

Evaluation of pubertal and hormone development in boys who stored testicular tissue for fertility preservation before a treatment possibly leading to later fertility problems

Submission date 30/03/2020	Recruitment status Recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 02/06/2020	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 11/01/2021	Condition category Nutritional, Metabolic, Endocrine	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

Plain English summary of protocol

Current plain English summary as of 11/01/2021:

Background and study aims

Worldwide, many children suffer from cancer or hematological disorders and this number is on the rise. However, due to advances in treatment, the survival rate of these children is continuously improving being nowadays above 80%. One of the most prevalent long-term side effects of these treatments is life-long sterility or subfertility. Because sterility affects an individual's psychological and social wellbeing, it is relevant to develop an adequate fertility preservation strategy in order to guarantee the patient's quality of life on the long-term. Since pre- and peripubertal boys have not yet entered puberty, they do not produce mature spermatozoa and consequently they cannot benefit from sperm banking before being exposed to gonadotoxic treatment. Currently, the only option for pre- and peripubertal boys who do not yet produce mature spermatozoa is to bank testicular tissue before gonadotoxic treatment followed by auto-transplantation at adulthood. Since 2002, more than 100 pre- and peripubertal boys banked their testicular tissue for fertility preservation purposes at the Universitair Ziekenhuis Brussel. Some of these young boys are followed-up by an endocrinologist to monitor their pubertal and endocrine development, however, this follow-up is currently far from regular and standardized. Furthermore, the impact of removing testicular tissue (biopsy) at a young age on the pubertal and endocrine development is difficult to predict. Although evidence demonstrates that immediate surgical complications of such a biopsy procedure are rare (2 - 3 %), nothing is known on the possible adverse effects in the long-term. The aim of this study is first to establish a more standardized follow-up protocol for young boys diagnosed with cancer or hematological disorders and undergoing a testicular tissue biopsy procedure at a young age as a fertility preservation strategy. Secondly, we aim to investigate how a testicular tissue biopsy procedure performed at a young age may affect the pubertal and endocrine development of young boys diagnosed with cancer or hematological disorders.

Who can participate?

Pre- and peripubertal boys (<18 years) who do not yet produce mature spermatozoa, who have been diagnosed with childhood cancer or childhood hematological disorders.

What does the study involve?

All available data related to the pubertal and endocrine development will be collected from the patients' medical records over several years and compared between patients who underwent a testicular tissue biopsy procedure and those who did not.

What are the possible benefits and risks of participating?

In the short term, former childhood cancer patients will be followed-up in a more standardized way. Participating patients will receive additional information regarding their pubertal and endocrine development and hormonal status. In case of problems, immediate action can be taken, such as starting hormonal substitution therapy. As a result, patients interested in fertility preservation will be better counseled and better informed at the start of their cancer treatment. In the long term, the study will provide better insight into whether the removal of testicular tissue (testicular biopsy) at a young age may affect the pubertal and endocrine development. This knowledge could lead to improved fertility preservation strategies which will improve the patient's quality of life.

Where is the study run from?

1. Universitair Ziekenhuis Brussel (Belgium)
2. Vrije Universiteit Brussel (Belgium)

When is the study starting and how long is it expected to run for?

January 2016 to December 2030

Who is funding the study?

1. Research Programme of the Research Foundation - Flanders (FWO) (Belgium)
2. Kom op tegen Kanker (KOTK) (Belgium)

Who is the main contact?

Prof. Dr Eileen Goossens (scientific), ellen.goossens@vub.be

Prof. Dr Inge Giles (public), inge.gies@uzbrussel.be

Previous plain English summary:

Background and study aims

Worldwide, many children suffer from cancer or hematological disorders and this number is on the rise. However, due to advances in treatment, the survival rate of these children is continuously improving being nowadays above 80%. One of the most prevalent long-term side effects of these treatments is life-long sterility or subfertility. Because sterility affects an individual's psychological and social wellbeing, it is relevant to develop an adequate fertility preservation strategy in order to guarantee the patient's quality of life on the long-term. Since pre- and peripubertal boys have not yet entered puberty, they do not produce mature spermatozoa and consequently they cannot benefit from sperm banking before being exposed to gonadotoxic treatment. Currently, the only option for pre- and peripubertal boys who do not yet produce mature spermatozoa is to bank testicular tissue before gonadotoxic treatment followed by auto-transplantation at adulthood. Since 2002, more than 100 pre- and peripubertal boys banked their testicular tissue for fertility preservation purposes at the Universitair

Ziekenhuis Brussel. Some of these young boys are followed-up by an endocrinologist to monitor their pubertal and endocrine development, however, this follow-up is currently far from regular and standardized. Furthermore, the impact of removing testicular tissue (biopsy) at a young age on the pubertal and endocrine development is difficult to predict. Although evidence demonstrates that immediate surgical complications of such a biopsy procedure are rare (1%), nothing is known on the possible adverse effects on the long-term. The aim of this study is first to establish a more standardized follow-up protocol for young boys diagnosed with cancer or hematological disorders and undergoing a testicular tissue biopsy procedure at a young age as a fertility preservation strategy. Secondly, we aim to investigate how a testicular tissue biopsy procedure performed at a young age may affect the pubertal and endocrine development of young boys diagnosed with cancer or hematological disorders.

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Prof. Eileen Goossens (scientific), ellen.goossens@vub.be

Prof. Inge Giles (public), inge.gies@uzbrussel.be

Contact information

Type(s)

Scientific

Contact name

Prof Ellen Goossens

ORCID ID

<http://orcid.org/0000-0001-7601-9689>

Contact details

Vrije Universiteit Brussel

Laarbeeklaan 103

Brussels

Belgium

1090

+32 24749213

ellen.goossens@vub.be

Type(s)

Public

Contact name

Prof Inge Gies

ORCID ID

<http://orcid.org/0000-0002-8571-0858>

Contact details

Universitair Ziekenhuis Brussel

Laarbeeklaan 101

Brussels

Belgium

1090

+32 24744180

inge.gies@uzbrussel.be

Additional identifiers

EudraCT/CTIS number

Nil known

IRAS number**ClinicalTrials.gov number**

Nil known

Secondary identifying numbers

B.U.N. 143201733195

Study information

Scientific Title

Follow-up of pubertal and endocrine development in boys who stored testicular tissue for fertility preservation before high-risk gonadotoxic treatment

Study objectives

Harvesting testicular tissue from pre- and peripubertal boys does not have an additional negative impact on their pubertal and endocrine development

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 08/11/2017, Medical Ethics Committee of the Universitair Ziekenhuis Brussel (Vrije Universiteit Brussel (VUB) Laarbeeklaan 101, 1090 Brussels, Belgium; +32 2 477 55 84; commissie.ethiek@uzbrussel.be), ref: B.U.N. 143201733195

Study design

Single-center prospective comparative observational cohort study

Primary study design

Observational

Secondary study design

Cohort study

Study setting(s)

Hospital

Study type(s)

Diagnostic

Participant information sheet

Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied

Childhood cancer, childhood hematological disease

Interventions

Current interventions as of 11/01/2021:

The study population consists of pre- and peripubertal boys (<18 years) diagnosed at the Universitair Ziekenhuis Brussel (UZ Brussel) or at the Hôpital Universitaire Des Enfants Reine Fabiola (HUDERF) with cancer or hematological disorders for which they need high-risk gonadotoxic treatment (with an $\geq 80\%$ risk of later fertility problems). All examinations and procedures required for the present study will take place exclusively at the UZ Brussel for all included patients (UZ Brussel patients as well as HUDERF patients).

Data on their pubertal and endocrine development (Tanner stage, testicular volume, reproductive hormones and other endocrine markers, bone age, and density) will be collected at diagnosis and yearly from the end of the gonadotoxic treatment until the age of 18 years. These collected data will be compared between young boys who did and those who did not undergo a

testicular tissue biopsy procedure at a young age as a fertility preservation strategy in order to identify a possible association between the biopsy procedure (which is performed to harvest testicular tissue) and the pubertal and endocrine development.

The following data will be collected from the patient's medical records:

- The patient's medical background: the diagnosis and the patient's age at the time of diagnosis, the type of treatment received with mention of the cumulative dose (chemotherapy, radiotherapy, total body irradiation, bone marrow transplantation, type and frequency of surgery, ...).
- Whether or not a testicular tissue biopsy procedure has been performed at a young age with mention of the testis portion biopsied (orchietomy, hemi-orchietomy or smaller portion), the site of biopsy (left, right or bilateral), the patient's age at the time of biopsy and the reason why the patient and his parents accepted or refused testicular tissue banking.

The following examinations and procedures will be performed at diagnosis and yearly until the age of 18 years (starting from the end of the gonadotoxic treatment):

- A physical examination to measure the patient's weight, height, body mass index, blood pressure, and testicular volume using a Prader orchidometer and to determine the patient's Tanner stage (scoring of patient's pubertal maturation).
- A scrotum ultrasound to measure the patient's testicular volume and to investigate potential abnormalities in the testicular parenchyma.
- A morning blood sample to evaluate the serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), estradiol (E2), inhibin B (INHB), anti-Müllerian hormone (AMH), thyroid-stimulating hormone (TSH), free thyroxine (FT4), insulin-like growth factor 1 (IGF1), prolactin (PRL), cortisol and adrenocorticotrophic hormone (ACTH) with mention of possible hormonal substitution treatment (start, duration, and dose prescribed).
- An X-ray of the left hand and wrist to determine the patient's bone age.
- An X-ray at two different locations (i.e. trabecular bone and lumbar bone) and the total body to assess the patient's bone density.

These data will be compared between young boys who did (biopsy group) and those who did not (control group) undergo a testicular tissue biopsy procedure at a young age using the appropriate statistical tests in order to identify a possible association between the biopsy procedure and the pubertal and endocrine development.

Previous interventions:

The study population consists of pre- and peripubertal boys (<18 years) diagnosed at the Universitair Ziekenhuis Brussel with cancer or hematological disorders for which they need high-risk gonadotoxic treatment (with an $\geq 80\%$ risk of later fertility problems).

Data on their pubertal and endocrine development (Tanner stage, testicular volume, reproductive hormones and other endocrine markers, bone age and density) will be collected at diagnosis and yearly from the end of the gonadotoxic treatment until the age of 18 years. These collected data will be compared between young boys who did and those who did not undergo a testicular tissue biopsy procedure at a young age as a fertility preservation strategy in order to identify a possible association between the biopsy procedure (which is performed to harvest testicular tissue) and the pubertal and endocrine development.

The following data will be collected from the patient's medical records:

- The patient's medical background: the diagnosis and the patient's age at time of diagnosis, the type of treatment received with mention of the cumulative dose (chemotherapy, radiotherapy, total body irradiation, bone marrow transplantation, type and frequency of surgery, ...).
- Whether or not a testicular tissue biopsy procedure has been performed at a young age with mention of the testis portion biopsied (orchiectomy, hemi-orchiectomy or smaller portion), the site of biopsy (left, right or bilateral), the patient's age at time of biopsy and the reason why the patient and his parents accepted or refused testicular tissue banking.

The following examinations and procedures will be performed at diagnosis and yearly until the age of 18 years (starting from the end of the gonadotoxic treatment):

- A physical examination to measure the patient's weight, height, body mass index, blood pressure and testicular volume using a Prader orchidometer and to determine the patient's Tanner stage (scoring of patient's pubertal maturation).
- A scrotum ultrasound to measure the patient's testicular volume and to investigate potential abnormalities in the testicular parenchyma.
- A morning blood sample to evaluate the serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), estradiol (E2), inhibin B (INHB), anti-Müllerian hormone (AMH), thyroid-stimulating hormone (TSH), free thyroxine (FT4), insulin-like growth factor 1 (IGF1), prolactin (PRL), cortisol and adrenocorticotrophic hormone (ACTH) with mention of possible hormonal substitution treatment (start, duration and dose prescribed).
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These data will be compared between young boys who did (biopsy group) and those who did not (control group) undergo a testicular tissue biopsy procedure at a young age using the appropriate statistical tests in order to identify a possible association between the biopsy procedure and the pubertal and endocrine development.

Intervention Type

Other

Primary outcome measure

Current primary outcome measure as of 11/01/2021:

Impact of a testicular tissue biopsy procedure performed at a young age on pubertal and endocrine development using the following measurements at diagnosis and yearly until the age of 18 years (starting from the end of the gonadotoxic treatment):

1. A physical examination to measure the patient's weight, height, body mass index, blood pressure, and testicular volume using a Prader orchidometer and to determine the patient's Tanner stage (scoring of patient's pubertal maturation)
2. A scrotum ultrasound to measure the patient's testicular volume and to investigate potential abnormalities in the testicular parenchyma
3. A morning blood sample to evaluate the serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), estradiol (E2), inhibin B (INHB), anti-Müllerian hormone (AMH), thyroid-stimulating hormone (TSH), free thyroxine (FT4), insulin-like growth factor 1 (IGF1), prolactin (PRL), cortisol and adrenocorticotrophic hormone (ACTH) with mention of possible hormonal substitution treatment (start, duration, and dose prescribed)

4. An X-ray of the left hand and wrist to determine the patient's bone age
5. An X-ray at two different locations (i.e. trabecular bone and lumbar bone) and the total body to assess the patient's bone density

Previous primary outcome measure:

Impact of a testicular tissue biopsy procedure performed at a young age on pubertal and endocrine development using the following measures at diagnosis and yearly until the age of 18 years (starting from the end of the gonadotoxic treatment):

1. A physical examination to measure the patient's weight, height, body mass index, blood pressure and testicular volume using a Prader orchidometer and to determine the patient's Tanner stage (scoring of patient's pubertal maturation).
2. A scrotum ultrasound to measure the patient's testicular volume and to investigate potential abnormalities in the testicular parenchyma.
3. A morning blood sample to evaluate the serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), estradiol (E2), inhibin B (INHB), anti-Müllerian hormone (AMH), thyroid-stimulating hormone (TSH), free thyroxine (FT4), insulin-like growth factor 1 (IGF1), prolactin (PRL), cortisol and adrenocorticotrophic hormone (ACTH) with mention of possible hormonal substitution treatment (start, duration and dose prescribed).
4. An X-ray of the left hand and wrist to determine the patient's bone age.
5. An X-ray at two different locations (i.e. trabecular bone and lumbar bone) and the total body to assess the patient's bone density.

Secondary outcome measures

Current secondary outcome measures as of 11/01/2021:

1. The patient's medical background: the diagnosis and the patient's age at the time of diagnosis, the type of treatment received with mention of the cumulative dose (chemotherapy, radiotherapy, total body irradiation, bone marrow transplantation, type and frequency of surgery, ...)
2. Whether or not a testicular tissue biopsy procedure has been performed at a young age with mention of the testis portion biopsied (orchiectomy, hemi-orchiectomy, or smaller portion), the site of biopsy (left, right or bilateral), the patient's age at the time of biopsy and the reason why the patient and his parents accepted or refused testicular tissue banking

Previous secondary outcome measures:

1. The patient's medical background: the diagnosis and the patient's age at time of diagnosis, the type of treatment received with mention of the cumulative dose (chemotherapy, radiotherapy, total body irradiation, bone marrow transplantation, type and frequency of surgery, ...)
2. Whether or not a testicular tissue biopsy procedure has been performed at a young age with mention of the testis portion biopsied (orchiectomy, hemi-orchiectomy or smaller portion), the site of biopsy (left, right or bilateral), the patient's age at time of biopsy and the reason why the patient and his parents accepted or refused testicular tissue banking

Overall study start date

01/01/2016

Completion date

31/12/2030

Eligibility

Key inclusion criteria

Current inclusion criteria as of 11/01/2021:

1. Pre- and peripubertal boys (<18 years) who do not yet produce mature spermatozoa
2. Diagnosis of childhood cancer or childhood hematological disorders (<18 years) at the Universitair Ziekenhuis Brussel or the Hôpital Universitaire Des Enfants Reine Fabiola
3. High-risk gonadotoxic treatment (with an $\geq 80\%$ risk of later fertility problems)
4. Did or did not undergo a testicular tissue biopsy procedure at a young age as a fertility preservation strategy

Previous inclusion criteria:

1. Pre- and peripubertal boys (<18 years) who do not yet produce mature spermatozoa
2. Diagnosis of childhood cancer or childhood hematological disorders (<18 years) at the Universitair Ziekenhuis Brussel
3. High-risk gonadotoxic treatment (with an $\geq 80\%$ risk of later fertility problems)
4. Did or did not undergo a testicular tissue biopsy procedure at a young age as a fertility preservation strategy

Participant type(s)

Patient

Age group

Child

Upper age limit

18 Years

Sex

Male

Target number of participants

100

Key exclusion criteria

1. Diagnosis of testicular cancer

Date of first enrolment

01/01/2018

Date of final enrolment

31/12/2029

Locations

Countries of recruitment

Belgium

Study participating centre

Universitair Ziekenhuis Brussel

Laarbeeklaan 101

Brussels

Belgium

1090

Study participating centre

Vrije Universiteit Brussel

Laarbeeklaan 103

Brussels

Belgium

1090

Sponsor information

Organisation

Universitair Ziekenhuis Brussel

Sponsor details

Laarbeeklaan 101

Brussels

Belgium

1090

+32 24774111

info@uzbrussel.be

Sponsor type

Hospital/treatment centre

Website

<https://www.uzbrussel.be/>

ROR

<https://ror.org/038f7y939>

Organisation

Vrije Universiteit Brussel

Sponsor details

Laarbeeklaan 103

Brussels

Belgium

1090

+32 26292010

info@vub.ac.be

Sponsor type

University/education

Website

<https://www.vub.be/>

ROR

<https://ror.org/006e5kg04>

Funder(s)**Funder type**

Government

Funder Name

Research Programme of the Research Foundation - Flanders (FWO)

Funder Name

Kom op tegen Kanker (KOTK)

Results and Publications**Publication and dissemination plan**

The study results will be disseminated with Belgium colleagues and other international scientists through presentations at scientific meetings and peer-reviewed publications in scientific journals.

General practitioners will be informed through journals of medicine.

The press service of the Universitair Ziekenhuis Brussel will encourage the publication of important results in national papers in layman's terms for the public.

Patients will be informed through the Centre for Reproductive Medicine (CRG) website (<http://www.brusselsivf.be/>) and the website of the Biology of the Testis (BITE) research group of the Vrije Universiteit Brussel (<https://bite.research.vub.be/>).

Intention to publish date

01/01/2031

Individual participant data (IPD) sharing plan

The current data-sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file			02/06/2020	No	No
Protocol file	version v3	19/10/2020	11/01/2021	No	No