Fertility preservation in women with vasculitis: experiences from the *Ferti*PROTEKT network

J.C. Henes[1,4], M. Henes[2,4], M. von Wolff[3,4], M. Schmalzing[1,4], I. Kötter[1,4], B. Lawrenz[2,4]

[1]Centre for Interdisciplinary Clinical Immunology, Rheumatology and Autoimmune Diseases – INDRA and Department of Internal Medicine II (Oncology, Haematology, Immunology, Rheumatology, Pulmonology), Tübingen, Germany; [2]University Hospital for Women, University of Tübingen, Germany; [3]Department of Gynaecological Endocrinology and Reproductive Medicine, University Hospital for Women, Bern, Switzerland; [4]For the Centres of the FertiPROTEKT Network

*Joerg C. Henes, MD**
*Melanie Henes, MD**
Michael von Wolff, MD
Marc Schmalzing, MD
Ina Kötter, MD
Barbara Lawrenz, MD

**These authors made an equal contribution.*

Please address correspondence to:
Dr Joerg Henes,
Internal Medicine II,
Otfried-Müller Straβe 10,
72076 Tübingen, Germany.
E-mail: joerg.henes@med.uni-tuebingen.de

Received on February 7, 2012; accepted in revised form on February 16, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 70): S53-S56.

Key words: autoimmune disease, vasculitis, fertility preservation, cyclophosphamide, fertiprotect

Competing interests: none declared.

ABSTRACT

Objectives. *Fertility preservation is not only important for malignant diseases but should also be offered to patients with autoimmune diseases (AID) like vasculitides, prior to cyclophosphamide therapy. No recommendations are available for patients with AID.*

Methods. *Analysis from the Fertiprotekt registry of all female patients with age <40 and the diagnosis of a vasculitis. The number of counselled patients, their diagnosis and age, the number of children before the start of therapy as well as the fertility preservation treatment chosen were evaluated.*

Results. *From January 2007 to November 2011, 47 patients with the diagnosis AID were counselled at 17 of the 69 Fertiprotekt centres. 80.9% decided for at least one of the offered preservation methods. Ovarian cryopreservation was performed in 6 patients, 36 patients opted for GnRH-analogue treatment. Two patients decided for a stimulation therapy for cryopreservation of oocytes.*

Conclusions. *Regarding the experiences from the registry and the literature gonadotropin releasing hormone analogues are evaluated best and recommended to most of the patients with AID. Cryoconservation of ovarian tissue is a promising option. Stimulation for oocyte cryopreservation can be offered to patients with vasculitis. A combination of the methods might have the biggest preservative effect.*

Introduction

Vasculitides are a heterogeneous group of autoimmune mediated inflammatory diseases of blood vessels. Especially Takayasu arteritis (TAK) and Behçet's disease (BD) as well as anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitides (AAV) but also panarteritis nodosa (PAN) and other/undifferentiated vasculitides can be found in young patients during childbearing age (1). In some patients cyclophosphamide (CYC) as an immunosuppressive alkylating agent is used for induction of remission.

The risk for premature ovarian failure (POF) – defined as premature depletion of ovarian follicles before the age of 40 – after CYC treatment has been described for autoimmune diseases with up to 54% depending especially on the age at the time of the CYC therapy and on the cumulative dose of CYC (2-4). A very recent work has shown that CYC has a negative influence on the ovarian reserve in patients with GPA (4).

The *Ferti*PROTEKT network (www.fertiprotekt.eu) aims on optimising fertility preservation techniques in young patients facing a gonadotoxic therapy. Sixty-nine centres specialised in fertility preservation in Germany, Switzerland and Austria counsel patients and report every counselled patient to the network. Compulsory documentation has been made of all patients and treatments since 2007. All approved fertility preservation techniques must be discussed and offered to the patient.

A detailed description of the various fertility preservation methods, the implementation, efficacy and risks has already been published elsewhere as open access (5). The choice of fertility preservation treatments includes the administration of gonadotropin-releasing hormone (GnRH) analogues. Cryopreservation of ovarian tissue and is another possible method. Approximately one-third to a complete ovary is removed laparoscopically and cryoconserved. Part of the ovary can be retransplanted laparoscopically in case of premature ovarian failure. A further option of fertility preservation is controlled ovarian stimulation for cryoconservation of oocytes.

Materials and methods

In this registry data analysis we included all female patients ≤40 years

who were counselled at one of the *Ferti*PROTEKT network centres before being treated for a vasculitis with CYC. The registry collects data on the number of counselled patients, their diagnosis and age as well as the number of children before the start of therapy. Furthermore, the fertility preservation treatment chosen and the occured complications are assessed. No data on disease activity or disease duration are documented.

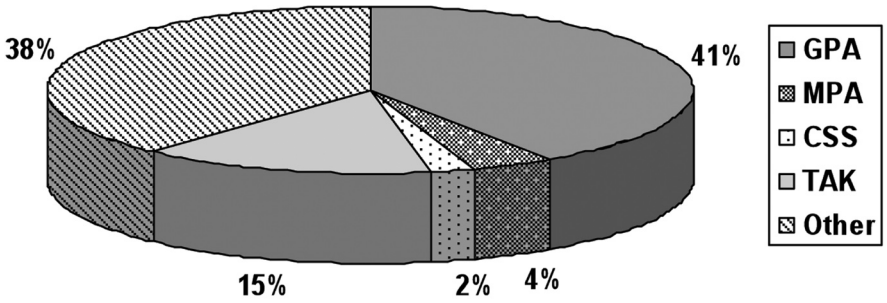

Fig. 1. Distribution of the different vasculitis entities included in the analysis

Results

All together, 2836 patients were counselled within the *Ferti*PROTEKT registry between 01/2007 and 11/2011 prior to a gonadotoxic therapy. In 47/2836 patients (1.66%) the diagnosis vasculitis was the reason for the consultation. Only 17 (24.6%) of the 69 centres counselled patients with vasculitis.

The mean age of the patients was 26 (15–40 years). Twenty-two patients (46.8%) suffered from an ANCA-associated vasculitis (19x GPA, 2x MPA, 1x CSS), 7 patients (14.9%) from Takayasu arteritis and in 18 patients (38.2%) no further differentiation was made (Fig. 1). The 47 patients had only 7 children at the time of consultation which comes to a mean number of children of 0.15/patient.

Table I summarises the decisions for fertility preservation made by the patients in correlation to their age and number of children before treatment. Thirty-eight patients (80.9%) decided for at least one of the offered preservation methods. The nine patients who decided against fertility preservation were with 27.4 (19–36) years older than the mean age of 26 years and had a comparable number of children (0.22/patient). 36 patients (76.6%) opted for GnRH-analogue treatment; 4 pts. in combination with ovarian cryopreservation. Ovarian cryopreservation was performed in 6 patients, in 5 patients <1 ovary was removed, in one patient one whole ovary was preserved. All ovarian resection was done laparascopically. No complications were reported.

Two patients (4.3%), 24 and 26 years old, decided for a stimulation therapy for cryopreservation of oocytes. The two patients suffered from an undifferentiated vasculitis and had no children at this time. Both wished to use a GnRH-analogue in addition. The stimulation was performed with a total dose of 2250IE and 1200IE follicle stimulating hormone (FSH) for 10 and 8 days, respectively. In both patients 6 unfertilised oocyted were cryopreserved. No ovarian hyperstimulation-syndrome was documented.

Discussion

Chronic autoimmune diseases (AID) seem to have a negative influence on the ovarian reserve themselves (6). Therefore especially young women with AID facing a CYC treatment should be given the possibility of fertility preservation. The *Ferti*PROTEKT network offers guidelines for patients with malignant diseases. Recommendations for systemic lupus erythematosus are on their way. This is the first data on fertility preservation strategies in female patients with vasculitis.

Regarding the literature there is no specific data on effectiveness or risks of the fertility preservation techniques in patients with vasculitis. Two recent metaanalyses on GnRH analogue therapy during CYC treatment have been shown to be effective in other AID (7, 8). If necessary, CYC treatment can be started immediately when adding a GnRH antagonist to the agonist therapy for the first 7 days.

Regarding the impact of female hormons or even a stimulation therapy on the disease activity in vasculitis patients there are no publications available. Reports on pregnancies in women with vasculitides are rare but most publications found no increased risk for mother and child (9-13). Especially in Behçet's disease and Takayasu's arteritis – which are more common during childbearing age – disease activity seems to be unchanged or even improve during pregnancy (11.13). In AAV relapse-rates during pregnancy range between 0% and 5% (8, 9). With this very limited available data even stimulation therapy for cryoconservation of fertilised or unfertilised oocytes – which up to now is the most effective fertility preservation treatment (5) – can theoretically be offered to patients with vasculitis; in contrast to patients with SLE where stimulation therapy might be associated with the risk of a disease flare and thrombembolic complications. The limiting factor of this treatment is the time (approximately 14 days) needed for stimulation and oocyte harvest which can lead to a delay of the necessary treatment. In the two documented patients in the *Ferti*PROTEKT network 8 and 10 days of stimulation were performed and no complications were reported.

Cryoconservation of ovarian tissue is still an experimental approach but more and more data on retransplantation and effective hormonal function of the transplanted tissue is available; even spontaneous pregnancy has been reported (14, 15). Besides the risk of the laparascopic surgery this procedure is a promising method also for patients with vasculitis. The additional time needed for this strategy is 1-2 days. In contrary to cryoconservation of oocytes the hormonal function of the ovary can be preserved as well.

All 8 patients who decided for a more invasive treatment with cryopreservation of either oocytes or ovarian tissue had no children at the time of the consultation. With a mean age of 24.4 years they were little younger than the mean age of all patients. This might

Table I. Distribution of all counselled patients according to their age and number of children before cyclophosphamide treatment. Multiple choices were possible.

	All patients	GnRH analogue	Stimulation	Cryo Ovar	No Therapy
Age	n=47 (100%)	n=36 (76.6%)	n=2 (4.3%)	n=6 (12.8%)	n=9 (19.1%)
< 20 years	n=8 (17%)	n=7 (87.5%)	n=0	n=2 (33.3%)	n=1 (11.1%)
20-29 years	n=23 (49%)	n=18 (78.3%)	n=2 (100%)	n=2 (33.3%)	n=4 (44.4%)
30-40 years	n=16 (34%)	n=11 (68.8%)	n=0	n=2 (33.3%)	n=4 (44.4%)
Total mean age in years (range)	26 (15-40)	25.5 (15-40)	25 (24-26)	23.7 (15-34)	27.4 (9-36)
Number of children	n=7	n=3	n=0	n=0	n=2
0	n=41	n=33	n=2	n=6	n=7
1	n=5	n=2	n=0	n=0	n=2
≥2	n=1	n=1	n=0	n=0	n=0
Mean number of children	0.15	0.08	0	0	0.22

reflect their stronger wish to preserve their fertility. The different preservation methods can also be combined, a chance that was realised by only 6 of the 38 patients who decided for a therapy.

As especially the cumulative dose of CYC plays an important role for the risk of developing a premature ovarian failure the lowest dose possible should be administered. Especially in AAV Rituximab has been shown to be equally effective and should be considered in young patients (16, 17). In other AID a reduced duration of CYC treatment partly substituted by mycophenolate mofetil preserved ovarian function (18).

As in other AIDs, pregnancy should be planned and patients counselled regarding the optimal time point and the possible complications of a pregnancy. Disease activity at the time of conception is the main prognostic factor and should be low on a stable therapy. All pregnancies in patients with vasculitis should be considered as high risk pregnancies and followed up closely during and after pregnancy by an interdisciplinary team of rheumatologists and gynaecologists.

This registry data has some limitations. The sample size for vasculitis patients is still very small and heterogeneous and the decisions made by the patients are biased by their counselling gynecologist and rheumatologist as well as by the patients actual life situation. No data are available on the effectiveness of the different preservation treatments but more and more experiences will be gained by the ongoing documentation by the attending oncologists, haematologists, gynecologists and rheumatologists. Of special interest will be the report of pregnancies or cases of sterility to the network. Hopefullly this will further enhance fertility preservation methods even in rare diseases like vasculitis.

From the current available literature, the data from the *Ferti*PROTEKT network as well as our experience over recent years in counselling vasculitis patients, we recommend the following approach:

- All women between the ages of 14 and 40 years who receive CYC for vasculitis should be counselled by a centre specialised in reproductive medicine on fertility preservation methods, in agreement with the responsible rheumatologists;
- Use of GnRH analogues prior to CYC treatment can be recommended for all patients;
- GnRH administration in combination with ovarian tissue cryoconservation can be performed especially in patients under the age of 35 years;
- GnRH administration in combination with stimulation therapy and subsequent cryoconservation of fertilised or unfertilised egg cells can be offered but should be performed under particular consideration of the individual risks.

References

1. DE MENTHON M, MAHR A: Treating polyarteritis nodosa: current state of the art. *Clin Exp Rheumatol* 2011; 29 (Suppl. 64): 110-6.
2. BOUMPAS DT, AUSTIN HA 3RD, VAUGHAN EM YARBORO CH, KLIPPEL JH, BALOW JE: Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. *Ann Intern Med* 1993; 119: 366-9.
3. MCDERMOTT EM, POWELL RJ: Incidence of ovarian failure in systemic lupus erythematosus after treatment with pulse cyclophosphamide. *Ann Rheum Dis* 1996; 55: 224-9.
4. CLOWSE ME, COPLAND SC, HSIEH TC *et al*.: Ovarian reserve diminished by oral cyclophosphamide therapy for granulomatosis with polyangiitis (Wegener's). *Arthritis Care Res* (Hoboken). 2011; 63: 1777-81.
5. VON WOLFF M, MONTAG M, DITTRICH R, DENSCHLAG D, NAWROTH F, LAWRENZ B: Fertility preservation in women-a practical guide to preservation techniques and therapeutic strategies in breast cancer, Hodgkin's lymphoma and borderline ovarian tumours by the fertility preservation network FertiPROTEKT. *Arch Gynecol Obstet* 2011; 284: 427-35.
6. LAWRENZ B, HENES JC, HENES M *et al*.: Impact of systemic lupus erythematosus on ovarian reserve in premenopausal women: Evaluation by using anti-Muellerian hormone. *Lupus* 2011; 20: 1193-7.
7. BEN-AHARON I, GAFTER-GVILI A, LEIBOVICI L STEMMER SM: Pharmacological interventions for fertility preservation during chemotherapy: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2010; 122: 803-11.
8. CLOWSE M, BEHERA MA, ANDERS CK *et al*.: Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis. *J Women's Health* 2009; 18: 311-9.
9. TUIN J, SANDERS JS, DE JOODE AA, STEGEMAN CA: Pregnancy in women diagnosed with ANCA-associated vasculitis: favorable outcome for mother and child. *Arthritis Care Res* (Hoboken). Epub 2011 Dec 12.
10. PAGNOUX C, LE GUERN V, GOFFINET F *et al*.: Pregnancies in systemic necrotizing vasculitides: report on 12 women and their 20 pregnancies. *Rheumatology* (Oxford) 2011; 50: 953-61.
11. ISHIKAWA K, MATSUURA S: Occlusive thromboaortopathy (Takayasu's disease) and pregnancy. Clinical course and management of 33 pregnancies and deliveries. *Am J Cardiol* 1982; 50: 1293-300.
12. JADAON J, SHUSHAN A, EZRA Y *et al*.: Behçet disease and pregnancy. *Acta Obstet Gynecol Scand* 2005; 84: 939-44.
13. UZUN S, ALPSOY E, DURDU M, AKMAN A:

The clinical course of Behçet's disease in pregnancy: a retrospective analysis and review of the literature. *J Dermatol* 2003; 30: 499-502.

14. DONNEZ J, DOLMANS MM: Preservation of fertility in females with haematological malignancy. *Br J Haematol* 2011 54: 175-84.
15. DITTRICH R, LOTZ L, KECK G *et al*.: Live birth after ovarian tissue autotransplantation following overnight transportation before cryopreservation. *Fertil Steril* Epub 2011 Dec 16.
16. JONES RB, TERVAERT JW, HAUSER T *et al*.: European vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363: 211-20.
17. HELLMICH B: Update on the management of systemic vasculitis: what did we learn in 2009? *Clin Exp Rheumatol* 2010; 28 (Suppl. 57): 98-103.
18. LASKARI K, ZINTZARAS E, TZIOUFAS AG: Ovarian function is preserved in women with severe systemic lupus erythematosus after a 6-month course of cyclophosphamide followed by mycophenolate mofetil. *Clin Exp Rheumatol* 2010; 28: 83-6.