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Autoimmune diseases and pregnancy

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Pregnancy in autoimmune diseases remains an argument of debate. In last years great improvements were done and with the correct medical support women with disease such as Systemic Lupus Erythematosus or Antiphospholipid Syndrome can afford a pregnancy and have healthy babies. The starting point is a good counselling. Women should be informed about risks that can occur taking some medications while pregnant and, on the other hand,

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that there are medications that can be safely assumed during pregnancy. Furthermore, there are known maternal risk factors such as the presence of antiphospholipid antibodies or anti-Ro/SSA antibodies that must be carefully managed by both rheumatologists and obstetricians. In addition, also disease activity during pregnancy can represent an issue. For all these reasons, a multidisciplinary approach is mandatory in order to give our patients an optimal medical support, before, during and after pregnancy.

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Introduction

For a longtime patient with autoimmune diseases were advised not to conceive because of the flares of their own condition possibly occurring during gestation and because of the reported increased rate of pregnancy adverse outcomes. In the last 20 years, however, the general management of these diseases greatly improved conditioning a much better quality of life of the patients. In this view, it becomes more and more important to understand if affected women can have a family life including the possibility to have one or more children.

In the last 30 years, many data have been accumulating on the effect of the different autoimmune diseases on pregnancy outcome and on the possible evolution of the maternal disease during pregnancy. It has to be underlined that each disease such as rheumatoid arthritis (AR), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) etc. carries its own potential maternal and fetal risks that need to be clearly evaluated during the pre-pregnancy counselling.

Part of the problem is certainly related to the drugs that the patients have to take in order to treat and maintain under control their own disease. It is generally assumed that pregnant women need to avoid any drug during pregnancy. This general view obviously is also the one of our patients and of their family and friends. Therefore, the women with autoimmune rheumatic diseases need to be informed of the different aspects of pharmacological treatment including the need to avoid some drugs while others are safe. In this respect if the patient needs to take teratogenic drugs for the treatment of her disease, the problem of contraception has to be faced.

All the above listed problems should be faced through a multidisciplinary counselling with the contribution of obstetricians, experts in the high-risk pregnancy and in autoimmunity, and of dedicated rheumatologists or internists.

The following paragraphs, realized through the collaboration of colleagues of different disciplines, aim to provide some simple concepts that should practically help the best management of patients with systemic autoimmune disorders in childbearing age, before, during and after pregnancy.

Counselling and risk stratification of patients with autoimmune rheumatic diseases

Reproductive issues are influenced by concerns about the effect of pregnancy on the rheumatic disease, the impact of disease on fetal health, the parenting experience, and the possible harms of medications on the child, both during gestation and breastfeeding. Many patients report that their disease affects their personal relationships and, consequently, their decision to have children.

Counselling is still an unmet need for young patients with rheumatic disease; it has been recently reported that about one third of the patients with autoimmune disease, both Connective Tissue Disease and Chronic Arthritis, were never asked about the desire for a pregnancy or contraceptives [1].

Some rheumatologists may not consider family planning to be among their clinical responsibilities or may feel underqualified or uncomfortable when discussing reproductive health issues. Usually patients will not initiate family planning conversations; in several surveys, it is reported that women desired counseling but they generally preferred their clinicians to initiate these conversations [2].

However, this topic plays a dramatic role in increasing patients' knowledge: the great majority of patients who had received a counselling declared a positive influence on their family planning, confirming the importance of an efficacy physician-patient communication.

Although the counselling is ideally a responsibility of the specialists in charge for the patients, the follow-up during and after pregnancy should be preferably performed by a multidisciplinary team composed of rheumatologists and/or internists, gynecologists, obstetricians, and other medical specialties (i.e. neurology, hematology, cardiology, nephrology, psychology, etc.), if indicated, in a medical institution that includes Neonatal Intensive Care Unit.

In any case, preconception counselling is essential in order to estimate the possibility of both fetal and maternal problems, related to disease activity, serological profile or eventual organ involvement as contraindication to pregnancy.

A recent diagnosis of systemic autoimmune condition and an active disease are prognostical bad factor for the mother and the baby and therefore the patients should be encouraged to postpone pregnancy.

SLE activity, disease flares at conception or in the last 6–12 months prior to pregnancy increase the risk for maternal disease flares during pregnancy and puerperium and for a fetal morbidity (in particular pregnancy loss, intrauterine growth restriction - IUGR, preterm delivery). A history of lupus nephritis or active renal disease at conception is a strong predictor for the recurrence of renal flare, during or after pregnancy, and for a poor fetal outcome (fetal loss and preterm delivery). In addition, active serology at conception (low serum C3 and C4 complement fractions, positive anti-dsDNA) increases the risk for maternal SLE flares during pregnancy and lead to pregnancy loss.

In APS patients, previous adverse pregnancy outcome and history of vascular thrombosis, especially if in the last 6–12 months, are related to pregnancy complications, as well as high-risk antiphospholipid antibodies (aPL) profile (lupus anticoagulant positivity, triple aPL positivity, moderate to high titre aPL, IgG isotype) and co-existing SLE [3].

In patients with Chronic Arthritis, an uncontrolled disease at conception could mean a flare during pregnancy and a need for an additional therapy. On the other side, an active disease during pregnancy has been demonstrated to increase the risk of preterm delivery and placental insufficiency and, consequently, to a low birth weight infants [4].

The definition of patient's antibodies profile, particularly focusing on autoantibodies with potential negative impact on pregnancy and fetal outcomes, is advisable in every autoimmune patient. The rheumatologist should search for: a) anti-ENA antibodies, especially anti-Ro/SSA and anti-La/SSB, which can be related to the occurrence of neonatal lupus; and b) antiphospholipid antibodies (by the 3 available tests: antiBeta2Glycoprotein I IgG/IgM, anticardiolipin antibodies IgG/IgM, Lupus Anticoagulant) that can be related to a poor pregnancy outcome.

Finally, medications: which drugs can be consumed during pregnancy? One of the critical issues in the management of a pregnancy in autoimmune patients is to choose the right medication to treat the mother without harming the fetus [5].

Non-steroidal anti-inflammatory drugs (NSAIDs) can increase the rate of miscarriages, and the risk is increased when they are taken at the conception or for several days long. Fluorinated corticosteroids can cross the placenta and should be prescribed when their effect is needed for the fetus. Less than 10% of the not fluorinated corticosteroid compounds, can cross the placenta, however they can cause side effects in the mother, such as maternal diabetes, hypertension, pre-eclampsia and the premature rupture of the membrane, so caution is indicated when especially in the third trimester. Chloroquine (CQ) and hydroxychloroquine (HCQ) are often indicated in patients with SLE and are safe during pregnancy. Discontinuation of HCQ during pregnancy can result in a flare of the maternal disease. Most immunosuppressive drugs are contraindicated during pregnancy with the exceptions of azathioprine (AZA), cyclosporine and tacrolimus. Cyclophosphamide (CYC) and Methotrexate (MTX) are mutagenic and teratogenic drugs so conception should be delayed at least until 3 months after the cessation of therapy. Mycophenolate mofetil (MMF) is associated with an increased risk of congenital anomalies (especially facial dysmorphism) and should be discontinued at least 6 weeks before conception. Regarding biological agents, patients should be counselled to avoid pregnancy for at least 6–12 months after rituximab infusion (anti-CD20 monoclonal antibody). Belimumab (a fully humanized IgG1 γ monoclonal antibody directed against soluble B lymphocyte stimulator) has not been associated with

an increased rate of fetal abnormalities or adverse pregnancy outcome [6]. However, data of the literature are not sufficient to clearly define its safety during pregnancy: the EULAR task force recommended alternative medications in young women who desire pregnancy [5].

Continuation of anti-TNF inhibitors (anti-TNFi) during the first part of pregnancy should be considered. Etanercept and Certolizumab Pegol may be considered as therapy throughout pregnancy due to low (or absent for certolizumab) rate of transplacental passage [7].

No specific pattern of abnormalities was observed in pregnancies exposed to statins. There is no evidence to demonstrate that use of statins in pregnancy increases the risk of foetal abnormalities [8]. Limited, but promising evidence exists for their efficacy in treating and preventing preeclampsia [9].

Drugs to be avoided or permitted according to EULAR recommendations are shown in Table 1.

A good counselling in women with autoimmune disease should include also contraception that can help patients in family planning and to avoid pregnancy during disease flare or while on teratogenic medications. A recent survey demonstrated that most patients (e.g. 60–70% of SLE/APS women), did not receive any counselling from rheumatologist even if this topic needs to be discussed because of the possible effects of estrogens on disease activity and on thrombosis occurrence [1].

Women with SLE should be counselled on the use of effective contraceptive measures (oral contraceptives, subcutaneous implants, intra-uterine devices) based on their disease activity and thrombotic risk (particularly aPL status). In patients with stable/inactive disease and negative aPL profile one should considered combined hormonal pill. In women with positive aPL, either with or without definite APS, hormonal contraception with progesterone only could be proposed considering the profile risk of thrombosis for each patient. Finally, all the patients with SLE and/or APS, without gynecological contraindication, could use Intra Uterine Device – IUD [3].

Patients with chronic arthritis do not show any particular contraindication to consume combined contraceptive pill, but they need to be screened for have thrombophilic status, including for aPL positivity.

The obstetric corner

Over the last 30 years, obstetrician-gynecologist increased the chance to meet patients with autoimmune diseases in their practice. This is because the frequency of autoimmune diseases is increasing, their diagnostics and differential diagnosis are improving. On the other hand, new methods of treatment and medicines have emerged that can lead to a long-term remission of the disease, which allows the patient to be advised about planning pregnancy together with rheumatologists and specialists of related disciplines. Advances in the treatment of autoimmune diseases and the management of pregnant women with these diseases have similarly improved the prognosis for the mother and the child. If pregnancy is planned during periods of inactive or stable disease, the result often is a birth to healthy full-term babies without increased risks of pregnancy complications. Nonetheless, pregnancies in most autoimmune diseases are still classified as “high risk” because of the potential risk for major complications. These complications include disease exacerbations during gestation and increased perinatal mortality and morbidity in most autoimmune diseases [10]. During pregnancy, genetic material and cells are bi-directionally exchanged between the fetus and mother following which there

Table 1
EULAR “Points to consider” for the prescription of antirheumatic drugs during pregnancy [5].

Drugs to be stopped before pregnancy	Drugs with insufficient data	Drugs permitted in pregnancy
Methotrexate (stop 3–6 months before a planned pregnancy), Cyclophosphamide (stop at least 3 months before a planned pregnancy), Mycophenolate Mofetil (stop at least 6 weeks before a planned pregnancy), Warfarin/acenocoumarol (discontinuation at the moment of positive pregnancy test)	Leflunomide, Mepacrine, Biologic agents other than anti-TNFi (e.g. rituximab, anakinra, tocilizumab, abatacept, belimumab, ustekinumab and anti-JAK), selective COX-2 inhibitors, statins.	Steroids, Hydroxychloroquine, Chloroquine, AINS (until 32 week of gestation), Azathioprine, Cyclosporine, Tacrolimus, Sulfasalazine, Colchicine, Intravenous immunoglobulin, TNFalfa inhibitors

can be a persistence of cells and/or DNA of fetal origin in the mother acquired during pregnancy. This naturally acquired microchimerism may impart beneficial or adverse effects on human health and has been associated with the occurrence of several different autoimmune diseases as well as implicated in tissue repair and immunosurveillance [11].

Increasing evidence in the literature suggests an important role for the microenvironment and for hormones in the physiology and pathology of the immune system. Females display an increased incidence of autoimmune diseases, with a sexual dimorphism in the immune response. Hormones, in general, and in particular steroid hormones may act at multiple steps of the autoimmune process with different (and contrasting) effects, depending on the type of the steroid (natural or synthetic), the concentration and co-presence of the ligands and the binding to their specific receptors. The classic view has been that steroid hormones have well-defined effects, with one type, estrogens, being “pro-inflammatory” and the other two progestogens (progesterone and its synthetic analogs) and androgens being “anti-inflammatory” [12].

Systemic autoimmune diseases are a heterogeneous group of disorders and currently there is no agreement on a common classification. The most frequent in obstetrician-gynecologist's practice –antiphospholipid syndrome, systemic lupus erythematosus and rheumatoid arthritis and they will be discussed below.

On the other hand, the most frequent organ-specific immune disease are Hashimoto's diseases (autoimmune thyroiditis), and type 1 diabetes mellitus (T1D).

The relationship between autoimmune thyroid disease to pregnancy has been the object of considerable interest particularly with the recognition of the postpartum thyroid disease syndrome [13]. In 1990 anti-thyroid antibodies were suspected as one of cause of pregnancy wastage. Since then many studies confirmed the association of these antibodies with recurrent pregnancy loss but their pathophysiologic role is still unclear. Fetal loss among patients with thyroid antibodies could be induced by several putative mechanisms [13]. The most obvious one is thyroid dysfunction, as is commonly seen in Hashimoto's thyroiditis which is the most frequent cause of hypothyroidism. Persons with classic Hashimoto's thyroiditis have serum thyroid autoantibodies (TAb) reacting with thyroglobulin and thyroid peroxidase (TPO). These antibodies (particularly antibodies against thyroid peroxidase) are complement-fixing immunoglobulins and may be cytotoxic. Women with TAb may have higher plasma TSH levels, within the normal range, reflective of subtle thyroid dysfunction. The fetus starts to produce thyroid hormones (THs) by the end of the 1st trimester. Before this time, the fetus is dependent on maternal hormones which are controlled by the placental deiodinase enzymes and the TH cell transporters. Normal maternal thyroid function is, therefore, critical in order to provide adequate THs for early fetal development and, in particular, early central nervous system development [14].

Recent advances in the diabetes have begun to cross into the obstetric field. Diabetes complicates up to 10% of all pregnancies. Of these, 0.2%–0.5% are patients with type 1 diabetes mellitus (T1DM) [15]. Pregnancy itself is usually regarded as a diabetogenic state in which postprandial glucose levels are elevated and insulin sensitivity is decreased. Early pregnancy is a time of insulin sensitivity, lower glucose levels, and lower insulin requirements in women with type 1 diabetes. The situation rapidly changes as insulin resistance increases exponentially during the 2nd and early 3rd trimesters and levels off toward the end of the third trimester. In women with normal pancreatic function, insulin production is sufficient to meet the challenge of this physiological insulin resistance and to maintain normal glucose levels. However, in women with preexisting diabetes, hyperglycemia occurs if treatment is not adjusted appropriately. Pregnancies affected by T1DM are at increased risk for preterm delivery, preeclampsia, macrosomia, shoulder dystocia, intrauterine fetal demise, fetal growth restriction, cardiac and renal malformations. Classically, the decreased response to insulin activity observed in pregnancy is associated with increases of cortisol, progesterone, estrogen, prolactin, and human placental lactogen [16]. Most recently, new molecules such as leptin, tumor necrosis factor- α (TNF- α), and resistin have been implicated in this matter. TNF- α is the strongest independent predictor of insulin sensitivity during the late gestational period. In vitro studies showed that TNF- α disrupted insulin signaling and inhibited glucose uptake [17]. Additional research and clinical trials are needed to determine the safety and efficacy of new insulin. Although some novel insulin formulations lack US Food and Drug Administration approval for use in pregnancy, their use is widely accepted [15].

Pregnancy itself can be a factor that provokes an exacerbation of the underlying disease, which is mainly associated with changes in hormonal levels, increased levels of estrogen, changes in immune status and increased pro-inflammatory tendencies. Of course, much depends on the nosology itself, that is with what specific autoimmune disease a woman enters the disease.

Systemic autoimmune diseases and pregnancy

Systemic lupus erythematosus and antiphospholipid syndrome

Systemic lupus erythematosus is a chronic autoimmune disease that mainly affects young females during their reproductive years; therefore, pregnancy is a topic of major interest. Pregnancy outcome has greatly improved in last years, along with a better management of the disease, but should be still considered a high risk period, with a spectrum of potential complications that can influence maternal and fetal health.

As previously reported, active disease in the 6 months before conception, active lupus nephritis (LN), the discontinuation of useful medications (in particular hydroxychloroquine), the presence of aPL, anti-Ro/SSA and/or anti-La/SSB antibodies are all considered risk factors for maternal and fetal complications.

In last years, serum complement level, that physiologically increases during pregnancy, has shown to play a role in pregnancy outcome. In the PROMISSE study, where authors identified predictors of adverse pregnancy outcome in a cohort of nearly 500 pregnant women with SLE, authors demonstrate that complement pathway activation is associated with adverse pregnancy outcome: it seems that complement activation could trigger or amplify Inflammation and interfere with physiological changes at the maternal–fetal interface [18].

Maternal complications mainly include disease flares and hypertensive disorders (such as gestational hypertension, preeclampsia/eclampsia – PE/E, Hemolysis, Elevated Liver Enzymes, Low Platelets – HELLP syndrome).

Pregnancy can have a direct impact on systemic lupus erythematosus: in females with SLE most of the studies have shown that risk of SLE flare is higher during pregnancy [19]. The impact of SLE flares on pregnancy outcome depends on their type and number [20].

For example, cutaneous or articular involvement are not life-threatening, while hematological and renal flares can be severe. These manifestations can occur at any time during pregnancy but more frequently in the 1st and 2nd trimester, and, in addition, the risk of flare is high up to 1 year after delivery [21].

In the PROMISSE study, that mainly recruited patients in a stable remission, less than 10% of women had mild or moderate flares and only 3% of them developed severe flares during pregnancy. Notably, 65% of all patients received HCQ before and during pregnancy [22].

To prevent renal flares during pregnancy is mandatory: SLE patients with active lupus nephritis are at higher risk of pregnancy complications than SLE patients without renal disease. In a recent multi-center study, Moroni et al. showed that immunological disease activity (low C3 and C4 serum levels and/or positive anti-dsDNA at conception) were the best predictors of renal flares during pregnancy [20]. On the other hand, women with quiescent disease (proteinuria <500 mg/day, inactive urinary sediment) and normal renal function are reasonably at low risk during pregnancy.

In addition, other pregnancy complications may mimic a renal flare and this is the case of PE and HELLP syndrome that, in SLE, sometimes may develop early in pregnancy (even around the 20th week) and should be promptly recognized in order to prevent rapid progression.

Preeclampsia is defined as a persistent systolic blood pressure ≥ 140 mmHg or diastolic ≥ 90 mmHg after the 20th week of gestation, associated with proteinuria ≥ 300 mg/24 h or protein/creatinine ratio ≥ 0.3 [21].

PE represent a major concern for SLE pregnant women since it occurs in 2–35% of cases, 10 times more commonly than in general population [23].

The PROMISSE cohort showed PE in 15% of SLE women, rising to 22% in case of positive aPL; Moroni et al. observed PE in 8.4% of patients with anamnestic LN. Some of the discrepancies can be

related to the possible overlap of PE related features with those of LN also because PE and LN can occur in the same patient, which is critical since these manifestations require different therapeutic strategies.

Several predictive factors of PE have been identified over the years, some are the same as in general population (e.g. diabetes mellitus, hypertension, nulliparity, obesity and previous PE), others are specific of SLE (active disease at conception, LN in the 6 months before gestation or a history of LN, presence of aPL, thrombocytopenia and low C3/C4 serum levels) [23].

In general obstetric population, low dose aspirin (LDA) is given to prevent PE in patients at a high risk. According to the EULAR recommendations for women with SLE and APS, also in this particular subpopulation LDA was highly recommended, especially in those with lupus nephritis or positive aPL. Furthermore, in women with SLE associated to APS, combination treatment with LDA and heparin is recommended [3].

The best time to introduce LDA during pregnancy remains a matter of debate [24]. Recently, also HCQ was investigated in a cohort of 151 pregnancies in 122 SLE women: authors found that in treated pregnancies, the incidence of PE was significantly lower and neonatal birth weight was significantly higher ($p = 0.001$) [25].

PE represents one of the most consistent predictors of HELLP syndrome and they can coexist in up to 80% of cases [26]. In a recent multicenter study, in 71 pregnancies of SLE patients, HELLP syndrome was observed in only two patients, whereas HELLP and/or PE occurred in 11% of cases [20].

Higher rate of HELLP syndrome were observed in patients with SLE and secondary APS, compared to patients with only SLE ($p < 0.01$), suggesting that aPL can have a significant role in the pathogenesis [27].

Poor fetal outcomes in patients with SLE also include IUGR, small for gestational age (SGA), preterm delivery, fetal loss/stillbirth, need of cesareans section and neonatal SLE.

Pre-term delivery, before 37 weeks of gestation, is the most common complication in patients with SLE. The incidence seems to range between 23 and 28%, with spikes of 33% [28].

Preterm birth is a possible consequence of IUGR, defined as birth weight below the 10th percentile according to week gestation at delivery and fetal gender. This condition is rare in healthy women but can range from 10 to 30% of pregnancies in SLE patients. One possible explanation, beside prematurity, may be placental insufficiency, mainly due to the presence of aPL [29].

SGA fetuses or newborns are defined as neonates' weight below the 10th percentile for gestational age. Moroni et al. recently observed SGA in 16.4% of patients with LN. Interestingly, the probability of having a baby with SGA decreased by 85% in patients who were treated with HCQ, underlining the important role of this drug [20].

Pregnancy loss involves 20% of SLE pregnancies: beside the presence of SLE itself, concomitant APS or the presence of aPL, especially Lupus Anticoagulant, are often associated with this major obstetrical complication [30]. Also active disease and a history of LN were reported as risk factor.

Finally, the presence of maternal anti-Ro/SSA and/or La/SSB could be related to neonatal lupus (NL). These antibodies can cross the placenta during the second trimester and affect the baby in several different ways, with different degrees of severity, ranging from mild cutaneous manifestations to cardiac manifestations, being conduction abnormalities (first-, second-, third-degree congenital heart block (CHB)) the most frequent [31].

Cardiac NL is less common than other NL manifestations, it affects approximately 2% of exposed offspring with a recurrence rate in subsequent pregnancies estimated between 12% and 17% [32].

It is debated if women diagnosed in utero with CHB need a specific treatment and which one [33]. Anyway, the livebirth rate in affected pregnancies ranges from 84% to 71% as supported by several registries. An important achievement has been reached with the early application of pace maker after birth of affected children, which in the majority of cases allows a normal physical and psychological development [34,35].

HCQ was shown to be helpful in decreasing the rate of CHB recurrence leaving open its possible role in limiting also the CHB occurrence [36].

Antiphospholipid Syndrome is one of the most important acquired causes of pregnancy loss. It is a systemic autoimmune disorder defined by the occurrence of venous and arterial thromboses, often multiple, and pregnancy morbidity, in the presence of antiphospholipid antibodies [37].

Criteria for obstetric APS, as mentioned in classification criteria, are:

1) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; 2) One or more premature birth of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia, or recognized features of placental insufficiency; 3) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

APS can occur in patients without concomitant definite autoimmune condition (primary APS) or it may be associated with other diseases, mainly SLE. aPL antibodies can be found in patients with autoimmune diseases or in healthy subjects without any anamnestic thrombotic events or pregnancy complications. aPL antibodies can affect pregnancy outcome in several ways, mainly through placental thrombosis and infarction with subsequent early miscarriage or fetal loss, early onset pre-eclampsia, IUGR, placental abruption and premature delivery. Prematurity, as a consequence, seems to be the most frequent neonatal complication of APS in pregnancy.

HELLP syndrome has been reported in APS pregnancy [38]. Usually HELLP in APS pregnancy appears earlier than in the general obstetric population, occurring more frequently in the second trimester.

One fundamental step in the approach of women with aPL is the stratification of risk, considering both aPL profile and anamnestic features: it is crucial in order to choose the best therapy for each patient. As described in the EULAR recommendations, high-risk aPL profile (lupus anticoagulant positivity, triple aPL positivity, moderate to high titre aPL, IgG isotype) and co-existing SLE identify possibly more complicated pregnancies [3].

Therapeutic approach in women with APS/aPL positivity mainly depends on the previously described stratification of risk. A recent European review evaluated all the preexisting guidelines or expert-opinion in order to identifying a consensus, in both diagnostic criteria and therapeutic approach. Combined low-dose aspirin and low molecular weight heparin seems to be the most effective treatment in order to prevent APS/aPL-related pregnancy complications. However, sometimes this approach could not be enough, so alternative strategies were proposed, even if not standardized: they mainly include increasing of anticoagulation dose or immunomodulation (corticosteroids, HCQ, intravenous immunoglobulins, plasmapheresis) [39,40].

Observational/retrospective studies on the protective role of HCQ on pregnancy complications in APS were recently proposed. A Multinational Randomized Controlled Trial of HCQ versus Placebo in Addition to Standard Treatment in Pregnant Women with Antiphospholipid Syndrome or Antibodies was launched in September 2017: HYPATIA [41]. Then, the HIBISCUS trial: it was hypothesized that HCQ added to standard therapy could significantly improve birth and thrombosis rate in primary obstetrical APS [42].

Inflammatory arthritis

Rheumatoid arthritis (RA) is a chronic articular inflammatory disease characterized by joint swelling, joint tenderness and destruction of synovial joints, leading to severe disability and premature mortality. Annual incidence of 8.7 per 100,000 between the ages of 18 and 34 years further increases to 36.2 per 100,000 between the ages of 35 and 44 years [43].

RA and other chronic inflammatory arthritis, such as polyarticular juvenile idiopathic arthritis (JIA), tend to improve spontaneously during pregnancy in the majority of patients, even though less frequently than described in the past. During pregnancy, active disease can be found in about 35%–52% of patients [44].

A better disease preconceptional control, achieved during the last years, can probably explain this trend. Nowadays the RA management is based on early diagnosis, early treatment to achieve remission by a treat to target strategy. Such drug-induced remission allows women with RA to have a quality of life similar to that of peers including the desire to have a family.

Furthermore, over the last decade, evidences were provided on the safe use of the majority of disease-modifying antirheumatic drugs and TNFi during pregnancy and lactation with a consequent dramatic impact on the general management of women with RA [5].

Good treatment of patients with RA before/during pregnancy and lactation should aim to prevent or suppress disease activity in the mother: maternal disease activity is detrimental for a good pregnancy outcome and it needs to be clarified that most drugs are helpful – not harmful-to the baby.

In fact, it was demonstrated that women with active RA during pregnancy have an increased risk for both preterm delivery and small for gestational age (SGA) offspring, as well as others inflammatory diseases such as Inflammatory Bowel Disease. The association between active RA and pre-eclampsia and gestational hypertension is still debated [45]. Studies showed conflicting results about possible explanations, it has been suggested that a common auto-immunologic factor may exist between pre-eclampsia and RA but no clear answers were given [46].

Postpartum follow-up reveals a worsening of symptoms. There is an increased incidence of RA following the first pregnancy, especially in the first 9 months. Postpartum flares may occur in up to 90% of RA patients, usually in the first 3 months, also more often after the first pregnancy [47].

A recent big study confirmed that disease activity during pregnancy and the use of non-fluorinated corticosteroids, still largely employed to obtain a rapid disease control, are both related to an increased risk of preterm delivery. The OTIS (Organization of Teratology Specialists) Autoimmune Disease in Pregnancy Project evaluated 657 women with RA, 170 with JIA, and 564 women without autoimmune disease who delivered live-born infants from 2004 to 2017. In particular, it demonstrated that corticosteroid use in any trimester increases the risk for pre-term delivery (2 to 5-fold than in controls) in both RA and JIA, independently of disease activity [48]. Nowadays, because of the above quoted data of the disease modifying drugs safe use during pregnancy, corticosteroid administration should be limited in term of dosage and time with consequent improvement of pregnancy outcome.

Another point to consider is that often women with RA are requested to postpone pregnancy to reach a better disease control while the raise of maternal age increases the rate for obstetrics complications.

Risk factors for complicated pregnancy in patients with RA are pre-existing comorbidities such as hypertension, diabetes mellitus and thyroid disease. The increased frequency of concomitant problems among RA patients may be associated with the long-term systemic inflammation characteristic of the disease or with the use of corticosteroids during the general management of RA [49].

Women with RA are also considered to be a greater risk than general obstetric population to delivery by caesarian section and to have postpartum wound complications. However, the association still remains unclear [50].

Spondyloarthritis (SpA) include psoriatic arthritis (PsA) and ankylosing spondylitis (AS) that share similar pathogenic and clinical features.

These diseases tend to be stable or to get worse during pregnancy, even if the available literature is scarce and various: some studies report a flare in 60%–80% of patients with axial SpA [51], more recently others find the 25% of flare rate [52].

A recent study in small cohorts of SpA and RA patients showed a reduced disease activity in 70% of AS patients. The risk of flare during pregnancy in patients with axial SpA, as well as RA, is associated with active disease, high C reactive protein levels and TNFi discontinuation in early pregnancy. The aggravation of disease were experienced several weeks after withdrawal of TNFi [52].

Moreover, several SpA symptoms such as lumbar night pain, morning stiffness and fatigue could be influenced by pregnancy itself and, as a consequence, disease activity might be overestimated.

Regarding PsA, few data are available, mainly due to small size samples studied. In a recent study on 29 PsA women with 42 pregnancies, a worsening of the joint and skin activity was found in 31.7% and 42.9% respectively, both during pregnancy and the first year after delivery [53].

Few reports regarding birth outcomes in SpA have been published in the past with consequent uncertain conclusions. Recently, a population-based study using large national births registers was performed in Sweden. The results showed that some comorbidities such as diabetes, renal disease and hypertension may affect birth outcomes in patients with AS more than controls. In addition, AS had a higher frequency of preterm birth versus controls, mainly due to pre-eclampsia. The authors concluded that pregnancies in women with AS could be associated with preterm birth and SGA. In addition, a high risk for caesarian section was noted, that could be related to musculoskeletal impairment or pain in relation to delivery [54].

Systemic vasculitis

Small and medium vessels vasculitis are rare diseases usually affecting women beyond their reproductive years, making the challenges of pregnancy management difficult to study. Reports of pregnancies in these patients are very limited: common feature of almost all the reported cases is the relationship between disease activity and pregnancy outcome, in term of preterm birth and cesarean section [55,56].

ANCA-associated vasculitis, a Th2-cytokine-mediated diseases, usually experience a worsening of disease course during pregnancy. The described most common complication in patients with granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) was preterm delivery. Others complications have been reported, such as preeclampsia, premature rupture of membranes, spontaneous abortion, parturition hemorrhage, and retroplacental hematoma [57,58].

Limited data are reported for microscopic polyangiitis (MPA) and primarily are case reports: complications included maternal death, low birth weight, prematurity, and the occurrence of an MPA-like syndrome in the neonate [59].

On the other hand, complications of maternal vasculitis could be very severe if pregnancy occurs during a flare or when the disease is not controlled. GPA flares during pregnancy mostly consisted of respiratory complications, subglottic stenosis, skin lesions, arthritis, and renal deterioration; maternal death was reported in EGPA. Furthermore, it can be difficult to differentiate renal impairment from a disease flare or preeclampsia. In patients with MPA symptoms are mainly rash, joint swelling, pain, and fever.

Pregnancy outcomes in patients affected by Polyarteritis nodosa (PAN) are generally good. Reported complications include preterm delivery and intrauterine growth restriction (IUGR) [60].

A number of studies focus on pregnancy in patients with Takayasu arteritis (TA) and Behcet's disease (BD), primarily because they both affect young adults under 40 years old, and, for TA, especially women.

The most frequent reported maternal complications in patients with TA (nearly 45% of women) were hypertensive disorders, particularly during the peripartum period (gestational hypertension, preeclampsia, eclampsia). Fetal complications included IUGR and neonatal low birth weight (LBW), mainly due to preterm delivery, ranging from 8% to 50% and estimated about 23% in a systematic review [58].

Pregnancy seems not to have a great impact on disease outcome: in another recent systematic review, only less than 5% of flare were described. The highest rate was recorded in patients with active disease or onset of vasculitis during pregnancy as expected [61].

In any case, if complications do occur, their consequences can be severe. Development of aortic aneurysm, stroke, congestive heart failure, aortic insufficiency, myocardial infarction, and aortic dissection are rare but very difficult to manage when occurring during pregnancy [59].

Up to now 396 cases of pregnancy in BD women have been published and data showed that pregnancy outcomes in these patients are quite similar to that occurring in general obstetric population [62].

Regarding disease flares, they were reported in approximately 30–36% of cases in a systematic review; BD usually improves or remains stable during pregnancy. Flares mainly consist of oral or genital ulcers, but also arthritis, uveitis, erythema nodosum, and, less frequently, thrombosis may occur [60].

One point to consider in these patients is the risk for thrombosis during pregnancy and puerperium, per se carrying higher thrombotic risk; in fact, several reports describe vascular events, including venous thrombosis and transient ischemic attacks in BD affected women [55].

Patients with prior thrombosis should be strongly considered as candidates for anticoagulation during pregnancy.

Other systemic autoimmune diseases (including scleroderma, Sjogren syndrome, myositis)

Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by various degrees of vascular involvement, fibrosis of connective tissues and inflammation/autoimmunity. Women are more likely to experience SSc than men so pregnancy is a major topic of interest. Pregnancy in women

with SSc in the past was mostly considered problematic but recent research has revealed a more favorable picture. Premature births and low birth weight were described as frequent pregnancy outcome in SSc patients. This trend was confirmed in a big Italian multicenter study of 109 pregnancies among 99 women with SSc collected prospectively from 2000 to 2010. When compared with a control population, preterm deliveries were significantly increased among women with SSc (25% vs. 12%). IUGR and low birth weight were also increased and the use of corticosteroids was associated with preterm deliveries. In general, the disease stayed stable during pregnancies. On the other hand, progression of the disease during or after pregnancy is rare, but possible; obviously, patients with severe organ involvement should be counselled to avoid the pregnancy. Authors concluded that women with SSc may have successful pregnancies but appropriate counselling and multidisciplinary approach is always needed [63].

Sjogren Syndrome (SSj) is more frequent in postmenopausal women but possibly could affect women at every age. It is an autoimmune systemic disease characterized by dysfunction of exocrine glands and possible multiorgan involvement with an high prevalence of anti-Ro/SSA and/or anti-La/SSB antibodies. It could be primitive but more frequent associated with other autoimmune disease, mainly RA and SLE. Main concern in pregnancy in women with SSj is related to the presence of these autoantibodies and their possible role in causing neonatal lupus, as previously described. In a recent review the authors evaluated 6 papers (from 1994 to 2014) and concluded that these pregnancies could be complicated and multidisciplinary approach remains the best chance for these patients [64].

Dermatomyositis (DM) and polymyositis (PM) are inflammatory myopathies mediated by autoantibodies characterized by proximal symmetric muscle weakness and, in DM, a large variety of skin manifestations. Pregnancy are rare in these patients, mainly because these diseases usually not involved women in childbearing age; it was estimated that in women from 25 to 34 years old prevalence was 4–11% [65].

A review was published in 2014 reported 78 pregnancies from 59 women with myositis [66]. As in other connective tissue diseases, pregnancy complications were related to disease activity at conception and during pregnancy itself. Pregnancy outcome was reported as generally good, with preterm delivery and SGA as the main complications described. In 2014 a single center study was published. Authors evaluated retrospectively 102 pregnancies in 51 women with inflammatory myositis and did not find any pattern of adverse pregnancy outcome and both pregnancy and disease were generally uneventful. Furthermore, clinical improvement tended to occur during pregnancy with common postpartum relapse [67].

Conclusions

Rheumatologists, obstetricians and gynecologists have to deal every day with the difficult task of managing pregnancy in a patient with a particular autoimmune disease. Both maternal and fetal mortality and morbidity are still significantly increased despite improvements in outcomes. A multidisciplinary strategy for the management of pregnancy and childbirth and often a well-coordinated team of specialists from other clinical disciplines is needed. Pregnancy in these patients should be attributed to high-risk pregnancy clinic and implies monitoring in medical hospitals with the presence of a NICU of 2 or 3 levels. Treatment options during pregnancy are also limited and maternal benefit has to be weighed against fetal risk. Furthermore, pre-conceptional counseling and a coordinated approach, with close monitoring by a multidisciplinary team, are essential for optimal outcomes.

Practice points

- Counselling and the stratification of risk is mandatory for a good management of pregnancy in women with rheumatic diseases.
- Most of drugs used in rheumatology are helpful, not harmful to the baby; discontinuation of safe medication could compromise the good outcome of pregnancy.

- As a general rule, a pregnancy should be avoided: while taking teratogenic drugs, if diagnosis of autoimmune disease is recent (usually 6 months), if there is major organ involvement, if there is disease activity or flares at conception or in the last 6–12 months prior to pregnancy.
- Multidisciplinary approach is advisable. A team composed by rheumatologist, gynecologist, neonatologist and all clinicians involved in the management of women with autoimmune disease is the best way to afford a pregnancy.

Research agenda

- Guidelines are lacking, therapeutic and clinical approach is often still based on expert opinion.
- More studies are needed to demonstrate safety during pregnancy of medications currently in the armamentarium of rheumatologists.

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