



# Oncofertility in Canada: gonadal protection and fertility-sparing strategies

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## ABSTRACT

### Background

Cancer can be a devastating diagnosis. In particular, malignancy and its indicated treatments have profoundly negative effects on the fertility of young cancer patients. Oncofertility has emerged as a new interdisciplinary field to address the issue of gonadotoxicity associated with cancer therapies and to facilitate fertility preservation. In Canada, fertility issues are often inadequately addressed despite the availability of resources. The goal of this four-part series is to facilitate systemic improvements in fertility preservation for adolescent and young adult Canadians with a new diagnosis of cancer.

### Methods

Here, we review the fertility preservation measures currently available. Medical and surgical strategies are both outlined.

### Results

Fertility-preserving strategies and gonadal protection have demonstrated variable success in a number of approaches. The value of hormone suppression is still in question for women. Progestins for endometrial cancer and alternative chemotherapies are other medical approaches. Gonadal shielding and protective surgical approaches have also been attempted.

### Conclusions

The techniques discussed here may be selectively considered and integrated into patient care in an attempt to preserve future fertility before initiating cancer treatment.

## KEY WORDS

Oncofertility, fertility preservation, cryopreservation, gonadotoxicity, young adult, adolescent

## 1. INTRODUCTION

This four-document series was created to facilitate improved education and communication for fertility preservation in adolescent and young adult Canadians with a new diagnosis of cancer. The present review outlines gonadal protection options and fertility-sparing strategies for the young cancer patient. Cryopreservation and later use of gamete and gonadal tissue will be addressed in a subsequent article.

Several strategies aimed at the preservation of male and female fertility have been developed. They have been categorized into several distinct areas. Initially, an attempt should, whenever possible, be made to preserve the functional capacity of the gonads. This attempt may include gonadal protection or fertility-sparing approaches using both medical and surgical strategies.

## 2. MEDICAL STRATEGIES FOR GONADAL PROTECTION

### 2.1 Hormone Suppression in Women

Gonadotropin-releasing hormone (GnRH) analogues emerged in the 1980s as a potential intervention to decrease the gonadotoxic effects of cancer therapy. The proposed mechanisms have varied, most involving some suppression of the hypothalamic–pituitary–gonadal axis during treatment<sup>1–5</sup>. The GnRH agonists (GnRHAs) and antagonists (which function with identical end-results) have both been used in gonadal protection<sup>2,3</sup>, but their efficacy continues to be debated.

Some studies have been encouraging and have included both cancer-related and non-malignant indications for chemotherapy. Earlier reviews of the

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literature, which came from small prospective or observational studies, demonstrated similar overall premature ovarian failure rates of 8%–11.1% in recipients of GNRHA pre-chemotherapy, compared with 51.6%–59% in appropriately matched non-recipient controls<sup>6–8</sup>. A more recent review by Del Mastro *et al.* noted short-term resumption of menses in 36%–96% of GNRHA-treated patients in five phase II trials<sup>9–13</sup> and preserved ovarian function in 70%–89% of patients in three of four phase III trials (compared with 33%–57% of patients who did not receive GNRHA pre-chemotherapy)<sup>5</sup>, but disappointingly, recent randomized trials showed inconsistent results<sup>12,14–17</sup>. Most meta-analyses have still managed to show statistically significant protective effects of GNRHA on post-chemotherapy ovulation and resumption of menses<sup>3,8,18,19</sup>, but subsequent pregnancy rates have been inconsistent<sup>8,18,19</sup>.

Although the literature has been encouraging, the results still lack uniform conclusions, thus limiting implementation of GNRHA. This lack of conclusions might be a reflection of study methodology (small sample sizes, lack of randomization and long-term follow-up). Many of the studies have also demonstrated inconsistency in their methods of assessing ovarian reserve. Menstrual status is the most common outcome, but provides a poor surrogate for fertile status, and use of other reporting markers (follicle-stimulating hormone, inhibin B, estradiol, anti-Müllerian hormone, and antral follicle count) is variable<sup>3,19</sup>. Still, although the literature is unclear, the potential advantages of GNRH analogues in fertility preservation, combined with an acceptable side-effect profile, may justify their use. They may even provide additional benefits during chemotherapy, such as prevention of menorrhagia secondary to severe thrombocytopenia during myelosuppression<sup>20</sup>.

## 2.2 Hormone Suppression in Men

Hormone suppression of testicular function and spermatogenesis has shown poor results in male fertility preservation. Although suppression was initially believed to effectively protect the gonads in men as it did in women, only one of eight clinical trials (based on 15 patients) showed enhanced gonadal protection with testosterone use<sup>21</sup>; the others showed no effect with hormone suppression<sup>22</sup>. This method has therefore not been endorsed for male fertility preservation<sup>23</sup>.

## 2.3 Apoptosis Inhibitors

The complex processes involved in chemotherapy- and radiation-induced gonadotoxicity have been shown to involve oocyte apoptosis<sup>24</sup>. The sphingomyelin pathway, involved in the generation of sphingosine-1-phosphate from the proapoptotic lipid molecule ceramide, has been implicated in programmed cell death in ovarian germ cells<sup>25</sup>.

Preliminary animal models and *in vitro* evidence have suggested that disruption of this pathway may provide an additional strategy to circumvent cancer therapy-related oocyte destruction<sup>25–27</sup>. Still, this research has not yet reached human application.

## 3. FERTILITY-SPARING STRATEGIES

### 3.1 Progestins and Endometrial Cancer

A number of case reports and small case series in the literature have presented fertility-sparing medical management in early endometrial carcinoma. Although standard management would involve removal of the reproductive organs<sup>28</sup>, progestin agents have been used in effort to spare fertility in well-differentiated early disease with no evidence of progression<sup>28,29</sup>. Response to treatment has been high (rates of 73%–81%), but not absolute<sup>28–31</sup>. Recurrence rates are also appreciable (18%–40% with follow-up times up to 357 months)<sup>28–30,32–34</sup>. Although progestin management of early endometrial carcinoma has shown success (recent pregnancy rates of 40% and subsequent live birth rates up to 47%<sup>30</sup>), this management route is evidently not without risk. Concurrent ovarian malignancy poses a risk estimated at 11%–29% in premenopausal women with endometrial carcinoma<sup>28</sup>. Additional drawbacks include a lack of consensus on progestin specifics, dose specifics, and length of treatment<sup>29,35</sup>. Also, no randomized controlled trials have yet compared this treatment with the standard of care, and no consensus on definitive treatment after childbearing has been reached<sup>35</sup>.

### 3.2 Alternative Chemotherapy

Alternative chemotherapeutic regimens might be a realistic consideration for some patients. Regimens that result in less gonadotoxicity without compromising disease outcome have increasingly become available<sup>36</sup>. For example, BEACOPP (bleomycin–etoposide–doxorubicin–cyclophosphamide–vincristine–procarbazine–prednisone) and ABVD (doxorubicin–bleomycin–vinblastine–dacarbazine) are arguably two similarly effective treatment regimens in Hodgkin lymphoma<sup>37</sup>; however, the latter combination resulted in significantly less amenorrhea and more resumption of spermatogenesis<sup>38,39</sup>. Treatment of colorectal cancer often involves 5-fluorouracil in combination regimens with oxaliplatin. The latter agent is considerably more gonadotoxic and might potentially be withheld in certain circumstances<sup>40</sup>.

Efforts made to aggressively control disease without first taking into account patient priorities for future fertility may result in overtreatment and unnecessary gonadal damage. For example, certain subgroups of breast cancer might be treated using agents that are less gonadotoxic<sup>41,42</sup>.

### 3.3 Ovarian Transposition and Gonadal Shielding

Irradiation to the ovaries can be quite damaging, and successful ovarian protection in this circumstance has been achieved through ovarian transposition. In this technique, the ovaries are transposed, laparoscopically or in a laparotomy, to a location outside of the field of radiation<sup>43</sup>. This procedure not only has the advantage of sparing fertility, but also of maintaining ovarian function and evading premature menopause<sup>44</sup>. However, it also carries risks, including those associated with surgery, increased ovarian cyst formation, postoperative adhesions, chronic pelvic pain, migration of the ovaries back to their native position, and premature ovarian failure<sup>45–47</sup>. Damaged or dysfunctional fallopian tubes may also preclude a spontaneous pregnancy. Finally, in a minority of cases (1%), metastatic disease may exist within the ovaries<sup>40,45,46,48,49</sup>, and transposition may facilitate spread of disease<sup>50</sup>. Unfortunately, ovarian transposition does not protect the ovaries from the effects of chemotherapy<sup>51</sup>, and therefore the risk of the procedure may outweigh the benefits if treatment also involves systemic gonadotoxic drugs<sup>52,53</sup>.

Wide variations in surgical technique, individual patient characteristics, and treatment characteristics can affect success rates. Radiation protocols vary in type (external-beam or brachytherapy), dose, degree of scatter, and use of shielding<sup>45</sup>. In cervical cancer, for example, external-beam radiation in conjunction with lead block shielding reduced radiation doses by 96%–98% at each laterally transposed ovary<sup>54</sup>. From a patient standpoint, vascular damage, adjuvant chemotherapy<sup>55</sup>, and patient age greater than 40 years<sup>44,56</sup> can affect success<sup>51</sup>. The increasing application of laparoscopic techniques has resulted in improved patient tolerance of the procedure<sup>57</sup>, with overall success rates (defined by continued menses or ovarian function, or both) ranging from 65% to 89%<sup>44,49,58</sup>. Gonadal shielding should be an additional consideration in patients undergoing radiotherapy. Shielding does not protect the gonads completely, but significant radiation dose reductions may be achieved<sup>59,60</sup>. In rectal cancer, for example, gonadal shielding has reduced testicular doses by as much as 66%–74%<sup>61</sup>. Significant dose reductions have also been noted with ovarian shielding<sup>54</sup>.

### 3.4 Other Fertility-Sparing Surgery

#### 3.4.1 Cervical Cancer

Fertility-sparing surgery affords a number of options to the cervical cancer patient. Traditional management often involves a radical hysterectomy and groin node dissection for early-diagnosed disease or a combination of chemotherapy and radiotherapy when disease has already progressed. In women with early-stage cervical cancer (<2 cm in size) who have not yet completed their childbearing, radical

trachelectomy may be of particular benefit. Many authors consider the procedure safe with respect to oncologic results<sup>57,62</sup>.

In a recent systematic review by Xu *et al.*<sup>63</sup>, 587 patients with early cervical cancer who underwent either radical trachelectomy or radical hysterectomy were prospectively studied. No significant differences between the groups were noted for rates of recurrence (documented as 5% in other studies<sup>73</sup>), mortality, 5-year recurrence-free survival, or 5-year survival. Operative morbidity was increased in the radical hysterectomy group<sup>63</sup>. In 2010, Ottosen<sup>64</sup> reported more than 900 cases in the literature and more than 200 live births. Pregnancy rates ranged between 41% and 79%, but with increased second-trimester miscarriage rates of 8%–10%, preterm delivery rates of 20%–30%, and increased incidences of chorioamnionitis and premature preterm rupture of membranes<sup>64</sup>.

Cervical conization and simple trachelectomy (which theoretically improves pregnancy outcomes compared with radical trachelectomy) might also be considered in select patients, depending on the extent of tissue invasion<sup>62</sup>. These procedures carry potentially increased antenatal risks: preterm delivery, low birth weight, cesarean section in conization, and increased cervical incompetence in trachelectomy<sup>57</sup>.

#### 3.4.2 Ovarian Neoplasms

In the case of ovarian neoplasms, fertility-sparing surgery may also be pursued depending on tumour histologic subtype, stage, extent of disease, preexisting ovarian reserve, and willingness of the patient to proceed in the face of potentially recurrent disease<sup>65</sup>.

More than 30% of borderline tumours of the ovary affect women under 40 years of age<sup>29</sup>. Traditional management of these neoplasms involves removal of the uterus, fallopian tubes, and ovaries. However, fertility-sparing surgery may also be pursued using unilateral removal of an ovary and fallopian tube (with extensive staging), even with implants present (if noninvasive) and with advanced disease (stages II–IV)<sup>66</sup>. Among such patients, 20% have been estimated to have extra-ovarian implants<sup>29</sup>. Unilateral cystectomy may also be considered in serous borderline tumours; however, recurrence rates run as high as 25%. An exception to this approach would be the mucinous tumour varieties, given their tendency to recur as invasive cancer<sup>29,65</sup>. Ovarian cystectomy may play an additional role in cases of bilateral ovarian involvement<sup>29,65</sup>. Recurrence rates for early borderline tumours have been reported to be similar to or slightly higher than those for traditional surgical management, but survival rates are not compromised because recurrences are well-treated with repeat and definitive surgical management<sup>66</sup>.

Invasive epithelial ovarian tumours are more challenging to manage with fertility-sparing surgery

alone. Among these tumours, 3%–17% affect women less than 40 years of age<sup>77</sup>. Conventional management includes removal of the uterus, fallopian tubes, ovaries, and omentum, together with extensive staging and subsequent chemotherapy if beyond very early disease. Fertility-sparing techniques would involve unilateral removal of the ovary and fallopian tube, with staging and subsequent close follow-up. Suggested prerequisites for conservative surgery include well-differentiated unilateral disease, with no sign of extra-ovarian metastasis<sup>29,65</sup>. However, gonadotoxic chemotherapy may still be recommended, countering the benefits of conservative surgical management. Survival data have been encouraging. The analysis by Kajiyama *et al.*<sup>77</sup> of 572 women with stage I epithelial ovarian cancer (126 of whom were 40 years of age or younger) showed no differences in 5-year overall survival or disease-free survival between women who had undergone radical hysterectomy and those who had undergone fertility-sparing surgery (univariate and multivariate analysis). Despite small numbers of cases and the need for further research, preliminary evidence suggests that early stage I and lower-grade (I and potentially 2) epithelial ovarian tumours might be able to be managed with fertility-sparing surgery without compromising 5-year survival<sup>67,68</sup>. Still, reconsideration of a switch to definitive surgical management may be considered after childbearing, given the persistent chance of recurrent disease and its associated poor prognosis<sup>65</sup>.

Nonepithelial malignant ovarian tumours, particularly germ-cell tumours, are excellent candidates for fertility-sparing surgery. Sex-cord stromal tumours and mixed histology tumours have been sparingly reported in the literature. Germ-cell tumours are routinely managed by removal of the unilateral ovary and fallopian tube, often with staging. High cure rates have been reported (90%–95%), and despite the usual need for postoperative chemotherapy<sup>29</sup>, resumption of menses occurs in at least 80% of patients<sup>69</sup>.

#### 4. SUMMARY

Gonadal protection and fertility-sparing approaches have each separately demonstrated variable success. Hormone suppression pre-chemotherapy and progestin treatment for endometrial cancer may be of value in women. Alternative chemotherapies might be considered to minimize gonadotoxicity. Fertility-sparing surgical approaches and gonadal shielding are also valuable strategies. None of these techniques can be considered universally applicable or a guarantee of success. However, in the context of likely gonadotoxic cancer treatment, the health care team and the patient should be aware of these options and consider the possibility of their integration into fertility preservation when appropriate.

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