FertiTOX – a retrospective systematic data analysis and a prospective cohort study to implement an internet platform on gonadotoxicity of cancer therapies to improve counselling of patients regarding fertility and fertility preservation by the network FertiPROTEKT

Abstract

Introduction

Cytotoxic treatments such as chemo and radiotherapy but also immune therapies are required in cancer diseases. These therapies have the potential to cure patients, but also have an impact on gonadal function and therefore on fertility. Therefore, fertility preservation treatments such as freezing of oocytes, ovarian tissue, sperm and testicular tissue might be required.

However, data about the necessity to perform fertility preservation treatments is very limited.

Methods and analysis

First, previously published data will be systematically analysed regarding the gonadotoxicity of chemo and radiotherapies in cancer patients.

Second, a prospective cohort study will be set up by around 70 centers in Germany Switzerland and Austria and will collect the following data: Ovarian function will be evaluated by analysing AMH, FSH, LH and E2 concentrations and testicular function by analysing sperm parameters and total testosterone, FSH and LH concentration just before and around 1 year after gonadotoxic therapies (short term fertility).

Follow up of these fertility parameters including history of conceptions will be performed 5 and 10 years after gonadotoxic therapies (long term fertility).

Furthermore, proportion of patients undergoing fertility preserving methods, efficacy and satisfaction with these methods will be analysed.

Third, the data will be merged to create the internet based data platform FertiTOX. The platform will be structured according to the ICD classification of cancer diseases and will be easily accessible using a specific App.

Ethics and dissemination

Ethical approval has been approved by the Cantonal Ethical Committee of Berne, Switzerland (KEK-BE 2022-02284). Data about the progress of the study will be disseminated through a study website www.fertitox.com. The findings will be disseminated through journal articles, conference presentations and the platform FertiTOX.

Strength and limitations of the study

- The platform will present previously published data in a similar and thereby comparable way.
- The prospective data set will be very large, will be based on the same parameters and will include new cancer treatments.
- The internet based platform will be easily accessible by the interested international community.
- The study will also provide data on the efficacy of and the satisfaction with fertility preserving methods.
- Most of the existing data are based on fertility associated parameters such as ovarian reserve and sperm count parameters but not on fertility.

Introduction

Since the first three milestones in fertility preservation had been reached such as the first birth after transplantation of cryo-preserved ovarian tissue (1), the introduction of luteal phase and thereby random start stimulation (2) and vitrification of oocytes (3), fertility preservation treatments have been introduced almost all over the world. Fertility preservation has now been accepted and defined as an important element to be considered before cancer treatments in females and males.

Medically, this has been shown by several national and international guidelines stating that fertility preservation counselling is required before gonadotoxic therapies (4-9).

Politically, this has been shown by many countries which have introduced reimbursement / coverage of fertility preservation treatments.

Different criteria have to be met to recommend fertility preserving treatments. A very important criterium is the risk of infertility due to the gonadotoxicity of the applied cancer therapy (Figure 1). However, data about the gonadotoxicity of the numerous cancer treatment protocols are mostly very limited. A recent study in mice has revealed that even immune therapies such as checkpoint inhibitors have substantial impact in the ovarian reserve (10) but data in humans are not available yet.

Accordingly, indications for or against fertility preserving therapies are not well defined with either the risk of over-treating patients with fertility preservation therapies, imposing unnecessary medical risks and burdens to the patients and therefore unnecessarily postponing the gonadotoxic therapies. On the other hand, the risk of under-treating patients with fertility preservation therapies imposes the risk of infertility, which can have a substantial impact on quality of life after cancer (11).

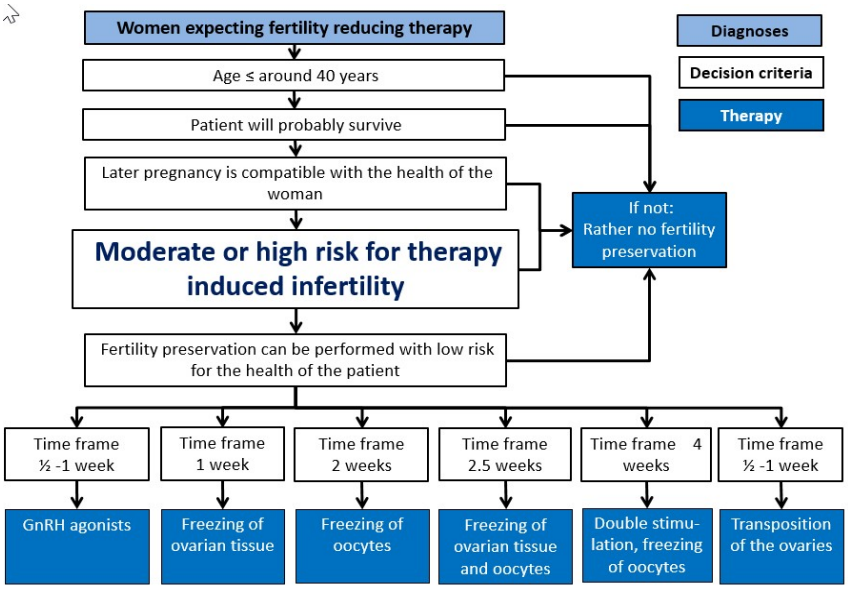
Meanwhile effective methods are available to reliably quantify the gonadotoxicity of cancer therapies. In females ovarian function can be evaluated by analysing AMH, FSH, LH and E2 concentrations and testicular function by analysing sperm counts as well as total testosterone, FSH and LH concentrations.

However, even though these methods are available, a prospective and systematic short and long term data analysis of the impact of cancer therapies on fertility has never been introduced. It can be assumed that this is due to a lack of effective fertility preservation network structures in most countries. However, in Switzerland, Germany and Austria such network structures have been established which permits a systematic and continuous large scale data analysis.

These data should be presented on an easily accessible internet platform merged with already published data on the gonadotoxicity of cancer therapies and other relevant data such as the 5 years survival rates of the cancer diseases. Such a data platform will support physicians and other experts and also patients in counselling about cancer treatment imposed fertility risks and the necessity to undergo fertility preserving measures.

Figure 1

Algorithm for indicating fertility preserving therapies in females (adapted from von Wolff & Nawroth, 12).



Methods and analysis

Study design

The study consist of two parts. First, a series of systematic reviews is performed in Switzerland which are registered at PROSPERO (www.crd.york.ac.uk/prospero/). Second an international multicenter prospective exploratory observational study of fertility related parameters with a long term follow-up of cancer patients` fertility in university and non-university public hospitals and private infertility centers in Germany, Switzerland and Austria.

Study period

The study has been initiated in 2022. Systematic reviews of published data of most ICD classified cancer diseases will be performed until 2025. Prospective data regarding short term fertility will be collected and analysed until 2026/2027 and regarding long term fertility at least until 2036. A first version of the FertiTOX internet platform is expected to be set up in 2025/2026.

Inclusion criteria for contributing centers

Each center that counsels patients regarding fertility issues, that can provide the fertility associated parameters and patients` information shown below in cancer patients and which is willing to add them to the Redcap study registry may participate. Prerequisite requirement is that each center has an Ethical approval for the study. Even though the study is intended to mainly include centers of the FertiPROTEKT (www.fertiprotekt.com) and FERTISAVE (www.sgrm.org/de/kommissionen/fertisave-main-de) networks Germany Switzerland and Austria, any other center worldwide can participate if the inclusion criteria are fulfilled.

Inclusion criteria for patients

- Female and male patients undergoing cancer therapies using chemotherapy, radiotherapy or immune therapy
- Willing to participate
- No language barrier
- Signed consent
- Age 14-50 years

Recruitment and informed consent procedure

Patients are recruited by reproductive physicians, associated to participating infertility centres. Around 70 centers (Germany 44 centers, Switzerland 21 centers and Austria 5 centers) will participate in the study and will collect data (Supplement).

Patients who need gonadotoxic therapies will be counselled before the onset of the therapies. During counselling, patients will be screened for eligibility to be included in the study.

Patients will receive counselling sheets to give informed consent before the onset of the gonadotoxic therapy to collect patients` specific basic data and data on gonadal function. Data will also be collected 12-15 month and 5 and 10 years after gonadotoxic therapy.

The project participants will be informed that they will be contacted by the infertility center or a defined co-worker of the study by telephone, e-mail or by mail to collect the data after the gonadotoxic therapy. The project participants will also be informed that they will not receive any compensations.

Primary and secondary objectives

Primary objective

To analyse if cancer therapies and chemotherapies reduce the AMH concentration (ovarian reserve) and sperm concentration.

Secondary objectives

To analyse the impact of cancer therapies and chemotherapies on other fertility parameters.

To analyse the probability of undergoing fertility preservation treatments in relation to:

- the cancer disease and chemotherapy and the treatment protocol,
- the number of children and the future wish to have children,
- other confounding factors such as age etc.

To assess

- the satisfaction with the decision to have undergone fertility preservation measures or not,
- the proportion of females and males who use their frozen gametes to generate a pregnancy and with what kind of outcome.
- To analyse the effect of different gonadotoxic therapies on long term fertility.

Primary and secondary endpoints

Primary endpoints

To be determined before gonadotoxic treatment and 12-15 months (exceptionally also during cancer therapy) after the end of the gonadotoxic treatments:

- In females the AMH concentration before and after specific gonadotoxic treatments.
- In males the sperm concentration before and after specific gonadotoxic treatments.

Secondary endpoints

To be determined before gonadotoxic treatment and 12-15 months after the end of the gonadotoxic treatments:

- Females: FSH, LH and E2 concentration
- Males: total sperm count, sperm motility

To be determined before gonadotoxic treatment:

- number of patients who freeze oocytes and embryos,
- number of patients who freeze ovarian tissue,
- number of patients who freeze sperm or testicular tissue.

To be determined after gonadotoxic treatment:

- Females: FSH, LH and E2 concentration,
- Males: total sperm count, sperm motility, total testosterone, FSH and LH concentration,
- Satisfaction with the decision to have undergone fertility preservation measures or not.

Long term endpoints

To be determined 5 and 10 years after the end of the gonadotoxic therapy:

- Females: AMH, FSH, LH and E2 concentration,
- Males: total testosterone, FSH and LH concentration and sperm parameters,
- Number of patients who become pregnant spontaneously after gonadotoxic therapies,
- Number of patients who use their frozen gametes and who became pregnant after using the frozen oocytes/embryos/sperm or the frozen tissue.

Sample size calculation

Determination of sample size

A power calculation was performed to assess whether the expected number of patients is sufficient to detect an effect of cancer treatment on fertility with a reasonable power.

The power was calculated for the primary outcome (i.e., sperm concentration for males and AMH for females), for males and females separately. Calculations were performed within each cancer for each treatment protocol separately based on a paired t- test, using Stata (Release 17.0).

No data have been previously published on the effect of cancer treatment on male and female fertility. We set the effect size not to miss a reduction of 50%. For the sperm count where the mean value in healthy men is 64 million with a standard deviation (SD) of 47 (13), this would correspond to an effect size of 0.67. For the AMH concentration where means and standard deviations (SD) can be assumed to be equal (14) it would correspond to an effect size of 0.5. The intraindividual correlation was set to 0.5 (13, 14). To account for multiple testing (analysis will be performed in 43 treatment groups for males and females separately), the Šidák correction was used and adjusted the significance level to 0.0006 (two sided).

Table 1

Expected number of cases and resulting power reached per specific treatments (treatment protocols) in the most common ICD cancer groups (www.krebsdaten.de/Krebs/DE/Home/homepage_node.html).

ICD cancer group	**Cases, n ***	**Specific treatments (treatment protocols), n**	**Effect size (females/ males)****	**Power, % (females/ males)****
Breast	2000	6	0.5/ -	100/ -
Hodgkin`s lymphoma	1000	2	0.5/0.68	100/100
Bone and articular cartilage	400	3	0.5/0.68	98.6/100
Female genital organs	350	3	0.5/ -	96.5/ -
Male genital organs	2000	4	-/0.68	-/100
Digestive organs	200	7	0.5/0.68	14.3/41.4
Mesothelial and soft tissue	200	3	0.5/0.68	67.2/96.7
Eye, brain & central nervous system	300	2	0.5/0.68	99.5/100
Non-Hodgkin's lymphoma	300	8	0.5/0.68	26.2/64.4
Leukaemia	200	5	0.5/0.68	30.6/70.8

* The estimation of the number of cases is based on the number of cases previously counselled and documented in the *Ferti*PROTEKT and FERTISAVE registries.

**Power is calculated for each treatment protocol, for male and female separately. The number of patients per protocol is calculated as the number of cases divided by the number of treatment protocols. The sex ratio is assumed to be 1:1 except for cancer of breast and genital organs.

Table 1 reveals that sufficient power of > 80% will be reached for most treatments.

If the number of cases were twice as high and the intra-patient correlation was 0.7, power > 80% would be reached for all treatment levels.

Data analysis

The impact of cancer therapies and chemotherapies on the primary outcomes will be assessed for each ICD cancer group (www.krebsdaten.de/Krebs/DE/Home/homepage_node.html) and for each specific treatment protocol separately, by comparing values measured before and after the gonadotoxic

therapy using paired t-tests. P-values will be adjusted for multiple testing using the false discovery rate (FDR) controlling procedure.

Consequences on other fertility parameters measured before and 12-15 months after the gonadotoxic therapy (i.e., females: AMH, FSH, LH and E2 concentration, males: total testosterone, FSH and LH concentrations and total sperm count, sperm concentration and motility), will be assessed using the same methodology, but without FDR adjustment. Long term consequences will be investigated later, by comparing values measured before and 5 years and 10 years after the gonadotoxic therapy. However, due to the long time period until the final analysis, statistics might be adapted in relation to future development of cancer and the fertility preservation therapies.

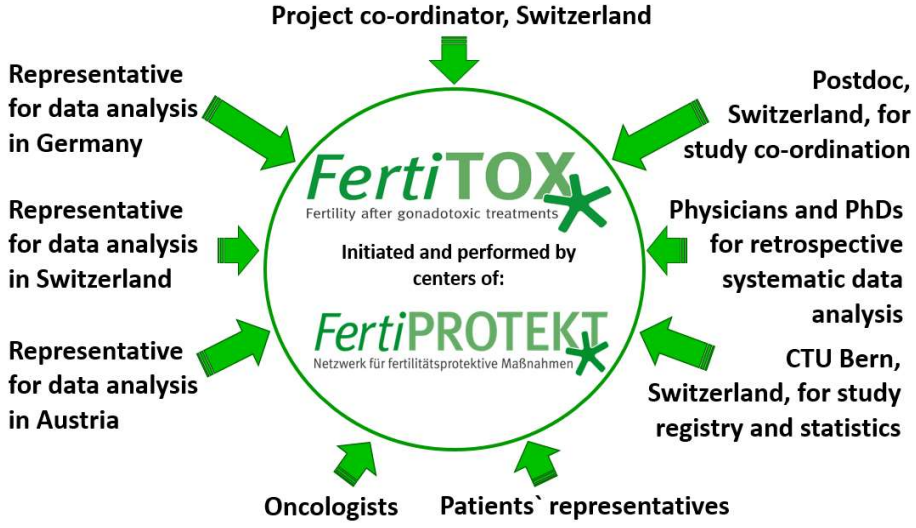
As age was identified to potentially modify the effect of gonadotoxic therapy on female fertility, we will additionally conduct stratified analyses and document the impact of gonadotoxic therapy in the different female age groups.

Finally, the effects of cancers, treatment protocol, age, and own children before cancer therapy on primary and secondary fertility outcomes will be analyzed using linear mixed effect models.

The frequency of patients undergoing fertility preservation treatments, freezing ovarian tissue, oocytes and embryos will be calculated for each ICD cancer group and for each specific treatment protocol separately and presented with the associated 95% Wilson confidence interval. Potential effects of the patients' characteristics on the binary outcomes mentioned above will be analysed using logistic regression.

Figure 2

The consortium of experts which control the project



FertiTOX platform

The FertiTOX platform is an internet based information platform which will be accessible for everybody. The platform will be structured based on the ICD cancer disease groups (Figure 3). The brand name FertiTOX has been registered and the domains www.fertitox.com/de/ch/at/ have already been blocked. A study website is currently being set up with the domain www.fertitox.com.

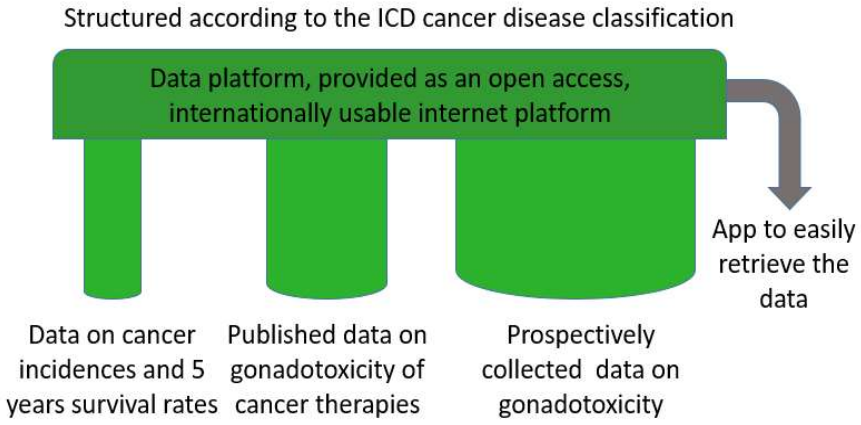
Data of females and males will be presented on the FertiTOX platform in 3 hierarchies:

- 1st hierarchy: Presentation of data regarding incidences and 5 years survival per ICD classified cancer diseases.
- 2nd hierarchy: Presentation of already published data regarding gonadotoxicity and fertility preservation issues regarding specific ICD classified diseases.
- 3rd hierarchy: Presentation of prospective short term and long term data on ovarian reserve and sperm quality before and after gonadotoxic therapies per ICD classified diseases.

Once the internet platform is successfully established, a platform specific App will be developed to retrieve data easily.

Figure 3

The internet platform FertiTOX. The thickness of the columns reflect the clinical relevance of the data.



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