Severe Autoimmune Diseases

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Indications and Prognosis

Autoimmune diseases often affect young women of reproductive age. Approximately 7% of all patients presenting at *Ferti*PROTEKT network clinics suffer from benign diseases, which include autoimmune diseases. Of these 7% of women, about 25% suffer from systemic lupus erythematosus (SLE) and 8% from vasculitis [1].

Above all, rheumatological systemic diseases such as connective tissue diseases and vasculitis and also haematological or neurological diseases such as multiple sclerosis, despite great therapeutic progress in recent years, continue to be an indication for the use of relatively undirected but highly immunosuppressive cytotoxic drugs. Cyclophosphamide (CYC) is used almost exclusively for this purpose orally or as intravenous pulse therapy. CYC also forms the cytotoxic central pillar for autologous stem cell transplantation, as the maximum therapy for immunosuppression in autoimmune diseases.

Diseases in which CYC therapy may be necessary:

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- Severe organ manifestations (glomerulonephritis, alveolitis or manifestations in the central nervous system) in *connective tissue diseases* (SLE, systemic sclerosis, Sjogren's syndrome, Sharp's syndrome, polymyositis or dermatomyositis)
- Severe organ manifestations (mostly pulmonary or renal) in anti-neutrophil cytoplasmic antibodies (*ANCA*) *associated vasculitis* (granulomatosis with polyangiitis [formerly: Wegener's granulomatosis], eosinophilic granulomatosis with polyangiitis [formerly: Churg–Strauss syndrome] or microscopic polyangiitis)
- Treatment-refractory forms of *large vascular vasculitis*, whereby only Takayasu arteritis occurs during reproductive age
- Autoimmune *neurological disease*s: e.g. multiple sclerosis
- *Non-malignant haematological diseases*: e.g. immune thrombocytopenia, acquired haemophilia, auto-immune haemolysis

With the exception of ANCA-associated vasculitides, these diseases usually peak before family planning is complete. A cure is not possible. However, by early diagnosis and initiation of the appropriate treatment, most patients can now be treated adequately on a permanent basis. As a result, their life expectancy has also become increasingly closer to that of the normal population, which means that the desire to have children and fertility preservation also plays an important role for these patients.

Gonadotoxity of the Treatments

The ovarian reserve, determined by the concentration of Anti Müllerian hormone (AMH), is limited in many autoimmune diseases due to the chronic disease per se and especially in cases of high disease activity [2–6]. For this reason, advice on fertility preservation should be given prior to CYC therapy, especially in autoimmune diseases.

CYC significantly increases the risk of premature ovarian insufficiency (POI) in autoimmune diseases. The percentages in the literature vary between 12 and 54% and are mainly influenced by the age of the patient at the time of therapy and the cumulative dose of CYC (Table 1).

The age and dose dependency of cyclophosphamide on ovarian toxicity are shown in a Chinese study of 216 women and in a study by Di Mario et al., in which ovarian toxicity was determined by AMH concentration [6, 16] (Fig. 1). According to these studies, other immunosuppressive drugs used in the treatment of SLE, such as mycophenolate, azathioprine, prednisolone, ciclosporin, tacrolimus and hydroxychloroquine, do not lead to a significant reduction in AMH concentration [6, 16].

Table 1 Studies on POI-rate after cyclophosphamide (CYC) treatment (SLE = systemic lupus erythematosus, GPA = granulomatosis with polyangiitis) and identified risk factor for premature ovarian insufficiency (POI)

Study	Origin of study	Diseases	Number of women	POI-rate (%)	Risk factors identified
Boumpas et al. 1993 [7]	USA	SLE	39	12–39	Age, CYC dose
Mc Dermott et al. 1996 [8]	UK	SLE	52	54	Age, CYC dose
Mok et al. 1998 [9]	China	SLE	70	26	Age, CYC dose
Ioannidis et al. 2002 [10]	Greece	SLE	67	31,3	Age, CYC dose disease duration
Huong et al. 2002 [11]	France	SLE, GPA	84	22,6	Age
Park et al. 2004 [12]	South Korea	SLE	67	14,9	Age
Singh et al. 2007 [13]	India	SLE	35	31,4	Cytochrome P450 polymorphism
Appenzeller et al. 2008 [14]	Canada	SLE	57 (CYC 750 mg/m^2) 50 (CYC 500 mg/m^2)	17,5 0	Age, CYC dose
Alarfaj et al. 2014 [15]	Saudi Arabia	SLE	188	13,1	Age, CYC dose
Di Mario et al. 2019 [6]	Italy	SLE	14	–	Age, CYC dose

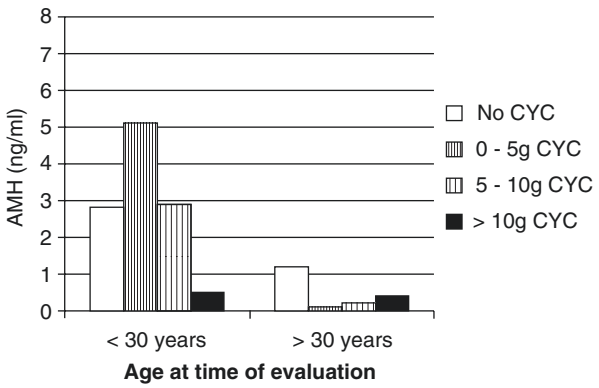

Fig. 1 AMH serum concentration after CYC treatment in women with SLE is dependent on age and dose (modified according to [16])

Probability of Exacerbation of the Underlying Disease

CYC treatment for autoimmune diseases is only indicated if there is high disease activity. A rapid initiation of therapy is usually necessary; however, the influence of fertility preservation therapy on the underlying disease must also be considered.

Due to the pathogenesis and gender distribution of many autoimmune diseases, it must be assumed that an increase in female hormones has a negative influence on the disease, and further exacerbation of the underlying disease can occur during ovarian stimulation for egg collection. Furthermore, other studies suggest that downregulation with a GnRH agonist has a positive effect on SLE [17]. A transfer of these findings to other autoimmune diseases is reasonable, but due to the rarity of the diseases, they have not been sufficiently and conclusively investigated.

Overall, there are only a few studies/recommendations on fertility preservation specifically for autoimmune diseases [18–21]. The other recommendations are mostly based on findings from the treatment of SLE patients. The European League against Rheumatism (EULAR) also includes fertility preservation in its 2017 recommendations [22].

Effectiveness and Risks of Fertility Preservation

The ovarian reserve is often reduced in autoimmune disease. Lawrenz et al. [3] and Di Mario et al. [6] found a 32% and 29% lower AMH concentration in women with systemic lupus erythematosus compared to a control collective. Lower AMH concentrations were also found in women with rheumatoid arthritis, Bechet's disease and spondyloarthritis [2], multiple sclerosis [5] and Takayasu's arteritis [4]. However, according to one study in lupus patients, AMH reduction appears to occur only in a severe form of autoimmune disease [6].

However, it is questionable whether the lowered AMH concentration also leads to fertility preservation measures being less effective. If oocytes are to be cryopreserved, the stimulation dose can often be adjusted. If ovarian tissue is cryopreserved, the AMH concentration plays a rather minor role. Important, however, is the density of primordial follicles, which in contrast to the AMH concentration, is not reduced in women with Hodgkin's lymphoma [23].

GnRH Agonists

The effectiveness of GnRH agonists (GnRHa) (see chapter "GnRH Agonists") has now been proven in patients with breast cancer (see chapter "Breast Cancer"). For autoimmune diseases only very limited data is available. However, it can be assumed that the data on efficacy in breast cancer can also be transferred to autoimmune diseases, since the risk of POI is comparable in both disease groups and the same cytotoxic drug is used (CYC).

Somers et al. [24] and Koga et al. [25] treated women with lupus erythematosus with CYC and GnRHa and compared the POI rate with a control group without GnRHa. The cumulative CYC doses administered were 12.9 g and approx. 5.0 g, respectively. The POI rate was 5% and 6% with GnRHa therapy and 30% and 50%

in the control group. Further studies investigated the effect of GnRHa [26] and its tolerability in children with SLE based on AMH concentration [27].

GnRHa can therefore be considered in individual cases as a singular method if a higher cumulative cyclophosphamide dose is planned.

Ovarian Stimulation

The procedure (see chapters "Ovarian Stimulation to Collect Oocytes" and "Cryopreservation of Unfertilized and Fertilized Oocytes") should be discussed individually if stimulation therapy for cryopreservation of fertilised or unfertilised eggs is to be carried out.

In principle, two risks should be emphasised:

1. Risk of Exacerbation of the Disease Under Stimulation

   In cases of connective tissue diseases in particular, especially SLE, stimulation can lead to a deterioration in disease activity. However, the available data are limited. Guballa et al. examined 17 women (10 with anti-phospholipid antibody syndrome (APS) and 7 with SLE) who underwent stimulation [28]. Stimulations with clomiphene citrate and with high-dose gonadotropins were included in the evaluation. No exacerbation was documented in women with APS. Women with SLE showed a slight exacerbation in 3/7 (43%) women in 3/16 (16%) stimulation cycles.
2. Risk of Thrombosis

   In general, the risk of thrombosis is increased in autoimmune disease, particularly in connective tissue diseases, and especially in SLE. Antiphospholipid antibodies are found in 40% of SLE patients, depending greatly on the patient's ethnicity [29–31]. The risk of thrombosis is highest in active APS and active SLE. According to a meta-analysis, if the serum marker "lupus anticoagulant" is increased, the risk of thrombosis increases by about six times, even in patients without SLE [32]. Other markers such as anticardiolipin antibodies, anti-β2 glycoprotein antibodies, anti-prothrombin antibodies, anti-phosphatidylserine antibodies and anti-phosphatidylethanolamine antibodies were only associated with a slight and insignificant increase in the risk of thrombosis in this study.

   There are little data available on the risk of thrombosis during stimulation. In the above-mentioned study by Guballa et al. [28], none of the 17 women stimulated with clomiphene citrate or gonadotropins had a thrombosis. However, all women received a thrombosis protection (heparin, aspirin or corticosteroids).

   In assisted reproduction, stimulation is also possible in SLE patients with special caution [28, 33]. In the event of an acute worsening of the underlying disease with the need for therapy escalation, the basic requirements for safe stimulation are not met. Therefore, this option should only be indicated with extreme caution in cases of active APS or SLE. Adequate thrombosis protection, depending on the risk profile, must be ensured [34].

Cryopreservation of Ovarian Tissue

Cryopreservation of ovarian tissue (see chapters "Removal of ovarian tissue" and "Transportation, cryopreservation and storage of ovarian tissue") is a good option for young women under the age of 35 and up to a maximum of approximately 40 years. Good pregnancy rates are particularly evident in women up to 35 years of age, and the method can also be successfully carried out in SLE patients [35, 36]. Since autoimmune diseases are chronic diseases, this method offers fertility preservation even if renewed CYC therapy is necessary. Due to the often reduced ovarian reserve, however, an adequate reserve should first be ensured by AMH measurement and determination of the AFC using ultrasound. A case report of a successful pregnancy in a patient with SLE after retransplantation of cryopreserved ovarian tissue is available [36].

Practical Approach

The choice of fertility preservation methods is always an individual decision, which should be made in close consultation with the patient, the gynaecologists and rheumatologists in charge.

In principle, patients should be introduced to a reproductive medicine centre as early as possible in order to ensure the greatest possible time frame for the implementation of fertility preservation methods. Figure 2 shows the procedure for carrying out fertility preservation measures for autoimmune diseases.

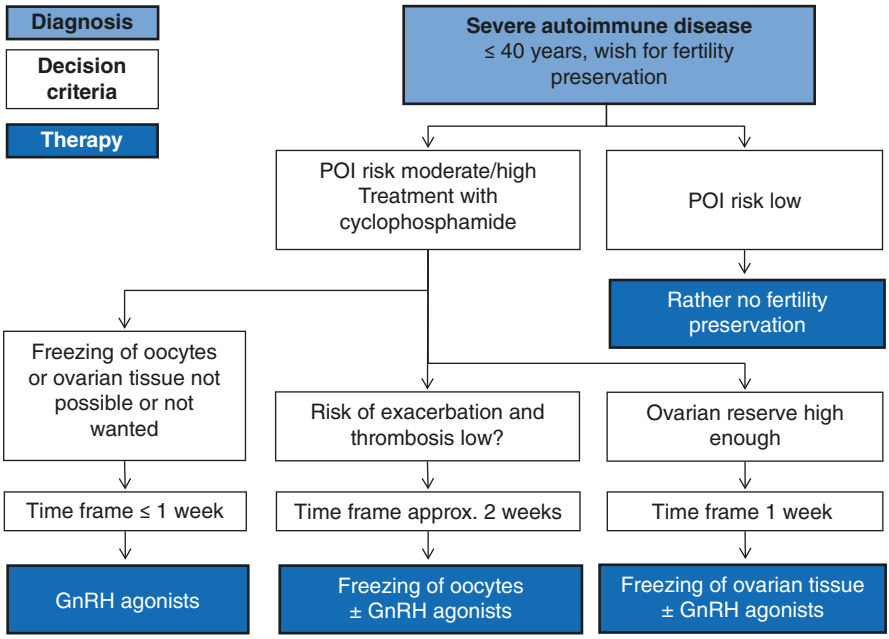

Fig. 2 Algorithm for fertility preservation in women with autoimmune diseases

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