Reproductive function, ovarian reserve and risk of premature menopause in Dutch female childhood cancer survivors

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Ethical review	Approved WMO
Status	Pending
Health condition type	Endocrine disorders of gonadal function
Study type	Observational invasive

Summary

ID

NL-OMON31794

Source
ToetsingOnline

Brief title
n.v.t.

Condition

- Endocrine disorders of gonadal function
- Nervous system neoplasms benign
- Reproductive tract disorders NEC

Synonym
fertility and ovarian reserve

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: KWF Kankerbestrijding

Intervention

Keyword: childhood cancer, fertility, ovarian reserve, premature menopause

Outcome measures

Primary outcome

Sexual activity, childwish at time of completion of the questionnaire, mean time to pregnancy, pregnancy resulting in live birth (yes/no), number of pregnancies, duration of pregnancy, risk of specific adverse pregnancy outcomes (miscarriage, stillbirth), birth weight, age at menopause, age at start of different stages of the menopausal transition, risk of menopause before the age of 40, hormonal levels in blood, uterus volume, and the number of antral follicles as assessed by ultrasound.

Secondary outcome

n.v.t.

Study description

Background summary

Advances in childhood cancer treatment over the past decades have significantly improved survival, resulting in a rapidly growing group of childhood cancer survivors (CCS). There is much concern, however, about the effects of treatment on reproductive potential. In females there is evidence that both chemo- and/or radiotherapy may adversely affect ovarian function, ovarian reserve and uterine function, clinically leading to sub- or infertility, premature menopause and/or adverse pregnancy outcomes.
In the literature to date, ovarian function and reserve are traditionally assessed by measurements of the pituitary and sex hormones. These markers, however, are of limited value when aiming to assess reproductive potential and risk of premature menopause. New techniques (ultrasound measurements of the ovaries and serum anti-Müllerian hormone (AMH) concentrations), which may

provide a better insight into ovarian function and reserve, are currently restricted to research or to the assisted reproduction setting and have, to our knowledge, rarely been used in CCS. In addition, the issue of premature menopause has only gained attention in recent years since it is only now that the first generation of female CCS is reaching their 40*s. Only two large questionnaire-based studies have suggested a relationship between treatment and risk of premature menopause. However, with the current Dutch trend to postpone childbearing to the thirties, more insight into the effect of various cancer treatments on ovarian reserve is important, not only to prevent involuntary childlessness but also to prevent menopause-associated conditions such as symptoms of oestrogen deficiency, osteoporosis and cardiovascular disease.

Study objective

The overall aim of this study is to examine, in adult female CCS in the Netherlands, the effects of treatment in general, and the effects of different types of treatment, doses of drugs, radiation sites and doses, and age at time of treatment, on: 1) ovarian function and actual fertility; 2) ovarian reserve and premature menopause; 3) uterine function and pregnancy outcome.
This will enable us to:
• provide adequate counseling on family planning to female CCS
• identify subgroups of female CCS who are at high risk of premature menopause and, therefore, are potential candidates for future testing of ovarian function and
reserve

Study design

The study, set up as a retrospective cohort study, is coordinated by the VU university medical center (VUmc), but performed in collaboration with the Dutch Paediatric Oncology - and Stem Cell Transplant Centers, which are united in a nationwide collaborative group for Late Effects Registration of Childhood Cancer (LATER). Each center screens their CCS for late effects of treatment on a regular basis with the intention to provide early diagnosis and treatment, and to register morbidity in survivors in order to quantify treatment-specific risks.

The study consists of two parts: a questionnaire and a clinical part. Eligible CCS will receive a study invitation letter explaining the questionnaire survey and the clinical study. In the clinical study, ovarian function and reserve will be assessed from 1) blood levels of the hypothalamic-pituitary hormones, sex hormones, inhibin A an B, and AMH, a novel marker of ovarian reserve exclusively expressed in the gonads; 2) ultrasound measurements of ovarian volume and the number of antral follicles in the ovaries. Uterine size and blood flow, also assessed by ultrasound, will evaluate uterine function while actual fertility, pregnancy outcomes and menopausal status will be assessed

from the mailed questionnaire.

In statistical analysis we will compare the outcomes of interest between the 5-year CCS and the control group and calculate the risks associated with specific treatments within the CCS group.

Study burden and risks

Judging from the many questions female childhood cancer survivors have at the different Late Effects of Treatment Outpatient Clinics in the Netherlands, many young female CCS have serious concerns about their reproductive potential. Since relatively little research has been performed in the area of female reproductive potential and premature menopause after treatment for childhood cancer, many of these questions remain unanswered.

With relatively simple methods (a questionnaire, a blood sample, and a transvaginal ultrasound of the reproductive organs), which are not associated with high burden or risk, it is possible to assess female fertility, reproductive function and ovarian reserve.

This increased knowledge should lead to adequate counseling on family planning and use of hormone replacement therapy. Potentially this study will also contribute to the improvement of current gonadotoxic treatment protocols without compromising survival but with improved quality of life.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Female
Treated for malignancy or a central nervous system tumour before the age of 18
Treated between 1965 and 2001
5-year survivors
At least 18 years at study entry

Exclusion criteria

For questionnaire:
- survivors who do not speak or read Dutch
- survivors with severe mental sequelae
For the clinical part of the study (blood sample and transvaginal ultrasound)
- females who have had both ovaries removed
- females who are pregnant or lactating at time of study
- females who have not had sexual intercourse are excluded from the ultrasound measurement

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2006
Enrollment:	1250
Type:	Anticipated

Ethics review

Approved WMO Date:	04-01-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-03-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-05-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL15106.029.06