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Laparoscopic ovarian tissue collection for fertility preservation in children with malignancies: a multicentric experience

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Introduction: Long survivors after childhood cancer are increasing thanks to oncological improvements. Their quality of life and fertility-sparing should be considered in the early phases of each oncological pathway. Cryopreservation of ovarian tissue removed before starting gonadotoxic therapies is the only fertility sparing procedure available for prepubertal children affected by cancer and it does not affect the timing of the start of the treatment.
Materials and methods: The present study shows the surgical and clinical outcomes following laparoscopic ovarian tissue collection (LOTC) for a total of 311 patients aged between 0 and 17 years old from four different European Centers.
Results: Only two major complications were reported according to the Clavien Dindo classification (0.6%).
Discussion: LOTC can be considered a safe procedure.

KEYWORDS

fertility-sparing, cryopreservation, cancer survivors, pediatric cancer, ovarian tissue collection, minimally invasive surgery

1 Introduction

Survival after childhood cancer has improved over the past two decades and is now up to 80% considering all diseases. Nearly 75% of young cancer patients will be living more than 10 years after diagnosis (1). Moreover, the long-term survival rate of children undergoing hematopoietic stem cell transplant (HSCT) is constantly increasing. Improving in survival implies, on the other hand, an increase in morbidity for long term survivors.

Among all the late effects, infertility is reported as a major concern, especially in female cancer survivors due to the use of gonadotoxic treatments, like radiotherapy or chemotherapy, which may permanently impair reproductive functions.

Total body irradiation (TBI) and an older age at the time of HSCT can negatively affect the persistence of ovarian function and the onset of premature ovarian failure (POF).

When administered before puberty, TBI is less gonadotoxic, with 40%–60% of patients experiencing spontaneous recovery, vs. 10%–14% in post-pubertal girls (2).

Loss of ovarian function after chemotherapy with an alkylating agent (cyclophosphamide, busulfan) could result in both sterilization and endocrine function deficiency.

Due to all these factors the risk of infertility in patients undergoing a conditioning regimen for HSCT has been defined as higher than 80%.

Fertility preservation is a key component of POF management in children and should be considered for all young patients undergoing potentially gonadotoxic cancer treatments or at high risk for ovarian failure.

Cryopreservation of ovarian tissue is currently the main option available to preserve fertility in prepubertal patients who require cancer treatment but cannot postpone the beginning of chemotherapy.

The advantage of this technique is that it requires just a few days to be planned and performed, with a minimally invasive approach and, as the retrieval of ovarian tissue is not dependent on the menstrual cycle, no delay in treatments is required.

Furthermore, it has been demonstrated that laparoscopic ovarian tissue collection (LOTC) is a feasible technique even after abdominopelvic surgery (3). This technique allows the storage of a great number of primordial follicles that are relatively resistant to cryodamage (about 70%–80% survival) (4).

The aim of the study was to describe and compare the experience of four high-volume European pediatric Centers in terms of surgical outcomes, where oncological female patients at high risk for infertility are enrolled in the program of LOTC.

2 Materials and methods

Data from four European high-volume pediatric Centers were considered for this study; the hospitals involved were the Regina Margherita Children's Hospital in Turin, Italy (Center 1), the Sant' Orsola-Malpighi University Hospital in Bologna, Italy (Center 2), the Giannina Gaslini Children's Hospital in Genoa, Italy (Center 3) and the Gregorio Maranon Children's Hospital in Madrid, Spain (Center 4).

This was a retrospective study including girls and adolescents up to 17 years of age, who had undergone LOTC in the past two decades, before a highly gonadotoxic treatment for malignant diseases was initiated.

The indication for LOTC was established when the treatment planned included conditioning for autologous or allogeneic hematologic stem cell transplantation, high-dose chemotherapy or *in toto* abdominal irradiation or pelvic irradiation.

The clinical and demographic features of each patient were collected (Table 1).

The surgical outcomes were evaluated considering different variables: the duration of the hospital stay, the operative timing, the need for laparotomic conversion intraoperatively, and the postoperative complications were registered during a postoperative follow up of six months for each patient (Table 2).

The postoperative complications were evaluated according to the Clavien-Dindo classification (5).

In Center 1, surgeons collected tissue from both ovaries by performing a bilateral sampling. The surgical procedure consisted in a 3-trocars 5 mm laparoscopy, collecting 50% of tissue of each gonad (ovarian cortex biopsies) without tissue cauterization to optimize the viability (only for hemostatic purpose after tissue removal), or draining the pelvis.

Trocar position was the following: the zero degrees camera port was positioned in the navel and the two operative ports were placed in the right and left iliac fossa respectively.

The sampling was then submitted for histological examination to detect any neoplastic contamination and, if negative, frozen, following the slow freezing procedure and cryopreserved in liquid nitrogen.

A hemoglobin check was planned in the first post-operative day and discharge was planned on the same day or on the second postoperative day.

TABLE 1 Demographic and clinical patients' characteristics.

Demographic and clinical characteristics	Center 1 93 pts	Center 2 164 pts	Center 3 36 pts	Center 4 18 pts
Age at diagnosis mean (range)	11.12 (0–17)	11.12 (3–17)	12.1 (7–17.2)	4 Leukemia pts 4.86 (2–10) 14 other pts 13.7 (1–17)
Age at surgery mean (range)	13 (2.7–17)	13 (1.8–17)	15.5 (7–31)	5 (2–15)
Prepubertal at surgery *n* (%)	24 (25.8%)	42 (25.6%)	10 (27.8%)	15 (83.3%)
LOCS pathological indication *n* (%)	Sarcomas 13 (13.9%) Acute leukaemia 60 (64.5%) HL 10 (10.8%) NHL 10 (10.8%)	Sarcomas 47 (28.7%) Acute leukaemia, HL, NHL 93 (56.7%) CNS tumors 10 (6.1%) Wilms tumor 6 (3.6%) Others 8 (4.9%)	Sarcomas 12 (33.3%) HL, NHL 15 (41.7%) CNS tumors 4 (11.1%) Ovarian teratoma 1 (2.8%) BM aplasia, chronic granulomatous disease 4 (11.1%)	Sarcomas 2 (11.1%) HL 8 (44.4%) NHL 3 (16.7%) Leukemia 4 (22.2%) BM aplasia 1 (5.6%)

Qualitative data are *n* (%); quantitative data are median (range).
Pts, patients; HL, Hodgkin Lymphoma; NHL, Non-Hodgkin Lymphoma; CNS, central nervous system; BM, bone marrow.

TABLE 2 Surgical patients' characteristics.

Surgical characteristics	Center 1 93 pts	Center 2 164 pts	Center 3 36 pts	Center 4 18 pts
Operative time (min) mean (range)	45 (35–55)	40 (35–45)	55 (45–65)	65 (55–75)
Type of ovarian sampling	Bilateral sampling 93 (100%)	Monolateral sampling 164 (100%)	Monolateral sampling 31 (86.1%) Bilateral sampling 5 (13.9%)	Monolateral sampling 18 (100%)
Intra/postoperative complications[a] *n* (%)	1 Dindo 3 (1%)	0 (%)	0 (%)	1 Dindo 3 (5.6%)
Laparotomic conversion *n* (%)	0 (%)	0 (%)	1 (2.8%)	0 (%)
Number and type of trocars	Three 5 mm trocars	One 10 mm trocar, Two 5 mm trocars	One 12 mm trocar, Two 5 mm trocars	Three 5 mm trocars
Use of drainage	No drains	Routinely inserted	No drains	No drains
Hospital stays (postoperative days) median (range)	2 (0–5)	1 (1–2)	2 (2–3)	1 (0–1)

Qualitative data are *n* (%); quantitative data are median (range).
Pts, patients.
[a]According to Clavien-Dindo classification (5).

In Center 2, a monolateral sampling was performed and the harvesting technique also consisted of a three-portal laparoscopy with a 10 mm umbilical port for a zero degrees camera and two 5 mm trocars for forceps and hemostatic devices. Only one ovary was subjected to biopsy, based on the pre-operative pelvic ultrasound. Surgical steps were the stabilization of the ovary by means of grasping forceps, followed by cutting the tissue to be removed with a cold blade. The tissue was excised with atraumatic forceps in a single point. Then the piece was externalized from the navel and accurate hemostasis was carried out with a monopolar hook or bipolar forceps. At the end of the procedure, a drain was routinely left in place and removed in the first postoperative day, after performing a control blood count. Discharge took place on the first or second post-operative day.

In Center 3, both a monolateral and a bilateral sampling was performed based on a pelvic ultrasound performed pre-operatively to check the presence and the numerosity of follicles in each ovary. The operative technique involved the use of 3 trocars, one 12 mm umbilical port for a 30-degree camera and two operating trocars, 5 mm on left hand and 12 mm on right hand. Surgical steps included identification of both ovaries and evaluation of the bigger one (confirming the pre-operative ultrasound findings), then stabilization of the ovary and removal of approximately half of the parenchyma of only one ovary, except in cases where the preoperative ultrasound and the surgical evaluation did not demonstrate dimensional superiority of one ovary, for which ovarian tissue was collected from both ovarian parenchymas. The sample was retrieved in an endobag and externalized through the umbilical access. Accurate hemostasis was carried out with a monopolar hook or scissor, in some cases the use of a vessel sealer device was needed. Drainage was not routinely inserted.

In Center 4, a monolateral sampling was collected and for the procedure, three 5 mm trocars were used. Antibiotic prophylaxis with Cefazolin was administered and only one ovary was sampled. For the cortex removal, a careful dissection with scissors was performed, avoiding the medulla of the ovary, fimbriae and vessels. Throughout the procedure, every attempt was made to avoid coagulation because of the risk of decreasing the viability of the primordial follicles.

To control hemostasis a hemostatic agent was preferred. No drains were left in place. The sample was removed through the umbilical trocar without an endobag. A member of the biology department was present during the entire procedure to ensure the correct and rapid transport of the sample, once it had been removed. The tissue was transferred to the laboratory where it was analysed and prepared for subsequent cryopreservation.

2.1 Cryopreservation/pathologic evaluation

The same cryopreservation process and pathologic evaluation criteria was applied to all the Centers involved in the study. The ovarian cortex is located a little deeper below the capsule and contains most of the primordial follicles. These primordial follicles represent the child's ovarian reserve. In the tissue cryopreservation technique, the cortex is dissected from the medulla and cut into cortical strips, washed to remove blood cells and then passed through a series of cryopreservation media (Figure 1). The processed strips are placed in cryovials and undergo a slow-freezing process to −40 °C. The tissues are then transported to a long-term reproductive tissue storage facility in liquid nitrogen. The intraoperative biopsy undergoes pathology evaluation for the presence and stage of ovarian follicles and the eventual presence of neoplastic cells. The quality of the ovarian tissue collected laparoscopically was directly proportional to the cold blade cut and inversely proportional to the surgical cauterization; the dimensions of the ovarian fragments collected were found to be satisfactory in all the Centers that provided the laboratory with a sufficiently represented quantity of three-dimensional tissue.