Study protocol: Follow-up of pubertal development in boys who stored testicular tissue before gonadotoxic treatment

Aangepast studieprotocol in kader van amendement (2017/278 studie).

Promoter and co-promoters

Prof. Dr. Ellen Goossens

Biology of the testis, Vrije Universiteit Brussel

Laarbeeklaan 103, 1090 Brussels

Telephone: 02/4749213

E-mail: ellen.goossens@vub.ac.be

Prof. Dr. Herman Tournaye

Centre for Reproductive Medicine, UZ Brussel

Laarbeeklaan 101, 1090 Brussels

Telephone: 02/4776612

E-mail: tournaye@uzbrussel.be

Prof. Dr. Inge Gies

Department of Pediatrics, Division of Pediatric Endocrinology, UZ Brussel

Laarbeeklaan 101, 1090 Brussels

Telephone: 02/4744180

E-mail: Inge.Gies@uzbrussel.be

Co-workers

Dr. Veerle Vloeberghs

Centre for Reproductive Medicine, UZ Brussel

Laarbeeklaan 101, 1090 Brussels

Telephone: 02/4744017

E-mail: veerle.vloeberghs@uzbrussel.be

Prof. Dr. Koen Norga

Department of Pediatrics, Hematology, UZ Brussel

Laarbeeklaan 101, 1090 Brussels

Telephone: 02/4774189
E-mail: Koenraad.Norga@uzbrussel.be

Dr. Sophie Bravo
Department of Pediatrics, Hematology, UZ Brussel
Laarbeeklaan 101, 1090 Brussels
Telephone: 02/4774392
E-mail: Sophie.Bravo@uzbrussel.be

Prof. Dr. Alina Ferster
Department of Hemato-Oncology, Hôpital Universitaire des Enfants Reine Fabiola (HUDERF)
Jean Joseph Crocqlaan 15, 1020 Brussels
Telephone: 02/4773113
E-mail: alina.ferster@huderf.be

Dr. Emily Delgouffe
Biology of the testis, Vrije Universiteit Brussel
Laarbeeklaan 103, 1090 Brussels
Telephone: 02/4774644
E-mail: Emily.Delgouffe@vub.be

M. Sc. Ellen De Beer
Biology of the testis, Vrije Universiteit Brussel
Laarbeeklaan 103, 1090 Brussel
Telephone: 02/4774644
E-mail: Ellen.de.beer@vub.be

Clinical problem and background

Cancer patients and patients suffering from haematological disorders require gonadotoxic treatment (like chemo- and radiotherapy) and/or total body irradiation as a conditioning therapy before bone marrow transplantation. For long, it was assumed that children were more resistant to gonadotoxic treatments. However, now, there is enough evidence that, just as adults, children face significant adverse effects as a consequence of the treatments. One of the possible side effects is life-long sterility or subfertility. Because sterility affects an individual's psychological and social wellbeing, prevention of sterility using fertility preservation methods is required to guarantee the patient's quality of life on

the long term. Unfortunately, since spermatogenesis only starts at puberty, pre-pubertal boys cannot benefit from sperm banking before being exposed to gonadotoxic treatments. To prevent later fertility problems, an alternative fertility preservation strategy is proposed: testicular tissue banking (as spermatogonial stem cells are present in the testis since birth) followed by auto-transplantation at adulthood. The Biology of the Testis research group at the VUB has performed pioneering work concerning translation of fertility preservation strategies towards the clinic. Since 2002, the UZ Brussel has stored testicular tissue from more than 100 pre-pubertal boys for future fertility restoration purposes. These boys were diagnosed in the UZ Brussel or in another hospital (such as the Hôpital Universitaire Des Enfants Reine Fabiola) and referred to the oncofertility centre of the UZ Brussel for fertility preservation. These boys are followed-up during and after treatment to assess their development at the UZ Brussel and HUDERF. However, this follow-up is far from standardized and therefore, a more standardised protocol for the follow-up of these young patients is needed. Furthermore, for these boys, the impact of the testicular tissue biopsy procedure at young age on the pubertal development is difficult to predict. Although evidence suggests that the biopsy procedure itself is unlikely to cause gonadal dysfunction, it is important to follow these patients' pubertal development to ensure that there are no late effects related to the biopsy procedure.

Aim

The aim of this project is

- To establish a standardized follow-up protocol for young patients with cancer or haematological disorders who underwent testicular tissue biopsy based on findings from a previous retrospective study (see 2016/396 and 2017/141).
- Design a database containing all patient data collected using the standardized follow-up protocol.
- To collect and combine follow-up data (collected using the standardized follow-up protocol) available on the hormonal status and pubertal development of all included paediatric patients diagnosed in the UZ Brussel or in HUDERF with cancer or haematological disorders but followed at the UZ Brussel in the context of this study.
- To compare these follow-up data between patients who did or did not undergo testicular tissue biopsy to identify a possible association between the biopsy procedure (which is performed to harvest testicular tissue) and pubertal development.

Material and Methods

The study population for this project consists of paediatric (<18 years) patients diagnosed in the UZ Brussel or in HUDERF with cancer or haematological disorders and who require/required high-risk

gonadotoxic treatment (with a ≥80% risk of facing later fertility problems). The patients diagnosed in the UZ Brussel will be recruited by the endocrinologist and the study nurses of the UZ Brussel. The patients diagnosed in HUDERF were already included in previous retrospective studies performed at the UZ Brussel (reference 2016/396 and 2017/141). The parents of these HUDERF patients will be informed about the present study by letter (see 'informatiebrief' attached to this study protocol) and contacted by the study nurses of the UZ Brussel to invite their son to participate in this UZ Brussel/VUB project. The young boys who agree to take part in the present study, will be followed at the UZ Brussel by the standardised follow-up protocol at diagnosis and yearly until the age of 18 years. 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).

For this project, we will perform a prospective analysis of follow-up data (collected using the standardized follow-up protocol) on the hormonal status and pubertal development of the included patients, with collection of at least following data at diagnosis and until 18 years old:

Data collected at diagnosis	**Data collected regularly until 18 years old**

• The age of the patient
• Data on bone age (x-ray)
• Hormonal analyses: serum levels of LH, FSH, T, E2, INHB and AMH
• Tanner staging: scoring of the pubertal development
• The testicular volumes measured with Prader orchidometer and a testicular ultrasound
• Testicular tissue banking:
  ○ The reason why it was offered and why it was performed
  ○ The portion of testis that is biopsied: orchidectomy, hemi-orchidectomy or one third of the testis
• The type of (oncological) disease and the type of treatment:
  ○ Chemotherapy with cumulative dose calculation for all pharmaca
	• The age of the patient
	• Data on bone age (x-ray) up to Tanner stage IV
	• Hormonal analyses: serum levels of LH, FSH, T, E2, INSL3, INHB and AMH
	• Hormonal substitution treatment if needed: start date, duration and hormone doses
	• Tanner staging: scoring of the pubertal development
	• The testicular volumes measured with Prader orchidometer and a testicular ultrasound
	• The number of endocrine evaluations

○ Type and frequency of surgery ○ Radiation therapy with cumulative dose calculation ○ Total body irradiation before bone marrow transplantation	

Follow-up frequency is every six months between Tanner stages II and IV (puberty development period). Follow-up frequency is once a year at Tanner stage I and V. At each follow-up visit, all examinations should be repeated.

In addition, available data on the hormonal status and pubertal development of the included patients that were recorded prior to inclusion in the present study (date of signed informed consent) will be retrospectively collected from their medical records.

Additional follow-up data could be collected according to the lacks identified in the retrospective study. These additional data will be submitted as an amendment to this application.

The collected follow-up data will be compared between boys who underwent a testicular tissue biopsy procedure and those who did not using the appropriate statistical tests in order to identify possible associations between the biopsy procedure and the pubertal development.

Study design

All follow-up data of included paediatric patients who did or did not perform testicular tissue banking as fertility preservation strategy will be collected according to the standardized follow-up protocol at diagnosis and yearly until the age of 18 years. A prospective analysis of these collected data will be performed and differences between patients who underwent a testicular tissue biopsy and those who did not will be identified.

Ethical considerations

Informed consent

For this project, an informed consent signed by all included patients and their parents is needed to approve the collection of the follow-up data. UZ Brussel patients as well as HUDERF patients and their parents will need to sign this informed consent. You can find a copy of the informed consents in attachment to this application.

Privacy

All the data needed for this prospective analysis will be collected and anonymized by the study nurses assigned to this project and under the responsibility of the treating physician. Only these anonymized data will be processed by the PhD student. An anonymized database will be kept as an Excel-file on a UZ Brussel (study nurses) and VUB computer (PhD student).