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SPECIAL ARTICLE

Oncofertility in Canada: cryopreservation and alternative options for future parenthood

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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, these 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

This article reviews fertility preservation options that use cryopreservation techniques. It also outlines some of the alternative options for future parenthood.

Results

Cryopreservation of a woman's gametes and gonadal tissue may involve embryo, oocyte, and ovarian tissue cryopreservation with or without ovarian stimulation. Similarly, male gametes and gonadal tissue may be cryopreserved. Techniques and success rates continue to improve. Third-party assistance through gamete donation, gestational carriers, and adoption are also alternative options for parenthood.

Conclusions

Cryopreservation techniques are especially feasible options for fertility preservation in the newly diagnosed cancer patient.

This article has not been peer reviewed.

KEY WORDS

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

1. INTRODUCTION

This article is part of a four-document series created to improve education and communication about fertility preservation in adolescent and young adult Canadians with a new diagnosis of cancer. It reviews cryopreservation strategies and touches on alternative options for parenthood.

2. CRYOPRESERVATION OF GAMETES AND GONADAL TISSUE FOR WOMEN

2.1 Embryo Cryopreservation with Ovarian Stimulation

Ovarian stimulation followed by oocyte aspiration has facilitated a number of cryopreservation techniques. Embryo cryopreservation has become a well-established and highly endorsed form of fertility preservation in young female cancer patients (American Society for Reproductive Medicine, American Society of Clinical Oncology, European Society of Human Reproduction and Embryology, British Fertility Society)[1–3]. The first pregnancy after a frozen and thawed embryo cycle was reported in 1983, followed by the first live birth 1 year later[4,5]. Success rates have been improving continuously since. Canadian Assisted Reproductive Technologies Register data from 2007, involving more than 2700 frozen embryo transfer cycles in women less than 40 years of age, showed clinical pregnancy rates and live birth rates of 24.7% and 18.6% respectively per cycle started. Overall embryo survival rates after thawing have ranged from 35% to 90%, and implantation rates, 8% to 30% per embryo transferred[6]. However, many of the quoted success rates have not yet taken into account the improved survival and outcomes

seen with new cryopreservation techniques (vitrification rather than slow freezing) and the younger age at oocyte retrieval in this patient population[7].

Although the benefits of using embryos for cryopreservation include improved pregnancy rates and widespread availability in fertility centres[8], multiple drawbacks still have to be considered.

- The time required to achieve ovarian stimulation, in addition to that necessary for referral, may delay cancer treatment. The stimulation process alone takes about 2 weeks, and there may be additional delays of 2–6 weeks to achieve ideal cycle timing[9].
- Concern has been raised about exposure to high levels of estrogen and the potential for neoplastic effects associated with traditional gonadal stimulation. This concern would particularly resonate in estrogen receptor–positive breast or ovarian malignancies, whether current, historical, or in the presence of a high genetic predisposition (for example, in *BRCA1/2*-positive patients)[9–12].
- The requirement for an established partner or donor sperm might be considered a future limitation on a woman's reproductive autonomy, possibly also imposing additional anxiety or stress on an emotionally burdened new cancer patient[13].
- Ethical, legal, and religious implications have been raised regarding the disposition of embryos in the event that the woman does not survive long enough to achieve a future pregnancy, or should the couple no longer be together[5,14,15].

2.2 Oocyte Cryopreservation with Ovarian Stimulation

Some of the drawbacks of embryo cryopreservation have been addressed by turning to oocyte cryopreservation as a reasonable alternative. Early on, pregnancy rates were much lower than those with preserved embryos and were limited by poor survival of oocytes after thawing[14,16,17]. The difficulties of preserving oocyte structural and functional integrity were significantly greater than those encountered in the freezing of embryos, in part because of the high volume-to-surface ratio of oocytes and inherent problems with the formation of ice crystals that easily damage the cell membrane and internal structures.

Improvements in cooling techniques, cryoprotectants, and protocols have since dramatically improved oocyte survival and pregnancy rates[18–20]. The introduction and refinement of vitrification has minimized structural damage to oocytes and has improved survival rates, currently in the range 87%–97% (about a 15% improvement compared with slow freezing)[17,21]. A 2011 meta-analysis reviewing more than 4200 vitrified oocytes (compared with either fresh or slow-frozen oocytes) has further confirmed significantly higher fertilization rates [odds ratio (OR): 1.50], higher-quality embryos (OR: 3.32), and higher rates of embryo cleavage (OR: 2–2.25) with the new technique[22].

Pregnancy and live birth rates after use of the newer cryopreservation techniques have also improved. Cobo *et al.*[22] randomized 600 patients to receive either fresh donor oocytes or frozen oocytes post vitrification and found no difference in the pregnancy rate per transfer (55.4% vs. 55.6%) or ongoing pregnancy rate per transfer (49.1% vs. 48.3%). Those results have been replicated in multiple other retrospective studies[23–25]. Other authors have also commented on the lack of differences noted in embryo quality between fresh and frozen oocytes from the same donor[26,27]. Finally, as with embryo cryopreservation, the younger age of this patient population at oocyte retrieval would favour even better success rates. To date, more than 4000 live births from cryopreserved oocytes have been estimated (Kawayama, M. Personal communication, 2012).

Improving success rates have led to wider acceptance of oocyte cryopreservation and the mounting view that the technique has overcome its experimental status[20,28,29], although currently no consensus has been developed in Canada or elsewhere regarding removal of the "experimental" label. The technique has also eliminated the need for concurrent spermatozoa, facilitated reproductive autonomy, and eliminated some of the burdens associated with embryo disposition. However, as with embryo cryopreservation, the drawbacks of ovarian stimulation and the protracted time to cancer treatment have persisted. Alternative ovarian stimulation protocols, natural-cycle protocols, and *in vitro* maturation (IVM) have therefore all been increasingly used in effort to resolve those challenges (overview follows in the next subsection). One final disadvantage, common to all techniques using oocyte aspiration, is the finite number of attempts for pregnancy thereafter and the limitations of oocytes obtained from a single collection.

2.3 Embryo and Oocyte Cryopreservation with Limited Ovarian Stimulation

The risks of hormonal fluctuations and the additional time required to undergo ovarian stimulation may generate considerable anxiety in patients and concern in care providers, who often strive to start cancer therapy as soon as possible. In an effort to address concerns both about time constraints and the hormonal fluctuations of traditional ovulation induction, a variety of methods have been described for altered ovarian stimulation, including limiting stimulation altogether and using IVM.

2.3.1 Alternatives in Ovarian Stimulation

Natural-cycle oocyte retrieval is the quickest and least hormone-altering option, but it unfortunately has very low success rates. Oktay *et al.*[30] obtained only 0.6

embryos per patient using this technique. Time-limiting factors have also been addressed by performing luteal-phase ovarian stimulation[31] or random-start stimulation, described in selective case reports[32].

Reductions in hormonal peaks have also been achieved in cancer patients by using tamoxifen or aromatase inhibitors (for example, letrozole, anastrozole), with or without gonadotropins. These agents or combinations of agents selectively induce ovulation while still exerting anti-estrogenic effects[33,34]. Use of these medications allows for estrogen levels to remain much lower than the potentially 10- to 20-times rise seen in traditional ovarian stimulation[30,35,36]. In 29 patients, Oktay *et al.*[30] showed substantially reduced peak estradiol levels after stimulation with tamoxifen, letrozole, or tamoxifen and low-dose gonadotropins (peak estradiol level: 419 pg/mL, 380 pg/mL, and 1182 pg/mL respectively) than with traditional ovulation induction with gonadotropins; no increased rate of cancer recurrence was observed for the treated women compared with untreated controls (follow-up time: 5–48 months).

Aromatase inhibitors are associated with lower estrogen levels than are seen in natural-cycle *in vitro* fertilization (IVF) used alone, while still effectively inducing ovulation[34]. More commonly, continuous letrozole has been used (from cycle day 2 until triggering of ovulation) with gonadotropins, which increases estradiol levels while still maintaining significantly lower levels than are seen in traditional ovulation induction[34]. Oktay *et al.*[16] again demonstrated significantly lower peak estradiol levels in 47 patients treated with letrozole and follicle-stimulating hormone, with no quantitative differences in the rates of oocytes obtained or fertilization, compared with traditional ovulation induction in controls. Thus far, there have also been no demonstrable effects on disease recurrence, as shown in the Azim *et al.*[36] study of letrozole and follicle-stimulating hormone compared with no-stimulation controls. No difference in disease recurrence (on 2-year follow-up) was noted between 79 breast cancer patients who had undergone fertility preservation and 136 who had not.

Finally, a suggestion has also recently been made that estradiol levels may be additionally reduced by triggering ovulation with gonadotropin releasing-hormone agonist (rather than traditional human chorionic gonadotropin)[37,38]. Results thus far are encouraging, but larger sample sizes and continued research are still needed.

2.3.2 IVM

In vitro maturation offers another feasible alternative for women avoiding ovarian stimulation. It may also be used in combination with other techniques to increase efficiency. The process involves aspiration of immature oocytes after minimal to no stimulatory medication, followed by meiotic maturation *in vitro* from the germinal vesicle to the metaphase II stage[39]. Matured oocytes can then be cryopreserved or fertilized and cryopreserved in embryo form[40].

Although oocytes are usually collected in the window of the pre-ovulatory follicular phase, IVM has also contributed time flexibility to cancer patients[41] by successfully maturing oocytes retrieved during the luteal phase[42–44]. In patients who are time-limited and unable to postpone their gonadotoxic cancer treatment for 2 weeks, IVM with or without ovarian tissue extraction is a suitable option[19]. Finally, IVM of oocytes aspirated from antral follicles of harvested ovarian tissue may be an option for prepubertal females. This technique has been performed experimentally and with good success in girls as young as 5 years[45].

Although techniques in IVM are well established and have been adopted for use in fertility preservation, the method was initially created for the treatment of polycystic ovarian (PCO)–related infertility. Caution must therefore be exercised in extrapolating the data for both efficiency and safety to the young cancer patient population[46]. Variations on IVM techniques applied to cancer patients (for example, with respect to the degree of ovarian stimulation) make outcomes and success rates even more challenging to elucidate. In reality, the live births reported to date with IVM-related fertility preservation have been limited in number. In combination with embryo freezing, IVM has led to case reports of live births at a variety of cleavage stages[47]. Successful live births ($n = 4$) have also been reported with IVM in combination with oocyte vitrification (20% of the cycles started in a prospective study of 20 patients); however, the participants were all PCO patients[46].

Other than having to exercise caution with respect to reliance on IVM success rates, another drawback includes lower implantation rates. These rates have been maximally estimated at 10%–15% per transferred embryo, about 50% of what would be expected in IVF with intracytoplasmic sperm injection (ICSI)[48,49]. However, the reported rates may have been a result of an inadequately developed endometrial lining in the IVM cycle and might theoretically be overcome by proper endometrial preparation in a subsequent cycle, after cryopreservation[47]. Overall pregnancy outcomes do not seem to be worse with IVM than with other methods of assisted reproductive technology (ART), which have a baseline increased risk of miscarriage; but the comparison is again largely extrapolated from PCO data and from a population with a predisposing level of infertility.

Finally, given the low numbers of live births reported after IVM with cryopreservation, and the limited data and long-term follow-up of offspring, caution should once again be exercised in routinely recommending this technique. The 4 live births after IVM and oocyte vitrification demonstrated no congenital anomalies or perinatal morbidity[46]. In PCO patients, IVM outcomes have also been studied sparingly, but

offspring have thus far shown no increased rates of congenital anomalies[50] or early developmental abnormalities at 2 years of age[51,52]. Buckett *et al.*[50] studied 344 ART pregnancies, of which 55 were achieved through IVM. No significant differences in major or minor abnormalities were noted between IVM infants and spontaneously conceived controls (OR: 1.21; 95% confidence interval: 0.63 to 2.32)[50].

In vitro maturation is performed on oocytes at an extremely vulnerable period, prone to epigenetic changes and imprinting defects[49]. Superimposing cryopreservation may introduce an added element of instability and should therefore be performed with caution until further safety data become available.

2.4 Ovarian Tissue Cryopreservation and Transplantation

Ovarian tissue cryopreservation is another potentially promising technique, but it is still in experimental phases. The procedure involves harvesting areas of the ovary—most often cortical tissue, rich in primordial follicles. The tissue is then cryopreserved. Later, in the presence of premature ovarian failure when cancer treatment is complete, it is orthotopically or heterotopically autotransplanted[33,53]. Orthotopic transplantation involves re-implanting the thawed ovarian tissue back into the pelvis, either on the pelvic sidewall, or on the remaining or remnant ovary. Spontaneous pregnancy might then occur without further ART[33]. Heterotopic transplantation, commonly involving transplantation to the forearm or abdominal wall[54], avoids intra-abdominal surgery, but necessitates ART for a possible future pregnancy[33].

Many of the advantages of this technique mirror those of oocyte cryopreservation. There is no need for a partner or donor sperm. The method also avoids ovarian stimulation and the passage of protracted amounts of time before chemotherapy can begin[8]. Additional advantages include the possibility that primordial follicles within the ovarian tissue are more resistant to cryopreservation than are oocytes themselves[19]. A much larger pool of oocytes and follicles may also be available for preservation than would be the case in oocyte aspiration[33]. The potential resumption of ovarian endocrine function may also be a unique advantage. Multiple studies have shown 100% success rates in resumption of ovarian hormonal function, lasting from several months to more than 5 years after transplantation[55,5654].

Finally, the potential of this technique to preserve fertility in prepubertal girls should not be undervalued, especially given the inability to apply most other fertility-preserving or -sparing techniques in this population. Jadoul's review of seven studies involving 266 children (173 less than 16 years of age, and some as young as 0.8 years) described unilateral oophorectomy or ovarian cortical resection followed by cryopreservation of ovarian tissue, with the possibility of combining it with oocyte aspiration, IVM, and gamete cryopreservation as well[57]. Although no autotransplantations of tissue harvested from prepubertal girls have yet been reported in humans, the well-tolerated procedures and successful cryopreservation of ovarian tissue and oocytes makes this option a promising one for facilitating future parenthood in childhood cancer[57].

Despite the potential advantages of tissue cryopreservation, the drawbacks are still many (largely pertaining to the still-experimental nature of the procedure) and warrant cautious use. Success rates are based on small numbers of patients. One 2009 report estimated that of 100 cases of frozen ovarian tissue orthotopically autotransplanted, 9% resulted in an eventual spontaneous pregnancy and delivery[58]. Most recently, the total number of live births reported in the literature after frozen ovarian tissue transplantation has been estimated at 17[59]. Although ovarian function has been successfully restored after heterotopic transplantation, the only live births reported from this procedure (3 in 1 patient) were spontaneous and therefore not clearly linked to the heterotopically transplanted tissue[16,54,60]. These relatively low pregnancy rates may relate to the high rate of follicular loss (25%–95%), tissue ischemia, and the challenge of revascularization upon thawing and autotransplantation[54]. Other drawbacks include the need for at least two separate operations (removal of ovarian tissue, autotransplantation, additional need for ART) should premature ovarian failure develop[33].

There is also the possibility of reintroducing malignant cells back into the body. Recent evidence has supported a very cautious approach to autotransplantation. The American Society for Reproductive Medicine has classified leukemias and neuroblastomas as higher risk and intermediate risk respectively for ovarian metastasis, with most other cancers posing a lower risk for ovarian involvement[61]. Azem *et al.* most recently found no evidence of neoplastic involvement in 40 ovarian biopsy specimens of various cancer patients intending to undergo ovarian tissue cryopreservation[62]. Similar results have previously been obtained, particularly in cases of breast cancer and lymphoma[63–65]. However, in 2010, Rosendahl and colleagues used polymerase chain reaction to examine the extracted ovarian tissue of 26 patients with leukemia and found that 75% of cells showed leukemic infiltration, contrary to the 0% rate of abnormality noted on histologic examination[66]. Other studies have similarly shown positive molecular markers for disease in ovarian tissue deemed histologically to be "safe"[67,68]. Patients harbouring the *BRCA1* or *BRCA2* gene may also be at particular risk. Colgan *et al.* showed that more than 8% of women (5 of 60) undergoing prophylactic oophorectomy for *BRCA1* gene status harboured occult or more advanced carcinoma[69]. The safety of autotransplantation of ovarian tissue to a breast cancer patient should be carefully

considered; a prophylactic oophorectomy is, in fact, the current recommendation.

No official recommendation and no long-term data are available regarding the safety of autotransplantation and the risk of reinoculation with cancerous tissue[70]. However, the relevant evidence and still-limited success warrant extreme caution in patients undergoing ovarian tissue extraction for the purpose of cryopreservation. Those at higher risk of ovarian metastasis, even in the absence of microscopic pathology, might want to consider pursuing a different modality of fertility preservation. Temporary heterotopic autotransplantation, followed by removal of the tissue after childbearing is complete might be another option for at-risk specimens[61].

2.5 Cryopreservation and Future Progress

Innovative new strategies have continued to improve oocyte cryopreservation techniques, survival, and success rates[71]. Although whole-ovary cryopreservation and autotransplantation have been attempted[72], inadequate perfusion by cryoprotectants, reperfusion injuries, and inadequate neovascularization after freezing have resulted in significant ischemia, reductions in follicular density, and limited success[53]. The technique has thus far shown success in animal models including rat, rabbit, and sheep[72]. In 2006, Imhof *et al.* published an account of successful pregnancy and delivery of a lamb after whole-ovary cryopreservation and orthotopic autotransplantation[73]. Prolonged ovarian function has also been noted in animals up to 6 years after whole-ovary autotransplantation[74]. Although human transplantation of cryopreserved whole ovaries has not yet been performed, *in vitro* examination of slow-cooled ovaries has demonstrated the overall viability of 75%–78% of primordial follicles[75]. Another consideration is that this technique still does not eliminate the problem of possible contamination by and reintroduction of neoplastic cells[76].

In vitro culture of primordial follicles has also shown particular promise. The demand for this technique is further emphasized by concerns about the reintroduction of cancer cells with autotransplantation of ovarian tissue or whole ovaries[77]. Moreover, pregnancy attempts with oocyte aspiration are quantitatively finite—particularly in fertility preservation patients who would likely have undergone only one collection before cancer treatment. The ability to culture a much larger pool of oocytes to maturity from primordial follicles creates the potential for many more attempts at pregnancy.

The first oocyte grown entirely *in vitro* and subsequent live birth of a mouse occurred in 1996. Multiple successful models of *in vitro* culture with resultant healthy offspring have since been demonstrated in animal studies[77]. However, extrapolating these results to humans has been problematic. One of the main challenges has been to overcome the long period (84 days) required *in vivo* for follicular development[77]. Telfer *et al.*[78] were able to shorten that period to 10 days *in vitro,* but with still-unknown effects on oocyte development. Human studies pursuing the ideal combination of growth factors and hormones and the composition of the extracellular matrix structure also continue[79].

A 2010 review of 15 studies demonstrated the pro-developmental and inhibitory effects of multiple hormones and growth factors, but also suggested that a multi-step culture would be required in conjunction with IVM to achieve oocyte maturity[77].

The effort to translate functional animal models to human application, to understand the methodical and selective development of follicles that range in stage from primordial to ovulatory, and to determine the ideal follicular stage for growth continues[80].

2.6 Combining Approaches in Women

Despite the improving success rates in multiple modalities, no method of fertility preservation has yet been perfected. Moreover, as discussed earlier, not every method of fertility preservation is universally appropriate. A strategic combination of approaches may maximize efficiency and yield the best success rate per patient, while avoiding any compromise to cancer treatment. For example, some studies have combined ovarian tissue cryobanking with immature oocyte aspiration and IVM immediately beforehand, avoiding any added time or prognostic risk to the patient[45,81]. Huober–Zeeb *et al.*[82] described ovarian tissue excision and cryopreservation, followed by ovarian stimulation and oocyte cryopreservation, as a way of maximizing efficiency in their study of 40 patients. This combined approach did not lengthen the time before cancer treatment could begin. Other examples of such approaches have been noted in the literature with good success[83].

3. CRYOPRESERVATION OF GAMETES AND GONADAL TISSUES FOR MEN

Cryopreservation of gametes tends to be less invasive and often better tolerated for men than for women. Currently, cryopreservation of spermatozoa is the most reliable[84] and the only well-endorsed method of fertility preservation in postpubertal men[2]. Successful cryopreservation of sperm (defined as motile sperm observed after freezing and thawing) was achieved for 85%–100% of patients, depending on age (15–40 years) and diagnosis (including testicular cancer, lymphomas, leukemias, bone cancer, other cancers) in one study of more than 900 patients[85]. In another retrospective study of 557 patients who successfully cryopreserved semen over a 20-year period, 9.6% of cancer survivors attempted use of their cryopreserved samples and were successfully

followed through 101 cycles, with banked time averaging 57 months. Live birth rates were 14.3%, 25%, and 28.3% per cycle for intrauterine insemination, IVF, and ICSI respectively, and overall parenthood success rates were 51% per patient (18 of 35)[86]. Other studies have noted parenthood rates of 33%–73% per patient[86]. However, those studies remain largely confounded by the partner's variable response to fertility treatments.

Obtaining adequate sperm samples through ejaculation may pose a challenge secondary to patient illness or discomfort[87], and malignancy itself may affect the quality and quantity of sperm[88]. Spermatozoa may be obtained from ejaculation, electro-ejaculation, microsurgical epididymal sperm aspiration, or testicular biopsy, and thereafter be used for oocyte injection in IVF or before embryo cryopreservation[33]. When sperm aspiration is performed in azoospermic (non-obstructed) patients by the microsurgical epididymal sperm aspiration procedure, sperm is successfully obtained approximately 60% of the time[89]. Moreover, when sperm quantity or quality is limited, ICSI has largely facilitated the success of fertilization by requiring minimal numbers of viable sperm[84]. Sperm samples may also be frozen for future use, with live births being reported at up to 21 and 28 years after cryopreservation[90]. Several studies have noted no significant difference in pregnancy outcomes with fresh or frozen spermatozoa in combination with ICSI[91,92]. Habermann *et al.*[91] examined outcomes with fresh and thawed spermatozoa in 46 cycles. No significant difference between the two was found in fertilization rate (56% vs. 61%, $p = 0.45$), cleavage rate (92% vs. 95%), implantation rate (26% vs. 17%, $p = 0.46$), and pregnancy rate per embryo transfer (33% vs. 45%, $p = 0.72$).

3.1 Cryopreservation and Future Progress

Increasing interest and success have been generated in the cryopreservation of testicular tissue and spermatogonial stem cells. Proposed techniques for restoring fertility have included autologous stem-cell transplantation and recolonization of the male testes after gonadotoxic treatment, thereby restoring natural fertility; or heterotopic autotransplantation of testicular tissue, with local spermatogenesis thereafter[93]. In prepubertal boys, cryopreservation of immature testicular tissue has also shown promise in restoring fertility through germ-cell autotransplantation (after gonadotoxic therapy), testicular tissue xenografting, or *in vitro* differentiation and maturation of spermatogonial stem cells[84]. However, although fertility restoration has been achieved in animals, research on humans is still required for any of the foregoing methods[94].

Maintaining proper storage and structural integrity of the testicular tissue after cryopreservation has also remained a challenge. Dimethyl sulfoxide has facilitated cryopreservation of prepubertal testicular tissue, and recently, the use of vitrification rather than the traditional slow-freezing techniques has improved tissue survival[84].

4. OTHER OPTIONS FOR FUTURE PARENTHOOD

4.1 Oocyte and Sperm Donation

Oocyte donation may be a suitable option for women who do not wish to undergo oocyte collection, who cannot wait any time before commencing gonadotoxic cancer therapy, who want to avoid even minimal hormone elevations, and who have experienced failed cryopreservation or who have exhausted their physiologic fertility despite their best efforts. Donation has the added advantage of preventing the passage of genetic material that may be associated with the patient's cancer (for example, *BRCA* genes)[8]. Despite pregnancy and live birth rates being comparable or better in donor cycles than in cycles using autologous oocytes (donor oocytes often come from young, healthy women)[95], accessibility is a limitation[96]. Canada places restrictions on financial compensation to oocyte donors (only reimbursement of expenses incurred by the oocyte donor are allowed) and also prohibits oocyte sharing programs in which the donor receives financial incentives[97]. Additional challenges include the heavy burden of health care expenses for both the patient and the oocyte donor, the difficulties associated with seeking out a suitable oocyte donor, and the potential fears and psychosocial consequences of having a genetically unrelated child[8,98].

Sperm donation may be a similar option for men experiencing failed cryopreservation of their own spermatozoa. The gravity of the supply problem may be less with donor sperm than with donor oocytes; however, the legislative restrictions of the *Assisted Human Reproduction Act* (instituted in 2004, prohibiting the purchase of gametes) and of Health Canada's strict screening protocols have highlighted the still-limited supply of Canadian sperm for donation. Previous studies indicated the potentially altruistic intentions of most sperm donors and supported the implementation of the *Assisted Human Reproduction Act*[99]. However, a recent Canadian survey study (301 potential sperm donors) indicated that fewer than 1% of the men initially interested in donation would actually complete the process, the limiting factors being the lack of financial compensation and the need to meet Health Canada screening criteria[100].

4.2 Gestational Carriers and Adoption

Finally, the options of gestational carriers ("surrogate pregnancy") and adoption are additional routes that patients should not discount as possible options for future parenthood. Particularly in the context of the

physical morbidities that may linger after cancer, either as a result of the process itself or of the treatment (for example, cardiac toxicity, renal dysfunction, respiratory disease with certain chemotherapies, removal of female reproductive organs), the ability to maintain a pregnancy may not be possible or may be too high a risk even if cryopreserved gametes are available. In a study involving 122 cancer patients, the perceived acceptability of alternative family-building options (after pregnancy with autologous oocytes) was highest for adoption (43%, 53 of 122) and second highest for surrogacy (34%, 42 of 122)[96].

In Canada, adoption is provincially mandated, as is surrogacy. In Quebec, contracts for carrying a pregnancy are considered illegal. Although these possibilities provide suitable alternatives for parenthood, some of the greater challenges include the prohibition on financial compensation to surrogates above and beyond expenses, the lack of legal validity to surrogacy agreements, daunting costs (adoption costs can range from $3000 to $30,000), and the long waiting times associated with adoption (the process can take up to 9 years) or finding a suitable surrogate[101,102].

5. SUMMARY

Fertility preservation and the ability to maintain future parenthood are issues that present and persist from the moment of a cancer diagnosis. Medical and surgical methods for gonadal protection may help partially to counter the effects of gonadotoxic treatments. However, cryopreservation of gametes and embryos remains the current mainstay of fertility preservation. Despite the major drawbacks of time sensitivity and potentially unwarranted hormone exposure in the female cancer patient, alterations in ovarian stimulation and *in vitro* technologies have helped to overcome the challenges. Continued advancement in the areas of gonadal tissue cryopreservation and *in vitro* culturing techniques also creates promise. Still, such methods of fertility preservation are far from perfect, and therefore other options for future parenthood may include gamete donation, surrogacy, or adoption. An awareness of these options is important for both the patient and the health care provider.

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7. CONFLICT OF INTEREST DISCLOSURES

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