



A review of reported surgical techniques in fertility preservation for prepubertal and adolescent females facing a fertility threatening diagnosis or treatment



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ABSTRACT

Background: Ovarian tissue cryopreservation is increasing as a preferred option for fertility preservation for prepubertal and young adolescent females facing a fertility threatening diagnosis or treatment.

Data sources: Ovid MEDLINE and PubMed searches for terms related to ovarian tissue removal for fertility preservation revealed there is no current consensus on operative technique for surgical ovarian cortical tissue removal in adult females. Additionally, there are limited published reports of surgical approach and outcomes in the pediatric population. In total, 22 publications were reviewed for their operative approach, ovarian tissue harvesting techniques, complications and outcomes.

Conclusions: Reported operative approaches and techniques for ovarian tissue cryopreservation for pediatric and adolescent patients are variable. Further investigations into operative technique and tissue harvesting that maintains healthy ovarian follicles for transplant will help establish standard technical principles for surgery in pediatric and adolescent females undergoing fertility preservation.

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1. Introduction

Pediatric female patients with a variety of cancer, genetic, endocrine, and rheumatologic conditions may be candidates for fertility preservation as part of their comprehensive care. Currently, children who receive a new cancer diagnosis can anticipate a five-year survival of 80% as compared to 60% in the late 1970s due to continued advancement in medical therapies.¹ This remarkable improvement in survivorship has prompted increased awareness of long-term quality of life concerns, including the risk of infertility and premature ovarian insufficiency amongst adult female survivors of childhood cancer.²

Many of the common pediatric cancer diagnoses require multimodal treatments that expose patients to gonadotoxic therapies such as alkylating agents, pelvic irradiation, and/or stem cell transplant that increase their risk for post-therapy infertility.

Historically, oophoropexy was the only fertility preservation option for prepubertal girls. While shown to be an effective means of mitigating radiation exposure and preserving ovarian function post radiotherapy, it does not provide protection from systemic therapies.^{3–5} In addition, very young prepubertal girls have limited area for anatomic transposition, making oophoropexy less likely to be technically successful.⁶

Currently, embryo and oocyte cryopreservation are the only assisted reproductive techniques that are considered to be non-experimental by the American Society for Reproductive Medicine.⁷ Unfortunately, there are limitations to these modalities when they are applied to the young adolescent population. Both require 3–4 weeks of ovarian stimulation with gonadotropins for oocyte harvest and typically involve use of transvaginal ultrasound and needle oocyte retrieval techniques, which could require general anesthesia or be technically not feasible in a sexually immature patient. This delay is often not acceptable for females requiring urgent therapy. Young girls are typically not candidates for embryo cryopreservation as it requires the use of sperm for embryo development. Additionally, oocyte cryopreservation cannot be offered to prepubertal females due to their immature hypothalamic-pituitary axis and inability to produce mature eggs.

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Ovarian tissue cryopreservation (OTC) was first described by Hovatta et al. in 1996 and involves surgically removing ovarian cortical tissue, independent of hormone stimulation, that is cryopreserved for potential future fertility and hormone restoration.⁸ While OTC remains experimental and requires prior approval by the healthcare institution's Institutional Review Board (IRB), it has become a viable method for fertility preservation and is currently the only pre-treatment option for prepubertal girls.⁹ Currently, there are over 60 reported successful pregnancies resulting in live births through ovarian tissue transplant after OTC from adult patients,¹⁰ one live birth following transplant of tissue preserved when the patient was peri-pubertal,¹¹ and news reports of one live birth from OTC performed in a prepubertal patient.¹²

Despite the increasing use of OTC, there is no current standard technique for surgical removal of ovarian tissue. Many operative techniques are described in the adult literature, but very few studies identify a technique that is applicable to the pediatric population. Therefore, this summary aims to review the currently described operative techniques for surgical removal of ovarian cortical tissue for cryopreservation and to discuss special considerations for prepubertal and young adolescent females undergoing surgical procedures for fertility preservation.

2. Methods

Ovid MEDLINE and PubMed searches were performed to identify articles published in the English language with the keywords of "fertility preservation", "cryopreservation", "ovarian tissue", "surgical technique", "operative technique", "ovarian biopsy", and "oophorectomy". Only human studies between January 2000 and December 2016 were reviewed. Three hundred and sixty-three articles resulted of which 133 had mention of operative approach after review of the title and/or abstract by one author (KC). The remaining manuscripts were reviewed for descriptive details of operative technique for OTC including operative approach, tissue harvest method, dissection technique, intraoperative complications, and postoperative outcomes and complications. Articles with the same first author that described similar operative techniques were included only once in the review. Overall, 22 manuscripts were found to report descriptive details in regards to the operative technique for OTC.

3. Results

Of the 22 manuscripts reviewed, 4 described using ovarian cortical biopsy, 6 partial oophorectomy, and 8 unilateral oophorectomy as their technique for OTC. Four studies reported multiple techniques used at their institution. Four manuscripts specifically reported on pediatric cohorts, defined as younger than 20 years of age. Refer to [Table 1](#) for manuscript review details.

3.1. Ovarian cortical tissue biopsy

Ovarian cortical tissue contains the primordial follicles, known as the follicle reserve, irrespective of the female patient age.¹³ Ovarian cortical tissue biopsies can be performed either laparoscopically or in conjunction with another open procedure such as a primary tumor resection.^{14,15} Regardless of technique, an area away from the hilum that is free of visible predominant follicles and/or luteal tissue is preferred as the site of biopsy. The goal is to maximize the number of primordial follicles per specimen without compromising vascular supply to the remaining ovarian tissue.¹⁶ Meirrow et al. describe using a three-port laparoscopic approach in which they stabilize the utero-ovarian ligament with a grasper and obtain five or six pieces (5 mm × 3 mm) of cortical tissue using

a laparoscopic biopter. Hemostasis was achieved with bipolar electrocautery after biopsy.¹⁷ Similarly, another group described using laparoscopy to obtain up to ten biopsies with 5 mm³ volume each depending on the volume and size of the ovary.¹⁸ Of those that included postoperative outcomes, there were no intraoperative or postoperative complications noted and an average length of stay less than 24 h was reported. Patients did not experience any delays in anticipated medical therapy in either study.^{17,19}

3.2. Partial oophorectomy

Partial excisions of ovarian cortical tissue can also be performed by either laparotomy or laparoscopy, but was most commonly reported as an elective laparoscopic procedure in the studies reviewed. Both three-port and reduced/single-port surgeries are described.^{20,21} Unlike cortical tissue biopsies, the partial excision technique extracts a single block of cortical tissue from either one or both ovaries.^{22,23} Anywhere from 1/4 to 2/3 of ovarian tissue is removed for cryopreservation purposes leaving a partially intact ovary in situ.^{17,18,20,22,24,25} In many cases, the right ovary was selected due to its preferred anatomic location away from the sigmoid colon.²⁶ Dissection was carried out with the use of sharp scissors out of fear for follicle damage secondary to electrocautery burn.

When reported, hemostasis was most often achieved using bipolar electrocautery.^{20,22,25} One report noted the use of a thrombin hemostatic matrix and another the use of argon beam coagulation to gain a more superficial level of hemostasis out of concern for cautery damaging to the remaining ovarian tissue.^{21,23} Data in the adult gynecology literature suggests that both bipolar and ultrasonic electrocautery have effects on the reserve of remaining ovarian tissue after laparoscopic ovarian cystectomy.^{27–29} Poirot et al. modified their approach after observing thermal injury of their partial oophorectomy specimens and proceeded with unilateral oophorectomy for the remainder of the study.³⁰

Of the studies that included postoperative outcomes, the majority reported no complications and an average length of stay ranging from same-day surgery to two-day hospital admission.^{18,20,22,24} One incident of clinically significant intraoperative blood loss requiring transfusion was described in a pediatric patient.²³

3.3. Unilateral oophorectomy

Laparoscopic unilateral oophorectomy was carried out for the purposes of ovarian cortical tissue cryopreservation, as well as whole ovary cryopreservation. Both standard two to four-port and reduced/single-port laparoscopy were described.^{3,19,31–33} Division of the infundibulopelvic (suspensory) and utero-ovarian ligaments was carried out by a wide range of techniques and devices including bipolar electrocautery, Endo-GIA stapler, Ligasure, Harmonic scalpel, Endoloop, as well as vascular clips.^{3,19,21,31,33,34} No study addressed the superiority of one technique compared to another in regards to division of the vasculature. Feigin et al. reported institutional variability due to surgeon preference for which device to use for dissection and vascular ligation, but did not address or compare outcomes according to technique.¹⁹ Again, the right ovary was cited as preferable for oophorectomy due to its anatomic positioning.^{3,11} The specimen was removed with the use of an Endocatch in all cases that reported extraction methods.^{3,21,33}

Of those that describe postoperative outcomes, one superficial surgical site infection requiring antibiotics was described, otherwise no postoperative complications were reported.^{19,33,35,36}

When single-site was compared to conventional laparoscopy, there were no statistically significant differences in surgical or

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