Evaluation of gonadotoxicity of cancer therapies to improve counselling of patients regarding fertility and fertility preservation measures: Protocol for a retrospective systematic data analysis and a prospective cohort study

Michael von Wolff[1*], Ariane Germeyer[2], Bettina Böttcher[3], Isotta Magaton[1], Irene Marcu[1], Janna Pape[1], Nicole Sänger[4], Verena Nordhoff[5], Marie Roumet[6], Susanna Weidlinger[1]

[1]University Women`s Hospital, Division of Gynaecological Endocrinology and Reproductive Medicine, Bern, Switzerland

[2]University Women`s Hospital, Department of Gynaecological Endocrinology and Fertility Disorders, Heidelberg, Germany

[3]Department of Gynaecological Endocrinology and Reproductive Medicine, Medical University of Innsbruck, Austria

[4]University Women`s Hospital, Department of Gynaecological Endocrinology and Reproductive Medicine, Bonn, Germany

[5]University of Münster, Centre of Reproductive Medicine and Andrology, Department of Clinical and Surgical Andrology, Münster, Germany

[6]Clinical Trial Unit, University of Bern, Bern, Switzerland

***Corresponding author:**

Prof. Dr. med. Michael von Wolff

University Women`s Hospital, University of Berne, Switzerland.

E-Mail: Michael.vonwolff@insel.ch

Abstract

Background

Cytotoxic treatments such as chemo- and radiotherapy and immune therapies are required in cancer diseases. These therapies have the potential to cure patients, but may also have an impact on gonadal function and therefore on fertility. Consequently, fertility preservation treatments such as freezing of oocytes, ovarian tissue, sperm and testicular tissue might be required. However, as detailed data about the necessity to perform fertility preservation treatment is very limited the following study was set up to fill this gap of data.

Objectives

Primary objective of the study is to analyse the impact of cancer therapies and chemotherapies on ovarian reserve and on sperm quality. Secondary objectives are to analyse the impact of cancer therapies and chemotherapies on other fertility parameters and to analyse the probability of undergoing fertility preservation treatments in relation to specific cancer diseases and treatment protocol and the probability to use the frozen games and gonadal tissue to achieve pregnancies.

Methods

The following methods will be involved:

First, previously published studies are systematically analysed regarding the gonadotoxicity of chemo- and radiotherapies in cancer patients.

Second, a prospective cohort study has been set up by approximately 70 centres in Germany, Switzerland and Austria and the following data will be collected: evaluation of ovarian function by analysing AMH concentrations and testicular function by analysing sperm parameters and total testosterone just before and around 1 year after gonadotoxic therapies (short-term fertility). A follow up of these fertility parameters including the history of conceptions will be performed 5 and 10 years after gonadotoxic therapies (long-term fertility). Additionally, the proportion of patients undergoing fertility preserving methods, the satisfaction with the methods and the amount of gametes and gonadal tissue and the children achieved by using the frozen material 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 be accessible using a specific App.

Results

Financing of the study is given by several founding bodies. Six systematic reviews are in progress and the first systematic review has been submitted for publication. All Swiss and many ethics committees in Germany and Austria have given their permission for the prospective cohort study. The study registry has been set up and a study website www.fertitox.ch has been uploaded. 50 infertility centers have already been prepared for data collection which has started December 1st 2023.

Conclusions

The study can be expected to fill the data gap of the gonadotoxicity of cancer therapies to better counsel patients regarding their infertility risk and their need of perform fertility preservation measures. First data will be expected to be uploaded on the FertiTOX® platform in 2026.

The trial was registered at ClinicalTrials.gov: NCT05885048.

Background

After reaching the first three milestones in fertility preservation such as the first birth after transplantation of cryo-preserved ovarian tissue [1], the introduction of luteal phase and thereby random start gonadotropin stimulation [2] and vitrification of oocytes [3], fertility preservation treatments have been introduced in most countries and fertility preservation has been accepted and defined as an important element to be considered before cancer treatments (Figure 1).

Medically this has been shown by several national and international guidelines stating that fertility preservation counselling is required before gonadotoxic therapies [4-9] and politically it has been shown as many countries have introduced reimbursement / coverage of fertility preservation treatments.

However, data about the gonadotoxicity of the numerous cancer treatment regimes are mostly very limited. Additionally, a recent study in mice has revealed that immune therapies such as checkpoint inhibitors have substantial impact on ovarian reserve [10], but human data is not yet available.

Accordingly, indications for or against fertility preserving therapies are not well defined with either the risk of over-treating patients with 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 respective 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 in males testicular function is evaluated by analysing sperm counts as well as total testosterone, FSH and LH concentrations.

Even though these functional parameters exist, prospective and systematic short and long term data of the impact of specific cancer therapies on fertility based on these parameters hardly exist. 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 permit a systematic and continuous large-scale data analysis.

Data should be made available as an easily accessible internet platform which is merged with already published data on the gonadotoxicity of cancer therapies and other relevant data such as the 5-year survival rates of the cancer diseases. The data platform will support physicians and other experts and also patients in counselling about fertility risks imposed by cancer treatments and the necessity to undergo fertility preserving measures.

We therefore set up a study to collect data on the gonadotoxicity of cancer therapies by systematically analysing already published data and by setting up an international multicentre prospective cohort

study to collect data in females and males on the gonadotoxicity of chemotherapies, radiotherapies and immune therapies and to upload summarized data on an internet based data platform.

Objectives

Primary objective

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

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

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

Methods

Study design

The study consist of two parts: First, a series of systematic reviews performed in Switzerland, which are registered at PROSPERO (www.crd.york.ac.uk/prospero/). Second, an international multicentre 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 centres in Germany, Switzerland and Austria.

Study period

The study was initiated in 2023. Systematic reviews of published data of most ICD classified cancer diseases will be compiled until 2025. Prospective data regarding short term fertility was started December 1st 2023 and will be collected and analysed until 2028, and long-term fertility data until at least 2036. A first version of the FertiTOX internet platform is expected to be set up in 2026.

Inclusion criteria for contributing centres

Each centre that counsels cancer patients regarding fertility issues and can also provide the fertility associated parameters and patients` information shown below may participate. Prerequisite requirement is that each centre has Ethical approval for the study. Even though the study is intended to mainly include FertiPROTEKT network centres (www.fertiprotekt.com) and FERTISAVE (www.sgrm.org/de/kommissionen/fertisave-main-de) networks in Germany, Switzerland and Austria, any other centre 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 (Figure 1)
- Willing to participate
- No language barrier
- Signed consent
- Age 14-50 years (Germany 18-50 years due to national regulations)

Recruitment and informed consent procedure

Patients are recruited by reproductive physicians who are associated to participating infertility centres. Approximately 70 centres (Germany 44 centres, Switzerland 21 centres and Austria 6 centres) will participate in the study and will collect data (see Supplement I).

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

Furthermore, patients 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 months and 5 and 10 years after the end of gonadotoxic therapy.

The project participants are informed that they will be contacted by the fertility centre or a defined co-worker of the study by telephone, e-mail or by mail to collect the respective data after the gonadotoxic therapy. Participants are informed that they will not receive any compensation.

Study registry

Data will be collected using the RedCap software, a secure web application for building databases (www.project-redcap.org). The RedCap registry has been set up and optimized by the study consortium with the support of the Clinical Trials Unit in Bern, RedCap technicians and statisticians. The contents of the study registry (consultation before and 12-15 months after the end of the gonadotoxic therapy) are shown in the paper version of the registry (Supplements II-V). The participating centers will add the data to the registry without adding any definite identifiers such as

name and date of birth. The participating centers can only see their patients.Patients can be traced with an individual code which is kept safely by the centers. Only very few authorized persons will get access to all data in order to check the data quality and to remind the centers to invite the patients for follow up consultations.

Primary endpoints

To be determined before gonadotoxic treatment and 12-15 months after the end of the gonadotoxic treatments (melanoma patients receiving adjuvant checkpoint inhibitor treatment will be evaluated every 3 months):

- In females, Anti mullerinan hormone (AMH) concentration before and after gonadotoxic treatments.
- In males, perm concentration before and after gonadotoxic treatments.

Secondary endpoints

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

- Females: Follicle stimulating hormone (FSH), Luteinizing hormone (LH) and estradiol (E2) concentration
- Males: total sperm count, sperm motility

To be determined only 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 only 12-15 months after the end of 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 became pregnant spontaneously after gonadotoxic therapies or males who have desired a pregnancy,

- 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

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 calculation was performed 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 entity and for each specific treatment protocol separately based on a paired t- test, using Stata (Release 17.0). We set the effect size so that a relative risk of 50% was not missed. 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 female 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 the significance level adjusted 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 males and females 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. As the study is expected to be extended a sufficient number of patients to reach this goal can be expected.

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 regimes 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 end of 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 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 different cancers, the treatment protocol, age, and the presence of own children before cancer therapy on primary and secondary fertility outcomes will be analysed using linear mixed effect models.

The frequency of patients undergoing fertility preservation treatments, namely freezing of ovarian tissue, oocytes and embryos, testicular tissue and sperm will be calculated for each ICD cancer group and for each specific treatment protocol separately and additionally 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.

Consortium of experts involved in the study

The project is supervised by several experts in Germany, Switzerland and Austria (Figure 2). Each country provides the logistics, manpower and experts to collect and control data collection and analysis. Interpretation of data will be supported by oncologists. Data are added to a RedCap study registry, which is provided by the Clinical Trial Unit Bern, Switzerland which is also responsible for statistical analysis. The data platform will be programmed by an IT company and data presentation will be optimized by the involved experts and by patients` representatives. The data platform called FertiTOX® will be part of the network FertiPROTEKT.

FertiTOX® platform

The FertiTOX® platform is an internet-based information platform that will be accessible for everybody and 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/ will be used. A study website (www.fertitox.com) has been set up.

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 allow easy retrieval of data.

Dissemination

Data about the progress of the study will be disseminated through a study website www.fertitox.com. The findings will be propagated through journal articles, conference presentations and the platform FertiTOX®.

Ethics considerations

Ethical approval is granted by the relevant ethical committees. In Switzerland all seven cantonal ethical committees have given consent for all 21 participating centers. In Germany the ethical committee in

Heidelberg and in Austria the committee in Innsbruck were chosen as national leading ethical committees. Based on the ethical votes approved by these two committees all other participating centers in Germany and Austria submitted an ethical application to their ethical committee.

Written consent is given by the participants. The participants are informed about the processing of data and their rights. The participants also give written consent that anonymized data can be transferred to other registries for further analysis if the other registry have the same high security standards as the RedCap registry. The data are collected in a RedCap study registry that complies with several data security and confidentiality conditions. Specific identifiers are not added to the registry, only the year of birth. The data are stored in Bern, Switzerland.

The participating centers can only access the patient's data they have been added to the registry. The patients can be identified by an individual code, generated by the RedCap system, which is locked in a safe place by the investigator of the participating center. Tracebility of the data is ensured by these identification codes. Patients give permission to be followed up. Patients are only contacted by the center or by authorized personal employed by the principal investigator or the national representatives of the study. Statistical analysis will be based on anonymized data.

No compensation will be offered to users for participating in the study.

Results

By December 1st 2023 the following achievements have been made:

The first systematic review, analysing the impact of cancer therapies on bone tumours has been submitted for publication. Five more systematic reviews have been initiated. They are covering the impact of cancer therapies on fertility in breast cancer, testicular cancer, hodgkins lymphoma, soft tissue cancer and the impact of bone marrow transplantation.

The prospective cohort study has been prepared. All Swiss ethics committees and the leading ethics committees in Germany and in Austria have given their permission. 70 infertility centers (Supplement I) have been prepared for data collection. The study registry has been set up and activated and a study website www.fertitox.ch has been completed.

Financing of the study is given by several funding bodies such as Swiss cancer league (Grant number KLS-5650-08-2022: CHF 349.000,-) and pharmaceutical companies such as IBSA Institut Biochimique SA, Theramex Switzerland GmbH and Ferring AG Switzerland. Pharmaceutical companies are not involved in any issues regarding the study concept, the analysis and the dissemination of data. A grant application has been submitted to the German "Krebshilfe".

Recruitment of patients has started December 1st 2023 and first data will be expected to be uploaded on the Fertitox platform in 2026.

The study has been internationally registered at ClinicalTrials.gov: NCT05885048.

Discussion

The systematic reviews which we have already prepared revealed that data on specific chemotherapy regimes is mostly too limited to allow adequate counselling of patients regarding their infertility risks and their need to perform fertility preservation measures. This finding clearly supports the necessity to perform the large prospective cohort study as described in this manuscript. This cohort study has already successfully been set up and data collection has been started December 1st 2023.

Solid data on the gonadotoxicity of different treatment regimes, mainly in cancer therapies, is the last major deficit in fertility preservation. All other requirements have been established in many countries such as fertility preservation measures and specialized centers to counsel patients and to perform these measures. Furthermore, many oncologists have been sensitized to address the fertility risk of cancer therapies and the possibility to perform fertility preservation measures.

However, what is still missing are comprehensive data about the specific gonadotoxicity of different treatment regimes which are required to counsel patients and to decide if fertility preservation measures should be recommended or not.

Previous studies have addressed fertility issues in cancer patients and the impact of cancer therapies on fertility but these studies are mostly based on spontaneous pregnancies following cancer therapies or are based on data such as the onset of puberty, cycle regularity and on few sperm counts. Studies based on pre- and post-chemotherapy treatment levels of AMH concentration and sperm counts are very limited and mainly limited to female breast cancer patients [15-18].

To close this data gap we set up a study in which we analyse data which have already been published and data which will be collected in at least three countries by centers belonging to the network FertiPROTEKT. The data will be analysed und disseminated via a web based platform called FertiTOX® to give patients, researchers and clinicians access to the analysis which will graphically illustrated. By including patient`s representatives in the data analysis we will ensure that the data will be presented in a way which is also understandable for patients. The data will not only be presented as a single curve presenting the means and showing odd ratios and confidence intervals which presents an average impact of therapies on gonadal function but will also show individual variations by presenting a set of curves.

The study has been designed to follow up patients for at least 10 years. Such a long follow up will enable us to evaluate how many patients have undergone fertility preservation measures but unfortunately did not survive. Furthermore, we will be able to estimate how many patients conceived spontaneously or by using the frozen gametes and gonadal tissue. Such an analysis is essential to evaluate the long term efficacy of fertility preservation counselling and treatment. We are aware that

some patients might be lost from the follow up process. But as the number of included patients is expected to be very high it can be assumed that the amount of data will still be sufficiently high.

The limitation of the study is that data are mainly collected in Germany, Switzerland and Austria. Accordingly, data will not be available for other treatment regimes which are performed elsewhere. However, as other countries are also invited to participate to join this study this limitation could possibly be reduced.

Another limiting factor is that children will not be evaluated. The main reason is that the study is based on AMH values and sperm parameters which can hardly be interpreted in children (AMH) or cannot be collected (sperm).

The last limiting factor is that new therapies are evolving very fast and that new combination therapies combining conventional chemotherapy agents and immune therapies will be developed which will increase the complexity of our data analysis. However, it is expected that this limitation can at least in part be compensated by the prospective design of the study which will include a higher number of new therapies. Furthermore, as checkpoint inhibitors which have been shown to be gonadotoxic in female mice will be analysed separately in women undergoing adjuvant therapy with checkpoint inhibitors for melanoma. These study results can be used to better estimate the gonadotoxicity of combination therapies involving checkpoint inhibitors.

In conclusion,

the study can be expected to fill the data gap of the gonadotoxicity of several therapies and gonadotoxic treatment regimes to better counsel patients regarding their infertility risk and their need of perform fertility preservation measures.

Acknowledgements

We would like to thank all participating centers for their support in preparing this study and collecting data.

Competing interests

No competing interests regarding the study.

Data availability

Participants have given written consent that data can also be analysed by others if sufficient data safety can been confirmed. Accordingly data can be considered by the study consortium to be transferred to others if sufficient data safety has been proven.

References

1 Donnez J, Dolmans MM, Demylle D et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet. 2004;364:1405-10.

3 Cobo A, Meseguer M, Remohí, J et al. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum Reprod. 2010;25:2239-46.

2 von Wolff M, Thaler CJ, Frambach T et al. Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. Fertil Steril. 2009;92:1360-5.

4 Loren AW, Mangu PB, Nohr Beck L et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2013;31: 2500-10.

5 AWMF. German, Austrian, Swiss guideline "Fertilitätsprotektion bei onkologischen Erkrankungen», 2017. Valid until September 30th, 30.09.2022. https://www.awmf.org/uploads/tx_szleitlinien/015-082l_S2k_Fertilitaetserhaltung-bei-onkologischen-Therapien_2017-12-verlaengert.pdf. Last access: April 23rd 2023.

6 Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2019 Dec;112:1022-1033.

7 ESHRE Guideline Group on Female Fertility Preservation, Anderson RA et al. ESHRE guideline: female fertility preservation. *Hum Reprod Open*. 2020;2020:hoaa052.

8 Suzuki N. Clinical Practice Guidelines for Fertility Preservation in Pediatric, Adolescent, and Young Adults with Cancer. International journal of clinical oncology 2019;24: 20-7.

9 Harada M, Kimura F, Takai Y et al. Japan Society of Clinical Oncology Clinical Practice Guidelines 2017 for fertility preservation in childhood, adolescent, and young adult cancer patients: part 1. International journal of clinical oncology 2022;27: 265-80.

10 Winship AL, Alesi LR, Sant S et al. Checkpoint inhibitor immunotherapy diminishes oocyte number and quality in mice. Nat Cancer. 2022;3:1-13.

11 Ussher JM, Perz J. Infertility-related distress following cancer for women and men: A mixed method study. Psychooncology. 2019 Mar;28:607-14.

12 von Wolff M, Nawroth F. Fertility preservation in oncological and non-oncological diseases. Eds. M. von Wolff & F. Nawroth, Springer 1st edition. 2020.

13 Cooper TG, Noonan E, von Eckardstein S et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16:231-45.

14 Segawa T, Omi K, Watanabe Y et al. Age-specific values of Access anti-Müllerian hormone immunoassay carried out on Japanese patients with infertility: a retrospective large-scale study. BMC Womens Health. 2019;19:57.

15 Dezellus A, Barriere P, Campone M, Lemanski C, Vanlemmens L, Mignot L, Delozier T, Levy C, Bendavid C, Debled M, Bachelot T, Jouannaud C, Loustalot C, Mouret-Reynier MA, Gallais-Umbert A, Masson D, Freour T. Prospective evaluation of serum anti-Müllerian hormone dynamics in 250 women of reproductive age treated with chemotherapy for breast cancer. Eur J Cancer. 2017;79:72-80.

16 Perdrix A, Saint-Ghislain M, Degremont M, David M, Khaznadar Z, Loeb A, Leheurteur M, Di Fiore F, Clatot F. Influence of adjuvant chemotherapy on anti-Müllerian hormone in women below 35 years treated for early breast cancer. Reprod Biomed Online. 2017;35:468-474.

17 Trapp E, Steidl J, Rack B, Kupka MS, Andergassen U, Jückstock J, Kurt A, Vilsmaier T, de Gregorio A, de Gregorio N, Tzschaschel M, Lato C, Polasik A, Tesch H, Schneeweiss A, Beckmann MW, Fasching PA, Janni W, Müller V. Anti-Müllerian hormone (AMH) levels in premenopausal breast cancer patients treated with taxane-based adjuvant chemotherapy - A translational research project of the SUCCESS A study. Breast. 2017 Oct;35:130-135.

18 Zhou B, Kwan B, Desai MJ, Nalawade V, Ruddy KJ, Nathan PC, Henk HJ, Murphy JD, Whitcomb BW, Su HI. Long-term antimüllerian hormone patterns differ by cancer treatment exposures in young breast cancer survivors. Fertil Steril. 2022;117:1047-1056.

Figures

Figure 1

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

Figure 2

The consortium of experts which control the project

Figure 3

The internet platform FertiTOX which will be used to distribute the data

Supplement I

Centers participating the prospective cohort study (in alphabetical order)

Supplement II

RedCap registry: Documentation in females before gonadotoxic therapy

Supplement III

RedCap registry: Documentation in males before gonadotoxic therapy

Supplement IV

RedCap registry: Documentation in females 12-15 months after the end of gonadotoxic therapy

Supplement V

RedCap registry: Documentation in males 12-15 months after the end of gonadotoxic therapy

Supplement I

Centers participating the prospective cohort study (in alphabetical order)

Germany

- Aachen: Universitätsklinik RWTH Aachen, Frauenklinik für Gynäkologische Endokrinologie und Reproduktionsmedizin – Dr. med. Nele Freerksen-Kirschner
- Berlin: Charité Universitätsmedizin Berlin, Centrum für Frauen-, Kinder- und Jugendmedizin mit Perinatalzentrum und Humangenetik, Klinik für Gynäkologie mit Zentrum für onkologische Chirurgie - Prof. Dr. med. Jalid Sehouli, Dr. med. Judith Altmann
- Berlin: Fertility Center Berlin - Prof. Dr. med. Heribert Kentenich, Dr. med. Andreas Tandler-Schneider
- Berlin: Kinderwunschzentrum an der Gedächtniskirche Berlin - Dr. med. Matthias Bloechle, Dr. med. Silke Marr
- Bielefeld: Bielefeld Fertility Center - Dr. med. Karl Völklein
- Bonn: Universitätsklinikum Bonn, Venuskind am UKB, Kinderwunschzentrum - Prof. Dr. med. Nicole Sänger, Dr. med. Julia John
- Bremen: Klinikum Bremen Mitte, Klinik für Gynäkologie - Dr. med. Mustafa Aydogdu
- Dortmund: MVZ Kinderwunschzentrum Dortmund GmbH - Prof. Dr. med. Stefan Dieterle
- Dresden: Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe - Dr. med. M. Goeckenjan-Festag
- Düsseldorf: Universitätsklinikum Düsseldorf, UniKid Universitäres Interdisziplinäres Kinderwunschzentrum Düsseldorf - Prof. Dr. med. Jan-Steffen Krüssel
- Erlangen: Uniklinikum Erlangen, Frauenklinik - Prof. Dr. med. Ralf Dittrich
- Frankfurt: Re-Pro Gyn Universitätsklinikum Frankfurt - Dr. med. Rahila Nuriyeva, Dr. med. Aynura Abbasova-Semiz
- Freiburg: Universitätsklinikum Freiburg, Klinik für Frauenheilkunde - Dr. med. Philipp Wiehle, Dr. med. Jasmin Asberger
- Gießen: UKGM Universitätsklinikum Gießen und Marburg GmbH, Standort Gießen, Klinik und Poliklinik für Urologie, Kinderurologie und Andrologie - Prof. Dr. med. H.-Chr. Schuppe, Prof. Dr. med. A. Pilatz, Prof. Dr. Florian Wagenlehner
- Gießen: UKGM Universitätsklinikum Gießen und Marburg GmbH, Standort Marburg, Klinik für Frauenheilkunde und Geburtshilfe - Prof. (apl.) Dr. med. Volker Ziller
- Göttingen: UMG Universitätsmedizin Göttingen, Klinik für Gynäkologie und Geburtshilfe - Priv.-Doz. Dr. Dr. G. Bauerschmitz
- Greifswald: Universitätsmedizin Greifswald, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe – Prof. Dr. med. Marek Zygmunt
- Halle: Universitätsklinikum Halle (Saale), Zentrum für Reproduktionsmedizin und Andrologie (ZRA) – Univ.-Prof. Dr. med. Hermann M. Behre
- Hamburg: amedes experts hamburg Facharzt-Zentrum für Kinderwunsch, Pränatale Medizin, Endokrinologie und Osteologie - Prof. Dr. med. Frank Nawroth
- Hannover: MHH Medizinische Hochschule Hannover, Klinik für Frauenheilkunde und Geburtshilfe – Prof. Dr. Cordula Schippert, Prof. Dr. Frauke von Versen-Höynck
- Heidelberg: Universitätsklinikum Heidelberg NCT National Center for tumor diseases Heidelberg - Prof. Dr. med. Carsten Müller-Tidow und Prof. Dr. med. Andreas Schneeweiss
- Hildesheim: Zentrum für Reproduktionsmedizin und Humangenetik Hildesheim - Dr. med. Jan-Simon Lanowski
- Karlsruhe: Städtisches Klinikum Karlsruhe, Frauenklinik - Prof. Dr. med. Andreas Müller
- Kassel: MVZ Medizinisches Versorgungszentrum für Reproduktionsmedizin am Klinikum Kassel - Dr. med. Marc Janos Willi, Dr. med. Oswald Schmidt

- Kiel: Universitäres Kinderwunschzentrum Kiel Lübeck Manhagen - Priv.-Doz. Dr. med. Sören von Otte
- Köln: MVZ PAN-Institut Köln - Dr. Irene Pütz
- Köln: Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe Klinikum der Universität zu Köln (AöR) - Prof. Dr. med. Gohar Rahimi
- Leipzig: Universitätsklinikum Leipzig, Klinik für Dermatologie, Venerologie und Allergologie - Prof. Dr. med. Sonja Grunewald
- Lübeck: Universitätsklinikum Schleswig-Holstein, Sektion für gynäkologische Endokrinologie und Reproduktionsmedizin - Prof. Dr. med. Georg Grisinger
- Magdeburg: Universitätsklinikum Magdeburg A.ö.R., Universitätsklinik für Frauenheilkunde, Geburtshilfe und Reproduktionsmedizin – Carina Strecker
- Mainz: Universitätsmedizin Mainz, Universitäts-Kinderwunschzentrum und Ambulanz für Gynäkologische Endokrinologie und Reproduktionsmedizin –
- Prof. Dr. med. Christine Skala, Dr. med. Susanne Theis
- München: Kinderwunschzentrum A.R.T. Bogenhausen – Dr. med. Stephanie Ziehr
- München: LMU Klinikum der Universität München, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, endo-repro-med – Univ.-Prof. Dr. med. Christian J. Thaler, Prof. Dr. med. Nina Rogenhofer
- München: TUM Klinikum rechts der Isar, Technische Universität München, Klinik und Poliklinik für Frauenheilkunde - Prof. Dr. med. Vanadin Seifert-Klauss, Prof. Dr. med. Marion Kiechle
- Münster: UKM Universitätsklinikum, Münster Kinderwunschzentrum – Prof. Dr. med. Hermann M. Behre
- Münster: UKM Universitätsklinikum, Münster Centrum für Reproduktionsmedizin und Andrologie – Prof. Dr. rer. nat. Stefan Schlatt, Prof. Dr. med. Sabine Kliesch
- Oldenburg: Tagesklinik Oldenburg – Dr. med. Jörg Hennefründ (Dipl. Biologin Gabriele Remek)
- Regensburg: Profertilita Fachklinik für Fruchtbarkeitsmedizin – Dr. med. K. Gisch-Pratsch, Dr. med. Ch. Reißmann
- Rostock: Praxiszentrum Frauenheilkunde – Priv. Doz. Dr. med. Heiner Müller, Dr. med. Anne Koenen
- Saarland: Universitätsklinikum des Saarlandes, Klinik für Frauenheilkunde, Geburtshilfe und Reproduktionsmedizin Homburg/ Saar – Dr. Simona Baus
- Tübingen: Department für Frauengesundheit Tübingen – PD Dr. Melanie Henes
- Ulm: UULM Universitätsklinikum Ulm Klinik für Frauenheilkunde und Geburtshilfe – Prof. Dr. med. Katharina Hancke
- Wiesbaden: MVZ TFP Rhein-Main GmbH, TFP Kinderwunsch Wiesbaden – Karin Schilberz
- Würzburg: Universitätsklinikum Würzburg Zentrum für gynäkologische Endokrinologie und Reproduktionsmedizin – Dr. med. Michael Schwab

<u>Switzerland</u>

- Baden-Dättwil: Baden Täfernhof - Dr. Mischa Schneider
- Basel: Regio Basel - Dr. Erika Ocon
- Basel: Universitätsspital Basel - Dr. Ursula Gobrecht–Keller
- Bern: Inselspital - Prof. Michael von Wolff
- Bern: Lindenhofspital - Dr. Eli Berger
- Biel: CARE - Dr. Susanna Crazzolara
- Chur: Kantonsspital Graubünden - Dr. Naomi Ventura
- Fribourg: HFR - PD Dr. Dorothea Wunder
- Genève: HUG - Dr. Federico Del Vento
- Küsnacht: GYNE INVITRO - Dr. Michael Singer

- Lausanne: CHUV - Dr. Anna Surbone
- Lausanne: CPMA - Dr. Nicolas Vulliemoz
- Locarno: Centro Cantonale di Fertilità - Dr. Alessandro Santi
- Luzern: Kantonsspital Luzern - PD Dr. Alexandra Kohl Schwartz
- Luzern: Klinik St. Anna - Dr. Sabine Steimann
- Olten: Fertisuisse - PD Dr. Gideon Sartorius
- St. Gallen: Yuna - Dr. Vera Hungerbühler
- Winterthur: Admira, Winterthur - Dr. Monika Fäh
- Zürich: 360 Grad, Zürich - Dr. Florian Götze
- Zürich: GYN-A.R.T. AG - Dr. Moritz Suerdieck
- Zürich: OVA - IVF Clinic - Dr. Michael Singer

Austria

- Graz: Medical University Graz - Dr. M. Neumayer
- Innsbruck: Medical University of Innsbruck - PD Dr. Bettina Böttcher
- Linz: Johannes Kepler University Linz - PD Dr. O. Shebl
- Salzburg: Private Medical University, Salzburg - Dr. K. Winkler- Crepaz
- Wien: Medical University of Vienna - PD Dr. J. Marschalek