Journal of Pediatric Surgery 56 (2021) 626–628

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg.org

Operative Techniques

Laparoscopic assisted extracorporeal ovarian harvest: A novel technique to optimize ovarian tissue for cryopreservation in young females with cancer

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ARTICLE INFO

Article history:
Received 3 June 2020
Revised 2 November 2020
Accepted 4 November 2020

Keywords:
Ovarian cryopreservation
Laparoscopic ovarian biopsy
Fertility
Primary Ovarian Failure

ABSTRACT

Background: Advances in pediatric cancer therapy have improved the long-term survival for many children with cancer. The awareness of quality of life aspects, specifically fertility preservation, has become a reality for many of these families and children. Ovarian tissue cryopreservation has emerged as an available fertility option for young females with cancer. Safe and effective removal of ovarian tissue in these girls is paramount. We report a laparoscopic assisted extracorporeal ovarian harvest technique that achieves this goal.

Operative technique: We place a 5 mm port at the umbilicus and in the right lower quadrant. Under laparoscopic guidance we place a 12 mm port in the left suprapubic area. Utilizing the 12 mm port site a monofilament traction suture is placed through the left ovary. The traction suture is used to translocate the ovary to an extracorporeal position via the 12 mm port site. Ovarian tissue is then excised utilizing standard surgical technique with the scalpel. Hemostasis is obtained and the capsule is closed with a running absorbable suture. The ovary is placed back in its native position laparoscopically.

Conclusions: The use of this extracorporeal ovarian harvesting technique is a safe and effective method to optimize removal and minimize tissue injury. Utilization of this technique, may have potential benefit to the young female with cancer.

1. Introduction

Cancer therapy have improved the long-term survival for many children with cancer. The 5-year overall survival rate for childhood cancer has increased from 58% in children diagnosed between 1975 and 1977 to 83% in those diagnosed between 2008 and 2014 [1]. The awareness of quality of life aspects, specifically fertility preservation, has become a reality for many of these families and children. Mainstay fertility preservation options for females undergoing gonadotoxic treatment typically include embryo and oocyte cryopreservation. However, for prepubertal patients or when urgent treatment is needed, ovarian tissue cryopreservation has emerged as the only available fertility option for this group of patients [2,3]. Successful studies documenting live births following this procedure in adult woman, and in at least 10 children, has led to a dramatic increase in the practice worldwide [4,5]. The oncofertility consortium has recently reported that ovarian tissue cryopreservation is a standard of care fertility option in young females with cancer [6,7].

Most ovarian harvesting techniques for cryopreservation employ oophorectomy. Our specialty has also reported this technique [8]. However, prediction of which patient will clearly benefit from ovarian cryopreservation remains a challenge and outcome data may be decades away. Because of this, some groups are adopting a more conservative harvesting approach with a more limited harvest and resection [9]. The objective in this report is to describe a novel extracorporeal ovarian harvest strategy that is safe, effective and may allow for more optimal tissue preservation in selected young females with cancer.

2. Operative technique

In this cohort of patients, we performed our ovarian harvest during the same anesthetic that is required for the child's chemotherapy catheter placement and/or bone marrow biopsy. Our selection criteria were based on criteria that predicted a greater than 80% risk of infertility and sterility following cure. Children who met these criteria were offered the option of ovarian cryopreservation where we utilized this technique. None of the children had received any gonadotoxic therapies. Consent was obtained from the parents/guardians and assent was obtained

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https://doi.org/10.1016/j.jpedsurg.2020.11.004
0022-3468/

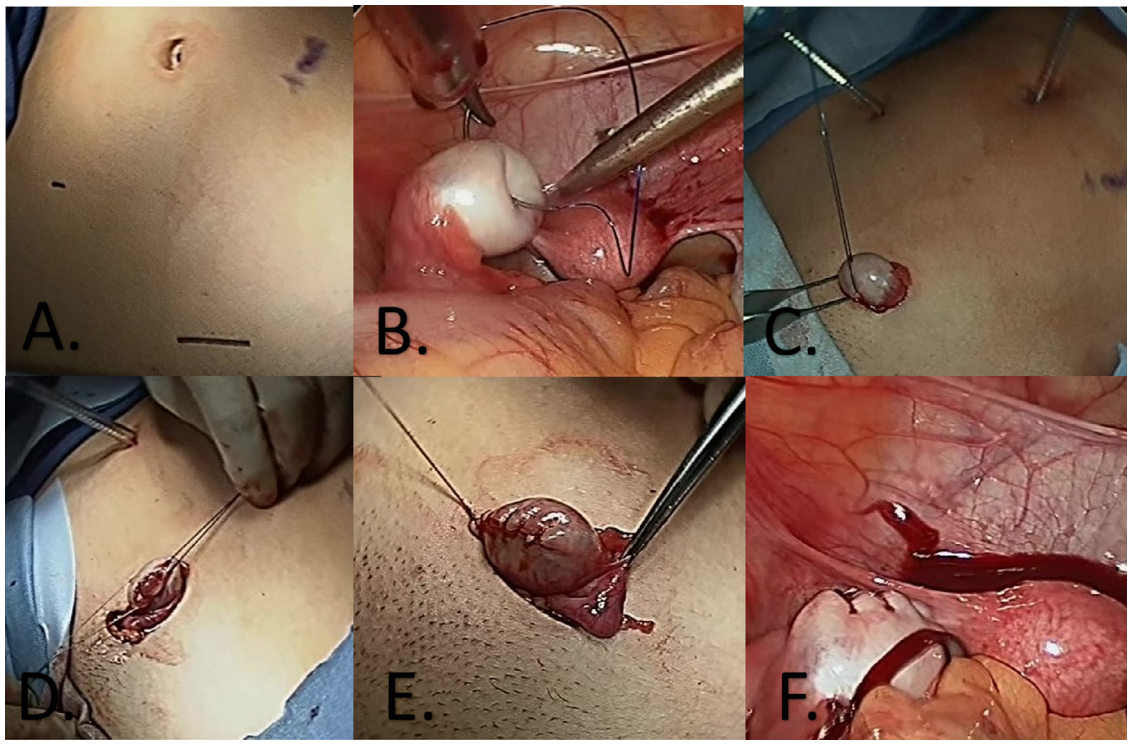

Fig. 1. A. Port sites locations; 5 mm at the umbilicus, 5 mm in the right lower quadrant, 12 mm in the left suprapubic area. B. Placement of the traction suture through the left ovary. C. Removal of the 12 mm trocar from the field and utilizing the traction suture to deliver the left ovary to an ex vivo position. May require extension of the incision. D. With suture stays and intermittent vascular control, a wedge resection of the left ovary performed with scalpel. E. Following removal of the ovarian tissue, hemostasis is obtained with electrocautery and the ovarian capsule is closed with running vicryl suture. F. Ovary is placed back in its native position and hemostasis ensured.

from girls who were of assenting age (greater than 8 years old). The consent discussion and risk/benefit discussion were carried out in partnership with the pediatric oncologist. In our discussion, we focused on the lack of efficacy data regarding the procedure and strategy. We stated unequivocally, that ovarian tissue cryopreservation has preserved the ability of a woman to have her own biologic child and in some cases reestablish hormonal function after cancer therapy and cure but that there is no guarantee that this same success will occur in this case.

The details of our technique are as follows. Five mm ports are placed at the umbilicus and the right lower quadrant. We prefer to harvest from the left ovary. Under laparoscopic guidance, we place a 12 mm port very low in the suprapubic space in very close proximity to the left ovary (Fig. 1A.). We introduce a 2–0 prolene on a CT1 needle via the 12 mm port. The suture is passed through the ovary (Fig. 1B.). Utilizing this traction suture, we translocate the left ovary to an extracorporeal position via the 12 mm port site incision (Fig. 1C.). In older teenagers, the 12 mm incision may need to be extended to allow safe evisceration of the ovary. With vascular control, ovarian harvest is carried out with the scalpel (Fig. 1D.). Following removal of the tissue, hemostasis is obtained and the ovarian capsule is closed with a running 3–0 vicryl suture (Fig. 1E.). The ovary is returned to its native position laparoscopically and hemostasis is verified (Fig. 1F.). The operation is completed in standard fashion. This patient population is at significant risk for post-operative bleeding complications. It is imperative that closure and repair of the ovarian capsule is done with meticulous attention to hemostasis.

In these patients we chose to remove approximately 30% of the left ovary (Video 1). We divided our specimen into 5 sections. The sections were placed into cryogenic vials and transferred to the assisted reproductive technology lab for cryopreservation. The specific technique of slow freezing ovarian tissue has been previously reported [10,11]. Ovarian cortex tissue was transferred to cryovials containing freezing medium (0.1 M sucrose/1.5 M PPD/20%SSS) that was used as a cryoprotectant. The cryotubes were cooled in a programmable freezer (Freeze Control CL-8000) using a slow-freezing program for ovarian tissue, with progressive reduction of the temperature curve, and stored at −196 C for each child.

We anticipate that each section will yield 2 cortical strips for a total of 10 cortical strips for each patient. We have successfully performed this technique on 16 young females with cancer (mean age 12 years, range 6 −18 years). We have had no difficulty with the extracorporeal translocation, no wound complications or complications related to laparoscopy including trocar sites,placement or post-operative bleeding.

3. Discussion

Childhood cancer treatment modalities are effective in achieving complete remission and cure. Aggressive chemotherapy and radiotherapy, as well as bone marrow transplantation, results in a greater than 80% cure in many children and young women with cancer [1]. A decrease in or loss of fertility in cancer survivors is a distressing issue that greatly impacts long-term quality of life. When the cancer patient is a child, the impact on future fertility is an important discussion for the parents/legal guardians and often for the patient [12].

Ovarian tissue cryopreservation and transplantation has emerged against this background [9,13–15] and over 100 live births have been reported in adult woman utilizing the strategy and at least 10 live births in woman who underwent pediatric ovarian tissue cryopreservation [7,16,17]. For young females with cancer, ovarian tissue cryopreservation has the advantage that the procedure can be performed on an urgent basis and does not require ovarian stimulation or in the case of prepubertal girls, the

strategy does not require active ovarian function [18–20]. In fact, in the prepubertal girl, ovarian tissue cryoprservation represents the only option available to potentially preserve fertility should they develop ovarian failure, following their cure [18–20].

The risk of primary ovarian failure (POF) and infertility is linked to the type and stage of cancer, type and dose of cancer therapy and the age of the patient at the time of initiation. There are likely genetic factors that are unique to each child that must be considered, such as the ovarian follicle density (FD) which can vary significantly amongst girls and women [21]. FD is a key predictor of reproductive potential and may serve as a tool to evaluate ovarian reserve, future fertility and response to ovarian cryopreservation and subsequent reimplantation [13]. FD is unique to each female and differs widely in adult women [21]. There is no data on FD in young females. Because of these issues, prediction of which girl with cancer will clearly benefit from ovarian tissue cryopreservation remains a challenge. To this end, the Committee on Best Practice of the Pediatric Initiative Network of the Oncofertility Consortium has recently reported guidelines that more precisely stratify the risk based on cancer therapy and this will assist in the consent and decision-making process [22]. Without mandated guidelines, the question of which child is offered ovarian biopsy, partial oophorectomy, unilateral oophorectomy for fertility preservation remains variable and there is no consensus. We currently offer the technique to all prepubertal females that are referred from pediatric oncology for a discussion on fertility preservation. The current recommendations are extrapolated from the adult experience and unilateral oophorectomy is commonly performed [7]. Children who are at a high level of increase risk, may benefit from unilateral oophorectomy. However, some groups are now considering a more conservative harvest strategy that maximizes the child's natural future reproductive and hormonal potential for those children who are deemed to have a minimally increased risk [9]. It would seem logical that this extracorporeal ovarian harvest technique may be most suitable for these females who have a minimally increased risk. The discussion of volume of ovarian tissue that is removed is carefully discussed as a team with the parents/guardians and patient. Surgical risks of post-operative hemorrhage are weighed against risk of infertility/sterility and adult efficacy data of the success of cryopreservation and subsequent reimplantation. The final decision on the ideal amount of tissue to be removed to optimize future fertility is unique to each child and is a synthesis of these factors.

Pediatric cancer treatment strategies have been modified to significantly mitigate the risk of POF and future infertility in girls, especially over the last decade. In light of these issues, the extent of ovarian tissue removal in young females with cancer is a critical consideration. Without mandated guidelines or clear risk stratification, the primary goal for our team in establishing this technique was one of nonmaleficence. We believe all girls who are at increased risk for ovarian failure and sterility from cancer therapy that are not candidates for other fertility preservation options should be offered ovarian tissue cryopreservation. Partial oophorectomy for girls at minimally increased risk and unilateral oophorectomy for girls who are at a significantly increased risk or a high level of increased risk may be a logical approach until there is more efficacy data in this patient population. The oncofertility guidelines and establishing a national registry, such as the one in France, will greatly enhance this decision analysis. The goal should be to obtain tissue in a manner that maximizes viable tissue that could be utilized for ovarian tissue cryopreservation and minimizes the risk and harm to the child. The extracorporeal ovarian harvest technique is a safe and effective procedure that accomplishes these objectives. Utilization of this technique, may have potential benefit to the young female with cancer that is at minimally increased risk for infertility/sterility following cure. mmc1.mp41

Declaration of Competing Interest

No competing financial interests for the author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jpedsurg.2020.11.004.

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