Conditionally recommend, but no available data§
Belimumab*	Not recommended (discontinue at conception)	Conditionally recommend, but no available data§

Table 1. Compatibility of use of anti-rheumatic drugs during pregnancy and lactation. Abbreviations: csDMARDs: conventional synthetic DMARDs; bDMARDs: biotechnological DMARDs; tsDMARDs: targeted synthetic DMARDs

Country	France	Germany	Italy	Norway	Switzerland	United Kingdom	United States/Canada
Name of the Registry/Study	EGR2	Rhekiss	P-RHEUM.it	RevNatus	RePreg	Pregnancy in Rheumatic Diseases Investigation Network	OTIS / MotherToBaby Pregnancy Studies
Year of establishment	2014	2015	2018	2016 (electronic registration); 2006 (paper registration)	2017	2018	2004
Number of enrolled pregnancies (up to first semester of 2021)	1941	1495	670	2109	340	351	8867 of which 2095 in Rheumatic Diseases
Number of participating centers	65	149	28	19	10	3	1
Funding / Support	French Society for Rheumatology (SFR), Patient's associations, UCB	German Rheumatism Research Centre Berlin, Rheumazentrum Rhein-Ruhr e.V. Düsseldorf	Italian Society for Rheumatology (SIR)	Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases	Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) register, Rheumastiftung, Swiss Society for Rheumatology (SGR), Pharmaceutical Industries	Rosetrees Trust, UCL, British Society for Rheumatology (BSR) Fellowship, Lupus UK, Arthritis Australia, UCB	Pharma, Federal and State funding
All autoimmune rheumatic diseases included?	YES	YES	YES	YES	Focus: RA, axSpA, PsA	YES	Focus: axSpA, JIA, RA, PsA. Also includes: SLE, APS, other connective tissue diseases, other AI, fibromyalgia
Type of platform for data collection	Online platform (Cleanweb®)	Online platform	Online platform (Red Cap®)	Online platform (MRS)	Online platform	Online platform	Maternal interviews, Records abstractions, Exam for subset
Enrolment during preconception counselling?	YES	YES	NO	YES	YES	YES	NO
Temporal limit for enrollment during pregnancy	Up to 12 GW	Up to 20 GW	Up to 20 GW	None	Up to 32 GW	None	For some <20 GW, some studies anytime in pregnancy (separate retrospective series)
Follow-up of children?	YES (up to 1 year of age)	YES (up to 2 years of age)	YES (up to 2 years of age)	None (follow-up of the mothers for 1 year after delivery)	YES (up to 4 years of age)	None	YES (to 1 year of age for all, 5 years of age for some)
Live birth rate (%)	87%	94%	89%	91%	98%	97%	88.5%

Box 1. Take-Home Messages.

- Reproductive health is of paramount importance in the management of women and men living with chronic conditions such as ARD.
- Preservation of fertility, contraception, and family planning should be addressed in all women of childbearing age, early in the disease course and regularly during the follow-up.
- Fertility of women with ARD might be reduced as compared with healthy women of the same age; infertility can be multifactorial and not only related to the disease and/or medications. Women with ARDs can be candidate to ARTs, provided individual risk assessment.
- Multidisciplinary preconception counselling, individual risk stratification and tailored approach are key points to minimize adverse pregnancy outcomes related to maternal disease factors.
- It is important to maintain disease remission or treat disease flares with drugs which are not harmful during pregnancy and lactation to pursue good pregnancy outcomes and wellbeing of the dyad mother-child. Preventative measures (e.g. LDASA for minimizing the risk of preeclampsia) should be considered in patients at higher risk for pregnancy complications.
- New drugs keep being introduced into rheumatology practice, therefore it is needed to assess their compatibility of use during pregnancy and lactation.
- Women should be supported during the puerperium as it can be characterized by disease flares, post-partum depression, and challenges in parenting.
- Prospective cohorts of pregnant patients and National Pregnancy Registries have been established in several Countries worldwide and they have been instrumental in addressing research questions about fetal-maternal outcomes and drug exposures.