Women's health and fertility, family planning and pregnancy in immune-mediated rheumatic diseases: a report from a south-eastern European Expert Meeting

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ABSTRACT

With current advances in medical treatment, reproductive issues have become more important for women with chronic immune-mediated diseases. Most, if not all, patients report that their disease affects their personal relationships, their decision to have children, and the size of their family. These decisions are multi-factorial, influenced mainly by concerns over the effect of pregnancy on the rheumatic disease, the impact of disease activity during pregnancy on foetal health, the patient's ability to care for the child, and the possible harmful effects medication could have on the child, both pre- and post-natally during breastfeeding. Apart from that, women's health issues tend to be overlooked in favour of the management of the underlying rheumatic disease. To this end, we convened an expert panel to review the published literature on women's health and reproductive issues and provide evidence- and eminence-based points to consider for the treating physicians. We conclude that there is a need for a change in mind-set from one which "cautions against pregnancy" to one which "embraces pregnancy" through the practice of individualised, pre- and post-conceptual, multi-disciplinary care.

Introduction

Immune-mediated rheumatic diseases (RDs) predominantly affect women of reproductive age. There is an unmet need to address issues related to women's health, family planning and pregnancy by improving education, communication and collaboration among the medical disciplines involved. A panel of specialists from south-eastern European countries met in Athens, Greece, in May 2013. The panel reviewed recently published literature on selected topics and discussed points to consider for physicians and health professionals who are involved in the care of women with RDs. Herein, we give a summary of the presentations and discussions held during the meeting, including general background information on women's health issues, specific considerations for women with RDs, and the use of immunosuppressive and biological treatments during pregnancy and lactation. We end by proposing a research agenda and future actions to undertake towards increasing the awareness on women's health, family planning and pregnancy issues.

Methodology

An expert panel was formed comprising of adult and paediatric rheumatologists, obstetricians-gynecologists, internists and paediatricians from south-eastern European countries. Pre-meeting electronic discussions were carried out to create a list of topics-of-interest related to women's health, fertility, family planning and pregnancy-lactation. Each topic was assigned to one panelist who reviewed the relevant literature with emphasis on peer-reviewed articles published in PubMed during the last five years. The results were presented, summarised and discussed upon during the expert meeting. Based on the presentations and discussions, provisional points-to-consider on selected topics were developed and circulated through the entire panel, and

were further discussed and modified using a consensus-based approach.

Women's health issues: general information health professionals need to know

General health issues in women

Certain medical diseases occur more frequently or have atypical presentations in women. These include osteoporosis (1), psychiatric disorders (such as anxiety and depression) (2), ischaemic heart disease (presenting with atypical symptoms and often negative work-up) (3), and urinary incontinence (4). In addition, there is a high burden of malignant diseases particularly breast cancer (5), cervical cancer (6), ovarian cancer (7), and increasing rates of lung cancer (8). Recommendations for the early detection of cancer in average-risk, asymptomatic women include annual mammography after the age of 40 years, and cervical cancer screening with smear Pap test and/or HPV DNA test after the age of 21 years (8). HPV immunisation reduces the risk for cervical pre-malignant and malignant lesions caused by certain HPV types, and it may prevent vulvar and vaginal pre-cancers and genital warts. It is recommended in girls 12–15 years old but its use can be extended from 9 to 26 years (9, 10).

Reproductive health issues in women

– Menstrual disorders

These include irregularities in menstrual cycle (from oligo- to absolute amenorrhoea) often due to underlying systemic illness, use of medications (including immunosuppressives), or unrelated common gynecological conditions such as polycystic ovarian syndrome (11). Abnormal uterine bleeding can be the result of bleeding diathesis (thrombocytopenia or platelet disorders, von Willebrand disease, clotting disorders) and is managed with low-dose oral contraceptives or cyclic progestogen given for 3-6 months (12).

– Contraception

For women with chronic diseases, pregnancy planning is important to reduce possible risks for maternal and foetal complications and includes prompt discontinuation of unsafe drugs, control of disease activity, and pre-pregnancy laboratory work-up. Hormonal contraceptives (combined oestrogen-progestogen and progestogen-only preparations), are associated with low rates of unwanted pregnancies (13). Issues to consider with their use include breakthrough bleeding and headaches, blood pressure elevations, and possible interactions with other medications. Some patients may discontinue contraceptives due to aforementioned harms or concerns regarding their safety in the setting of an autoimmune disease or thrombophilic diathesis, which may be exacerbated by their use (14, 15). Prolonged use of oestrogen-containing contraceptives is associated with increased risk (2 to 4-fold) for venous thromboembolism and therefore, they are contraindicated if there is coexisting thrombophilia. Other contraindications include uncontrolled hypertension and severe renal disease (13). In such cases, progesterone-based contraceptives can be used, including the progesterone-only pill, injectable progesterone methods (Implanon®, Depo Provera®) and the Mirena® intrauterine system (16).

– Infertility and fertility preservation

Infertility, defined as at least one year of attempted conception without success, affects more than 6 million couples in the US, and despite thorough work-up, no apparent cause can be identified in up to 26% of cases (17). Premature ovarian insufficiency (triad of amenorrhoea, sex steroid deficiency, and elevated/menopausal levels of gonadotropins) is a cause of female infertility associated with treatment with cytotoxic agents including cyclophosphamide (18). When no cause is identified, the management of infertility includes clomiphene citrate and intra-uterine insemination (IUI), combined gonadotropins and IUI, and *in vitro* fertilisation (IVF) (19). Female patients should be informed and properly advised with regards to the inverse relationship between increasing age and fertility (Table I) and the possible risks of delaying childbearing, including risks for miscarriage, gestational diabetes, pregnancy-induced hypertension, preeclampsia and intrauterine growth restriction (IUGR) (20, 21). Medical options for fertility preservation in female patients who are scheduled to receive gonadotoxic treatment include the use of gonadotropin-releasing hormone (GnRH) agonists and cryopreservation of oocytes, embryo, or ovarian tissue prior to drug administration (22).

– Pregnancy and medical issues

Approximately 25% of women will enter pregnancy with a chronic medical illness. For these women, it is crucial that they are in a quiescent disease state and on the safest possible medication profile. At the same time, however, more harm might be caused to the pregnant woman and the foetus by withholding any necessary treatments. *Pre-eclampsia* is a hypertensive disorder complicating 6-8% of pregnancies. It accounts for 15% of premature deliveries and 18% of maternal deaths (23). Risk factors include history of diabetes, diagnosis of systemic lupus erythematosus (SLE), renal disease, hypertension, thrombophilia, obesity, age extremes (>40 years or <18 years), and primigravida. Treatment includes blood pressure control, seizure prophylaxis, and delivery of the baby as soon as this is feasible. Low-dose aspirin is recommended for pregnancies at risk for pre-eclampsia (23, 24). For pregnant women with *hyperglycemia*, blood glucose control is crucial to prevent maternal and foetal complications. Oral hypoglycemic agents are contraindicated during pregnancy and thus, hyperglycemia should be managed with insulin to keep fasting plasma glucose levels in the range of 65–95 mg/dL and 1-hr post-prandial glucose <140 mg/dL (25).

Menopause is associated with significant physiologic changes particularly in the cardiovascular (progressive increase in LDL-cholesterol levels and heightened risk for coronary heart disease), skeletal (accelerated bone loss), and central nervous system (diminished feeling of well-being, cognition and mood) (26). During the peri- and post-menopausal period, women often (30-50%) experience vasomotor symptoms (hot flushes, chills, sweats), vaginal dryness and sleep disturbances, which vary in severity and gradually resolve over a period

Table I. Number of ovarian follicles and corresponding rates of maximum monthly fecundability, reduction in fertility and infertility rates according to age of women (modified from (112-115).

Age group	Number of ovarian follicles	Maximum monthly fecundability rate [1]	Reduction in fertility [2]	Infertility
19–30 years	79980 ± 15580	48%	6% (for women aged 25-29 years)	7.0–8.9%
31–35 years	25300 ± 4860	35%	14%	14.6%
36–40 years	21450 ± 2650	28%	31%	21.9%
41–45 years	7320 ± 1450	–	–	28.7%
>45 years	1880 ± 310	–	–	–

[1] Probability of clinical pregnancy following intercourse on the most fertile cycle day in women of average fertility; [2] Fertility is defined as the natural capability to produce offspring.

of 5–8 years. These symptoms generally respond well to hormone replacement treatment (HRT: oestrogen plus progestin), which, however, has a complex benefit-to-risk pattern. Specifically, there are possible risks for coronary heart disease (hazard ratio [HR] 1.18) and breast cancer (HR 1.24) (27). The absolute risks of major adverse events per 10,000 women annually taking conjugated equine oestrogens (CEE) plus medroxyprogesterone acetate (MPA) ranged from 12 excess cases in women aged 50–59 years to 38 excess cases in women aged 70–79 years; for women taking CEE alone, there were 19 fewer cases and 51 excess cases in the respective age groups (27). Accordingly, HRT is generally administered for the shortest possible time, and it should be avoided in women with a history of cardiovascular disease, venous thromboembolism, breast or endometrial cancer.

Fertility, family planning and pregnancy in immune-mediated rheumatic diseases: general considerations

Contraception

Although unintended pregnancy may be associated with increased risk for complications in women with RD, many of these patients are not counseled regarding contraceptive use or are counseled against their use based on concerns about the safety of contraceptives. In a study of 86 premenopausal women with SLE aged <45 years, 59% had not received contraceptive counseling in the last year; 22% reported inconsistent contraceptive use, and 53% depended solely on barrier methods, which are the least reliable (28). Main concerns for women with RDs using hormonal contraceptives include the possible risk of disease flare-up and thrombosis. Two randomised controlled trials (RCTs) have shown that combined oestrogen and progoestrogen or progestogen-only contraceptives do not increase the risk for flares in women with quiescent, mild- or stable- active SLE (14, 29, 30). Similarly, a systematic literature review concluded that hormonal contraceptives are unlikely to adversely impact on RA disease activity and progression (31). In women with positive antiphospholipid antibodies – especially if at moderate or high titers or when other thrombotic risk factors coexist – oestrogen-containing contraceptives should be avoided due to increased risk for thromboembolism (30). Additional considerations include the potential interactions of hormonal contraceptives with other medications and the risk for pelvic infection related to use of intrauterine devices in patients receiving immunosuppressive treatment.

BOX 1. Points to consider for fertility preservation and assisted fertility in immune-mediated rheumatic diseases.

- Develop proper counselling regarding fertility and family planning;
- High disease activity may adversely impact on fertility. Aim to have the disease in remission for at least 3 to 6 months before any attempt to conceive;
- With the exception of cyclophosphamide, most anti-rheumatic drugs do not reduce fertility;
- For women of childbearing years, favour therapeutic agents that do not impair fertility and are safe in pregnancy;
- Inform regarding the assisted reproductive methods including improved protocols and "natural cycle" methods;
- Establish a network of reference centres and proper communication between involved specialists.

Fertility and assisted fertility (Box 1)

– Fertility

In patients with RDs, childbearing decisions and the capacity to have children is negatively influenced by both physical (disease activity, damage and treatment) and psychosocial factors. Fertility *per se* might also be impaired in some patients (32-34). In a large population-based cohort study, women with RDs had lower number of births after disease diagnosis (average 1.7) and shorter reproductive period (average age at first baby 26.6 years, at last baby 29.4 years) compared to healthy individuals (average number of births 2.2; mean age at first baby 23.8 years, at last baby 30.8 years) (35). Accordingly, up to >50% of women with RDs reported that the disease affected negatively their decision to have children and their family size (36, 37). On the other hand, 40–50% of all pregnancies will have measurable activity of the underlying illness (38).

– Fertility preservation and assisted fertility

Although cyclophosphamide is broadly used in patients with severe rheumatic manifestations, there are no uniform recommendations for protection against its gonadal toxicity. GnRH analogs are often prescribed but there is weak evidence regarding their gonadoprotective effect (39). Among other options, cryopreservation is not favoured due to the need for prior hormonal stimulation, which may increase the risk for ovarian overstimulation syndrome (20). This complication also develops in approximately 30% of IVF cycles and may mimic flares of the underlying RD. Consequently, it is essential to proceed cautiously and individualise IVF and other assisted fertility procedures (*in vitro* maturation, fertilisation and vitrification of embryos, cryo-conservation of ovarian tissue) to the patient's profile (40-

42). The *natural cycle* approach, which avoids the use of exogenous gonadal hormones, is associated with lower, yet acceptable success rates compared with the ovarian stimulation protocols, depending on the age of the patient, the severity of underlying disease, and the degree of ovarian function impairment (43). Alternatively, patients with autoimmune diseases may undergo *low-dose* IVF with the least amount of necessary medications.

Reproductive health concerns in adolescents with rheumatic diseases

RDs often start at adolescence when most girls would not yet have had an encounter with a gynecologist. Thus, the rheumatologists in care of such patients need also to address reproductive health issues including sexuality, screening for risk-taking behaviour, contraception, protection from sexually-transmitted diseases, and human papilloma virus (HPV) vaccination. Two out of three adolescents with chronic illness engage in risky sexual behaviour because of a false perception of subfertility or as an expression of anger, depression and low self-esteem (44). There is a misconception that adolescents are "*small adults*". However, this population poses unique traits and health issues requiring special handling (45). Table II shows a "checklist" to facilitate the gynecological care of these patients. Although there is a concern about the possible influence of medications used for disease treatment on fertility, there no long-term or controlled data on this issue.

Pregnancy (Box 2)

Most frequent issues in pregnant women with RDs include prematurity (birth before 37 completed weeks of gestation) and IUGR (failure of the foetus to achieve intrinsic growth potential due to impairment of placental function) (46). Diseases with the potential to affect the kidneys, particularly SLE and antiphospholipid syndrome (APS), are more likely to impact negatively on pregnancy outcomes (25, 46). No definitive data exist with regards to long-term psychomotor development of children born from mothers with RDs and/or complicated pregnancies (47).

Table II. Check-list for reproductive health issues.

Reproductive health issues	Suggested actions
Menstrual history	Refer if: a) amenorrhoeic after the age of 15 years; b) >3 menstrual cycles in past year <21 days or >35 days; c) no periods for >3 months; d) periods reported as heavy or lasting longer than 7 days.
Sexual history	If sexually active or over 18: a) ask if smear test has been done; b) offer HPV vaccination for ages between 12-15 years; c) explain the importance of both partners to be informed about infection transmissions.
Contraception	• Ask for contraception methods; • Suggest hormonal contraception if not contraindicated.
Pre-conception or trying for pregnancy	Offer preconception counseling: • Consider previous pregnancy complications; • Current disease activity; • Determine presence of irreversible damage; • Reconsider treatment options with aim to achieve disease remission preconception and suggest timelines and folate supplementation.
Vaginal symptoms	• Ask for vaginal dryness or dyspareunia; • If yes, gynecological referral to rule out autoimmune skin involvement (lichen sclerosus).

Menopause

Menopause-associated hormonal changes might influence the risk and severity of immune-mediated RDs, although direct effects are difficult to show (48, 49). In a RCT of combined HRT versus placebo in 106 women with SLE who were in the menopausal transition or early or late post-menopause, 15 of the 21 evaluated menopausal symptoms were present in ≥50% of women at baseline (50). Over a 2-year follow-up, HRT resulted in more pronounced improvement in vasomotor symptoms compared to placebo, but not in psychological, subjective-somatic, and organic-somatic factor scores (50). Both this and another RCT (51) found that HRT did not significantly affect SLE activity but it increased the risk of thrombosis despite exclusion of patients with antiphospholipid antibodies (in the latter study) and history of thrombosis. In women with RA, HRT has demonstrated anti-osteoporotic effects without a worsening in disease activity (15). Together, HRT can be considered for short-term (up to 1–2 years) management of severe menopausal symptoms after assessment of patient's cardiovascular and thrombotic risk profile.

Fertility, family planning and pregnancy in individual rheumatic diseases

Systemic lupus erythematosus – Fertility

SLE can result in primary infertility in cases of: a) amenorrhoea accompanying severe lupus flares; b) moderate or

BOX 2. Points to consider for family planning and pregnancy.

- Discuss appropriate contraceptive methods;
- Oral contraceptives are not likely to aggravate disease activity;
- Oestrogen-based contraceptives are contraindicated in cases of thrombophilia (including the presence of antiphospholipid antibodies at moderate or high titers), uncontrolled hypertension, and renal involvement with nephrotic level proteinuria;
- Plan/counsel before pregnancy. Discontinue any unsafe drugs, control disease activity, and perform appropriate laboratory work-up;
- Pregnancy may affect the natural history of the disease. In SLE, if conception occurs at the time of quiescent disease, the risk of disease flare is low. In inflammatory arthritis, peripheral disease may improve with pregnancy.

severe renal insufficiency (glomerular filtration rate [GFR] <60 ml/min); c) ovarian failure secondary to cyclophosphamide therapy; d) sustained use of non-steroid anti-inflammatory drugs (NSAIDs) which may inhibit rupture of the follicle (52).

– Flares

There is a 5–10% risk for disease exacerbation, usually of mild-to-moderate severity, during pregnancy and postpartum. Risk factors include: a) active SLE during the 6 months prior to conception; b) multiple flares prior to conception; c) discontinuation of hydroxychloroquine; d) history of SLE nephritis (20–30% relapse rate) (53). New-onset SLE during pregnancy has been associated with more severe disease and higher prevalence of renal and haematological involvement compared with patients without pregnancy (54).

– Pregnancy outcome

There is an increased risk for obstetrical and medical complications including the need for Caesarean section, pre-eclampsia, preterm labour, IUGR, foetal mortality, and postpartum haemorrhage (55, 56). In a meta-analysis of more than 2,200 lupus pregnancies, active nephritis correlated significantly with premature birth and hypertension. Past history of nephritis was also associated with hypertension and pre-eclampsia (57). In a prospective study of 203 lupus nephritis patients, high disease activity during pregnancy was associated with a 3-fold increase in perinatal mortality, 10% reduction in live births, and a 50% rate of prematurity (58). Pre-eclampsia, can be difficult to distinguish from a nephritis flare. Levels of serum complement, anti-dsDNA antibodies and urine sediment analysis guide the differential diagnosis (59).

– Neonatal lupus (NL)

Offsprings of women with positive anti-Ro/anti-La antibodies carry a small risk to develop NL syndrome; the cutaneous form is more frequent (up to 16% (60), typically 3–5%) than the cardiac one (1–2%) (60, 61). Recurrence rate of cardiac NL approximates 17%, while having a child with cutaneous NL is associated with 6- to 10-fold increased risk for having subsequent children with cardiac NL (62, 63). In mothers with connective tissue disease and anti-Ro antibodies hydroxycholoquine may decrease the risk of first and recurrent foetal development of cardiac-NL by 54–86% (64-67).

Antiphospholipid antibody syndrome

APS-associated pregnancy morbidity includes the following: a) ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical or hormonal abnormalities, and paternal and maternal chromosomal causes excluded; b) ≥1 deaths of a foetus at or beyond the 10th week of gestation, with healthy foetal morphology documented by ultrasound or by direct examination of the foetus; c) ≥1 premature births of a morphologically healthy newborn baby before the 34th week of gestation because of eclampsia or severe pre-eclampsia (68). APS is diagnosed when at least one of the above clinical findings is present in association with the detection of at least one of the antiphospholipid antibodies (anticardiolipin antibodies, anti-β2-GPI antibodies, lupus anticoagulant) (68). Additional pregnancy complications in APS include (69): a) placental insufficiency, preterm birth (32-65%); b) oligohydramnios; c) HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low platelet count); d) vessel thrombosis. Risk factors for pregnancy failure include: a) co-existing SLE or other autoimmune disease; b) prior history of both thrombosis and pregnancy morbidity; c) positive lupus anticoagulant; d) triple antiphospholipid antibodies positivity (70, 71). Table III outlines the suggested management of APS during pregnancy (72-76).

Rheumatoid arthritis (RA)

In RA, 50–68% of patients improve during pregnancy and 25% reach remission during the 3rd trimester of pregnancy, although many may relapse within 3 months after delivery (77). Maternal RA is associated with modestly increased risk (7.8–13.6%) for obstetrical and foetal complications such as IUGR, prematurity, small for gestation age infants, and mild pre-eclampsia (78-81). Vaginal bleeding, elective cesarean section, and preterm delivery were reported more frequently among RA patients than the reference population both in first (ORs 1.5–2.0) and in subsequent pregnancies (ORs 1.4–1.5) (82). Higher disease activity and C-reactive protein levels have been correlated with increased risk for prematurity and low birth weight (83).

Juvenile idiopathic arthritis (JIA)

Adult JIA patients treated with synthetic and/or biological DMARDs constitute approximately 50% of all patients diagnosed in childhood and many of them have or will develop polyarticular disease. JIA patients may be at risk for reduced reproductive capacity and fertility as a consequence of their chronic inflammatory condition or the administered medications (adjusted relative fertility rate is 0.84 compared with the normal population) (84, 85). In an observational study of 78 births from 50 women with JIA, 53 (68%) were delivered by either Caesarean section (51%) or instrumental delivery (17%) (86). Women with JIA had significantly higher rates of pre-eclampsia, postpartum haemorrhage and severe maternal morbidity, and infants from mothers with JIA were more likely to be born prematurely (86).

Ankylosing spondylitis (AS)

Fertility in women with AS is generally unaffected except for cases of severe hip arthritis causing pelvic "mechanical" issues. During pregnancy, patients with AS tend to follow variable course; 20–50%, especially those associated with small joints disease, psoriasis and ulcerative colitis, experience improvement in disease activity, which, however, may deteriorate at later stages (87, 88). Flares are common during the first 3 months post-partum. A retrospective study in women with chronic inflammatory arthritides, including AS, reported increased risk for preterm deliveries, small for gestational age infants, lower mean birth weight and higher perinatal mortality (80).

Systemic sclerosis (SSc)

Women with SSc have a high likelihood

for a successful pregnancy but there is increased risk for preterm delivery (OR 2.5), severe preterm delivery (<34 weeks of gestation) (OR 2.2), IUGR (OR 4.4) and very low birth-weight (OR 4.9) (89). During pregnancy the disease remains stable, Raynaud's phenomenon tends to improve, yet gastro-oesophageal reflux may worsen.

Renal crisis is the most severe complication in pregnant women with SSc, particularly for those with early diffuse SSc, and must be differentiated from pre-elampsia. Pregnancy is contraindicated in cases of: a) severe cardiomyopathy (left ventricle ejection fraction <30%); b) moderate-to-severe pulmonary arterial hypertension (stage III); c) reduced lung volume (forced vital capacity <50%); d) renal insufficiency (serum creatinine [SCr] >2.9 mg/dL; in woman with SCr in the range 1.5–2.9 mg/dL there is 40% risk for decline in GFR by the end of pregnancy), and; d) rapid disease progression (90, 91).

Inflammatory myopathies (myositis, dermatomyositis) (IM)

Only 14% of IM cases develop during childbearing years. Therefore, little is known regarding the impact of the disease on fertility, although a reduction in parity is expected due to the chronic nature of the disease and the frequent use of immunosuppressives. A small case-control study has reported delayed menarche with normal cycles and low follicular reserve in juvenile dermatomyositis patients (92). A retrospective study of 78 patients found no major effect of the pregnancy on disease activity. The prognosis of pregnancy depends on the activity of maternal disease. Thus, in patients with quiescent disease, there is low risk for maternal and foetal complications. Conversely, poor foetal outcome tends to occur in patients who have active disease or disease onset during pregnancy, especially during the first trimester, in which cases foetal loss rates range 43–57% (93-95).

Immunosuppressive drug use in pregnancy and breast-feeding

(Box 3)

Data on the safety and efficacy of anti-rheumatic drugs during pregnancy are scarce and originate mostly from animal studies, case reports, and observational human studies (reviewed in (96, 97)). Nonetheless, there is a need for informed decisions, based on the best available data, so that an individualised treatment strategy can be planned (98). In a large Norwegian registry of >150,000 pregnancies, approximately 1% of women received anti-rheumatic drugs three months before and during pregnancy and 0.8% of fathers received anti-rheumatic drugs till the time of conception (99). A total of 723 individuals had NSAIDs, 633 prednisolone, 119 sulfasalazine, 101 azathioprine, 58 hydroxychloroquine, 37 etanercept, eight methotrexate, two leflunomide, and three adalumimab (99). None of the children whose mothers had received anti-rheumatic drugs were reported to be born with a major malformation. In women with autoimmune diseases, use of DMARDs does not significantly increase the risk for pre-eclampsia (100).

Methotrexate

Although classified as teratogen (FDA category X), there are only limited data about its safety in pregnancy. In a systematic review of 100 patients with RA, exposure to methotrexate at doses 5–25 mg/week from conception till the first trimester of pregnancy was associated with miscarriage and birth defects rates comparable to those in the general population (101). Nonetheless, the current recommendation is to discontinue methotrexate at least 3 months before conception.

Table III. Management of APS during pregnancy.

Planning and monitoring

- Antenatal surveillance for complications, foetal ultrasound for foetal growth assessment at 18-24 weeks of gestation, assessment of hypertension and proteinuria (after 20 weeks of gestation).
- Complete aPL profile before planning pregnancy (mainly in SLE).

Management

- The optimal management for obstetric APS is currently unknown. Use anti-thrombotic treatment as soon as pregnancy is confirmed.
- Warfarin should be switched to heparin, as warfarin must be avoided in the first trimester. Warfarin may be used in 2nd-3rd trimesters only in women who develop thrombosis - especially arterial thrombosis - during pregnancy despite combination treatment. Switch to heparin at least 15 days before the planned delivery time.
- Current management for the prevention of pregnancy loss in patients with positive aPL
  - Aspirin (in individuals with positive aPL but no history of thrombosis or pregnancy complications). Combination of aspirin and heparin (unfractioned or LMWH) in patients with history of thrombosis and/or pregnancy morbidity) results in less pregnancy loss and higher live birth rates
  - In selected cases, prednisolone or intravenous immunoglobulin can be considered
- Increased risk of thrombosis during postpartum. Anticoagulant coverage is critical if there is a history of thrombosis. However, there is currently no international consensus on long-term prophylaxis if there is no history of thrombosis.

BOX 3. Points to consider for the use of immunosuppressive drugs during pregnancy and breast-feeding.

- Know your patients' expectations; all patients should have appropriate counseling and planning.
- Use this information in your therapeutic strategy. Have a holistic approach.
- Strive for remission before conception and during pregnancy. In the majority of patients, maintaining remission with medical treatment outweighs the potential risk for adverse drug effects.
- Many drugs can be used during pregnancy. However, methotrexate, leflunomide and cyclophosphamide are contraindicated.
- When using monoclonal antibodies as biological agents, beware of the placental transfer and consequences for the newborn.
- There is no evidence that vaccination with non-live vaccines of children exposed to anti-rheumatic drugs in utero is affected, or associated with adverse effects. Vaccination with live vaccines should be done when there is no detectable anti-TNF in the blood (in most cases in the second half of the first year).
- Glucocorticoids, azathioprine, hydroxychloroquine and sulfasalazine are generally safe during pregnancy and breastfeeding. There are limited data on breastfeeding and use of biologics.

Table IV. Safety of biological anti-rheumatic drugs during pregnancy.

- Transfer of IgG through the placenta does occur after the 1st trimester and is an active process mediated by placental Fc receptors (116).
- Infliximab (INF) and adalimumab (ADA) are found in cord blood in the 2nd and 3rd trimester. Active INF and ADA transport across the placenta can be detected at birth and for up to 6 months thereafter.
- Due to the absence of the Fc fragment, certolizumab (CZP) has the lowest level of placental transfer, based on levels measured in cord blood and infants at birth due to lack of active transport in the absence of Fc fragment (117).
- Patients (mostly with inflammatory bowel disease) exposed to anti-TNF agents at conception or during the 1st trimester have good outcomes.
- In IBD, discontinuation of anti-TNF therapy (INF, ADA) appears to be safe for pregnant women with quiescent disease. However, these drugs are still detected in cord blood samples. In every day practice, treatment is usually discontinued around gestational week 22-23, and if there is a relapse steroids are used; however, this is not an evidence-based approach (117).
- Exposure to rituximab at conception or during pregnancy has been associated with increased rates of pre-term deliveries and spontaneous miscarriages, although these findings could be confounded by the severity of the underlying disease and/or the concomitant use of potentially hazardous drugs.
- Rituximab can cross the placenta during the 2nd and 3rd trimester and cause transient depletion of foetal and neonatal B lymphocytes therefore increasing the risk for infection.
- Data anakinra, abatacept, tocilizumab and belimumab, are scarce.

Table V. Suggested future actions.

- Need for recommendations for family planning and pregnancy in patients with rheumatic diseases.
- Inclusion of family planning and pregnancy in the rheumatology training curriculum.
- Create a slide collection of the meeting presentations to be used for educational purposes.
- Prepare a short, comprehensive booklet for physicians and patients with "ABCs" on women's health, family planning and pregnancy in immunological diseases.
- A "check-list" to be prepared by gynecologists and shared with other involved specialties to help in the discussion with their patients about the topic.
- Form working groups within National or European Societies.
- Initiate workshops in each country (use the teaching slide set that will be created)
- Include the topic in National Congresses of each specialty; Invite and involve experts from the different fields.
- Use web channels/webcasting to increase awareness, and for educational purposes, e.g. on-line training modules.
- Conduct a survey in all rheumatology centres in the countries gathering information on the topic (pregnancy issues, fertility, pregnancy planning, level of awareness, needs), and understanding of areas where there is a need to focus and improve.

Leflunomide

Embryotoxicity and teratogenicity has been demonstrated with the drug in animals but not in humans. In 64 pregnant women with RA who were exposed to leflunomide during pregnancy (95% of whom received also cholestyramine), the overall rate of major structural defects was similar to the 3-4% rate expected in the general population (102). In another study of 45 pregnant women, all 16 of the pregnancies with leflunomide exposure during pregnancy and 27 out of 29 of the pregnancies with exposure prior to conception resulted in liveborn infants (103). There were 2 infants with major malformations from mothers who were exposed during pregnancy, and no malformations reported in the preconception group. The standard recommendation is to discontinue the drug two years before conception, or follow a rapid washout procedure with cholestyramine.

Biologic agents

Most data are available for anti-TNF agents, including extensive experience in inflammatory bowel diseases (more than RA) (104-108) (see also Table IV). Exposure to anti-TNF therapies, especially if this occurs at the time of conception or during the first trimester, is generally not associated with increased risk of adverse pregnancy and foetal outcomes (including foetal malformations). During the 2nd and 3rd trimester, monoclonal antibodies may undergo transplacental transfer whereas fusion proteins containing the Fc part of IgG or modified antibodies with no Fc part show minimal passage. There are increasing reports of pregnancies in women exposed to rituximab (anti-CD20 mab) prior to or during pregnancy (109, 110). In an analysis of 153 pregnancies from the rituximab global safety database which included mothers with lymphoma, immune cytopenias and other autoimmune diseases, 60% resulted in live births (76% full-term deliveries) and 21% in first trimester miscarriages (111), although these findings could be confounded by the severity of the underlying disease and/or the concomitant use of potentially hazardous drugs. Exposure to rituximab during the 2nd and 3rd trimester results in transient B-cell lymphopenia in the child but the long-term effects on immune system development remain unknown. Data on other biologic therapies, including anakinra, abatacept, tocilizumab and belimumab, are scarce.

Breast-feeding

Glucocorticoids, azathioprine, hydroxychroquine, and sulfasalazine are generally considered as safe. There is limited data on breastfeeding and the use of biologics.

Future actions

The panel discussed different levels of actions to increase awareness in women's health, fertility, family planning and pregnancy, which are summarised in Table V.

Conclusions

Rheumatologists are eager to support the decision of women with RDs to raise a family by providing the best care for both them and their offspring. However, a change in the "mind-set" and practice guidelines must occur, confronting women's health issues and not overlooking them in the management of chronic RDs in female patients, shifting the attention from post-conception to pre-conception; from the disease to the patient; from single physician approach to multidisciplinary approach; and from avoiding pregnancy to embracing pregnancy.

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