Preserving ovARian function through cryoprEservation and informing girLs with cancer about infertility due to gonadotoxic treatment

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Patients will be included in 3 prospective cohorts, cohort A, B, C and 1 retrospective cohort, cohort 0. Cohort A: The primary objective of cohort A is to show that by implementing a standard infrastructure all newly diagnosed girls with cancer (or…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON52464

Source
ToetsingOnline

Brief title
PAREL

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Sexual function and fertility disorders

Synonym
childhood cancer, pediatric oncology

Health condition

alle kinderkanker

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie
Source(s) of monetary or material Support: Prinses Maxima Centrum en particuliere donaties via Stichting Steun

Intervention

Keyword: evaluation of care, fertility, ovarian tissue cryopreservation (OTC), pediatric oncology

Outcome measures

Primary outcome

Cohort A

Primary endpoint:

- Percentage of girls diagnosed with cancer who received fertility information

(verbal and written information), by documenting:

- Percentage of girls diagnosed with cancer who received fertility

information (verbal and written information)

Cohort B

Primary endpoint

- Percentage of girls to whom fertility counselling is offered prior to start

gonadotoxic treatment and who received additional fertility counseling by

fertility expert.

Cohort C

Primary endpoint: Evaluation of OTC in a national cohort

- Rate of complications within one month of the surgery and relatable to the surgery with CTCAE score of 3 or above, including:
- bleeding requiring blood transfusion or other treatment,
- bowel perforations requiring additional surgery or inter-operative repair,
- infection requiring antibiotics within one week of the surgery,
- other complications relatable to the surgery with CTCAE score of 3 or above.
- Percentage longer hospitalisation (in days) due to complications of the OTC,
- Percentage of laparoscopic procedures vs. laparotomic procedures,
- Delay in initiation of oncological treatment (days)(median range),
- Determinants of delay in initiation of oncological treatment (>48h),
- Success rate of combination of OTC with planned anesthesia/surgery (percentage of procedures).

Cohort 0

Primary endpoint:

- Percentage of girls diagnosed with cancer who received fertility information (verbal and written information).

Secondary outcome

Cohort A

Secondary endpoints:

- To determine characteristics of patients receiving fertility information, by documenting:

- Time interval between cancer diagnosis and fertility information (days)

- Percentage of girls in which fertility information is offered within 24-48 hours from diagnosis/treatment conversation (working days)

- Percentage of girls in which information is offered prior to start gonadotoxic treatment

- Percentage of girls with respectively low risk, intermediate risk and high risk of developing primary ovarian insufficiency (POI): premature menopause or acute ovarian failure (AOF) after cancer treatment

- to evaluate the impact of receiving information regarding fertility at the time of cancer diagnosis using standard of care questions in KLIK at the end of treatment and qualitatively analyzing these and documenting the percentage of girls > 12 year and parents who perceive to be well informed on their risk of infertility,

- to determine the influence of diagnosis and treatment on the remaining gonadal reserve, reflected by anti-müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol and luteinizing hormone (LH) levels and menstrual cycles (secondary amenorrhea) and longitudinal hormone level development over time, at diagnosis and after cessation of treatment.

Cohort B

Secondary endpoints:

- To determine characteristics of patients receiving fertility counseling,

- To evaluate the motivation for choosing for or against OTC 1-2 months (range 1-6 months) after counseling and identification of the barriers to referral for

counseling and for OTC, and at what stage of the referral pathway such barriers occurred

- To evaluate the impact of receiving fertility counseling fertility at the time of cancer diagnosis 1-2 months (range 1-6 months) after counseling and qualitatively analyzing these and documenting the percentage of girls > 12 year and parents who perceive to be well informed on their risk of infertility.
- to determine the influence of diagnosis and treatment on the remaining gonadal reserve, reflected by anti-müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol and luteinizing hormone (LH) levels and menstrual cycles (secondary amenorrhea) and longitudinal hormone level development over time, at diagnosis, after cessation of treatment and 1 year after cessation of treatment.

Cohort C

Secondary endpoints:

- to determine the number of OTC*s performed and the characteristics of patients undergoing OTC.
- to determine the influence of OTC on the remaining gonadal reserve, reflected by anti-müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol and luteinizing hormone (LH) levels and menstrual cycles (secondary amenorrhea).
- to biobank all of rest material after preparation of the tissue for clinical-use-cryopreservation (medulla tissue and tuba tissue).
- to biobank for research up to 15% of the harvested ovarian tissue.

The research on the 15% and rest material is focused on the safety and efficacy of future use of the tissue and may include, but is not limited to, identification of the presence of minimal residual disease (MRD) in the ovarian tissue (Supplemental Table S1), the presence of follicles in various stages in the medullar tissue, the viability of the germ cells and explore the techniques of ex vivo maturation of follicles in the cortex and medulla.

- Check for MRD. Supplemental Table S1 describes the currently available targets, and investigate whether the MRD presence in the ovarian cortex is also present in the medullar tissue.
- The number of follicles in various stages in the harvested ovarian tissue in the cortex and medulla
- To develop the optimal tools to identify and propagate oocytes in and from this tissue to allow and enhance the probability of autologous transplantation in the future if infertility has become apparent.
- To gain insight in the molecular profile of oocytes and supportive cells, before and after propagation in vitro to develop the most optimal and safe standard operation protocol for oocyte isolation and in vitro propagation, to prepare for optimal circumstances of oocytes to mature.

Cohort 0

Secondary endpoint:

- To describe characteristics of girls who did and did not receive fertility information.

- To evaluate in the counseled subset the motivation for choosing for or against OTC after counseling and identification of the barriers to referral for counseling and for OTC, and at what stage of the referral pathway such barriers occurred

- To evaluate the impact of receiving fertility counseling fertility at the time of cancer diagnosis after counseling and qualitatively analyzing these and documenting the percentage of girls > 12 year and parents who perceive to be well informed on their risk of infertility in the counseled subset.

Study description

Background summary

Childhood cancer treatment has resulted in excellent survival rates over the past decades. Hence, awareness for serious early and long term toxicity is increasing. Impaired fertility potential is one of the most relevant long term morbidities as rated by survivors and their families. Currently, at presentation of a new child with cancer, the focus is on an optimal and rapid diagnostic process, in order to start treatment as soon as possible. In that process, informing the girl with cancer and her family about toxicity of the treatment, and in particular about the risk of potential gonadal damage, does not always have the highest priority in pediatric oncology care.

This needs to be urgently changed, as patients and their families benefit from knowing when the risk is low, as that gives them, at least some, relief. On the other hand, subsets of patients with high risk of gonadal damage may benefit from referral to fertility experts, who may advise them to preserve gonadal material, for future purpose, preferably before childhood cancer treatment is started. Of course this requires careful consideration in terms of potential delays in anti-cancer treatment, balanced against the time required for fertility counselling and preservation. However, in principal, a standard infrastructure is needed to identify, assess on risk, inform all girls with cancer and their families, counsel and offer preservation if applicable. Thus a fertility care plan has been developed in the Princess Máxima Center.

Preservation options such as oophoropexy and oocyte vitrification are widely accepted as standard of care, but for many patients not an appropriate option

for preservation. Recently, preservation methods, such as ovarian tissue cryopreservation (OTC), have become available for children potentially at risk for gonadal damage. Currently, for prepubertal girls with cancer, OTC is the only possible way to potentially guarantee future biological offspring, by utilizing the preserved ovarian tissue for auto-transplantation in the future. Worldwide more than a 1000 children have undergone OTC without any major complications and 298 (29%) were under the age of 13 years at time of harvest. However, there is limited experience with autotransplantation of ovarian tissue in girls and adolescents, thus outcome, efficacy and safety data in large cohorts in this age group have not been published. In addition, 200 births after auto-transplantation of OTC material, harvested in postpubertal women, have been reported. Sixteen girls in which OTC was performed prepubertally or peripubertally already underwent ovarian tissue transplantation (OTT) with the aim to restore fertility, which led to 11 pregnancies and 9 live births. specifically. OTC in adult women and girls is considered safe and the Princess Máxima Centre offers OTC as standard of care. However, remaining challenges regarding autotransplantation of ovarian tissue include the infiltration of tumor cells in the harvested ovary, loss of primordial follicles in the neovascularization period after OTT and the options regarding oocytes in the medulla. Generally, medullar tissue is not cryopreserved for future use, however, it can be used to detect minimal residual disease (MRD) in the ovary and to develop maturation techniques. We aim to biobank all rest material after preparation of the tissue for cryopreservation (medulla tissue) and biobank 15% of the harvested ovarian tissue. The research on the 15% and rest material is focused on the safety and efficacy of future use of the tissue and may include, but is not limited to, identification of the presence of minimal residual disease (MRD) in the ovarian tissue (Supplemental Table S1), the presence of follicles in various stages in the medullar tissue, the viability of the germ cells and explore the techniques of ex vivo maturation of follicles in the cortex and medulla.
A gap of knowledge exists in the field of fertility care and OTC as a fertilty preservation method and this study aims to fill these gaps.

Study objective

Patients will be included in 3 prospective cohorts, cohort A, B, C and 1 retrospective cohort, cohort 0.
Cohort A:
The primary objective of cohort A is to show that by implementing a standard infrastructure all newly diagnosed girls with cancer (or relapse) and their families can be informed on fertility in a structured manner by the navigator (nurse practitioner), prior to the start of gonadotoxic cancer treatment about their particular risk of fertility impairment due to their gonadotoxic treatment.
The secondary objectives of cohort A are:
- to describe the impact of receiving information regarding fertility at the time of cancer diagnosis (at the end of treatment in the Kwaliteit van Leven In

Kaart (KLIK) portal),
- to determine the influence of diagnosis and treatment on the remaining gonadal reserve, reflected by anti-müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol and luteinizing hormone (LH) levels and menstrual cycles (secondary amenorrhea) at diagnosis and end of treatment.

Cohort B:
The primary objective of cohort B is to offer counseling about fertility preservation by the gynecologist to all families with a child with an intermediate to high risk of infertility, which is clinically evaluated according to the Edinburgh criteria and CED due to gonadotoxic treatment.
The secondary objectives of cohort B are:
- to explore the reasons for the decision to preserve or not,
- to qualitatively describe the impact of receiving information regarding fertility at the time of cancer diagnosis combined with the counseling (1 - 2 months (range 1-6 months) after counseling).
- to determine the influence of diagnosis and treatment on the remaining gonadal reserve, reflected by anti-müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol and luteinizing hormone (LH) levels and menstrual cycles (secondary amenorrhea) at diagnosis, end of treatment and 1 year after the end of treatment.

Cohort C:
The primary objective of cohort C is to provide safety data on the OTC procedure in a large pediatric oncology population with respect to surgical complications of ovarian tissue (OT) harvest for cryopreservation of ovarian tissue within one month of the surgery and relatable to the surgery, including the delay in initiation of cancer treatment.
The secondary objectives of cohort C are:
- to describe the number of OTC*s performed and the characteristics of patients undergoing OTC,
- to determine the influence of OT harvest on the remaining gonadal reserve, reflected by anti-müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol and luteinizing hormone (LH) levels and menstrual cycles (secondary amenorrhea)
- to biobank all of rest material after preparation of the tissue for clinical-use-cryopreservation (medulla tissue and tuba tissue).
- to biobank for research up to 15% of the harvested ovarian tissue.
The research on the 15% and rest material is focused on the safety and efficacy of future use of the tissue and may include, but is not limited to, identification of the presence of minimal residual disease (MRD) in the ovarian tissue (Supplemental Table S1), the presence of follicles in various stages in the medullar tissue, the viability of the germ cells and explore the techniques of ex vivo maturation of follicles in the cortex and medulla.
- Check for MRD. Supplemental Table S1 describes the currently available targets, and investigate whether the MRD presence in the ovarian cortex is also

present in the medullar tissue.
- The number of follicles in various stages in the harvested ovarian tissue in the cortex and medulla
- To develop the optimal tools to identify and propagate oocytes in and from this tissue to allow and enhance the probability of autologous transplantation in the future if infertility has become apparent.
- To gain insight in the molecular profile of oocytes and supportive cells, before and after propagation in vitro to develop the most optimal and safe standard operation protocol for oocyte isolation and in vitro propagation, to prepare for optimal circumstances of oocytes to mature.

Cohort 0:
The primary objective of the retrospective cohort 0 is to evaluate the fertility care since the opening of the Princess Máxima Center in 2015 by documenting number of informed patients
The secondary objectives of cohort 0 are:
- to describe the characteristics of informed and non-informed patients,
- to explore the reasons for the decision to preserve or not in counseled patients since the opening of the Princess Máxima Center in 2015,
- to qualitatively describe the impact of receiving information regarding fertility at the time of cancer diagnosis combined with the counseling in counseled patients since the opening of the Princess Máxima Center in 2015.

Study design

Prospective longitudinal observational registry study design (cohort A,B,C). Retrospective chart review in the first year of fertility care after opening of the Maxima (cohort 0).

Study burden and risks

For patients in cohort A, B, C and the counseled subset of 0 extent and burden are low. Cohort A receives standard of care only and no informed consent is obtained. A blood sample (LH, FSH, estradiol and AMH levels) will be taken from patients in cohort B and C as part of the research protocol one year after cessation of treatment, if possible using existing vascular access ports, at times when blood is collected for diagnostic/therapeutic purposes. In cases that OTC is performed, one additional blood sample is collected the next day preferably 27 hours after preservation (the timing may be altered for the individual patient). Approximately at the end of the treatment patients and parents in cohort A will answer a few questions in KLIK as SOC. 1-2 months (range 1-6 months) after counseling patients and parents in cohort B are asked to fill out a questionnaire on the impact of fertility information and fertility counselling and the reason for the decision for or against fertility preservation. Information concerning menses, weight and general health will be collected at these time points during a routine visit at the outpatient clinic.

Benefits for the participants receiving the standard of care fertility care may include a better knowledge on whether they carry a lower or higher risk of gonadal impairment which may positively influence quality of life during and after treatment, because patients and parents are informed on the effect of cancer treatment on fertility. Another benefit is that patients and parents have the possibility to improve fertility care and contribute to better fertility care and preservation options for future patients. Preservation options such as oophoropexy and oocyte vitrification are often not feasible for children. Ovarian tissue cryopreservation (OTC) is therefore the only option to preserve fertility and offered as SOC in the Princess Máxima Center.

To ensure standardized measurements and a complete follow up, all patients will be invited to the outpatient clinic at the Princess Máxima Centre for follow-up at these time points. (i.e. they will not go to *shared care hospitals* for follow up at these time points.)

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

Informed consent will only be asked of patients in cohort B, C and the counseled subset of cohort 0.
- Female gender
- Age 0-18 years
- Confirmed new diagnosis of pediatric cancer or relapse since start of the study or counseled since the opening of the Princess Máxima Center in 2015.

Additional inclusion criteria for cohort A
- none

Additional inclusion criteria for cohort B
- Written informed consent
- Intermediate to high risk of infertility defined as >50% risk of infertility or Premature Ovarian Insufficiency (POI) and received counseling by a fertility specialist.
- Low risk of infertility (<50%) with a strong wish for additional fertility counseling and received this counseling

Additional inclusion criteria for cohort C (OTC)
- Written informed consent
- Indication for gonadotoxic treatment
- Counselled regarding fertility preservation by a fertility specialist
- Opted for OTC

Additional inclusion criteria for cohort 0
- Patients newly diagnosed with pediatric cancer or relapse since the opening of the Princess Máxima Center in 2015 and start of the study or have undergone OTC or haven been counseled between the opening of the Princess Máxima Center in 2015 and the start of the study. Written informed consent will be asked from the counseled subset of cohort 0.

Exclusion criteria

Additionally a subject who meets any of the following criteria will be excluded from participation in the subgroup C opting for OTC
- Parents and/or patients > 12 years unable to understand the treatment-

and/or study information even in the presence of an interpreter

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-12-2020
Enrollment:	515
Type:	Actual

Ethics review

Approved WMO Date:	22-01-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-12-2022
Application type:	Amendment

Review commission: METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL72115.041.19
Other	NL8192