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Review

Pregnancy and reproduction in autoimmune rheumatic diseases

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Abstract

Despite evidence for the important role of oestrogens in the aetiology and pathophysiology of chronic immune/inflammatory diseases, the previous view of an unequivocal beneficial effect of oestrogens on RA compared with a detrimental effect on SLE has to be reconsidered. Likewise, the long-held belief that RA remits in the majority of pregnant patients has been challenged, and shows that only half of the patients experience significant improvement when objective disease activity measurements are applied. Pregnancies in patients with SLE are mostly successful when well planned and monitored interdisciplinarily, whereas a small proportion of women with APS still have adverse pregnancy outcomes in spite of the standard treatment. New prospective studies indicate better outcomes for pregnancies in women with rare diseases such as SSc and vasculitis. Fertility problems are not uncommon in patients with rheumatic disease and need to be considered in both genders. Necessary therapy, shortly before or during the pregnancy, demands taking into account the health of both mother and fetus. Long-term effects of drugs on offspring exposed *in utero* or during lactation is a new area under study as well as late effects of maternal rheumatic disease on children.

Key words: Oestrogen, Systemic lupus erythematosus, Rheumatoid arthritis, Pregnancy, Antiphospholipid syndrome, Pre-eclampsia, Neonatal lupus, Systemic sclerosis, Vasculitis, Fertility.

REVIEW

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Introduction

Rheumatic diseases occur preferentially in women, often during the childbearing years. The female preponderance has raised the confirmed conviction that sex hormones play an important role in both disease development and course.

During pregnancy, profound changes of the hormonal milieu take place. The increase of free steroid hormones including glucocorticoids, progesterones and oestrogens, induces changes in functions of immunocompetent cells such as B cells, T cells and monocytes [1]. As a consequence, clinical symptoms of immune-mediated rheumatic diseases are modified related to the prevailing pathophysiological disease process; some improve, while others remain relatively unchanged or worsen during pregnancy.

Pregnancy outcome may be threatened by severe organ involvement and the presence of autoantibodies. Rare diseases with anecdotal pregnancy experience, like most of the vasculitides, pose problems in pregnancy management.

Fetal and neonatal effects of maternal autoantibodies are well known, whereas the long-term outcome of children born to mothers with autoimmune rheumatic disease is still insufficiently studied. Likewise, causes of impairment of fertility in patients with rheumatic disease need more detailed investigation, particularly in males. This survey gives a concise overview of current basic and clinical research into the various aspects of reproduction in rheumatic diseases.

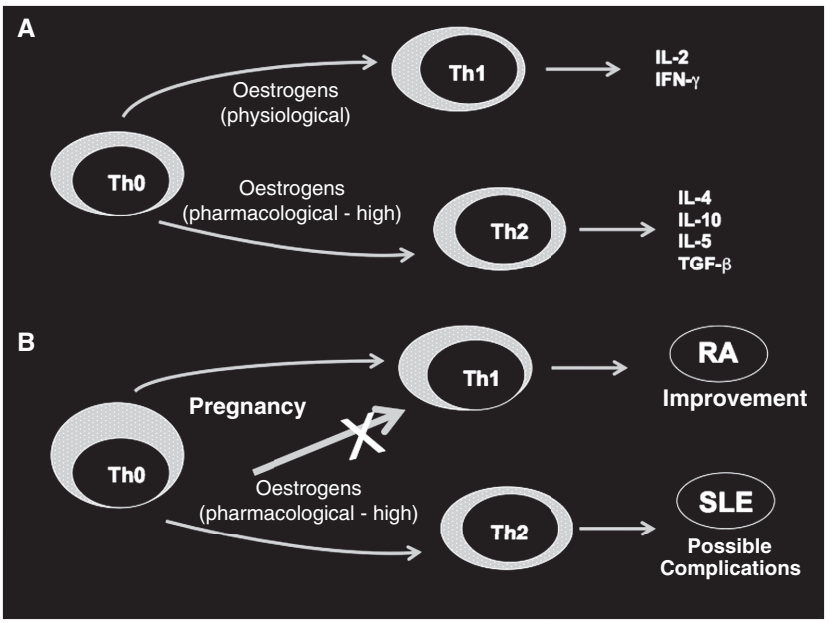
Sex hormones and autoimmune diseases

Immunological, epidemiological and clinical evidence suggest that female sex hormones play an important role in the aetiology and pathophysiology of chronic immune/inflammatory diseases [1]. Oestrogens are generally considered as enhancers of cell proliferation and humoral immune responses, whereas androgens have opposite effects [1]. However, the role of oestrogens in human autoimmune diseases has been under debate with partly confusing and opposite conclusions because of animal and cellular studies.

Today, important factors to be considered are the different effects of oestrogens on their different receptors or on different target cells, the influence of oestrogen concentrations (Fig. 1) and finally, opposite effects (especially on cell proliferation) exerted by different peripheral oestrogen metabolites in humans [2].

A preponderance of 16α-hydroxylated oestrogen metabolites as observed in RA SF is unfavourable in synovial inflammation since these metabolites enhance cell proliferation including that of synoviocytes [2]. In addition, since 17β-oestradiol administered during HRT will rapidly increase oestrone sulphate after conversion in adipose tissue by aromatases, HRT can have pro-inflammatory

Fig. 1 Immunomodulatory effects of oestrogens. (**A**) Serum oestrogens in physiological concentrations are generally implicated in maturation of Th cells (Th0) into Th1-type T cells. In pharmacological concentrations and pregnancy levels (high), they mainly support the maturation of Th0 T cells into Th2 type T cells (and B-cell activation). (**B**) During pregnancy, as serum oestrogen concentrations increase, a shift to a Th2 response is supported, therefore classical Th1-driven diseases such as RA are mitigated (improvement in 50–75%), whereas classical Th2-driven diseases such as SLE may be negatively influenced (complications in 40–70%).



effects by providing oestrone sulphate to the inflamed RA synovial tissue [1].

In SLE, peripheral blood mononuclear cells show an increase in anti-dsDNA and IL-10 in response to oestrogen [3, 4]. Women with SLE tend to have lower levels of DHEA, which are further reduced by treatment with prednisone. In clinical trials, DHEA supplementation was helpful both for disease activity and for BMD in SLE patients [5]. Oestrogen substitution in post-menopausal women with SLE increases mild/moderate, but not severe, flares significantly [6].

However, oral contraceptive (OCP) use is an established risk factor for SLE [7]. This risk is particularly elevated in women who recently started OCPs, suggesting an acute effect at least in a small subgroup of susceptible women [7]. OCPs do not increase flares in women with established SLE that is inactive or only moderately active [8]. In conclusion, it is now much better established that female gonadal hormones exert an important role in the aetiology and course of chronic inflammatory/autoimmune diseases as epidemiological, immunological and clinical evidence shows that menstrual cycle, pregnancy, menopausal status and OCPs are significant influencing factors [1].

Pregnancy and autoimmune rheumatic diseases

Pregnancy is a state of high concentration of sex hormones and cross-talk between mother and fetus. Throughout pregnancy, the hormonal, biochemical and immunological equilibrium in the mother changes related to the stage of pregnancy. However, at all stages tolerance to the semi-allogeneic fetus is maintained by a supportive immunological milieu [9]. Related to the pathogenesis, clinical symptoms of the autoimmune rheumatic diseases vary: some improve spontaneously during gestation, others remain active or even flare. Likewise, pregnancy outcome is different depending on disease extent and severity (Table 1).

RA and AS

Retrospective and some prospective studies have shown that RA improves during pregnancy and flares after delivery. The largest prospective study from the Netherlands assessing the effect of pregnancy on RA, and the impact of RA on pregnancy includes >200 women at present [10]. Forty-eight per cent of the RA patients improved during pregnancy according to the 28-joint DAS (DAS-28)-derived EULAR response criteria, whereas 41% flared after delivery according to reversed EULAR response criteria [10].

Neither improvement of disease activity of RA during pregnancy nor the post-partum flare was associated with changes in levels of anti-citrullinated protein antibodies (ACPAs) or RF [11]. However, women negative for ACPA and RF were more likely to improve during pregnancy [11].

Higher disease activity during pregnancy was associated with lower birth weight (multiple regression analysis −75 g (95% CI −142, −8.0 g) decrease in birthweight per 1.0 increase in DAS-28). Gestational age at delivery of patients using prednisone was significantly shorter (38 5/7 *vs* 39 6/7 weeks, $P = 0.006$), and their delivery more often premature (<37 weeks), 8.6% in the RA group compared with 6.2% in the control group [12].

The pregnancy-induced amelioration of RA presents a window of opportunity for insights into pathogenic mechanisms in this disease. Bi-directional trafficking of cells or DNA occurs routinely during normal pregnancy, from fetus to mother and mother to fetus.

Microchimerism (Mc) refers to a small number of cells (or DNA) harboured by one individual that originated in a genetically different individual. Pregnancy has immunological effects both in the short term and for the long term. Higher levels of fetal Mc were found in the circulation of women with RA who improved during pregnancy compared with those who did not [13].

Pregnancy also leaves a legacy for the long term as it is now known that decades after birth fetal Mc persists in the mother and maternal Mc in her offspring. Women with RA who were themselves negative for HLA alleles associated with RA risk were recently reported to harbour Mc with RA-risk alleles significantly more often than healthy women [14]. Thus, Mc could contribute to both health and disease.

Among factors influencing disease activity and immunological mechanisms of fetal–maternal tolerance are $CD4^+CD25^+FOXP3^+$ Tregs. Tregs suppress immune responses thereby preventing autoimmune disease and supporting maternal tolerance towards the fetus. In healthy women, the number of circulating Tregs increases during pregnancy and declines post-partum. The same pregnancy-related expansion of Tregs is found in patients with RA and AS [15, 16]. However, unlike in healthy women, Tregs of RA and AS patients are unable to suppress effectively the pro-inflammatory cytokine response of T-effector cells [16].

In RA, pregnancy restores Treg function creating an anti-inflammatory cytokine milieu in the third trimester at the time of maximal improvement of RA disease activity [15]. In contrast to RA, pregnancy does not substantially alter the disease activity in AS. This was reflected by a defective Treg function with impaired capacity to suppress pro-inflammatory cytokines [16]. Thus, the different clinical response of RA and AS to pregnancy corresponded to a different response at the cellular level.

SLE

In contrast to RA, SLE often remains active or even flares during pregnancy. There are clear differences in hormonal and cytokine levels in SLE *vs* control pregnancies [17]. Data from the Hopkins Lupus Pregnancy Cohort have shown an increase in renal flares in pregnant SLE patients [18]. However, a Canadian prospective study found changes in renal disease activity and deterioration in renal function in pregnant patients similar to those

Table 1 Interaction of pregnancy and some CTDs or vasculitis

Disease	Effect of pregnancy on disease	Risk of maternal complications in pregnancy	Risk for pregnancy complications	Risk for fetus/neonate
RA	Improvement in 48–75%	No	Moderate increase	Very rare
SLE	Flare in 50% of cases	Most frequent: haematological, and renal complications	Hypertension, pre-eclampsia, prematurity	Fetal loss, intrauterine growth restriction, low birthweight, neonatal lupus
APS	Aggravation	Thrombosis	Pre-eclampsia, prematurity, HELLP syndrome	Fetal loss, intrauterine growth restriction, low birthweight
SSc	No major effect on disease activity	Not more frequent than outside pregnancy	Prematurity	Reduced birthweight in premature infants
Takayasu arteritis	Unchanged in 72%, improvement in 20%	Progression of renal insufficiency, congestive heart failure	Hypertension in 30–44% Pre-eclampsia in 12–16%	Only at severe maternal disease, otherwise 85% good neonatal outcome
ANCA-positive vasculitis	Data insufficient to discern a particular effect	Renal and pulmonary disease	Pre-eclampsia, prematurity	Fetal loss, intrauterine growth restriction, low birthweight

HELLP: haemolysis, elevated liver enzymes low platelet.

which occur in non-pregnant patients with LN [19]. Other studies have shown that SLE flares are not more severe in pregnancy than in the non pregnant state [20].

The combination of high clinical activity and abnormal serology (complement or anti-dsDNA) is most predictive of a poor obstetric outcome [18]. Pregnancy loss is increased when there is proteinuria, aPL, thrombocytopenia or hypertension at the first pregnancy visit [18].

Concerning therapy, HCQ use is desirable in pregnancy, as HCQ-treated pregnancies have fewer preterm births and less severe clinical activity [21]. Prednisone, in contrast, at high concentrations, is associated with more diabetes, hypertension and pre-eclampsia.

The PROMISSE (predictors of pregnancy outcome: biomarkers in antiphospholipid syndrome and systemic lupus erythematosus) study is an ongoing prospective observational study to identify markers that predict poor pregnancy outcome (fetal growth restriction, pre-eclampsia, fetal or neonatal death) in patients with the named diseases. Particular focus is on complement activation and on angiogenic factors in predicting poor outcome [22]. Patients are grouped as: aPL; no SLE (goal 150, 93 recruited as of 1 September 2009); aPL and SLE (goal 100, 42 recruited); SLE with no aPL (goal 250, 220 recruited); and neither SLE nor aPL and prior successful pregnancies with no more than one early miscarriage (goal 200, 154 recruited).

As of 1 September 2009, surprisingly good outcomes are shown in all patient groups [48 (16%) of the 307 study patients and 2 (2%) of the 117 normal delivered patients had poor outcomes] with those with SLE and aPL faring worst. Preliminary analyses suggest that LA, formally defined by confirmatory tests after positive screening for activated PTT, KCT, DRVVT and/or dilute PT, is a far better predictor of poor outcome than is high titre aPL and anti-β_2-glycoprotein I immunoglubulin (Ig) G (IgG) antibody; IgM and IgA antibodies are not predictive.

Neonatal lupus syndromes

Transplacental transfer of Ro/SSA antibodies can induce neonatal lupus syndromes, either as a typical skin rash that resolves spontaneously within 6 months after birth or a congenital heart block (CHB) in the child. Atrioventricular (AV) block is defined as congenital if diagnosed *in utero*, at birth or within the neonatal period (0–27 days after birth).

The most common presentation is an unexpected advanced AV block in the fetus of a healthy asymptomatic mother (85% of cases) [23]. To differentiate these blocks into complete *vs* incomplete is difficult *in utero*. The risk of delivering a child with complete CHB for anti-Ro/SSA-positive mothers is 1–2% [23]. The risk of recurrence is 15–20%; unfortunately high dose IVIGs are not effective in reducing this risk [24].

Other minor ECG abnormalities may be present in infants born by anti-Ro/SSA-positive mothers [PQ interval (time between the beginning of the atrial contraction and the beginning of the ventral contraction) prolongation, sinus bradycardia]. Anti-Ro/SSA antibodies do not negatively affect other pregnancy outcomes [23].

APS

aPLs are associated with recurrent pregnancy losses. Different aPL-mediated pathogenic mechanisms have been described, such as: (i) placental thrombotic events; (ii) placental inflammatory events following local

complement (C′) activation; and (iii) direct aPL effect on trophoblast cells inducing defective placentation. In two previous investigations of placental tissue, placental thrombosis was no more frequent in patients with APS and recurrent miscarriage than in patients with recurrent miscarriage who were aPL negative. There were no specific placental lesions or patterns of abnormalities characteristic of the primary APS (PAPS) [25].

In a prospective study, histological and immunohistochemistry analysis of term placentas or abortive materials was carried out in 14 pregnancies of women affected by PAPS and compared with five matched controls [26]. No specific histological pattern or widespread inflammation was found. Complement activation was detected for the first time in APS placentas both in abortive specimens and in placentas at term, but there was no relationship with therapy or pregnancy outcome. These results suggest that complement activation may contribute to placental damage; however, whether it plays a key role is not clarified.

The poor pregnancy outcome in women with APS has been changed by therapy with anti-aggregation (low-dose aspirin) alone or in association with anti-coagulation (low-molecular-weight heparin) to a nearly 80% rate of live births. However, 20% of pregnancies still experience poor outcome despite conventional treatment. Various treatments have been suggested after failure of conventional therapy ranging from increasing the dose of low-molecular-weight heparin, or adding either steroids, HCQ or IVIG [27]. Recently, the Antiphospholipid European Forum promoted a multicentre project for collecting cases of pregnancy loss despite anti-aggregating and anti-coagulation treatment in women with APS and matched controls [28]. Preliminary results showed that women with unsuccessful pregnancies were more likely to be those with SLE, or with a history of thrombosis or thrombocytopenia.

A severe complication in both SLE and APS is the increased risk of pre-eclampsia triggered by placental dysfunction caused by maternal endothelial cell dysfunction. Both genetic polymorphisms, dysregulation of angiogenic factors [29] and a variety of other factors are involved in the pathogenesis of pre-eclampsia. It has been hypothesized that increased circulating, soluble Fms-like tyrosine kinase (sFlt-1) contributes to the endothelial dysfunction, hypertension and proteinuria of pre-eclampsia. Interestingly, elevated sFlt-1 levels have been detected in SLE pregnancies at risk for pre-eclampsia [30].

A recent study showed that cell-free, fetal nucleic acids (DNA and mRNA) are released by the placental trophoblast, and are elevated in cases with manifest pre-eclampsia [31]. Levels correlated with disease severity and were higher in early-onset than in late-onset pre-eclampsia. Furthermore, cell-free DNA levels were found to be elevated early in pregnancy (<24 weeks of gestation) in those cases that subsequently developed pre-eclampsia, but not in those with normal pregnancy outcome.

In addition, studies indicated that placentally derived cell-free nucleic acids were associated with microdebris released by syncytiotrophoblast turnover [32]. Placental microdebris could trigger neutrophil extracellular trap (NET) generation by the extracellular extrusion of their nuclear DNA. NETs have been found in greater quantities in pre-eclamptic placentae than in those with normal healthy deliveries. The role NETs play in the underlying aetiology of pre-eclampsia awaits further clarification.

SSc

In the past, pregnant SSc patients were thought to be at high risk for poor fetal and maternal outcome. In a recent Italian study considered the largest up to now, 17 centres prospectively followed 70 pregnancies in 62 women with SSc. Mean age at conception was 30.9 years, and duration of disease 56 months; diffuse disease was present in 47% of women. The control group was a cohort of 111 women with SLE followed in the same period at four centres.

Pregnancy losses occurred in 4% of SSc women *vs* 15% of SLE women ($P = 0.03$); with prematurity as the most prominent adverse outcome in SSc (25% in SSc *vs* 17% in SLE); pre-eclampsia and hypertension occurred more frequently in SLE (1.5 *vs* 7% SLE).

Pregnancy outcomes were similar in limited and diffuse SSc and were not correlated with disease activity. SSc skin involvement remained stable in 69% of women, RP improved in 40%, oesophageal reflux worsened in 24%, spirometry remained stable in 72% and echocardiography was stable in 98%. No renal crisis was observed, but pulmonary hypertension developed in one woman. The study confirms that women with SSc can have uncomplicated, successful pregnancies, provided the disease is stable and organ damage mild. High-risk pregnancy management should be standard, because of the high frequency of prematurity [33].

Vasculitis

Improvement in diagnosis of primary systemic vasculitides has led to an earlier detection and treatment with the consequent improvement of survival rate as well as quality of life. For these reasons, reproduction is becoming an important issue in patients with vasculitides. Data on pregnancy in patients with systemic vasculitides are scarce due to their low incidence, low female : male ratio or their frequent disease onset after childbearing age.

However, patients with Behçet disease tend to improve during pregnancy and are at low risk for preterm delivery, fetal and obstetric complications. Maternal and fetal outcome has been satisfactory in most patients with Takayasu arteritis, WG and Churg–Strauss syndrome when the disease activity was well controlled [34] (Table 1).

An assessment of microscopic polyangitis or PAN during pregnancy is not possible due to the few case reports published. Patients with active vasculitis at conception or disease onset during pregnancy are at increased risk for adverse pregnancy outcomes. The severity of the initial

manifestations of vasculitis does not predict the activity of the disease during pregnancy. A disease flare during pregnancy or post-partum is possible even when the vasculitis was quiescent at conception. Frequent control during pregnancy and post-partum is therefore mandatory.

Preconceptional counselling of high-risk pregnancies

Co-ordinated medical/obstetric care is essential to maximize the chance of successful pregnancy outcome in women with vasculitis or CTDs [35]. Optimum disease control and preferably remission or low disease activity before pregnancy is the requirement for good outcomes.

Previous complicated pregnancies, renal disease, irreversible organ damage, anti-Ro/SSA and aPL and treatment with high doses of glucocorticoids increase the risk of complications. Pregnancy is contraindicated in women with symptomatic pulmonary hypertension, heart failure, severe restrictive pulmonary disease, severe chronic renal failure, recent high disease activity and recent arterial thrombosis.

During pregnancy, HCQ, low-dose glucocorticoids and AZA can be safely used. Pulse i.v. steroids can be given in cases of severe SLE or vasculitis flares. CYC, MTX and MMF are contraindicated during pregnancy and lactation [36].

Follow-up of children

Apart from neonatal and perinatal disease induced by aPLs or Ro/SSA antibodies, very little information about the long-term outcome of children born to mothers with SLE or APS exists. A prospective study on the long-term outcome of children up to the age of 17 years born to mothers with SLE is now in progress [37]. In a follow-up study of 38 children born after the diagnosis of APS, delayed milestones or developmental abnormalities were reported in 9 (23%) compared with a national average of 4%. Attention-deficit disorders were found in three children and dyslexia was identified in two males.

Children born to APS mothers are more likely to be delivered preterm, have low birthweights and demonstrate neurological developmental abnormalities than those born to normal mothers. Neuro-developmental abnormalities result mostly from preterm birth rather than from the disease or medications. An increased rate of learning disabilities has been found in children of SLE mothers and women with aPL [38]. Genetic factors can be inherited and may predispose to autoimmunity in the children later in life.

Another concern is the long-term outcome of children exposed to immunosuppressive drugs *in utero*. Several studies assessed humoral and cellular immune responses of children exposed to glucocorticoids alone or in combination with AZA or ciclosporin or high-dose dexamethasone for anti-Ro/SSA-associated CHB [39, 40]. No significant differences from matched controls were found. Children exposed to HCQ during pregnancy and lactation showed no signs of ophthalmic or ototoxic toxicity [33].

The follow-up of children exposed to TNF blockers during pregnancy is still too short to draw definite conclusions on safety.

In Brescia, 10 children exposed to etanercept during 1–8 weeks of pregnancy were followed up for a mean period of 11 months (range 1–45 months). No particular complications at birth or developmental abnormalities were observed. In conclusion, follow-up of children exposed to immunosuppressive drugs needs to be constantly updated in order to support existing data on a growing number of cases.

Fertility

Infertility affects 10–15% of all couples, and is higher in male and female patients with rheumatic disease [41]. Normal values of sperm parameters were published by the World Health Organization (WHO) in 1992 and 1999 and, for morphology, by Kruger (1998). However, nearly all reference values (especially morphology) have been questioned. A Swiss study of proven fertile men whose partners were pregnant at the time of study inclusion showed high variability of several sperm parameters, especially morphology [39].

Similar results were found in young Swiss recruits [42]. This shows that there are wide ranges for most sperm parameters and no diagnosis of male infertility can be made because of a single abnormal parameter. A combination of several semen criteria is more predictive.

A Brazilian study revealed impaired testicular and sexual function in 35 male SLE patients [43]. SLE patients had lower median testicular volume in both testes ($P = 0.003$ and $P = 0.004$), total sperm count ($P = 0.002$) and total motile sperm count ($P = 0.004$) compared with 35 healthy controls.

A lower median sperm concentration ($P = 0.0001$), total sperm count ($P = 0.0001$), total motility sperm count ($P = 0.0001$), sperm motility ($P = 0.004$) and Kruger normal sperm forms were found in SLE patients under i.v. CYC (IVCYC) therapy ($P = 0.038$) compared with patients without this treatment [43].

Almost a quarter of SLE patients had Sertoli cell dysfunction according to low serum inhibin B, and the serum level was lower in SLE patients treated with IVCYC compared with those without this therapy ($P = 0.031$). Further evaluation of the 26 SLE patients with normal inhibin B and FSH levels revealed that medians of inhibin B : FSH ratio were lower in SLE patients with oligozoospermia compared with normozoospermia ($P = 0.004$) [44].

The inhibin:FSH ratio was also lower in SLE patients treated with IVCYC than those without this therapy ($P = 0.04$). Furthermore, the frequencies of sexual/erectile dysfunction were significantly higher in SLE *vs* controls ($P = 0.0001$) [44].

These are the first studies to identify sexual/erectile and gonadal dysfunction in male SLE patients. A multidisciplinary approach is essential in order to offer preventive measures, including sperm cryopreservation before IVCYC therapy, for these patients.

Conclusion

Some previously accepted paradigms such as spontaneous improvement for the majority of pregnant women with RA and predominantly unfavourable pregnancy outcomes in SLE, APS and SSc have lately been challenged.

Due to an increasing recognition of risk factors and an interdisciplinary approach in monitoring pregnancy, most women with autoimmune rheumatic diseases can have successful pregnancies, provided pregnancy is planned and occurs after a prolonged period of remission or low disease activity. Poor disease control and flares in pregnancy may result in low birthweight and prematurity, and these factors are more likely to cause short- and long-term adverse outcomes in the offspring than the maternal disease or the medication used during pregnancy.

Problems remain in patients not responding to standard therapy or with life-threatening organ manifestations. Some areas, previously neglected, such as fertility in male patients and long-term effects of maternal disease in offspring are now under more intense investigation.

Follow-up of children during childhood and adolescence will answer questions related to possible adverse long-term effects of maternal disease or therapy during pregnancy. Awareness of the risk for learning disabilities in children of SLE and APS mothers can assist in early recognition and proper management.

In addition, reproduction problems need to be addressed both in female and male patients, risk factors for adverse outcome of pregnancy or for offspring must be analysed and appropriate counselling and skilled management be given.

In conclusion, expert surveillance ensures a safe pregnancy for the majority of women with autoimmune rheumatic diseases.

Rheumatology key messages

- Female gonadal hormones have an impact on the aetiology and course of chronic inflammatory/autoimmune diseases.
- Use of OCPs and pregnancy can modify disease symptoms.
- Pre-pregnancy planning and interdisciplinary monitoring throughout pregnancy ensures a successful pregnancy outcome for most patients.

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