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

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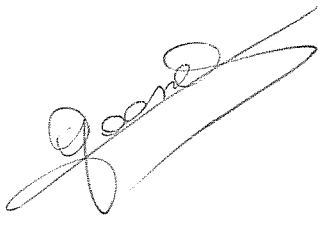

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Clinical problem and background

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 are followed-up on yearly basis at the UZ Brussel. 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 pediatric patients diagnosed in the UZ Brussel with cancer or haematological disorders and who did or did not perform testicular tissue banking as fertility preservation strategy.
- 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 pediatric (<18 years) patients diagnosed in the UZ Brussel with cancer or haematological disorders. These young boys will be followed by the standardised follow-up protocol at diagnosis and yearly until the age of 18 years through consultations by an endocrinologist.

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 these 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) • Data on bone density (x-ray) • Hormonal analyses: serum levels of LH, FSH, IGF1, TSH, FT4, PRL, T, E2, cortisol, ACTH, INHB and AMH • Tanner staging: scoring of the pubertal development	• The age of the patient • Data on bone age (x-ray) every year • Data on bone density (x-ray) every 2 years • Hormonal analyses: serum levels of LH, FSH, IGF1, TSH, FT4, PRL, T, E2, cortisol, ACTH, INHB and AMH every 6 months • Hormonal substitution treatment if needed: start date, duration and hormone doses

• The testicular volumes measured with Prader orchidometer and a testicular ultrasound
• Testicular tissue banking:
  o The reason why it was offered and why it was performed
  o 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:
  o Chemotherapy with cumulative dose calculation for all pharmaca
  o Type and frequency of surgery
  o Radiation therapy with cumulative dose calculation
  o Total body irradiation before bone marrow transplantation
	• Tanner staging: scoring of the pubertal development every 6 months
	• The testicular volumes measured with Prader orchidometer and a testicular ultrasound every 6 months
	• The number of endocrine evaluations

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.

Study design

All follow-up data of pediatric patients diagnosed in the UZ Brussel with cancer or haematological disorders and 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 the parents and the patient himself (if possible) to approve the collection of the follow-up data is needed. You can find a copy of this informed consent in attachment to this application.

Privacy

All the data needed for this prospective analysis will be collected under the responsibility of the treating physician. These data will be anonymized by a data manager and only these anonymized data will be processed by the student. Only a completely anonymous database will be kept on a personal or portable computer.