A Clinical Case of Fertility Preservation in an Adolescent with Hodgkin Lymphoma

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Case Presentation

NT is a 15-year-old post-menarchal girl; she was complaining of cervical enlargement, a weight loss of 21 kg in 3 months, night sweats, and fever. Clinical examination of the patient found a 2 cm fixed painless and firm right lateral jugular lymphadenopathy. The left cervical lymphadenopathy biopsy revealed a scleronodular Hodgkin's disease. The patient's disease was staged IIBb with mediastinal bulky according to the Ann Arbor classification system.

She was planned to receive two cures of OEPA (vincristine, etoposide, prednisone, doxorubicin) followed by an early PET scan assessment (according to the Euronet-Paediatric Hodgkin Lymphoma Group).

According to guidelines, hematologists addressed the issues of chemotherapy side effects including possible risk of ovarian toxicity. The patient and her parents (she was minor) were offered to be referred for fertility preservation. They consulted one day after being referred.

59.1 Assessment of Ovarian Reserve and Ovarian Function Loss Risk

The aim and headlines of oncofertility were explained before the individual evaluation of the gonadotoxicity. For this purpose (and on the same day), serum anti-Mullerian hormone (AMH) testing was performed and resulted on a level of 0.88 ng/ml suggestive of a decreased ovarian reserve. A decreased AMH level in patients with hematologic malignancies is reported by some authors [1] but still controversial [2]. The pathophysiology and the long-term implications are unknown, but extreme catabolic state could be one of the mechanisms.

In this case, risk of loss of ovarian function was considered intermediate. Indeed, the initially planned chemotherapy protocol contains no alkylant agent (the most gonadotoxic supress). On the other hand, the decreased initial ovarian reserve was a risk factor of premature ovarian failure [3]. In addition, a switch for a more aggressive chemotherapy (in case of unsuccessful first-line treatment) was estimated as possible by the hematologists.

59.2 Management

Considering all these parameters, the patient was advised to proceed with fertility preservation.

Oncofertility possibilities were explained to the patient and her parents. Because NT was postpubertal, she was offered ovarian tissue cryopreservation (OTC) or oocytes vitrification (OV). In our case, advantages and disadvantages of each technique were discussed with the patient and her parents.

Although preferred by many oncofertility teams, OTC is still considered as experimental. Despite this label, it was shown that OTC is an effective method that can restore fertility but also endocrine activity. Moreover, 18–23% pregnancy rates are reported [4, 5] with half of the pregnancy occurring spontaneously.

This method requires a laparoscopy and therefore, theoretically, allows the patient to start chemotherapy, one day after the surgical removal of the ovarian tissue. However, in our particular case, NT presented mediastinal compression due to large thoracic nodes, and the anesthetist recommended that she would need at least 10 days of prednisone before being able to have a laparoscopy, which would delay the start of chemotherapy. Long-term risks of OTC were also discussed including the risk of introducing malignant cells when grafting the ovarian tissue after recovery, even though Hodgkin Lymphoma is low risk [6]. Finally, we considered in this case, that in a patient with low ovarian reserve and low risk chemotherapy (which may not induce premature ovarian insufficiency), removing ovarian tissue may be more harmful than the chemotherapy itself.

Oocytes vitrification is the standard method according to the guidelines [7], and it has been shown to be associated with 32% of pregnancy rates [4]. It requires ovarian stimulation with gonadotrophins, which would delay the start of chemotherapy by 12–15 days using a random start protocol. The window of stimulation would allow for prednisone administration to reduce her thoracic compression. The patient and her parents gave consent for ovarian vitrification on the day of consultation, and ovarian stimulation was started (on day 15 of cycle).

Ovarian stimulation was started with human menotropins 300 international units per day with an GnRH antagonist for prevention of ovulation and a GnRH agonist trigger for oocyte maturation. This protocol minimizes the risk of ovarian hyperstimulation ovarian syndrome risk. In this case, the GnRH antagonist was started on day 10 (Table 59.1) as it

Table 59.1 Ovarian stimulation monitoring

	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14
HMG (UI)	300	300	300	300	300	300	300	300	300	300	300			Oocytes pickup
Gn-RH anta										0.25 mg	0.25 mg			
Gn-RH agonist												0.2 mg		
E2 (pg/ml)						188		369		1018				
Progesterone						22		20		9				
Right ovary[a]						10–9		2×12–10		3×16		2×18		
								2×9		2×15		17		
												2×16		
Left ovary[a]						7 + CL		10–12		16–13		18–15		
								+CL						

Gn-RH anta GN-RH antagonist, *CL* corpus luteum
[a]Follicles size are expressed in mm

is possible to delay the start of the GnRH antagonist when stimulation occurs in the luteal phase and endogenous progesterone remains elevated [8].

After 12 days of stimulation, we obtained seven follicles with four measuring more than 17 mm indicating a triggering with GnRH agonist. GnRH agonist triggering should be used only in women with proof of normal hypothalamic-pituitary-ovarian axis activity, and an LH assay should be performed 12 hours after GnRH agonist administration to verify the LH surge (>15 mIU/ml).

59.3 Outcome

The patient and her parents were uncomfortable with idea of transvaginal oocyte pickup procedure so we offered them the possibility of using perurethral transvesical pickup which represents an effective and safe alternative [9].

Eight oocytes were retrieved; seven of them were mature and then vitrified. No complications occurred, and the patient was referred the day after oocyte pickup to start chemotherapy, 15 days after being referred to the oncofertility unit.

59.4 Conclusion and Keypoints

- Malignant hemopathies especially Hodgkin Lymphoma are common indications for fertility preservation.
- Fertility preservation counselling should be individualized based on the patient, her diagnosis, and her ovarian reserve.

Clinical Pearls/Pitfalls

- Ovarian reserve markers may be low in hematologic malignancies before any chemotherapy.
- According to guidelines, every patient who had not achieved his parenthood should be referred to an oncofertility program.
- Both ovarian tissue cryopreservation and oocyte vitrification are effective techniques and offer realistic chances of becoming a parent.
- For oocyte vitrification, the preferred protocol for ovarian stimulation protocol is a Gn-RH antagonist with GnRH agonist trigger to maximize the oocyte yield in a safe and expeditious manner.
- Confirmation of an LH surge after a GnRH agonist trigger should be verified by an LH and possibly progesterone level performed 12 hours after Gn-RH agonist administration.

Review Questions and Answers

Q1. What are the most important factors for the evaluation of gonadotoxicity risk of chemotherapy?

A1. Age, pre-existing ovarian reserve, chemotherapy agents, and additional therapies (radiation, surgery).

Q2. What is the best cycle day to start ovarian stimulation for fertility preservation?

A2. Ovarian stimulation can be started at any day of cycle with the exception of the periovulatory window. Delaying ovarian stimulation to the 1st day of cycle is not recommended.

Q3. What are the alternatives to vaginal oocyte pickup in adolescents?

A3. Peruretheral transvesical, abdominal, or laparoscopic oocyte pickup may be more acceptable than transvaginal oocyte aspiration in some adolescents.

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