Fertility preservation counselling and treatment for medical reasons – data from a multinational network with >5000 women

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Abstract

Fertility preservation techniques for medical reasons are increasingly offered in national networks. Its introduction and improvement require knowledge about characteristics of counselled patients and fertility preservation techniques performed. Therefore the *Ferti*PROTEKT network registry was analysed over 7 years until 2013. In 39 (2007) to 85 (2013) university and non-university centers in Germany, Austria and Switzerland, 5159 women were counselled and 4060 women underwent fertility preservation therapies.

Fertility preservation counselling for medical reasons increased significantly, resulting in 1043 counsellings in 2013. Of these, mainly childless women and those between 21 and 35 years of age were counselled. Frequency of GnRH agonist applications slowly decreased whereas tissue and oocytes/zygote freezing increased between 2007 and 2013. In 2013, the main technique performed in breast cancer patients was tissue freezing whereas lymphoma patients received mainly GnRH agonists. Women <20 of age predominantly received GnRH agonists and cryopreservation of ovarian tissue, women between 20-40 years all kind of techniques and >40 years mainly GnRH agonists. Average number of aspirated oocytes per stimulation cycle decreased with increasing age and were <30y 12.9, 31-35y 12.3, 36-40y 9.0 and >41y 5.7. For ovarian tissue cryopreservation, removal and cryopreservation of less than one ovary was preferred and performed in 97% of cases.

Key words

Fertility preservation, registry, GnRH agonists, ovarian tissue, ovarian stimulation, oocyte

Introduction

The report of the first delivery following transplantation of ovarian tissue in 2004 (Donnet et al., 2004) has substantially accelerated the implementation of fertility preservation programmes for medical reasons. Furthermore, following the first reviews about the putative protective effect of gonadotrophin releasing hormone agonists (GnRHa) on ovarian function in 2008 (Blumenfeld & von Wolff 2008), and the report about the high efficacy of unfertilized vitrified oocytes in 2010 (Rienzi et al., 2010), the reproductive physician can currently choose between a broad spectrum of fertility preservation techniques. These techniques allow an individualized approach in relation to the patient's age, to the gonadotoxicity of the therapies, and to the available time frame.

At that time, it also became apparent that due to the complexity of the involved therapies and due to the need to integrate fertility preservation counselling and treatment into the oncological treatment protocols, local, national or even international co-operation and multidisciplinary networks were urgently required. Accordingly, networks such as *Ferti*PROTEKT (FertiPROTEKT), covering Germany, Austria and Switzerland and the Oncofertility Consortium (Oncofertility consortium) covering the U.S. were founded in 2006 and in 2007 respectively.

Furthermore, to support physicians and oncologists in this rapidly evolving complex area, these networks (von Wolff et al., 2011) as well as national (Practice Committee 2013; Loren et al., 2013) and international (ISFP 2012) societies have published several recommendations. According to these recommendations, the technique most frequently recommended is ovarian stimulation to cryopreserve oocytes, zygotes or embryos. Those techniques not explicitly been recommended such as cryopreservation of ovarian tissue and GnRHa have also been suggested to be effective by recently published studies (Donnez et al. 2013; Dittrich et al.;

2015; Liebenthron et al., 2015; Moore et al., 2015). In addition, ethics committees of national societies have prepared several statements about the ethical issues related to the welfare of both patients and offspring (Ethics Committee 2013).

In contrast, data about the actual number of patients being counselled and treated by fertility preservation techniques, about the distribution of the applied techniques and about the patients' characteristics is very limited. The network *Ferti*PROTEKT published such preliminary data, but analysis was not performed longitudinally during recent years. Rather it was limited to women between 15 and 40y, and a detailed analysis about the relationship between patients characteristics and the kind of treatment chosen as well as about any changes throughout the years was not performed (Lawrenz et al., 2011).

As data from representative multinational registries is essential to better understand the current status of fertility preservation in order to better implement or to improve fertility preservation programmes, data from the *Ferti*PROTEKT network registry (FertiPROTEKT), which involves 85 documenting centres, were analysed. The time span analysed was from the beginning of the era of fertility preservation in 2007 until 2013 when these techniques were already implemented in many oncological treatment protocols.

Material and methods

The *Ferti*PROTEKT network

The network was founded in 2006 to offer fertility-preserving techniques, initially in Germany, then also in the neighbouring German-speaking countries of Austria and Switzerland. The aim was to scientifically evaluate and improve the techniques and make them part of oncological treatment protocols. Initially all university fertility clinics were included, and then private fertility centres were also incorporated.

To ensure high quality counselling and therapy, and to keep up to date with the rapid developments in the specialty, all centres have to attend an annual two-day workshop. Standardized storage of ovarian tissue is ensured through central cryobanks. Support in treatments is further given by the networks recommendations published internationally (von Wolff et al., 2011) and by a bilingual website in German and English (www.fertiprotekt.com), which is available for doctors and patients.

The network's registry

A registry, which includes details of all treatments given, complications, and pregnancies was established in 2007. Physicians fill out a questionnaire about basic patient information such as age, disease, oncological therapy etc. Furthermore, details about the fertility preservation therapy chosen are added. In case of ovarian tissue cryopreservation, type of abdominal surgery, amount of ovarian tissue removed and site of storage are documented. In case of ovarian stimulation, timing of ovarian stimulation, number of stimulation days, gonadotrophin dosage, number of collected oocytes, fertilization technique, number of fertilized oocytes etc. are included. In addition, use of GnRHa, any combination of the specified therapies, data about transpositions and complications are documented. Finally, data about ovarian tissue retransplantation and embryo transfers are added. The data sheets are sent to a centrally located university based infertility centre, where data are added to the registry's software on a weekly basis.

The data is analysed annually, presented at the annual networks workshop and basic data are publicly available through the *Ferti*PROTEKT website. For this manuscript, data from 5159 counselled women was analysed. Data concerning the final outcome of the therapies such as ovarian tissue retransplantation has been described elsewhere (Dittrich et al., 2015; Liebenthron et al., 2015).

To better visualize the data in this paper, first total numbers of counsellings and treatments were calculated (Figure 1). Patients' characteristics were then analysed and all data was expressed as relative numbers in relation to the total number of counselled patients. Therefore, apart from the data in Figure 1 and 4c, all data is presented as relative numbers.

Institution review board permission was not required due to the analysis of anonymized registry data.

Statistics

The distribution of the different categories were reported with absolute and relative frequencies, possible differences were proofed using chi-square-tests. Possible increase over time (Figure 1) was proofed using linear regression models and reported by average increase per year. Statistics were not performed for data presented in Figure 3 as data were not disjunct (i.e. >1 different therapies in some women).

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Results

Counselling and treatment numbers

Number of counsellings increased significantly throughout the analysed time period, from 388 in 2007 to 1043 in 2013 (average: n=103/year) (Figure 1). Furthermore the number of treatments performed by university (average: n=32/year) an non-university-centers (average: n=42/year) increased significantly. As a result, the proportion of all fertility preservation treatments per counselling remained stable and was 82.2% in 2007 and 80.1% in 2013. The number of counselling centres also increased throughout the analysed time period. The number of centres was 39 in 2007, 59 in 2008, 68 in 2009, 78 in 2010, 84 in 2011, 85 in 2012 and 85 in 2013 (data not shown). On average, this resulted in 9.9 counsellings per centre in

2007 and 12.3 in 2013. The increase in the number of centres was mainly due to an increase in non-university centres. Accordingly, the total increase in counsellings and treatments was mainly due to the increase in non-university centres. The proportion of counsellings and treatments by non-university centres was 5.4% in 2007 and 5.3% and increased to 36.1% and 34.6% respectively in 2013.

Overall, the increase in counsellings was firstly due to the increase in counselling centres and secondly due to an increase in counsellings per centre.

Patient characteristics

Most women who were counselled were childless. In 2007, 86% were childless and in 2013 87%. The proportion of childless women remained stable (p=0.84).

The largest group of counselled patients in 2013 was the patient group between 26-30 years of age with a proportion of 30% of the total number of counselled patients, followed by the 31-35y group with 23% and the 21-25y group with 17% (Figure 2b). Overall, around 2/3 of all counselled patients were between 21 and 35 years of age. The age distribution of counselled patients remained stable throughout the analysed time period (p=0.11).

The analysis of the patients' diseases revealed that most patients in 2013 had breast cancer with a proportion 41% of the total number of counselled patients, followed by lymphoma with 28% (Figure 2c). Other malignancies played a minor role with 24%, and benign diseases with 7%. Among those with "other malignancies" were patients with acute myeloid leukaemia (10.8%), acute lymphoblastic leukaemia (8.3%), ovarian borderline tumours (6.5%), cervical cancer (6.1%), Ewing's sarcoma (5.7%), unclassified sarcomas (5.7%), unclassified ovarian cancers (4.3%), rectal cancer (3.4%) and among those with "benign diseases" were systemic lupus erythematosus (24.8%), unclassified vasculitis (8.2), Wegener's granulomatosis (6.4%), aplastic anaemia (6.2%), ovarian dermoid cysts (4.1%), Mosaic Turner syndrome (3%), thalassaemia (3%), scleroderma (2.7%) and multiple sclerosis (2.7) (data not shown). The

total distribution of the different diseases changed significantly over the analysed time period ($p<0.0001$).

The analysis also revealed the different age peaks of breast cancer and lymphoma patients (Figure 2d). Most women in the age group 16-25y were lymphoma patients, and most women in the age group >25y were breast cancer patients. The age distribution remained stable throughout the analysed time period (Figure 2d). The total distribution of the diseases in the different age groups changed significantly over the analysed time period ($p<0.0001$).

Fertility preservation treatments in relation to patient characteristics

The distribution of the total numbers of treatments changed slowly throughout the analysed period (Figure 3a). In 2007, 61% chose GnRHa, 35% tissue freezing and 14% oocyte/zygote freezing. In 2013, the distribution of these therapies changed to 41%, 38% and 21% respectively.

Women without children preferred the more invasive strategies such as tissue and oocyte/zygote freezing. In 2013 women without children preferred tissue freezing in 40% of cases and oocyte/zygote freezing in 23% of cases. In those with children, the numbers were 19% and 7% respectively (Figure 3b).

A further analysis (Figure 3c) was performed to better understand the distribution of therapies in relation to the diseases. Striking differences were found for the comparison of the breast cancer and lymphoma patients. In 2013 most breast cancer patients underwent tissue freezing (45%) followed by oocyte/zygote freezing (21%), whereas lymphoma patients predominantly received GnRHa (66%) followed by tissue freezing (33%).

The distribution of treatments varied throughout the analysed age groups (Figure 3d). Highest rates of GnRHa were found in the age groups <26 and >40y. Tissue freezing was chosen by >50% in young women <21y whereas in women >40y, only 21% chose this option in 2013. Oocytes/zygote freezing was performed frequently in all age groups between 21-40y.

Characteristics of fertility preservation treatments

Figures 4a-c depict more details about the characteristics of the GnRHa, tissue and oocyte/zygote freezing techniques. Figure 4a shows the proportion of patients receiving GnRHa as a sole treatment or in combination with tissue and oocyte/zygote freezing throughout the analysed period. Overall, around 40% of patients received GnRHa in combination with other therapies and this distribution remained stable between 2007 and 2013. The total distribution of the different GnRHa treatments changed significantly over the analysed time period ($p<0.027$).

Figure 4b shows the proportion of cases in which <1 ovary or ≥1 ovary was removed. Since 2008, the proportion of cases in which <1 ovary was removed increased and reached 97% in 2013. The distribution of these numbers changed significantly over the analysed 7 years ($p<0.0001$).

The average numbers of oocytes in relation to age are shown in Figure 4c. In 2013 the average number of oocytes per stimulation cycle were <30y 12.9, 31-35y 12.3, 36-40y 9.0 and >41y 5.7. The oocyte numbers in the age groups were significantly different ($p<0.0001$). The average number of collected oocytes did not significantly change since 2007 ($p=0.716$), and was around n=12/follicle aspiration.

Discussion

Fertility preservation for medical reasons is a topic which has encountered great interest in science, clinical routine and amongst the public in the last 10 years. Prior to this, transplantation of ovarian tissue and the administration of GnRHa were purely experimental techniques. This evolution is reflected in the number of Pub-med entries. In 2004, there were only 68 entries under the search terms „fertility preservation cancer“, and in 2014 there were already around 300. During this period, national and international networks and societies

were founded, such as, for example, the Germany, Austria and Switzerland-wide network, *Ferti*PROTEKT in 2006 (www.fertiprotekt.com), the Task Force of the European Society of Human Reproduction and Embryology, ESHRE (www.eshre.eu) in 2007, the Fertility Consortium in the USA (http://oncofertility.northwestern.edu) and the International Society of Fertility Preservation (www.isfp-fertility.org).

It has become clear over the last few years that the three main techniques appear to be effective in fertility preservation. So far, in 3 large case series with altogether 138 transplantations (Donnez et al., 2013; Dittrich et al., 2015, Liebenthron et al., 2015), transplantation of ovarian tissue has been shown to result in delivery rates per transplantation of around 20%, vitrified unfertilized oocytes have been shown to have the same pregnancy potential as fresh oocytes (Rienzi et al., 2010), resulting in a theoretical birth rate per stimulation in women <35y of 40 and between 35-39y of 30% (von Wolff et al., 2015) and the first meta-analyses and the results of looking at the efficacy of GnRHa co-treatment in breast cancer (Yang et al., 2013) and lymphoma (Zhang et al., 2015) chemotherapy as well as recently presented large prospective randomized study (Moore et al., 2015) have suggested a protective effects resulting in around 50% reduction of premature ovarian failure.

It is evident that the use of these techniques requires outstanding expertise in reproductive medicine and in oncology, as well as intensive networking with oncological specialities. This means that effective fertility preservation is only possible in a multidisciplinary and multicentre network. Some authors even stipulate that every oncology patient must be discussed with regard to the use of fertility preservation methods in a specifically arranged multidisciplinary board, in order to offer an ideal, individualised treatment (Wunder et al., 2012). In reality, however, such approaches are barely possible in daily clinical practice and under the given time pressure of beginning chemotherapy. Effective network structures and

registers are suitable as an alternative, which allow integration of the expertise of diverse centres and a register-based evaluation.

*Ferti*PROTEKT is such a network, whose aim was to ensure optimal, comprehensive patient care. The integration of multicentre expertise is shown, for example, by the first birth in the network after transplantation of ovarian tissue in 2011, for which the ovarian tissue was removed in one centre, was transported overnight to the central cryobank of a second centre, and was later transplanted at a third centre. The care of the pregnancy and birth took place in a fourth centre (Dittrich et al., 2012).

With the limitation that even a multinational register such as that of *Ferti*PROTEKT cannot be unreservedly transferred to the situation in other countries, it can be assumed that the register provides extensive representative data on fertility preservation and its development in recent years. The multicentre, multinational register evaluation carried out in this publication is the first published analysis of the use of fertility preservation techniques over a period of several years.

What does the register evaluation show? The first analysis block (Figures 1, 2) conveyed general data on counselling and patient characteristics. Figure 1 shows that comprehensive care involves not only a university structures, but also private centres. The increase in counselling over the last few years, which was equal to >1000 in 2013, is largely attributable to an increase in counselling in non-university centres. In the Fertility Consortium in the USA, the relatively dense network of treatment centres is only possible with the integration of university and non-university centres (FertPROTEKT, Oncofertility consortium5). However, it should be noted that private centres require particular support, since integration into an oncology network is often more difficult. Many private centres cannot offer all measures in the same way. In the *Ferti*PROTEKT network, annual workshops for continuing education with compulsory attendance are therefore organised and central cryobanks, to which the

centres who cannot store ovarian tissue themselves can send their ovarian tissue, have been installed.

Evaluation of the age distribution (Figure 2b) shows that predominantly adults are counselled. The age distribution reflects disorders such as breast cancer and lymphoma, where counselling was most often carried out. The figures show that oncologists who have specialised in lymphoma should also be involved in fertility protection programs as well as breast cancer patients to whom reproductive medicine specialists have very good access. The figures also show that up to now, very few children and adolescents were counselled, and an intensive cooperation with paediatric oncologists is necessary. A few years ago, children could only be offered the then highly experimental cryoconservation of ovarian tissue or GnRHa, which were then without proof of efficacy; meanwhile there are demonstrably effective treatments. Diverse recommendations on fertility preservation in children and adolescents have also been published since.

As the techniques have developed much further over the last few years, and because data on their efficacy has been increasingly published in recent years, the question arises of whether these developments have been reflected in the distribution of the treatments which are performed. Indeed, the evidence from recent years shows that a transplantation of ovarian tissue lead to pregnancy in a relevant percentage (Donnez et al., 2013; Dittrich et al., 2015; Liebenthron et al., 2015) and the evidence that effective cryoconservation of unfertilised oocytes is possible (Rienci et al., 2010) led to a relative reduction in GnRHa therapy (Figure 3a). GnRHa are still administered, but in over 40% of cases in combination with another fertility preservation treatment, in order to increase the effectiveness of the treatment by combining GnRHa as a toxicity-reducing measure with the creation of a fertility reserve (Figure 4a).

It is striking that the cryopreservation of oocytes, which is the only established technique according to recommendations such as those by the American Society of Reproductive Medicine (Practice Committee of American Society for Reproductive Medicine, 2010) has been chosen by only a minority of women. It can be assumed that the high costs of ovarian stimulations, the long period of time needed and the potential risks of stimulation therapies in breast cancer patients motivated physicians and women in many cases to opt for less established therapies such as cryopreservation of ovarian tissue or GnRHa.

The analysis also showed that the choice of method used is age-dependent. In children and adolescents, ovarian tissue is preserved in a high percentage, as this is considered to be particularly effective at a young age where there is a very high ovarian reserve (von Wolff et al., 2009a). GnRHa were also used very often. Since the administration of GnRHa is simple, minimally invasive and relatively cheap, this method is probably especially popular for use in children and adolescents. GnRHa dominate in patients over 40 years of age because other techniques are less effective at this age (Dolmans et al., 2013; Donnez et al., 2013; Dittrich et al.2014).

The comparison of the 31-35 and the 36-40 age groups is also interesting. Since cryoconservation of ovarian tissue is only recommended up to the age of ca. 35 years (von Wolff et al., 2009a), but IVF treatments are also carried out at a higher age, the distribution shifted with increasing age from ovarian tissue to cryoconservation of oocytes/embryos (Figure 3d).

There are marked differences in the choice of fertility preservation method depending on the various diseases. Cryoconservation of ovarian tissue dominates in breast cancer, as the question of whether ovarian stimulation and GnRHa can be performed or administered without risks is still open. GnRHa use dominated in lymphoma, although ovarian tissue in lymphoma, as in breast cancer, does not appear to lead to a risk of developing metastases after

retransplantation (Dolmans et al., 2013). Whether the large proportion of GnRHa is due to the fact that many chemotherapy agents used for hodgkin's lymphoma are less gonadotoxic (Behringer et al., 2005) and invasive treatments are therefore avoided, or whether the reason lies in the lower average age (Figure 2d), where the expensive invasive methods can be less well financed by many patients, is unclear.

Furthermore, the register data allowed the further analysis of ovarian tissue removal and ovarian stimulation. In the case of ovarian tissue removal, it has now become accepted that in most cases, only half an ovary is laparascopically removed. Even when some individual centres still favour the removal of a whole ovary, the high pregnancy rates in the *Ferti*PROTEKT network (Dittrich et al., 2014; Liebenthron et al., 2015), show that half an ovary should be sufficient.

The later chances of birth after cryoconservation of unfertilised and fertilised oocytes strongly depends on the number of oocytes collected. It has been shown that the number of collected oocytes prior to gonadotoxic treatment is not less than during regular IVF treatment (Lawrenz et al., 2010; Turan et al., 2013) and that stimulation with high effectiveness is possible in all cycle phases (von Wolff et al., 2009b; Cakmak et al., 2013; Germeyer et al., 2014). The register evaluation also showed that the number of collected oocytes has not increased over the years, despite the centres' increasing experience (Figure 4c). Therefore, an increase in pregnancy chances by freezing oocytes will be limited in the future.

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Figures

Figure 1

Total number of counsellings and fertility preservation therapies at universities and non-university centres from 2007 until 2013 (Overall increase of each category: $p<0.0001$).

Figure 2

Characteristics of women counselled. Proportion of women with and without children (2a), distribution of age (2b), of diseases (2c) and of diseases in relation to age (2d) (Overall distribution of diseases and of diseases in relation to age: $p<0.0001$).

Figure 3

Percentage of women who chose the mentioned fertility preservation therapy from 2007 until 2013 (3a), in relation to their child status (3b), their underlying disease (3c) and their age (3d). Note: some women chose more than one therapy.

Figure 4

Details of the different fertility preservation therapies such as GnRHa (4a), ovarian tissue freezing (4b) and ovarian stimulation plus oocyte/zygote freezing (4c). Figure 4a depicts the percentage of women choosing GnRHa as a sole treatment or in combination with other treatments, Figure 4b the percentage of cases in which <1 (less than 1 total ovary) or ≥1 ovary was removed and cryopreserved, and Figure 4c the number of collected oocytes per aspiration on average and in relation to age from 2007 until 2013 (Overall distribution of different

GnRH therapy combinations (4a): p=0.027; overall distribution of cases with <1 or ≥1 ovary removed (4b): p<0.0001; overall distribution of oocytes in the age groups: p<0.0001).