ISRCTN13057463 https://doi.org/10.1186/ISRCTN13057463

# 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

**Registration date**
02/06/2020

**Last Edited**
11/01/2021

**Recruitment status**
Recruiting

**Overall study status**
Ongoing

**Condition category**
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] 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.

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 counselled 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 2018 to December 2029

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. 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**
https://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**
https://orcid.org/0000-0002-8571-0858

**Contact details**
Universitair Ziekenhuis Brussel
Laarbeeklaan 101
Brussels
Belgium
1090
+32 24744180
inge.gies@uzbrussel.be

# Additional identifiers

**Clinical Trials Information System (CTIS)**
Nil known

**ClinicalTrials.gov (NCT)**
Nil known

**Protocol serial number**
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

## Study type(s)
Diagnostic

## 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 ≥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 (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.

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 adrenocorticotropic 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 ≥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 adrenocorticotropic 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.

## Intervention Type
Other

## Primary outcome(s)
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 adrenocorticotropic 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 adrenocorticotropic 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.

### Key secondary outcome(s))
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

### 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 ≥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 ≥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

### Healthy volunteers allowed
No

### Age group
Child

### Upper age limit
18 years

### Sex
Male

### 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

**ROR**
https://ror.org/038f7y939

**Organisation**
Vrije Universiteit Brussel

**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

**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? |
|---|---|---|---|---|---|
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |
| Protocol file | | | 02/06/2020 | No | No |
| Protocol file | version v3 | 19/10/2020 | 11/01/2021 | No | No |