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Infertility in women with systemic autoimmune diseases

Jamilya Khizroeva, MD, Professor of Obstetric and Gynecology [a], Cecilia Nalli, MD, Consultant Rheumatologist [b], Victoria Bitsadze, MD, Professor of Obstetric and Gynecology [a], Andrea Lojacono, MD, Gynecologist [c], Sonia Zatti, MD, Gynecologist [c], Laura Andreoli, MD, PhD, Professor of Rheumatology [b], Angela Tincani, MD, Professor of Rheumatology [b, d, *], Yehuda Shoenfeld, MD, FRCP, Ma, ACR, Professor of Rheumatology [d, e, f], Alexander Makatsariya, MD, Professor of Obstetric and Gynecology [a]

[a] *Department of Obstetrics and Gynecology of I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia*
[b] *Rheumatology and Immunology Unit, Department of Clinical and Experimental Sciences, University of Brescia, ASST Spedali Civili Brescia, Italy*
[c] *Obstetric and Gynecology Unit, Department of Clinical and Experimental Science, University of Brescia, ASST Spedali Civili Brescia, Italy*
[d] *I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Russia*
[e] *Department of Medicine 'B', The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Ramat Gan, Israel*
[f] *Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv-Yafo, Israel*

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Infertility consists by definition in" failure to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse" while the term subfertility means a delay to achieve pregnancy. Several factors can contribute to infertility or subfertility in patients with systemic autoimmune diseases. The association of systemic autoimmune conditions with endometriosis, celiac disease and thyroid autoimmunity that are well known

* Corresponding author. Rheumatology and Clinical Immunology Unit, Piazzale Spedali Civili 1, 25123, Brescia, Italy.
E-mail address: angela.tincani@unibs.it (A. Tincani).

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causes of infertility and/or subfertility need to be taken in consideration when difficulties in the onset of pregnancy is reported. The majority of the used antirheumatic drugs do not interfere with fertility. However, the use of cyclophosphamide, limited to severe disease, can provoke premature ovarian failure; to preserve fertility a preventive treatment is available. Nonsteroidal anti-inflammatory drugs can cause temporary infertility and corticosteroids are associated to a prolonged time to pregnancy in some rheumatic diseases. Data on the association of antiphospholipid antibodies (aPL) with infertility are still debated but in general an increased rate of aPL is described patients undergoing medically assisted reproductive techniques. In systemic lupus erythematosus aPL and other autoantibodies (i.e. antioocytes) can contribute to the infertility of some patients. Subfertility, rather than infertility, is observed in patients with rheumatoid arthritis; the particular physical conditions of these women can also account for this. Physicians should not forget the patients' age, that is mandatory in order to preserve their chance to have children.

Introduction: definition of infertility and subfertility

Autoimmune diseases, infertility and adverse pregnancy outcomes are the subject of close attention and increased interest of various researchers. The close relationship between autoimmune pathology and adverse pregnancy outcome have been confirmed in several studies but very few reports have linked autoimmune diseases with infertility. Currently the World Health Organization (WHO) defines infertility as a disability and "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse". The primary factors that impair the chances of pregnancy in infertile women are female factors such as chronic anovulation, blocked fallopian tubes or endometriosis or male factors such as sperm abnormalities, obstructions, or ejaculatory dysfunction or it can be due to unexplained factors.

The term subfertility means a delay in conceiving. This can be due to other factors such as older age, endometriosis, diabetes mellitus, ovarian dysfunction, polycystic ovarian syndrome, and previous infection of genital tract [1].

The terms subfertility and infertility are often used interchangeably, but they are not the same. Subfertile women have the possibility of conceiving naturally, but it takes longer than average. In infertility, the probability of conceiving without medical intervention is unlikely.

With « normal » fertility the probability of becoming pregnant is about 15–20 percent per month with timely intercourse in the fertile days. Eighty percent of women under age 30 years become pregnant within the first six cycles even with intercourse during the most fertile phase. The monthly fecundity varies between 30 and 35%. After six unsuccessful cycles, about 20% of couples are considered at least slightly subfertile. Half of these subfertile couples will conceive naturally in the next six cycles – before the definition of infertility sets in. After 12 unsuccessful cycles, 10% of remained unpregnant couples are considered at least moderately or seriously subfertile couples. Fifty percent of these couples will conceive spontaneously in the next 36 months, the remaining are complete infertile. After 48 months, about 5% couples are considered as complete infertile couples.

For women after the age of 35 years, the chance of being pregnant decreases even more rapidly. With age, the cumulative possibilities of conceiving decline because of heterogeneity in the fecundity increases due to a higher proportion of infertile couples [1].

Besides problems related to the specific disease and its systemic activity, some underlying health conditions of mother can contribute to subfertility and women with autoimmune diseases are more

likely to have premature ovarian insufficiency that can compromise their chances of getting pregnant [2]. Autoimmunity in infertile women may play a major role in fertilization, implantation and placental development. The pathogenic mechanisms that link autoimmunity and infertility remain uncertain and speculative due to the lack of controlled well designed studies. Most existent data we know through scarce information from experimental animal models or from uncontrolled studies with heterogeneous groups of patients with different types of infertility. Conclusions of all the studies are in favor of increased prevalence of women with autoimmune disorders attending infertility clinics. The association of thyroid autoimmunity with reproductive failures is the most studied and this association arose not a chance. A possible mechanism for this relationship is the fact that the presence of anti-thyroid antibodies reflects the generalized activation of the immune system and enhances the auto-immune process against the human reproduction. Prevalence of thyroid diseases is significantly higher among infertile women compared with fertile women, especially among those whose infertility is caused by endometriosis or ovarian dysfunction.

Altogether, several patients affected by systemic autoimmune conditions can report subfertility or infertility. Since in the same population some women also experience recurrent pregnancy loss, the overall fecundity results significantly decreased. This phenomenon greatly impacts on the patient's life expectance supporting the need to analyze all its possible different causes. The following lines will report what is known about infertility in autoimmune rheumatic diseases.

The main reasons of infertility in women with systemic autoimmune diseases

Patients with systemic autoimmune diseases have less children than expected in the general population. Some of these women do not have children at all, some others report a prolonged time to pregnancy resulting in smaller family size than they expected [3].

Certainly, in this population, the number of children can be also related to the frequently associated organ specific autoimmune disease (i.e.: thyroiditis or celiac disease), to endometriosis that is known to have an increased rate of occurrence in women with systemic autoimmune diseases or to the well-known increased rate of adverse pregnancy outcome such as miscarriages and fetal losses. However, many other factors should be taken into consideration. The disease itself and the musculoskeletal limitations linked to it can impair sexual function and psychologically impact on woman desire [4].

In addition, in several systemic autoimmune diseases, also the poor body image, the related poor self-esteem and depression can influence the personal and sexual relationships of these women [5,6].

The age is not a negligible influence that can also be attribute. Nowadays the general attitude is to postpone the pregnancy because of personal problems of the women. In patients with systemic autoimmune diseases there are several other reasons to postpone pregnancy. If the disease is diagnosed during childbearing age, pregnancy should be postponed until the disease activity results under complete control and the treatment is stable without the inclusion of teratogenic drugs [7]. It is not clear if and when the gonads can be directly affected by the inflammation related to disease activity causing a real reduction in the fertility rate. On the other hand, some of the drugs administered as a standard of care may impair the gonads function at different levels causing transient or permanent infertility.

The role of drugs in infertility

When addressing fertility issues among patients with autoimmune conditions, we also have to consider that some medications commonly prescribed in these settings might affect the reproductive function. Although in general not much has been published on the effect of antirheumatic drugs on women fertility, we will summarize below the available information.

Non-steroidal anti-inflammatory drugs (NSAIDs) represent the most employed and sometimes self-administered medications in patients suffering for joint pains. The two categories of NSAIDs, selective and non-selective cyclooxygenase inhibitors, preventing prostaglandins synthesis, can cause the luteinized unruptured follicle syndrome (LUF) which consists in the lack of oocyte release and therefore infertility [8]. The LUF syndrome was found significantly associated to the general use of NSAIDs but its rate of occurrence was significantly higher in patients taking the selective

cyclooxygenase 2 inhibitors [8]. It is of note that LUF syndrome cause only a transient infertility that can be reverted at the drugs withdrawal.

When used for chronic or acute treatments, corticosteroids (CSs) can influence ovarian function causing menstrual disturbance and infertility. This can happen through CSs influence on the hypothalamo-pituitary-gonadal axis causing impairment in the production of follicle stimulating hormone belonging to the group of luteinizing hormones [8]. However, CSs can also impair the ovarian function directly binding their specific receptors on cells surface. In patients with rheumatoid arthritis (RA) assuming chronic CSs treatment, a prolonged time to pregnancy was observed as manifestation of their subfertility state, although this effect was not shown in patients affected by systemic lupus erythematosus (SLE) undergoing analogue treatment [9–11].

Cyclophosphamide (CTX) is an alkylating drug that is used, although today less frequently, in patients with severe organ impairment, such as those with glomerulonephritis or central nervous system involvement within the spectrum of systemic lupus erythematosus. CTX is reported to deplete ovarian oocytes and to induce ovarian failure. The gonadotoxic effect in female patients is related to the cumulative dosage of drug and to the women age. A cumulative dose of 10 g or more is generally considered a significant risk factor for premature ovarian failure [7]. However, lower doses can also cause premature menopause when the patient is 35 (or more) years old. A recent paper shows that SLE patients that undergo sequential CTX and immunosuppressive treatment had significant lower levels of Anti Mullerian Hormone (AMH) as expression of the reduction of ovarian reserve [12]. The use of gonadotropin-releasing hormone analogue, causing a temporary artificial menopause, can preserve ovarian function even in patients receiving intravenous CTX pulse treatment. It is of note that in these patients, probably because of the limited time of exposure, is not observed an increased risk of cardiovascular disease, stroke or osteoporosis like it is reported after some years of natural menopause [13]. Other commonly used anti-rheumatic drugs such as sulfasalazine, azathioprine, cyclosporine and tacrolimus as well as Tumor Necrosis Factor inhibitors do not cause women infertility [2]. Methotrexate, a drug widely used in rheumatic diseases, particularly in rheumatoid arthritis, is also used by obstetricians to interrupt ectopic pregnancies and it is known for increasing the rate of miscarriages when pregnancy are exposed in the first trimester [14]. Interestingly, no effect on the ovarian reserve or on the levels of AMH were observed in patients after high dose methotrexate administration [15].

Thyroid disease

Autoimmune thyroid disease is defined by positive thyroid autoantibodies (abs), particularly thyroid peroxidase (TPO) auto-abs and anti-thyroglobulin (TG) auto-abs. It is a very common condition in women of childbearing age with a prevalence of 5–15% and can lead to either an overactive (Graves' disease, hyperthyroidism) or underactive thyroid (Hashimoto's thyroiditis, hypothyroidism). Autoimmune thyroid antibodies are 5–10 times more common in women than in men, and can often occur without thyroid dysfunction, and therefore remain undiagnosed. The effects of estrogen in triggering an autoimmune process, genetic factors, and possibly X chromosome abnormalities can potentially explain the predominance of thyroid antibodies in women [16]. Autoimmune thyroid pathology has been shown to be more common in women seeking treatment for infertility [17].

Iodine is an essential component for thyroid hormone synthesis. In the past, many countries including population of Western Europe lived in areas of iodine deficiency that became a significant public health issue. The recommended dose for iodine intake during pregnancy consists 250 μg/day.

The adequate level of circulating thyroid hormones is of a primary importance for the female reproductive system. Thyroid dysfunction itself interferes with normal ovarian function. The thyroid gland continuously interacts with hypothalamus–pituitary axis [18]. Ovarian surface epithelium and oocytes of follicles contain thyroid-stimulating hormone (TSH)-receptor and thyroid hormones receptor (TRα1 and TRβ1). TSH receptors and RNA messenger for TRα1, TRα2, and TRβ1 were also found in endometrial biopsy samples. RNA messenger for all receptors is present in ovarian epithelium. Granulosa cells expressed transcripts for deiodinases types 2 and 3, but not type 1, indicating the possibility of conversion of peripheral thyroid hormone thyroxin (T4). Triiodthyronine (T3) modulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) action; multiple T3 binding sites also have been identified in granulosa cells, stromal cells and oocytes [19,20].

Non-adequate delivery of T3 to granulosa and stromal cells may interrupt normal functioning of female reproduction [21]. Granulosa cells stimulated with TSH demonstrated an increase in adenylate cyclase-cAMP, indicating activation through TSH receptors in ovaries and endometrium. The role of these receptors needs further studies but it's obvious that thyroid system relates to different aspects of human reproduction. Hypothyroidism influences ovarian function by decreasing levels of sex-hormone-binding globulin and increasing the secretion of prolactin: forty-six percent of women with hypothyroidism are hyperprolactinemia. Hyperprolactinemia impairs pulsatile secretion of gonadotrophin-releasing hormone (GnRH) and causes ovulatory dysfunctions from inadequate corpus luteal progesterone secretion when TSH is mildly elevated to oligomenorrhea or amenorrhea and polycystic ovaries when levels are high. Highly elevated prolactin decreases the levels of estrogens in women and causes short luteal phase. Low progesterone level further cause failure to sustain a fertilized egg and may lead to loss of early pregnancy [22]. Thyroid hormones are involved in production of estrogens and progesterone, non-adequate level of which can cause infertility independently from hyperprolactinemia. Thyroid autoimmunity is significantly higher in women with infertility especially in those with endometriosis and the polycystic ovarian syndrome.

Infertile women undergoing *in vitro* fertilization protocol are faced with excessive estrogen concentrations, which in turn can severely impair thyroid function. This estrogen dominance stimulates the liver to produce a larger amount of thyroid binding globulin (TBG), which bind the thyroid hormones and decreases the available amount of hormones that can be utilized by the cells. In women without thyroid autoimmune diseases these changes are transient, but in women with thyroid autoimmunity estrogen dominance can lead to thyroid abnormal function throughout all further pregnancy and symptoms of clinical hypothyroidism can be present. Thyroid autoimmunity in pregnant women does not interfere with embryo implantation but carries an increased risk for miscarriage in the first trimester, compromises fetal neuropsychological development and increases the risk of preterm delivery, small for gestational age infants, fetal distress in labor, and probably gestation-induced hypertension and placental abruption [23]. Therapy with thyroxine in hypothyroid women can improve pregnancy outcome and avoids unnecessary assisted reproductive technologies.

Thyroid dysfunction is quite common in patients with other autoimmune diseases suggesting a shared immunogenetic background. In addition to organ-specific autoantibodies, in patients with thyroid autoimmunity, can also be directed to other components of the immune system. Autoimmune thyroid diseases are associated with pernicious anemia, vitiligo, myasthenia gravis, celiac diseases, chronic autoimmune gastritis, autoimmune damage to the adrenal gland, gluten enteropathy, rheumatoid arthritis, or lupus erythematosus. The role of these antibodies is currently being intensively investigated [24]. A very interesting question is the association of thyroid pathology with antiphospholipid antibodies. This finding is not accidental. After all, both autoimmune thyroid disease and the presence of aPL are a reflection of the generalized activation of the autoimmune process, the severity of which is exacerbated by a combination of autoimmune disorders. The presence of antithyroid antibodies itself is an unfavorable factor for the onset and preservation of pregnancy: with the simultaneous presence of aPL, the autoimmune process directed against the reproductive system is enhanced.

In this regard, also the increased prevalence of combination of thyroid autoimmunity with endometriosis is very interesting and noteworthy [25].

Celiac disease

In recent years, there has been an increased interest of impaired fertility in patients with celiac disease. Celiac disease, sometimes called celiac sprue or gluten-sensitive enteropathy, is a serious autoimmune disease that occurs in genetically predisposed people where the ingestion of gluten leads to damage in the small intestine. It affects around 1% in many developed countries. It is an immune reaction to eating gluten, a protein found in foods made with wheat, barley, rye, and triticale. This hypersensitivity reaction to gluten destroys the villi and prevents intestine's lining from proper absorbing nutrients from food (malabsorption). Tissue transglutaminase (tTG) is the autoantigen against which the abnormal immune response is directed and two main autoantibodies, anti-endomysium and anti-tTG, are currently the most useful serological markers to screen for the disease.

Celiac disease has a variety of symptoms, which range from diarrhea, fatigue, weight loss, bloating to iron deficiency anemia. Eventually, this may lead to malnourishment, loss of bone density, even to neurological diseases, or certain cancers. A strict gluten-free diet can help to manage symptoms and promote intestinal healing. In a 1999 study, Ventura, et al. found that for people with celiac disease, the later the age of diagnosis, and the greater the chance of developing another autoimmune disorder. Despite the generally accepted belief that celiac is a digestive illness, it is a systemic disease that affects all the body. Some studies have found that women with undiagnosed celiac disease may have an increased risk of infertility. Of particular interest has been the effect of celiac disease on fertility and pregnancy. It's not clear why women with undiagnosed or untreated celiac disease suffer from infertility. Possibly suggested mechanisms were associated with the malnutrition or immune-mediated mechanisms. Modern possible pathogenetic factors that may alter placental function and cause adverse pregnancy outcomes include maternal celiac disease autoantibodies binding to placental transglutaminase, and genetic mutations that may facilitate microthrombus formation. Recent studies estimating the role of genetic thrombophilia suggested that the 4G variant of the plasminogen activator inhibitor-1 gene was more frequent in the group of celiac women with early miscarriages. It was suggested that the intestinal injury, endothelial dysfunction, platelet hyperaggregation and enhanced apoptosis recently described in celiac disease are at the origin of the increased exposure of phospholipids or new epitopes representing autoantigens. Autoantibodies directed to these antigens may play a pathogenic role in the microthrombosis associated with celiac disease and represent markers for potential anticoagulant preventive therapy. Additional studies are needed to explore these mechanisms. However, after diagnosis of celiac disease and treatment with a gluten-free diet and preventive anticoagulants, some markers of infertility and miscarriage rates may be corrected.

Endometriosis

Endometriosis is a chronic and the most common (after fibroid) gynecological disorder affecting up to 10% of reproductive age women. Endometriosis is seen in 1 in 10 women of reproductive age especially in 30s and 40s years. It's diagnosed when there is the growth of endometrial like tissue outside the uterus lining. The exact etiology is still unknown and is under-explored. The most widely accepted theory for endometriosis etiology is the retrograde menstruation and abdominal dissemination of endometrial cells through the fallopian tubes [26]. Retrograde menstrual dissemination is present in many women but not all of them develop endometriosis. There is abundant evidence that endometriosis is associated with a variety of immunological changes. Current hypotheses of endometriosis pathogenesis include altered immunity and inflammatory responses in genetically susceptible women [27]. In healthy organism a general inflammatory response clears the peritoneal cavity from the endometrial implants. Modern interpretation of reflux menstruation suggests aberrations in the immune system of patients, preventing clearance of ectopic endometrial cells and allowing for implantation of these cells outside the uterus. Defective immune control creates an inflammatory response that may promote implantation and proliferation of endometriosis [28]. Studies have demonstrated an escape of cells from immune surveillance. Abnormalities of almost all types of immune cells have been identified, including increased levels of peritoneal neutrophils and macrophages, reduced cytotoxic activity of natural killer cells, and aberrant numbers of T and B lymphocytes that aid endometriotic cells growth, maintenance, invasion, and angiogenesis [29,30]. Symptoms of endometriosis include pelvic pain, painful periods, painful intercourse, and subfertility and altogether can affect the quality of woman's life. Women may also have asymptomatic endometriosis, so the actual incidence of disease should be much greater. It is an estrogen-dependent condition. Endometriosis implants respond to estrogen fluctuations and may grow and bleed like the endometrial lining does every month during periods. It causes the irritation and inflammation of the surrounding tissue and, in more advancing cases, leads to scarring and adhesion formation. The bleeding, the inflammation, and the scarring cause pain, especially associated with menstrual days. Swelling and scarring of tissue can involve all surrounding organs. Endometriosis implants can block the fallopian tubes. About 40% of infertile women have endometriosis. In addition to adhesion formation and the development of tubal and abdominal causes of infertility, inflammation from endometriosis may damage the sperm or the egg and can interferes with their movement through the fallopian tubes. Endometriosis requires a

personalized management with the treatment depending on symptoms, age and desire of pregnancy. The current therapeutic strategies include medical, surgical, or a combination of these approaches. For many women, adequate treatment requires a combination of treatments given over their lifetime.

Endometriosis requires a multidisciplinary team approach. The results from major medical databases and their published analysis demonstrate the association between endometriosis and autoimmune diseases. Five of the 26 studies provided high-quality evidence, and among these, four supported a statistically significant association between endometriosis and at least one autoimmune disease: systemic lupus erythematosus, Sjögren's syndrome (SS), rheumatoid arthritis, celiac disease, multiple sclerosis (MS), inflammatory bowel disease (IBD). It's unknown whether endometriosis is a risk factor for, or a consequence of, autoimmune diseases and whether these two types of disorders share pathophysiological mechanisms even if they arise independently. Further studies are needed before we will get answers to this question [31].

Antiphospholipid syndrome and systemic lupus erythematosus

Anti-phospholipid syndrome (APS) is a systemic autoimmune condition characterized by arterial as well as venous thrombosis, and/or pregnancy loss or complications, in the presence of persistently positive antiphospholipid antibodies detected at least with one test. The tests formally adopted to detect aPL and included in the classification criteria are lupus anticoagulant (LA, coagulation test), anticardiolipin antibodies (aCL, immunoassay) and anti-beta2glycoprotein I antibodies (anti-b2GPI, immunoassay) [32].

The putative association of aPL with infertility has been first postulated in the 80s [33]. Some years later in 1991 working on animal models Blank et al. demonstrated that, after infusion of IgM and IgG aCL antibodies, naive mice displayed a low fecundity rate and/or an increased rate of embryo absorption, leaving opened the possibility that aPL could provoke infertility. In fact, according to experimental data, aPL may impair female fertility interfering with endometrial decidualization thus with implantation [34].

The field remains still highly controversial. However, even though the association of aPL with infertility is debated, infertile women are commonly screened for aPL and their positivity rate is generally higher than expected.

Vega et al., in 2016, investigated 351 infertile female patients looking for an association between positive immune tests (antinuclear antibody, aPL, anti-thyroid antibodies and total immunoglobulin levels) and low AMH levels. Authors found that the presence of at least one aPL was significantly associated with low AMH in 50 women (14.2% of the studied group); none specific aPL or other immune marker demonstrated an association with AMH. A big limit of this study is that it was not clear if these women were healthy carriers or affected by an autoimmune disease and, in this last case, their disease activity at sample timing was not reported [35].

Recently, Chighizola et al., published a review focusing on the relationship between aPL and female infertility including a total of 46 papers. Among the three tests anticardiolipin antibody assay was the most frequently performed and almost half of available studies confirmed an association between aCL positivity and infertility. However, this reports do not considered the possible low specificity of isolated aCL positivity. In addition the Authors noted that the definition of aCL positivity itself was heterogeneous, not conforming to the international consensus definition in nearly all studies analyzed. When all the three tests were performed, the positivity rate of at least one aPL test was found in 6% of infertile patients, compared to 1% among control subjects. Furthermore, fifteen papers (48.4%) assessed non-criteria aPL tests: anti-phosphatidylserine antibodies (aPS) were the most commonly tested (42%); antiprothrombin antibodies (aPT) were investigated in only one study that showed a significant association between aPT positivity and infertile women. The application of these assays remains debated because it is not clear if testing for these antibodies provide relevant clinical information and because such tests are not recommended in international guidelines [36]. Authors concluded that it is still not clear whether the higher aPL frequency registered among infertile women underlies a clinically important association or if it was due to a bias of publications [37].

SLE affects young women. Although very few studies address this issue, infertility is not found more prevalent in SLE compared to the general population, underlying that the phenomenon, if present, is

not frequent. Usually, the premature ovarian failure observed in SLE patients is linked to immunosuppressive drug treatment that in fact can affects the gonads. However, today we are dealing with a relative wider choice of drugs including several non-gonadotoxic molecules, such as the biological ones. In addition, the old gonadotoxic drugs, such as CTX, still prescribed in severe cases, are administered with "lighter protocols" that usually do not cause ovarian failures [38].

Finally, if high doses of intravenous CTX are needed to control severe organ impairment, the use of gonadotropin releasing hormone analogue has been shown to significantly reduce premature ovarian failure.

On the other hand, SLE is known as the diseases of more than 100 autoantibodies [39]. It is of note to mention that also the above mentioned aPL are found in SLE patients in a rate that varies from 20% to 60% according to different reports with their consequence on the reproductive issues of the women [40]. But autoantibodies can directly affect also the male and female gonads. In women, anti-ovarian antibodies described as linked to ovarian aging and autoimmune oophoritis leading to impaired ovarian function, was reported in SLE patients and linked to premature menopause [41,42].

Menstrual irregularity and an ovulatory cycles are reported in SLE patients with high disease activity (and consequently undergoing important CSs treatments) so it becomes mandatory to be able to evaluate the ovarian reserve.

Recently, AMH has been shown as the more reliable measurement of ovarian reserve, independently form the different times of menstrual cycle. In normal women AMH, that is part of transforming growth factor beta family, reaches its higher levels immediately after puberty and declines to zero in menopause [43].

It is relevant the recent observation that AMH was found reduced in SLE patients with severe disease activity and undergoing prolonged immunosuppressive treatments [12]. These results suggest that AMH could be taken as a measure of the remaining ovarian reserve and could provide objective data to help patients and physicians in the discussion of the not easy topic of family planning.

Rheumatoid arthritis and other chronic arthritis

The idea that a link might exist between RA and infertility is not a new one but up to now no clear association with decreased fertility was demonstrated. It is still debated if the association between RA and family size is mainly due to a problem of fertility, to a patient choice, or a combination of both.

As underlined by Provost et al., since 1958 fertility in these patients was object of interest. Several Authors studied women with RA and noted that they seemed to have less children than controls and displayed higher incidence of nulliparity than general population [44].

Fertility seemed to be also impaired in women with RA. Decreased fertility before disease onset was firstly reported in 1993 in a study of 259 patients with RA compared with 1258 healthy controls, data not confirmed in a subsequent study in 1999 [45]. More recently, in 2004 a group of 113 women with established RA was studied. Purpose of Authors was to investigate if reproductive history before disease onset could be associated with disease activity, in particular with severity of joint destruction. This aspect was not confirmed but Authors found that fertility was decreased: according to the earlier studies, the time to pregnancy was found prolonged in a consistent group of patients (16%) [46,47].

Controversial data for family size in patients with RA were published. Nelson et al. demonstrated in 1993 a comparable family size between patients with RA and controls [45]. A more recent review, on the other side, listed works in which Authors found a family size reduced compared to general population reporting multiple explanations of their founding. They ranged from age-related fertility decline, decreased ovarian reserve, or systemic inflammation as well as medication side-effects to more psychosocial causes, such as decreased sexual desire or simply personal choice [48].

There were published studies suggesting that the follicular pool in the reproductive years may be particularly sensitive to external insults, such as inflammations or drugs [49]. Therefore, it is possible that RA medications or the disease process itself affects an already depleted follicular pool in these women. Following this idea, Flaisler et al. noticed significantly lower rates of ovulation when compared with controls in a prospective analysis of 16 patients with RA [50].

A recent review focused on infertility in women with RA and, after the already described medical reasons that RA shares with the other systemic autoimmune diseases, Authors commented on several

works investigating the personal choice of these women of having less children than desired. The main fears in these women are about their ability to care for children, or if medications would harm the baby and if their children would develop RA themselves [44]. This finding bring forth the problem of a correct counseling in women with rheumatic diseases [51]. As well as in other chronic diseases, clinicians should discuss the possibility of infertility in young women with RA in order to identify as early as possible every doubt or critical issue.

Another extremely important aspect to consider in a woman with RA, can be also the possible reduction of sexual desire. Through interviews to patients, some Authors found that nearby 30% of respondents felt that their health status significantly influenced their sexual activity and it was mainly due to higher levels of fatigue, mental distress, functional limitations, and lower levels of self-efficacy [52,53]. Therefore, sexual dysfunctions could be considered as possible actors in the impaired fertility in women with RA but probably more studies are needed in order to better define the impact of this aspect.

Conclusions

Patients with autoimmune rheumatic disease frequently complain about their difficulties in having children. According to the actual knowledge, this problem recognize multifactorial explanations. Among these explanations, infertility plays its role even if probably it is not the most frequent cause of the reduction of family size.

In these patients, several factors can result in permanent or transient infertility: this is the case of certain antirheumatic drugs, of particularly high disease activity, of the physicians' attitude to ignore the family planning in favor of an aggressive and, sometimes, not justified extended disease treatment leading to a decreased ovarian reserve because of the women age.

In this scenario, the patients' frequent choice to look for the medically assisted reproductive techniques can be easily understood. The safety of these procedures in women with autoimmune systemic diseases has been debated for a long time. However, recent findings [54,55] underline that medically assisted reproductive techniques do not expose these patients to particular risks, if the patients are in stable disease remission and if they receive an adequate treatment. In addition in the presence of congenital or acquired thrombophilia (i. e. positive aPL), a prophylactic treatment is required because of the increased thrombotic risk due to the hormonal stimulation administered during the assisted reproductive techniques cycles. Women with rheumatic diseases show a successful rate of these techniques comparable to that of the general population and the subsequent pregnancies complications are in line with those observed in spontaneous pregnancies of these patients.

Physicians involved in the management of women with systemic autoimmune diseases need to keep in mind the possible infertility risk of their young patients and to protect them with adequate protocols. In a larger perspective, physicians should include in their daily practice the counseling of women in childbearing age about their family planning. The result of this conversation is to understand the individual need to preserve fertility that obviously can vary according to the patients' life situation and personal choices.

Practice points

- Infertility could be an issue in women with rheumatic diseases, mainly because of the women's age and some anti-rheumatic drugs.
- Also endometriosis, celiac disease or thyroid disease could impair fertility.
- As a general rule, a pregnancy should be planned in a period of remission of the disease, while taking not teratogenic drugs and if there is no organ involvement.

Research agenda

- Guidelines for managing infertility in women with systemic autoimmune diseases are still lacking.
- More studies are needed to demonstrate safety of medications usually used by rheumatologists in women.

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