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Ovarian transposition as a minimally invasive fertility preservation technique: ten years of experience in a pediatric center

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ABSTRACT

Introduction. Ovarian transposition is a surgical procedure allowing gonadal mobilization from a radiation spotlight to a safer, radiation therapy-free place in patients receiving abdominal or pelvic radiation therapy. And these patients can be managed using minimally invasive surgery. Although some authors have reported good results in fertility preservation with this technique, there are no long-term studies in the pediatric population. We present our results with this procedure in our oncological patients from the last decade.

Materials and methods. Retrospective review of medical reports of patients who underwent laparoscopic ovarian transposition in our pediatric oncological surgery unit from 2008 to 2018. The technique varied depending on age, irradiation zone, and concomitant oncological resections.

Results. A total of 21 ovarian transpositions were successfully performed in 13 patients. Eight were bilateral, four were left and only one was right. An ovarian cortex cryopreservation was simultaneously carried out in all patients. Eleven procedures were completed laparoscopically, and the suspensory ovarian ligament was divided in sixteen cases. The Fallopian tube was divided in one case, and a simple ovarian transposition was conducted in five cases. Mean hospital stay was 2.4 days, and no complications in the immediate postoperative period were noted.

Conclusion. Ovarian transposition is a feasible, safe technique. These patients require an extended follow-up to assess ovarian function after oncological treatment.

KEY WORDS: Fertility; Child; Surgical procedures.

LA TRANSPOSICIÓN OVÁRICA COMO TÉCNICA DE PRESERVACIÓN DE LA FERTILIDAD EN EDAD PEDIÁTRICA: 10 AÑOS DE EXPERIENCIA EN UN CENTRO DE TERCER NIVEL

RESUMEN

Introducción. La transposición ovárica es una técnica quirúrgica que permite alejar los ovarios de la zona de irradiación en pacientes que van a recibir radioterapia abdominal o pélvica. Se han descrito buenas tasas de conservación de función. Sin embargo, no existen estudios en pacientes pediátricos. Presentamos nuestra serie de pacientes intervenidas en nuestro centro.

Material y métodos. Estudio retrospectivo de pacientes a las que se le realizó transposición ovárica en nuestra unidad de cirugía oncológica pediátrica entre los años 2008 y 2018. La técnica empleada dependió de la edad, la zona de la irradiación y de la asociación o no con la cirugía del tumor primario.

Resultados. Durante el periodo de estudio se realizaron un total de 21 transposiciones ováricas en 13 pacientes (8 bilaterales, 4 izquierdas y 1 derecha). En todos los casos se realizó criopreservación de corteza ovárica dentro del programa de preservación de fertilidad. Once de las 13 intervenciones fueron por laparoscopia, seccionándose el ligamento tubo-ovárico en 16 unidades y en 5 se realizó transposición ovárica simple. La estancia hospitalaria media fue de 2,4 días sin registrarse ninguna complicación en el postoperatorio. Actualmente 9 pacientes continúan seguimiento en sus unidades de oncología pediátrica de referencia, sin haberse notificado ninguna complicación.

Conclusión. La transposición ovárica es una técnica segura y reproducible. Estas pacientes requieren un seguimiento prolongado para conocer el estado de los ovarios tras el tratamiento oncológico.

PALABRAS CLAVE: Fertilidad; Ñiño; Procedimientos quirúrgicos.

INTRODUCTION

Fortunately, the number of pediatric and adolescent patients surviving cancer has increased in the last decades owing to the advances made in antineoplastic therapies. Therefore, concerns about long-term treatment sequels in this type of patients are of the utmost importance[5,6,9,10].

Abdominopelvic radiation therapy and chemotherapy, especially with alkylating agents, are two of the most com-

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mon treatments[2,6]. Both therapies have side effects at the gonadal level. The risk of early ovarian failure (EOF) has been described, associated with an increase in cardiovascular conditions, prevalence of osteoporosis, and a decrease in follicle reserve, thus entailing a loss of fertility[1,2,4,5]. As a result of this, from a global perspective and considering long-term sequels, implementing the necessary measures to preserve ovarian function as much as possible proves particularly important[9].

Patients undergoing these treatments can benefit from gonadal function preservation techniques, such as cryopreservation (of ovarian tissue or oocytes) or ovarian transposition (OT)[1,4,5,8,10]. The latter, described in 1958, moves the ovary away from the damaging field of pelvic radiation therapy, thus reducing the risk of EOF[1,3]. In addition, laparoscopic OT incorporates the advantages of this approach, such as fewer adhesions and shorter hospital stay[7,8,10]. In previous studies, fertility preservation rate using this technique can reach 89%[3,7].

Even though OT has been largely described in the literature, there are few studies where an extended follow-up of patients undergoing this technique has been carried out[1-3]. The objective of this work is to describe the results of OT in patients aged between 7 and 15 in our center over the last 10 years.

MATERIALS AND METHODS

Type of study

Retrospective and descriptive study of pediatric patients undergoing abdominopelvic radiation therapy and ovarian transposition from January 2008 to December 2018 in our pediatric oncologic surgery unit.

Inclusion criteria

All patients under 14 undergoing ovarian function preservation treatment were included. Patients referred to our hospital with a previous transposition were excluded. Unilateral or bilateral ovarian transposition with ovarian cortex cryopreservation (OCC) was performed. The technique used (open or laparoscopic surgery) depended on age, irradiation area, and association or not with primary tumor surgery.

Patients from all over Spain were referred to our department by our hospital's children's oncology department, as a reference center for pediatric fertility preservation therapies.

Study variables

Data collected included patient demographic data (age at surgery and reference center), oncologic diagnosis and treatment, data related with the technique used (transposed ovarian unit and OCC unit, type of surgery – open or laparoscopic –, and method used for unit marking in the abdominal wall), operating times, intraoperative and immediate postoperative complications, and mean hospital stay, as well as an outpatient control by their oncologist in their reference center.

Technique description

Prior to surgery, an abdominal ultrasonography is performed in all patients to identify the largest ovary. The laparoscopic approach is initiated by using a 5 or 10 mm Hasson port at the umbilical level for the introduction of a 5 mm, 30-degree scope. Entrance pressure and flows are programmed according to patient age and weight. The surgeon is placed in a contralateral position with respect to the ovary to be transposed, at the level of the patient's shoulders, with the videolaparoscopy screen at her feet. Two additional 5 mm ports without balloon are placed at the level of both flanks under direct visualization. The abdominal cavity is visualized, and both ovaries, the tubo-ovarian ligaments, and the uterus are identified. A partial oophorectomy of the ovarian cortex of the largest ovary is performed, and an ovarian surface fragment of at least 1 sq. cm is removed. Then, to transpose the ovary to the recommended area, the ovarian unit may have to be isolated from its tube by selecting the tubo-ovarian ligament, freeing it, or just mobilizing the ovary and the tube simultaneously. The technique used depends on the distance the ovary needs to be moved and on the patient's anatomy. Finally, both ovaries are marked with titanium metallic clips to determine their exact position in future controls. Following the procedure, the patient remains in hospital for 24 to 48 hours, prior to discharge. In those cases requiring primary tumor removal – for example, neuroblastoma –, the open approach is preferred, with both processes being carried out in the same surgical procedure.

Follow-up

A control was carried out by the surgeon in charge of the pediatric oncologic surgery unit following the procedure. Patients referred from other hospitals for surgical treatment in our center were controlled by the oncologists in their reference hospital. During follow-up, the patient's clinical situation was checked to determine if she had completed oncologic treatment, if she was still under follow-up, if she had amenorrhea, or if she was receiving hormone replacement treatment.

Other aspects

The procedure and its potential risks were explained to the patients and their relatives. In all cases, informed consent for surgery and research data exploitation purposes was obtained.

RESULTS

13 patients were included in the study. Study patient data are featured in Table 1.

Table 1. **Demographic and clinical characteristics.**

N	*Age (years)*	*Histology*	*Approach*	*OT*	*OCC*	*Marking*	*Time (min)*	*Hospital stay (days)*
1	13.61	Hodgkin's lymphoma	Laparoscopic	Bilateral	Right	Yes	87	1
2	12.68	Hodgkin's lymphoma	Laparoscopic	Bilateral	Right	Yes	117	1
3	14.73	Hodgkin's lymphoma	Laparoscopic	Bilateral	Right	Yes	152	1
4	10.6	Neuroblastoma	Open	Bilateral	Left	N/A	N/A	6
5	13.7	Rhabdomyosarcoma	Laparoscopic	Bilateral	Right	Yes	124	2
6	14.72	Ewing's sarcoma	Laparoscopic	Bilateral	Left	Yes	153	2
7	11.47	Ewing's sarcoma	Laparoscopic	Bilateral	Right	Yes	120	1
8	14.58	Ewing's sarcoma	Laparoscopic	Bilateral	Right	Yes	142	2
9	3.68	Rhabdomyosarcoma	Open	Right	Left	N/A	156	6
10	13.44	Ewing's sarcoma	Laparoscopic	Left	Right	N/A	N/A	5
11	14.51	Ewing's sarcoma	Laparoscopic	Left	Right	N/A	N/A	N/A
12	10.56	Ewing's sarcoma	Laparoscopic	Left	Right	Yes	52	1
13	15.34	Others*	Laparoscopic	Left	Right	N/A	N/A	1

N/A: not available.

21 ovarian transpositions were carried out in 13 patients (median age at surgery: 13.61 years; interquartile range: 3.615 years). In 8 cases, transposition was bilateral, in 4 cases only left, and in 1 case only right. In all cases, OCC of the largest ovary within the fertility preservation program, identified through ultrasonography prior to surgery, was performed. In 10 cases, the ovarian cortex was resected from the right ovary.

The most common surgical approach was the laparoscopic one, carried out in 11 of the 13 patients (84.6%). In 16 (76.19%) ovarian units, the tubo-ovarian ligament was divided, and simple ovarian transposition was performed in 5 units (23.81%). In one patient, both tubo-ovarian ligaments were divided, and ipsilateral salpingectomy and abdominal wall lipoma resection were conducted simultaneously in the same procedure. In another patient, an ovarian cyst was incidentally found and removed.

Titanium clips were the most widely used technique – 8 patients – for ovarian unit marking for future studies. In the other 5 patients, the surgical protocol did not specify the marking type used.

Operating times ranged between 52 and 156 minutes per patient, bilateral transpositions being the longest ones. In addition, ovarian cortex cryopreservation was performed in all cases, and a central venous catheter with reservoir was placed in some. In four patients, operating times could not be calculated as they were not specified in the surgical protocol. Mean hospital stay was 2.4 days. No immediate postoperative complications (first 24-48 hours) were noted.

At the time of drafting this article, patient follow-up times ranged between 12 months and 10 years. During follow-up, four patients died owing to the progression of their condition, so now only 9 patients are still under follow-up in their reference pediatric oncology units, with no surgical complication being recorded. Six of the nine patients completed oncologic treatment. In one case, the patient's oncologic state is not mentioned.

Two patients remain under treatment owing to the progression of their condition.

Of the six patients having completed treatment, three have regular periods without requiring hormone replacement treatment. The oldest patient, who completed oncologic treatment in 2009, presented regular periods and one pregnancy, which she voluntarily interrupted, and now she is under hormone replacement treatment. The other two patients – aged 13 and 8 – remain in pre-puberty stage (Tanner 2), so ovarian function is still unknown.

DISCUSSION

Concerns about sequels and quality of life in patients surviving such a compromising condition as cancer are a growing issue. Fertility-related problems represent one of the most important concerns in these patients, 81% of whom are interested in fertility preservation[12]. Multiple studies in the adult population demonstrate the benefits of OT when it comes to preventing the risk of early ovarian

Table 2. Patient inclusion criteria in La Fe University and Polytechnic Hospital (Valencia)'s fertility preservation program[11].

- > 18 months and < 15 years
- Diagnosed with neoplasia / hematologic disease with a high gonadotoxic risk treatment (high or medium-high risk according to the Valencia 2015 classification)
- Diagnosed with neoplasia / hematologic disease with a low-medium gonadotoxic risk treatment according to the Valencia 2015 classification and an additional determining factor (age or family interest)
- Clinically stable
- Patients who have received low doses of gonadotoxic chemotherapy or no doses at all
- Reasonable survival expectancy or at least first-line treatment healing intention

failure as well as to preserving fertility in patients undergoing pelvic or abdominal radiation therapy[1,3,7].

Of all fertility preservation techniques[1,10], OCC is the main option for pre-pubescent patients. The criteria for indicating this type of procedures are clearly established in our hospital's fertility preservation protocol (Table 2).

In the case of OT, various factors should be considered when performing an adequate patient selection. On the one hand, the pelvic area should be included in the irradiation area, and the dose to be administered to the patient should be gonadotoxic. A 1,000 cGy dose is considered as sufficient to cause a damaging effect and unleash an early ovarian failure in pediatric patients, with a 70% EOF in patients receiving > 2,000 cGy doses[1,6]. On the other hand, it should be anatomically possible to place the ovary aside from the irradiation area without damaging ovarian vascularization, so as to avoid ischemia and ovarian atrophy. However, this surgical procedure does not allow all distances to be covered; therefore, indication should be carefully and individually studied in each patient. In our unit, a detailed anatomical study is carried out using the data from the imaging studies previous to radiation therapy. This allows the main irradiation area and the peripheral area to be simulated, and the anatomical site from which the ovary can be sufficiently moved away from the problematic area to be clearly determined (Fig. 1). With these data and intraoperative findings, decision is made as to which surgical procedure should be performed. In our series, most patients required tubo-ovarian disconnection for OT purposes. We believe this technique provides good long-term results without the need for salpingectomy, which we find more aggressive, and which we only performed in one single patient. In single transposition cases, the mere joint manipulation of the ovary and the tube allowed the ovary to be moved away from the risk area.

Any OT technique involves a more complex surgery for the patient, with greater surgical aggression, and probably, higher likelihood of complications and/or postoperative discomfort.

The laparoscopic approach proves advantageous as it provides with a better visualization of the abdominal cavity and the contralateral ovary, with a smaller incision size[3,8,10]. Regarding long-term complications, ovarian cysts owing to manipulation following ovarian transposition have been described in the literature, with an incidence of

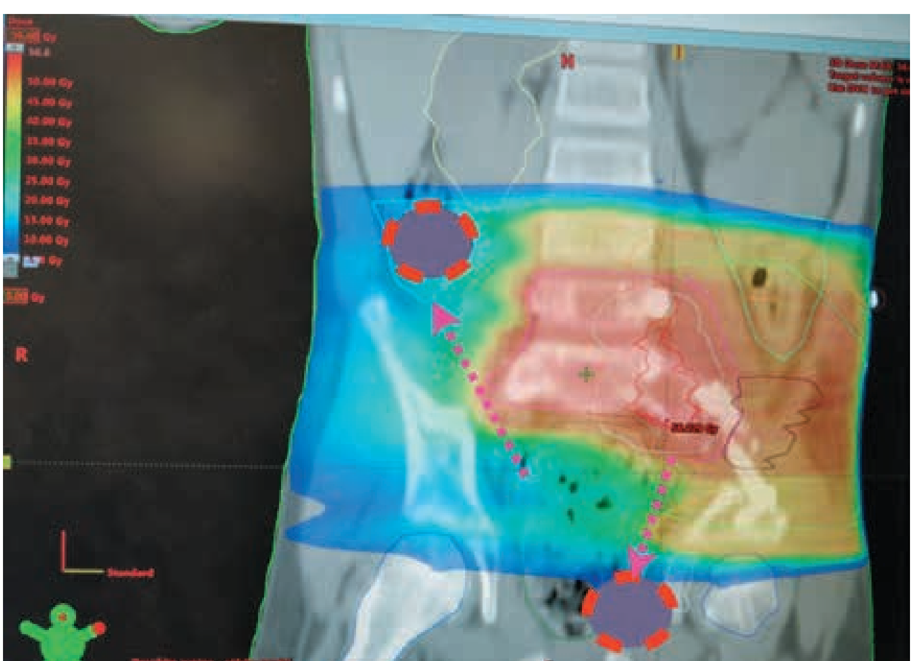

Figure 1. Radiation therapy simulation and ovary position after surgery.

up to 9.6%[3], which we did not note in our series. In addition, there are certain complications developing in adult patients which can hardly be detected in pediatric patients as they stem from metastasis, such as ovarian metastasis, which may be another cause of ovarian failure[3].

One of the causes which can explain EOF in spite of performing an OT is the fact that many patients receive high gonadotoxic chemotherapy doses (such as alkylating agents) concomitantly. Furthermore, in certain oncologic processes, a higher abdominopelvic radiation therapy dose, or total body irradiation, may prove necessary. In such conditions, despite ovarian transposition, the amount of Gy the ovary receives is high enough to cause a damaging effect on ovarian function, so OT is proposed as an option to attempt to mitigate radiation[1,3,7,8].

In the literature, fertility preservation following OT is described between 60 and 90% according to the type of radiation therapy used[10]. During our series' follow-up, four patients had regular periods or a voluntary interruption of pregnancy, with no complications such as ovarian torsion, ovarian cyst, or ovarian atrophy, which have been described in the series published up until now[1,10]. We believe a longer follow-up period for these patients is required to study ovarian function following this technique, as well as potential complications not observed during our series' follow-up.

CONCLUSIONS

Fertility preservation techniques should be offered in all pediatric cancer treatment centers, and long-term patient follow-up should be essential. More complex procedures such as OT should be carefully indicated after individualized assessment and carried out in expert facilities. The minimally invasive approach allows discomfort associated with these procedures to be reduced.

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