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Case Report

Hypergonadotropic hypogonadism after ovarian tissue cryopreservation on a 13-year-old female: A case report and review of the literature

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ABSTRACT

Ovarian failure is a major long-term adverse event following gonadotoxic treatment of malignant diseases. Ovarian tissue cryopreservation can be offered in some conditions to preserve fertility. We report the case of a 13-year-old female with a diagnosis of acute myeloid leukemia, who presented with hypergonadotropic hypogonadism after unilateral ovariectomy for fertility preservation and before highly gonadotoxic treatment. Even though damage seemed only partial, this case suggests that the remaining contralateral ovarian function may be compromised after ovarian tissue cryopreservation, leading *per se* to a hypergonadotropic hypogonadism. Although indication of ovarian cryopreservation is not called into question in situations of highly gonadotoxic therapy, this procedure should only be performed after evaluation by a specialized multidisciplinary team and provided a solid indication.

Introduction

While survival rates after childhood cancer have greatly improved over recent decades, one of the major adverse effects of oncologic treatments is the risk of gonadal function impairment [1]. According to the Childhood Cancer Survivor Study, the prevalence of acute ovarian failure is 6.3 % within 5 years [1].

Since infertility has a major impact on the quality of life of cancer survivors, the gonadotoxic effect of a therapy should be assessed early and appropriate fertility preservation modalities should be offered to the patient [2,3]. Ovarian tissue cryopreservation (OTC) is the only available method of fertility preservation for pre-pubertal girls, and pubertal females when oncological therapy cannot be delayed to allow ovarian stimulation for cryopreservation of mature oocytes [4]. OTC consists of the removal of ovarian tissue and cryopreservation of cortical fragments containing primordial follicles [5]. The ovarian tissue can be later orthotopically transplanted, with the purpose of restoring both endocrine and exocrine ovarian function [5]. In pre-pubertal girls, the whole ovary is removed because of its small size [3]. In post-pubertal females, some authors recommend removing the whole ovary in order to increase the harvested follicular pool [4], while others perform a partial ovariectomy to conserve sufficient primordial follicles that may permit recovery of ovarian function [6]. Since the first pregnancy obtained using this technique in 2004 [7], more than 130 live births have been reported worldwide [8]. However, data on OTC performed before or around puberty are scarce, because the large majority of these

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samples have not yet been used [4]. Currently, two live births have been reported after autograft of ovarian tissue cryopreserved before menarche [9,10].

According to the committee opinion published at the end of 2019 by the American Society for Reproductive Medicine, OTC is no longer considered as an experimental procedure [11]. However, the impact of unilateral ovariectomy on the overall ovarian function is not completely understood [2].

We report a case of hypergonadotropic hypogonadism after unilateral ovariectomy in a pubertal female.

Case report

A previously healthy 13-year-old female was diagnosed with an acute myeloid leukemia (AML) M2 subtype, without central nervous system involvement, and with high-risk cytogenetics. According to the AML-Berlin-Frankfurt-Münster (BFM) 2012 protocol, induction chemotherapy with cytarabine, idarubicin, etoposide and high dose cytarabine and mitoxantrone was administered for four cycles, with complete remission achieved at the end of cycle 1 and 2 (Fig. 1). Indication for intensification with allogenic hematopoietic stem cell transplantation (allo-HSCT) was established at diagnosis due to high-risk cytogenetics and molecular criteria.

OTC was discussed within the multidisciplinary team for fertility preservation and offered to the family after reaching consensus. Oocyte cryopreservation was not considered a good option for this patient because the start of oncologic treatment could not be delayed to allow time for ovarian stimulation, and because of the chemotherapy already received. Informed consent was obtained from the patient and her parents. The patient had experienced a normal pubertal development. Menarche occurred at 13 years of age, after the induction chemotherapy described above and one month before OTC. At the time of fertility preservation, pubertal development was Tanner 3 (B3, PP3).

Surgery was undertaken at Lausanne University Hospital. The decision to remove a whole ovary was made during the procedure. After inspection of both ovaries, the right ovary was chosen because of its size, seemingly sufficient for a partial ovariectomy.

TIMELINE (months)	EVENTS	SYMPTOMS	TREATMENTS
T-4	Diagnosis of AML	Tanner B3 PP3	Chemotherapy according to AML-BFM 2012 protocol
T-3			
T-2			
T-1		Menarche	
T0	Ovarian tissue cryopreservation		
T+1			
T+2			
T+3			
T+3.5			GnRHa
			Conditioning regimen
T+4	Allo-HSCT	Vaginal bleeding	
T+5			
T+6			

Fig. 1. Events' timeline, in relation to timing of the ovarian tissue cryopreservation (T0), expressed in months. The time scale is modified between the two oblique lines.
AML = Acute myeloid leukemia.
AML-BFM 2012 protocol = AML-Berlin-Frankfurt-Münster 2012 protocol.
GnRHa = Gonadotropin-releasing hormone agonist.
Allo-HSCT = Allogenic hematopoietic stem cell transplantation.

However, after opening the capsule, a 2 cm-follicular cyst was detected, occupying almost half of the ovarian volume. Hence, it led to the decision to perform a total right ovariectomy to obtain sufficient cortical tissue. The left ovary appeared normal during the procedure.

The patient was then referred to Geneva University Hospitals for allo-HSCT, where the pre-transplant assessment took place. The endocrinological evaluation, performed one month after the right ovariectomy but before the allo-HSCT, revealed a hypergonadotropic hypogonadism (follicle stimulating hormone (FSH) 130 UI/l, luteinizing hormone (LH) 93.1 UI/l, estradiol <17 pmol/l) (Fig. 2). Retrospective dosage on stored serum sampled one month before surgery revealed a normal ovarian function (FSH 8.4 UI/l, LH 21.7 UI/l, estradiol measurement not available). There was no familial history of premature ovarian insufficiency, autoimmune disorders or conditions suggesting a Fragile X syndrome. Hypergonadotropic hypogonadism was confirmed several times during a 2 month-period following cryopreservation. Three months after surgery, we noticed a decrease in gonadotropins levels and an increase in estradiol (FSH 86.9 UI/l, LH 36.1 UI/l, estradiol 128.5 pmol/l), suggesting a partial recovery of endocrine function, but without return of menses.

In preparation for transplant, gonadotropin-releasing hormone agonist (GnRHa) was routinely administered to prevent menstrual bleeding, after which interpretation of ovarian function became impossible. Nonetheless, two weeks after GnRHa administration, the patient experienced vaginal bleeding similar to menstruations, lasting 6 days. Pelvic ultrasound showed a uterus of pubertal morphology, with a thick endometrium, and a left ovary with visible follicles, the biggest one measuring 12 mm. As expected, blood tests showed suppressed ovarian function under GnRHa (FSH 2.8 UI/l, LH 4.10 UI/l, estradiol <17 pmol/l).

Conditioning regimen, consisting of myeloablative doses of busulfan (area under the curve of 96 mg*H/L) and cyclophosphamide (200 mg/kg), was administered before a matched unrelated donor hematopoietic stem cell transplant, with an uneventful course at 6 months from transplant.

No serum antimüllerian hormone (AMH) was measured before surgery, but it was done several times after the procedure and after the allo-HSCT: all measures were extremely low (AMH < 0.3 pmol/l), reflecting the follicular depletion after unilateral ovariectomy and gonadotoxic treatment respectively.

Discussion

We suspect that the removal of an ovary in our patient induced the hypergonadotropic hypogonadism observed one month after surgery, before administration of gonadotoxic treatment. The pubertal development had been spontaneous and the gonadotropin levels were normal before the OTC, suggesting previous normal ovarian function. Although the patient had received chemotherapy before OTC, these chemotherapeutic agents are all classified as low risk of gonadotoxicity. Moreover, gonadotrophin measurement after initial chemotherapy and before OTC was normal. It is therefore unlikely that the hypergonadotropic hypogonadism observed after surgery would stem from the chemotherapy previously received, although a sensitization cannot be excluded. The observed ovarian insufficiency seemed to be only partial and temporary, since a significant rise in estradiol and a slight decline in gonadotropins rates were observed 3 months after the unilateral ovariectomy. Partial recovery of the endocrine function is also supported by the withdrawal bleeding, occurring 2 weeks after GnRHa administration, attributable to a flare-up effect, and by signs of estrogenic impregnation of the endometrium on pelvic ultrasound. Thereafter, blood tests were not interpretable owing to GnRHa suppression of ovarian function.

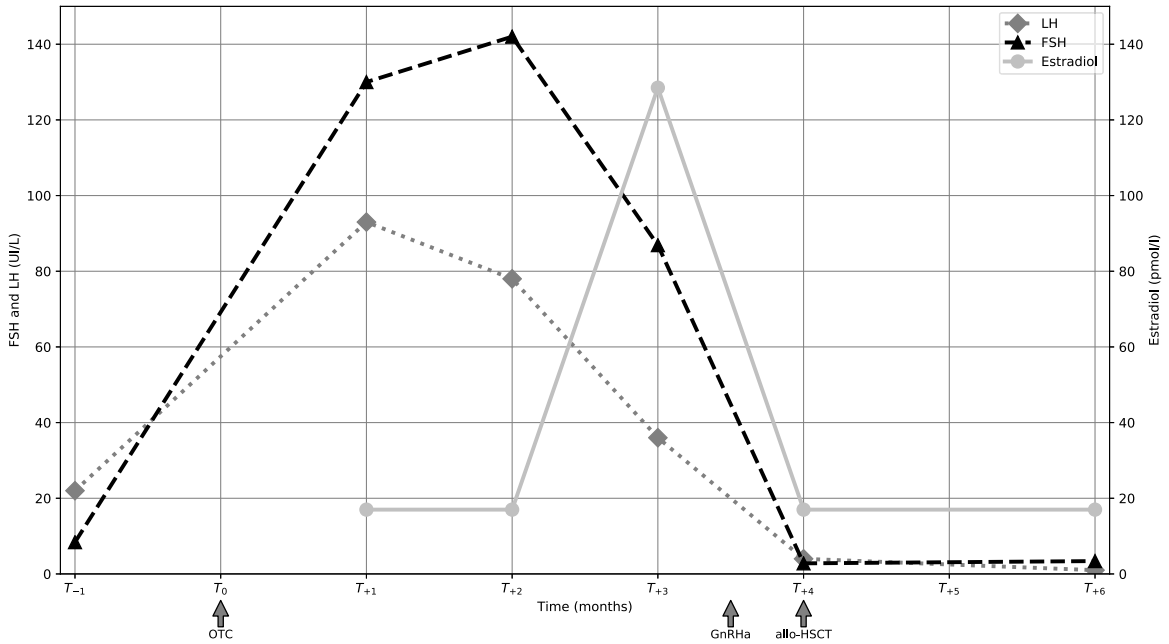

Fig. 2. Evolution of gonadotropins and estradiol in relation to timing of the ovarian tissue cryopreservation (T0), expressed in months.
FSC = Follicle stimulating hormone.
LH = Luteinizing hormone.
OTC = Ovarian tissue cryopreservation.
GnRHa = Gonadotropin-releasing hormone agonist.
Allo-HSCT = Allogenic hematopoietic stem cell transplantation.

This observation raises the question of the evolution of ovarian function after unilateral ovariectomy. Despite the existence of several other indications for unilateral ovariectomy (such as ovarian torsion, cysts, tumors and endometrioma), with an incidence in the reproductive population of 56–125 per 100'000 person years [12], there is no publication in humans addressing this question. Animal data suggest some compensatory mechanisms occurring after unilateral ovariectomy, with higher serum FSH levels and hypertrophy of the remaining ovary, although this compensation seems to be incomplete as mice with a single ovary have fewer litters and stop breeding at a younger age than mice with two ovaries [13]. In the field of oncology, data reports on ovarian function after OTC have always been collected after gonadotoxic treatment [14]. None of these studies differentiated the impact of ovariectomy on ovarian function from that of gonadotoxic therapy. One study provides a partial answer on ovarian function after unilateral ovariectomy in the oncological context: Rosendahl et al. investigated ovarian function during chemotherapy among patients aged 19–35 years with malignant disease, who were to receive their first gonadotoxic treatment [15]. Eight out of 17 patients had had unilateral ovariectomy for fertility preservation before they started chemotherapy. Hormonal measurements were not performed between unilateral ovariectomy and the first cycle of chemotherapy, allowing no conclusion to be made on the direct impact of unilateral ovariectomy on endocrine profile. However, authors compared the 8 patients who had an ovary removed before the first cycle of chemotherapy to the 9 patients who still had their both ovaries. After the first cycle of chemotherapy, AMH was significantly lower in patients with a single ovary compared with patients having two ovaries (0.59 vs 1.40 ng/mL, p = 0.039). The authors concluded that unilateral ovariectomy might contribute to the reduction of AMH levels.

In conclusion, we report the case of a pubertal female with hypergonadotropic hypogonadism after unilateral ovariectomy for OTC, prior to administration of gonadotoxic treatment. Even if the ovarian insufficiency was probably only partial or temporary, given the presence of a thickened endometrium on ultrasound and the withdrawal bleeding after GnRHa administration, this case suggests that unilateral ovariectomy for fertility preservation could induce an impairment of ovarian function. In this situation, indication of OTC is not called into question because the benefices of this procedure outpaced by far the risks of an extremely gonadotoxic treatment for high risk acute myeloid leukemia. Nevertheless, this observation raises the question of the evolution of ovarian function after unilateral ovariectomy and challenges the common belief that one ovary is sufficient for normal endocrine and reproductive function [12]. To the best of our knowledge, this is the first report of hypergonadotropic hypogonadism after unilateral ovariectomy in humans. There is no data in the literature on ovarian function after such a surgery, even outside oncological context. Further prospective studies on hormonal profile after unilateral ovariectomy would be valuable for improving the understanding of the dynamic evolution of ovarian function after unilateral ovariectomy.

Patient consent

Written informed consent for publication of the case report has been obtained from the patient and her parents.

Declaration of Competing Interest

The authors report no declarations of interest.

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