GONADAL FUNCTION AND FERTILITY IN CHILDREN WITH HODGKIN LYMPHOMA TREATED ACCORDING TO THE EURONET-PHL-C2 PROTOCOL

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The primary aim of this study is to assess the overall, and treatment arm specific, gonadotoxic potential of the protocol in both boys and girls treated for classical Hodgkin Lymphoma in Europe. Secondary aim is to evaluate the frequency of various...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gonadotrophin and sex hormone changes
Study type	Observational invasive

Summary

ID

NL-OMON54649

Source
ToetsingOnline

Brief title
Fertility study EuroNet-PHL-C2 protocol

Condition

- Gonadotrophin and sex hormone changes

Synonym
fertility, gondal function

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: funding door KiKa

Intervention

Keyword: (premature) menopause, fertility, Hodgkin lymphoma, late effects

Outcome measures

Primary outcome

In girls, the primary outcome measure is AMH. In all treatment arms, the distribution of serum AMH level (corrected for age, as AMH rises with age, sd z-scores will be calculated to correct (16) directly after chemotherapy and at two years, will be compared to the distribution at baseline level, using a Wilcoxon signed-rank test. If the data are normally distributed, a paired sample t-test will be used.

Next, the Kruskal-Wallis test will be used to compare the distributions of the change of AMH level (directly after chemotherapy compared to baseline), between all three treatment arms. If there is a significant difference between the arms, a Mann-Whitney U test with Bonferroni multiple testing correction will be applied as post-hoc test. If the data are normally distributed a one-way analysis of variance and two-sample t-tests with Bonferroni correction as a posthoc test, might be used instead. This analysis is repeated for the two years measurement.

To test the gonadotoxic effect of the intensified (DECOPDAC) chemotherapy, the distributions of the change of AMH after chemotherapy (compared to baseline) for the COPDAC- and the DECOPDAC-treatment groups will be compared in both TL2 and TL3, using the Mann-Whitney U test or a two-sample t-test in case of normality. This analysis is repeated for the two years measurement.

In boys the primary outcome measure is semen (TMSC, total motile sperm count = volume ejaculate (ml) x sperm concentration x progressive motility in % (31)).
For this outcome measure an identical statistical analysis will performed as in girls.
For the tests a significance level of 0.05 is used.

Secondary outcome

In girls, amenorrhea and changed menstrual cycle (both dichotomous) will be used as secondary outcome measures. For all arms the fractions of girls with amenorrhea or a changed menstrual cycle will be estimated.
In boys, Inhibin B, expressed continuously in pg/ml, and FSH expressed in U/l will be measured. Changes within individuals during follow-up will be assessed.

Other study parameters
In girls, ovarian volume as well as uterus dimensions (max length and max width) will be In girls, ovarian volume as well as uterus dimensions (max length and max width) will be assessed retrospectively from MRI*s that are performed in the context of patient care. In boys, these MRI*s will be used to measure testicular volume.

In a subset of patients, patient and parental experience on fertility care and fertility counseling will be collected using a questionnaire during follow up.

Study description

Background summary

Survival for children with Hodgkin lymphoma (HL) has increased rapidly over the years and with current multimodal treatment protocols over 90% survives (1). However, late effects of treatment, such as second malignant neoplasms, infertility and premature menopause, are of great concern given their impact on future health and quality of life. Young cancer survivors, particularly those with lymphoma diagnosis or radiotherapy to the pelvis (23,34), have an increased risk of infertility (> 1 year of unsuccessful attempts at conception) compared with sibling controls. In addition, a premature menopause is a well-recognised effect of HL treatment (19, 20, 22) which is very relevant in the light of todays trend to postpone childbearing to the early thirties. Risk factors for impaired gonadal function include abdominal/pelvic radiotherapy (23), TBI, and treatment with alkylating agents (Procarbazine in particular) and the risk increases with cumulative dose (2-5), and older age at time of treatment in females (6). In adult males with HL, alterations of sperm characteristics have been described already before treatment (24,25). Potential causes described are fever (26), stress (27) or inflammatory immune-mediated mechanisms (28). Twelve months after treatment containing doxorubicin and Dacarbazine, sperm count recovered to pretreatment values but this was not the case for patients receiving chemotherapy courses containing cyclophosphamide or Procarbazine. 24 months post-treatment, azoospermia rates were 22 % and 50 % respectively (29). After treatment with BEACOPP (containing Cyclophosphamide and Procarbazine) even 89% of HL patients had azoospermia (30). However, studies on fertility in boys with HL are lacking. In order to reduce the risk of adverse late effects, pediatric HL treatment protocols have been adapted over the years. The use of radiotherapy (RT) was limited in order to prevent its described secondary malignancies and Procarbazine was replaced by Dacarbazine to reduce gonadotoxicity (1). Studies in adult HL patients, however, have shown that gonadal damage was still present after treatment with Dacarbazine in a subset of patients (3). Since pelvic radiotherapy increases the risk of infertility (22), it is important to study whether radiotherapy can be omitted in patients with HL without compromising survival. The current EuroNet-PHL-C2 treatment protocol will answer that important question in a subgroup of patients. In this protocol, the use of radiotherapy will be reduced in the intensified chemotherapy arm (DECOPDAC-21) in contrast with standard COPDAC-28 courses (for EuroNet-PHL-C2 protocol see figure 1 and 2). However, the impact of the intensified chemotherapy on gonadal function is unknown. The intensified DECOPDAC courses are given every 3 weeks instead of every 4 weeks in the standard COPDAC-arm, allowing less time for gonadal recovery. Furthermore DECOPDAC-21 consists of a higher dose of (gonadotoxic) Cyclophosfamide, in addition to Etoposide and Doxorubicin and should therefore be investigated. The gold standard for assessing gonadal function in (post)pubertal males is sperm analysis. However, in prepubertal boys and in boys who are not able to provide a semen sample, surrogate markers are often used including pubertal staging and serum hormone levels of which the Inhibin

B/FSH ratio (IFR) has shown to be the best marker of male infertility (9,10). Direct assessment of gonadal function in females is impossible and relies solely on a combination of surrogate tests. Menstrual history, serum levels of early follicular phase FSH, estradiol, and Inhibin B, and ultrasound based antral follicle counts (AFC) and ovarian volume measurements are commonly used (11-13). However, all these measurements require specific timing within the menstrual cycle and in girls taking oral contraceptives their value is limited (37). Recently, anti-Mu*llerian hormone (AMH) has emerged as a promising marker of ovarian reserve (11-16,35). This hormone is presumed cycle independent, is stable from 8-25 years (17), has shown to decrease over time in normo-ovulatory women, long before changes in serum FSH, E2 and inhibin B (12-14), and is the only current marker reported to be useful in the assessment of ovarian reserve in prepubertal girls receiving cancer treatment (18). To preserve fertility, sperm may be banked for those young boys who are physically and emotionally able. In adolescent females, cryopreservation of oocytes or ovarian tissue are available options although still experimental and not possible in all centers.
In girls who need to be irradiated at the pelvic region, ovariopexy can protect the ovaries and preserve gonadal function. Some oncologists administer oral contraceptives or GnRH analogues as co-treatment to preserve fertility. It is hypothesized that resting follicles are more resistant to CT and that the hypo-estrogenic state may decrease utero-ovarian perfusion, resulting in a decreased exposure of the ovaries to chemotherapy (7, 8). However, reported effects of GnRH-a on ovarian function are contradicting and should be evaluated further. In summary, since the use of (gonadotoxic) chemotherapy will be intensified in the new EuroNet-PHL-C2 protocol, this study will prospectively study the overall, and treatment arm specific, gonadotoxic potential of the protocol in boys and girls treated for HL in Europe. In addition, the frequency and effect of various methods applied as co-treatment to preserve fertility will be evaluated.

Study objective

The primary aim of this study is to assess the overall, and treatment arm specific, gonadotoxic potential of the protocol in both boys and girls treated for classical Hodgkin Lymphoma in Europe.
Secondary aim is to evaluate the frequency of various methods applied as co-treatment to preserve fertility in European countries; if number are sufficient, the effect of these methods on gonadal function will be assessed subsequently.

More specifically, primarily this study:

1) will prospectively evaluate the gonadotoxic effect of 2, 3, 4 or 6 cycles of chemotherapy (with or without RT) in boys and girls treated for Hodgkin Lymphoma according to EuroNet-PHL-C2 protocol.
2) will evaluate the difference in gonadotoxicity between OEPA-COPDAC-28 and OEPA-DECOPDAC-21 (with or without RT) in both boys and girls treated according

to the EuroNet-PHL-C2 protocol.

Secondarily, the current study:
3) will assess the frequency of oral contraceptives or GnRH-a co-treatment and/or ovariopexy, given as part of standard patient care in a subset of patients. Subsequently, in case of sufficient numbers, the impact of these methods on gonadal function will be studied in young females.
4) will investigate the frequency of sperm banking in young boys, the differences in frequency between countries, and the reasons for doing or not doing so.
5) will investigate the frequency of cryopreservation of ovarian cortical tissue or oocytes in young females, the differences in frequency between countries, and the reasons for doing or not doing so.
6) will evaluate patient and parental experience on provided fertility care and counseling in a subset of patients (patients treated in the Netherlands).

Study design

General study design and study population This study is set up as a European, multi-center, prospective, observational cohort study, in children treated for classical Hodgkin Lymphoma according to the EuroNet-PHL-C2 protocol between 2016 and 2021. Children diagnosed with Hodgkin Lymphoma before the age of 18 years, in participating centers for pediatric oncology in 5 European countries, will be asked to participate in the study after approval of the country-specific ethics committee. The study will be initiated in the Netherlands and Belgium first and then expanded to Austria, Czech Republic and Germany. In order to perform all follow-up measurements of this study (see table 1 below), patients will be included during a period of five years (2017-2021). It is expected that approximately 700 patients will be eligible during the 5 year inclusion period, based on number of patients diagnosed per country: Netherlands: 27 patients/year, Belgium 11 patients/year, Germany 140 patients/year, Czech Republic 20 patients/year and Austria 20 patients/year. With a participation rate of approximately 50%, we expect to include over 300 newly diagnosed patients. The number of semen samples collected, however, will be lower than 150, i.e. in prepubertal boys it is not possible, but also some pubertal boys who are willing to provide a sample, will not be able to do so; the estimated % of boys who will provide semen for analysis is considered to be approximately 30%. Written informed consent for participation in the current study will be obtained from all patients and their parents prior to inclusion in the study. Participation in the study does not require extra visits for the patients to the hospital. Data collection Relevant clinical data according to the EuroNET-PHL-C2 protocol will be collected for all children with HL treated according to this protocol by the participating institutes of approximately 20 different European countries using CRFs. These data will be entered and stored in a central database at the EuroNet-PHL study office in Leipzig using the infrastructure which was already in place for the data collection relevant for the previous EuroNet-PHL-C1 protocol. The EuroNet-PHL-C2 database will contain

all clinical data, for instance treatment center and country, date of birth, gender, date of diagnosis, stage of disease, tumor site and regions involved (nodes and extra nodal involvement), treatment level (1,2, or 3), randomization group, detailed treatment data (chemotherapy per cycle: the dates and doses of each chemotherapeutic agent administered, RT: dose at each radiation site), dates of recurrence, dates of diagnosis of second malignancies, medical history, toxicity/complications. Furthermore, MRI*s of children will be stored at the central EuroNet-PHL Study office, University Leipzig for central review of the response assessment of the Hodgkin treatment (EuroNet-PHL-C2 protocol). For the current study, relevant clinical data of all patients will be extracted from the central EuroNet-PHL-C2 study database. R elevant data: • Treatment center and country, date of birth, gender • Date of diagnosis, stage of disease, tumor site and regions involved (nodes and extra nodal involvement) • Treatment level (1,2, or 3), randomization group, detailed treatment data (chemotherapy per cycle: the dates and doses of each chemotherapeutic agent administered; RT: dose at each radiation site) • Dates of recurrence, dates of diagnosis of second malignancies • Medical history Furthermore, additional data for this study will be collected by the centers participating in the study on additional CRF*s from diagnosis onwards until 5 years post-diagnosis/the age of 18 years (T5, see table 1). Data will be collected during regular visits in the context of patient care and/or will be retrieved from medical records. In girls, completed CRF*s will contain information on • menstrual cycle (menarche yes/no, length and regularity of menstrual cycle) • use of hormonal contraception(if yes, type, dose and frequency will be recorded) • GnRH-a co treatment (if yes, type, dose and frequency will be recorded) • menopausal status of the mother, and age at menopause if applicable. • height, weight , pubertal stage according to Tanner criteria, • smoking, drinking alcohol, • whether ovariopexy (when iliac/pelvic lymph node region is to be irradiated) was performed, • whether ovarian cortex or oocytes were harvested for cryopreservation (yes/no, if no: why not), For boys, data will be collected accordingly on • height, weight , pubertal stage according to Tanner criteria, • testicular volume measured with the Prader orchidometer, • smoking, drinking alcohol, • Whether or not sperm is banked for fertility preservation and if not (while Tanner stage 4 and/or testicular volume >15 mls as measured by Prader orchidometer), why not . These data will be sent to VU University medical Center and stored anonymously in the statistical (SPSS) database. In order to be able to trace data to an individual subject, a subject identification code list will be used which will be safeguarded by the principal investigator. To accomplish the highest achievable participation rates and to ensure solid data collection, the National chair of participating countries will recruit local champions/dedicated pediatric oncologists who will keep in close contact with the PhD student as well as the PI*s. The PhD student will provide the relevant CRF*s to the local champions well timed and will be responsible for the return of the CRF*s and proper storage of the data. A core working group consisting of the PI*s and the local champions/dedicated oncologists will be established, monitoring of the progress and content of the study on a regular basis i.e. accrual charts for each institution. Blood sampling Blood samples from both

boys and girls will be collected during regular visits at several time points to assess in blood values over time within and between treatment arms (table 1). In females 6 ml of extra blood will be drawn for measurement of anti-Mullerian hormone (AMH); timing within the menstrual cycle i.a. will be documented. In males 6 ml of extra blood will be drawn to assess serum levels of Inhibin B, and FSH. Blood for AMH (in girls only) and FSH and Inhibin B (in boys) should be collected in a serum-separating tube. To enhance and accelerate the clotting process, invert the tube at least 6-12 times immediately upon filling. Leave the tube for an hour to coagulate. After 1 hour the tube should be spinned for 10 minutes 1800g. Then the serum should be divided between 3 tubes, each containing at least 500-750 µL serum (and labelled with date of blood sampling and unique patient number). Serum should subsequently be frozen at -20 °C locally in each participating center. Frozen sera will be transported (frozen; on dry ice) in batch to VUmc for central evaluation on set occasions. In all children some serum and blood (DNA) will be stored for future research into reproductive function and ovarian reserve outcomes. Ovarian volume, uterus dimensions and testicular volume: In girls, ovarian volume as well as uterus dimensions (max length and max width) will be assessed retrospectively from MRI*s that are performed in the context of patient care by the PhD appointed to the project. This in order to assess changes over time within treatment arms and between treatment arms. In boys, these MRI*s will be used to measure testicular volume. These MRI*s are stored for central review of response assessment of the Hodgkin disease at the central EuroNet-PHL Study office, University Leipzig. Semen sampling: All young boys who are physically and emotionally able to provide a semen sample will be asked to do so on three occasions during the study (before treatment and 2&5 years post diagnosis; table 1). Semen analysis will be performed on site in fresh semen. Semen samples will be evaluated for sperm volume, sperm count, sperm forward motility according to World Health Organisation guidelines. Conditions of disturbed sperm quality will include hypospermia (volume <1.5 mls), oligozoospermia (sperm concentration <15 x 106/ml), asthenozoospermia (sperm with forward motility < 32 %), and theratozoospermia (sperm with normal morphology <4 %). Total motile sperm count will be calculated by multiplying the sample volume by the sperm concentration and the % motile sperm (31) since this is considered as the best indicator of male infertility. Fertility questionnaire A subset of patients (included in the Netherlands, provided separate informed consent) will receive a fertility questionnaire during follow-up. The questionnaire will be directed to the parents/guardians of the patients, containing questions on: - fertility counseling: was fertility counseling offered, and if so: what was the timing, and who was the interlocutor (pediatric oncologist, specialized nurse, gynecologist/urologist) - fertility preservation: was fertility preservation offered and if so: did they eventually choose to perform a treatment - participation of the child: did their child actively participate in the fertility counseling and were they incolved in the decision-process whether to use available fertility preservation methods - satisfaction and experience: do they feel like they received sufficient information on fertility and available fertility preservation methods. In addition, patients who were aged 12 years or

older at time of diagnosis will be asked to fill in a short questionnaire themselves. Patients will be asked whether they can remember conversations about fertility, how they experienced these conversations (was it important to them and was it understandable) and whether they currently of formertly feel worried about their fertility. Parents of boys and girls will receive distinct versions of the questionnaire. The questionnaire will be sent out at a single timepoint (2023), at approximately 1.5-3 years post-diagnosis for most patients. One full-time researcher (PhD.-student: *AIO*) is requested for a period of four years. Under the supervision of the principal investigators, the researcher will coordinate and conduct the study and will be responsible for the day-to-day management of the project.

Study burden and risks

The current study will be performed in children with Hodgkin disease and who will be treated according to the upcoming EuroNet-PHL-C2 protocol. This EuroNet-PHL-C2 protocol aims to reduce the use of radiotherapy in order to reduce secondary malignancies by intensifying the use of (gonadotoxic) chemotherapy. It is unknown whether this will lead to (increase of) gonadal damage. This is particularly relevant to the population of HL patients of whom the majority will survive. Therefore this European, multi center, prospective, observational study will be performed. Data will be collected before start of treatment as well as during and following treatment during regular visits to the hospital. The risks associated with participation in the current study can be considered negligible and the patient burden low. For the blood samples only some extra blood (max 1-2 ml per sample, maximum 7 samples) will be drawn. We do not expect to induce a lot of stress in boys when a second or third semen sample, 2/5 years after treatment will be requested.
A subset of patients aged 12 years or older (at time of diagnosis) and parents will be asked to fill in a paper questionnaire during follow-up at a single time point (Dutch participants who provided informed consent to participate in this survey). Questions can be considered personal as they comprise patient experience and satisfaction. Participants are allowed to skip questions if they do not wish to answer certain questions. Nevertheless, the questionnaire is short (time to complete is estimated at 10-15 for parents and 5 minutes for children) and mostly contains multiple choice questions.

This study will reveal the overall, and treatment arm specific, gonadotoxic potential of the EuroNET-PHL-C2 treatment protocol in both boys and girls treated for classical Hodgkin Lymphoma in Europe, and will provide information on whether and which patients are at risk of gonadal damage, which has been associated with a reduced quality of life if a survivor finds him or herself unable to procreate later in life.
In addition, the frequency of various methods applied as co-treatment in females (GnRH-analogues, oral contraceptives and/or ovariopexy) to preserve fertility will be evaluated and when numbers are sufficient the effect of these methods on gonadal function will be studied. Furthermore, this will evaluate

the frequency of banking of sperm, cryopreservation of ovarian cortical tissue or oocytes, and will provide insight in reasons for not doing so. Data on patient- and parental experience on provided fertility care and counseling will be collected in a subset of patients (patients treated in the Netherlands)

The results of the current study will allow us to better inform future patients at risk of (persistent) gonadal damage and their parents about the risk of the current Hodgkin lymphoma treatment and methods that can be applied to preserve fertility. In addition, it can help us to inform current female survivors at risk for a premature menopause about their possible reduced fertile life span, which may have implications for the timing of parenthood if they wish to have children in the future. This is particularly relevant given the trend of postponing childbearing to the early thirties in several countries throughout Europe. Also, if fertility appears to be reduced after treatment in women who still have a natural cycle there may still be options for fertility preservation in survivorship. Fertility preservation in survivorship might help alleviate the distress often associated with the urgency to start a family due to an imminent premature menopause, particularly if a woman is still very young and/or without a partner. When gonadal damage will be demonstrated in the boys who underwent treatment according to the EuroNet-PHL-C2 protocol, they might be reassured because their semen was also cryopreserved prior to treatment. Furthermore, if we find a protective effect of hormonal contraception, GnRH-analogues or ovariopexy in females, these co-treatments should be implemented in girls as standard supportive care during Hodgkin treatment. Moreover, if we find that methods that can be used to preserve fertility are applied infrequently in patients at risk of gonadal damage, this information will be used to inform and educate pediatric oncologists.
All in all, the risks associated with participation in the current study can be considered negligible and the patient burden low. Given this negligible risk and low burden, and the fact that this study has the potential to have major consequences for future HL patients as well as for current HL survivors, this study is considered to have a favourable risk-benefit assessment .

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Children (<18 years) with Hodgkin lymphoma, treated according to the EuroNet-PHL-C2 protocol

Exclusion criteria

no informed consent

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-01-2017
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO Date:	30-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2023
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	NL58283.029.16