

**Fertility preservation by ovarian tissue transportation and centralized cryobanking for a 20-year old woman with Hodgkin lymphoma**

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**Figure 1: Canadian Implementation of the “Hub-and-Spoke” model**

Provides access to expert counselling and specialized fertility preservation services while overcoming geographical and systemic barriers, maximizing patient comfort, ensuring timely cancer treatment, and offering a cost-effective and safe solution.

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**Fertility preservation by ovarian tissue transportation and centralized cryobanking for a 20-year old woman with Hodgkin lymphoma**

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**Key Points:**

- Reproductive risks due to cancer therapy should be discussed with all patients as an integral part of oncology care.
- Ovarian tissue cryopreservation is the only fertility preservation option for patients with ovaries who cannot undergo ovarian stimulation, including children, urgent cases and those living remotely from a fertility centre.
- Ovarian tissue transportation and centralized processing and cryobanking overcome barriers and improve access to care.
- This case demonstrates the feasibility of implementing ovarian tissue transportation and centralized cryobanking in Canada.

**Case:**

A 20-year-old, G3P2AB1, pediatric cancer survivor presented to her local oncology centre in Southwestern Ontario with right supraclavicular adenopathy. She had a history of Stage IIA Hodgkin lymphoma diagnosed at age 15 and treated with two cycles of OEPA chemotherapy (vincristine, doxorubicin, etoposide and prednisone), achieving complete response. Positron emission tomography-computed tomography revealed multiple lymphadenopathies in the neck and chest above the diaphragm, and biopsy confirmed the diagnosis of relapsed Hodgkin lymphoma, stage IIA. The patient was 8 weeks pregnant at presentation and subsequently underwent a surgical pregnancy termination. She expressed a desire for future fertility and was referred for urgent virtual counselling at an oncofertility centre providing fertility preservation care. We counselled the patient regarding the effects of repeated alkylating-based chemotherapy exposure, the high risk for future infertility and premature ovarian insufficiency, and the various fertility preservation strategies available. Due to the need to initiate immediate salvage chemotherapy and the remote location (380km from Toronto), the patient elected to proceed with ovarian tissue cryopreservation after considering surgical risks, tissue transportation, processing, storage and future transplantation of the ovarian tissue. We coordinated care remotely through a close collaboration with her local oncologist and gynecologist. The patient completed pre-procedure investigations locally, including viral

serology screening to ensure safe tissue handling and storage, and serum anti-mullerian hormone measurement to assess baseline ovarian reserve. A local gynecologist trained in specific oophorectomy techniques for ovarian tissue cryopreservation performed a laparoscopic unilateral oophorectomy using minimal coagulation and delicate tissue handling to preserve follicular viability. The contralateral ovary and both fallopian tubes remained in situ. We arranged for professional courier transportation of the ovarian tissue under continuous temperature monitoring, maintaining 4°C–8°C throughout the 380-km journey to our specialized embryology laboratory. Upon arrival, we stored the tissue overnight at 4°C until the tissue processing could be completed by an embryologist the following day. We completed tissue processing within 23 hours of retrieval, yielding over 60 tissue fragments. Additionally, during processing, we isolated 10 cumulus-oocyte complexes and successfully matured in vitro 8 oocytes that were cryopreserved, providing additional reproductive potential. The patient was discharged home on the day of surgery and started GDP salvage chemotherapy (gemcitabine, cisplatin, dexamethasone) within 6 days. Followed by autologous stem cell transplant with BEAM conditioning (carmustine, cytarabine, etoposide, melphalan) within 3 months. Four months after the procedure, the patient remains well, and no immediate complications related to the fertility preservation procedure or bone marrow transplantation have been reported.

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**Discussion:**

For reproductive-aged individuals diagnosed with cancer, the prospect of future fertility often becomes a critical concern alongside survivorship<sup>2</sup>. This case illustrates the complex challenges faced by young cancer patients who desire biological children but require urgent treatment that threatens their reproductive potential. Unfortunately, many life-saving interventions, including reproductive organ surgery, chemotherapy, and abdominopelvic radiation, increase the risk of infertility and reproductive endocrine dysfunction<sup>1</sup>. These advancements in cancer treatment and survivorship have led to the development of oncofertility, a discipline that integrates oncology and fertility care to preserve reproductive potential. For individuals with ovaries, the choice of fertility preservation strategy is individualized and depends on patient-specific factors, including age, pubertal and menarchal status, underlying diagnosis, urgency to initiate cancer therapy, baseline ovarian reserve, partnership status, physical and financial access to fertility care, and patient preference (Table 1<sup>3</sup>). The success of fertility preservation procedures in achieving a future live birth is closely tied to the quantity of stored samples and the patient's age at the time of the procedure.

For prepubertal and adolescent patients who cannot undergo ovarian stimulation and whose potential risk of infertility is considered high according to the internationally accepted standardized model for patients undergoing cancer treatment<sup>4</sup>, adults younger than 35 years who urgently need to start chemotherapy or patients who have limited access to a fertility clinic, ovarian tissue cryopreservation, declared no longer experimental in 2019<sup>5</sup>, is considered the best clinical practice by international fertility and oncology societies<sup>6</sup>. This multi-step procedure involves laparoscopic removal of a whole or part of an ovary, transportation to an expert embryology laboratory for processing, cryopreservation and storage (Figure 1). Processing ovarian tissue in preparation for cryopreservation can also yield mature oocytes that can augment reproductive potential. Ovarian tissue can be stored for over 10 years, and when conception is desired, the tissue is thawed, prepared for transplantation, and auto-transplanted into the patient's pelvis to restore fertility and endocrine function.

Despite Canadian obstetric and gynecology and fertility societies' clinical guidelines endorsing fertility preservation in cancer patients<sup>7-9</sup>, multiple barriers to the delivery of oncofertility care exist<sup>10</sup>. Patient barriers include a lack of awareness and high distress around survival, while healthcare providers' barriers include knowledge gaps and discomfort with discussing infertility risks, leading to low referral rates for counselling and procedures. Barriers at the health care system level include the lack of well-designed and accessible resources to provide urgent oncofertility counselling and the absence of care pathways for coordinating procedures. Funding for fertility preservation procedures also varies by province and can present a substantial barrier to accessing care in provinces where patients must pay out of pocket expenses for this service.

While the ability to perform laparoscopic oophorectomy is readily available in many primary centres, the main practical barrier to equitable access to oncofertility care is that the processing and storage of ovarian tissue require expertise and specialized equipment that are not commonly found in most fertility clinics that perform oocyte or embryo cryopreservation. Centralizing the processing and storage of ovarian tissue in a dedicated cryobank facility offers several advantages, particularly for patients residing in remote areas. Access to care provided by local tissue harvesting, with subsequent safe transportation of the tissue to a central facility, a process shown to be feasible and safe<sup>11</sup>. Given that ovarian tissue cryopreservation is a relatively rare procedure, centralization is also highly cost-effective, as it eliminates the need for maintaining multiple processing sites. Additionally, a centralized cryobank operating in a high-volume setting ensures improved quality control and assurance, as expertise can be concentrated, and standardized procedures can be consistently applied.

This approach is common in many European countries that have established centralized ovarian tissue cryopreservation programs and successfully incorporate tissue transportation across regions. Pioneered by the Danish Network, founded in 1999 with the slogan "the patient stays – the tissue moves," centralization of ovarian tissue cryopreservation in Denmark and southern Sweden, is enabling tissue retrieval locally and transport for processing and storage, leading to multiple live births<sup>12</sup>. One network spanning 125 centres in Germany, Austria, and Switzerland,

consolidates the processing into three main cryobanks, optimizing transportation logistics and achieving multiple live births<sup>13</sup>. Optimizing resources and outcomes, in 2018, the Netherlands merged seven fertility preservation centres into a centralized national program<sup>14</sup>. The UK's centralized cryobank in Oxford follows a "Hub-and-Spoke" model, providing cryopreservation services across England, Wales, and Northern Ireland<sup>15</sup>. Similar centralized models exist in Japan and the US.

This case demonstrates the feasibility of implementing a centralized "Hub-and-Spoke" model for ovarian tissue cryopreservation in Canada. As a proof-of-concept, we successfully delivered specialized oncofertility services through coordinated care pathways that overcome geographical barriers. The hub oncofertility centre provides specialized oncofertility expertise while collaborating with local healthcare teams, as spokes, through a multidisciplinary approach that includes urgent virtual consultations, coordination of local surgical procedures, professional tissue transportation, and centralized expert processing and storage. The described model aims to reduce infertility and reproductive endocrine dysfunction in cancer survivors, minimize the psychosocial impact of infertility, and enhance the quality of life for patients and their families by improving access and coordination of care.



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**Table 1:** Fertility preservation strategies in individuals with ovaries

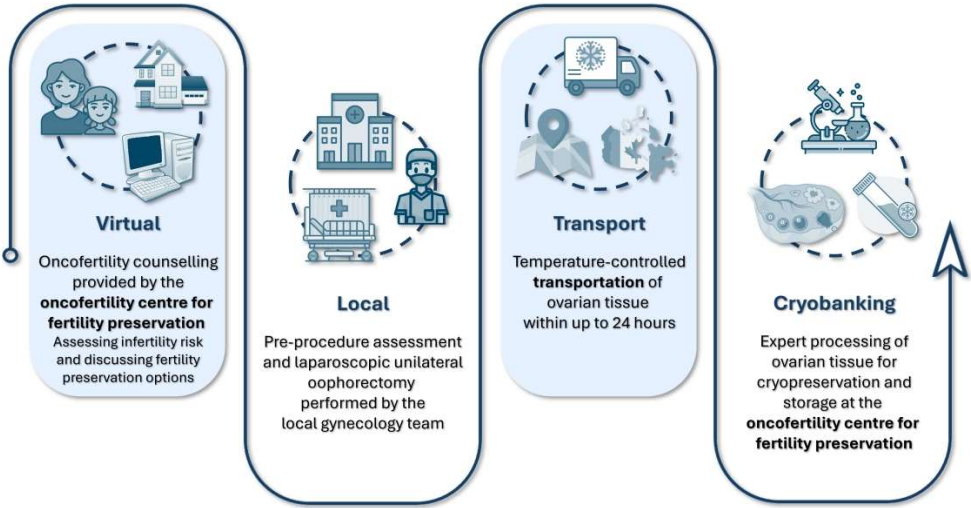
Strategy	Procedure involves	Advantages	Limitations
Embryo Cryopreservation	<ul style="list-style-type: none"> <li>2-3 weeks of ovarian stimulation</li> <li>Injectable medications administration</li> <li>Multiple visits for blood draws and ultrasounds to monitor response</li> <li>vaginal approach procedure</li> <li>fertilization of oocyte by sperm, in the lab, and freezing of embryos</li> </ul>	Well-established success rates: 35.3% live birth rate	<ul style="list-style-type: none"> <li>Only in post-pubertal patients</li> <li>Delays cancer therapy</li> <li>Requires sperm provider</li> <li>Limits reproductive autonomy</li> <li>Access – requires physical proximity to a fertility clinic</li> </ul>
Oocyte Cryopreservation	<ul style="list-style-type: none"> <li>2-3 weeks of ovarian stimulation</li> <li>Injectable medications administration</li> <li>Multiple visits for blood draws and ultrasounds to monitor response</li> <li>vaginal approach procedure</li> <li>freezing of unfertilized oocytes</li> </ul>	Well-established success rates: 25.8% live birth rate	<ul style="list-style-type: none"> <li>Only in post-pubertal patients</li> <li>Delays cancer therapy</li> <li>Access – requires physical proximity to a fertility clinic</li> </ul>
Ovarian Tissue Cryopreservation	<ul style="list-style-type: none"> <li>Surgery – Laparoscopic oophorectomy</li> <li>Transportation of tissue</li> <li>Processing and storage of ovarian tissue</li> </ul>	<ul style="list-style-type: none"> <li>Pre and post-pubertal patients (&lt;35y)</li> <li>No delay in cancer therapy</li> <li>No physical proximity to fertility clinic</li> <li>Restores endocrine and fertility functions</li> <li>Well-established success rates: 32.3% live birth rate (in international centres)</li> </ul>	<ul style="list-style-type: none"> <li>Requires surgery (at time of harvesting and again at time of re-transplantation)</li> <li>No live births reported in Canada</li> <li>Requires unique OTC expertise</li> </ul>

- For patients requiring pelvic radiation, ovarian and/or uterine transposition can be offered.
- Live birth rates from a meta-analysis comparing the success of oocytes, embryo, and ovarian tissue cryopreservation<sup>3</sup>

3. Ní Dhonnabháin B, Elfaki N, Fraser K, et al. A comparison of fertility preservation outcomes in patients who froze oocytes, embryos, or ovarian tissue for medically indicated circumstances: a systematic review and meta-analysis. *Fertil Steril* 2022;117(6):1266–1276; doi: 10.1016/j.fertnstert.2022.03.004.

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### Author Contributions Statement

JM conceived the study, established the ovarian tissue transportation and centralized cryobanking program, provided oncofertility counseling and coordinated patient care, wrote the original draft, and led the revision process. ME processed the ovarian tissue, coordinated care, and contributed to manuscript review. MS performed the surgical procedure and reviewed the manuscript. EMG supervised the project and reviewed the manuscript. All authors reviewed and approved the final manuscript for publication.

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