Oocyte and embryo cryopreservation before gonadotoxic treatments: Principles of safe ovarian stimulation, a systematic review

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Abstract

Objective: Review the safety of fertility preservation through ovarian stimulation with oocyte or embryo cryopreservation, including cycle and medication options.

Evidence review: A systematic review of peer-reviewed sources revealed 2 applicable randomized control trials and 60 cohort studies as well as 20 additional expert opinions or reviews.

Results: The capacity for future family building is important for the majority of reproductive age people, despite life-altering medical or oncologic diagnosis. Modern fertility preservation generates a high rate of oocyte yield while utilizing protocols that can be started at multiple points in the menstrual cycle and suppressing supra-physiologic levels of estrogen. Finally, more than one quarter of fertility preservation patients will return to later utilize fertility services.

Conclusion: For most patients, fertility preservation can safely be pursued and completed within 2 weeks without affecting disease severity or long-term survival.

Keywords

cancer, chemotherapy, cryopreservation, embryos, fertility preservation, oocytes, safety

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Introduction

Fertility preservation has become a common part of the infertility community vernacular, and yet only a minority of patients diagnosed with cancer, medical conditions, or genetic predispositions that result in subfertility utilize this option. To ensure access to care for all at risk people, clear evidence of safety and best practices for success should be easily available to referring oncologists, immunologists, nephrologists, gynecologists, as well as treating reproductive endocrinologists.

This review assembles the evidence regarding safety of fertility preservation across a range of medical indications. It discusses ovarian stimulation protocols and adjuvants that can increase the chances of a patient’s future fertility while facilitating the rapid transition to appropriate medical treatments that increase the probability of years of future good health in which to pursue family building goals.

Fertility preservation is a medical treatment field that encompasses preservation of gametes, embryos, and ovarian tissue cryopreservation. Ovarian tissue cryopreservation and in vitro maturation have, thus far, resulted in lower pregnancy rates and remain experimental with need for further evidence. Thus, we will review the literature guiding embryo and oocyte cryopreservation.

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Embryo cryopreservation through vitrification is an everyday part of modern-assisted reproductive care. However, of course, embryo cryopreservation requires fertilization of the oocyte either with a partner or sperm donor. This requirement limits the application of embryo cryopreservation to those who have an acceptable sperm source. For many women facing gonadotoxic treatment, such is not the case, and so embryo cryopreservation may limit reproductive autonomy making oocyte cryopreservation their best or only option.

Embryologists have strived since the early 1980s to arrive at safe clinical and laboratory techniques for cryopreservation of oocytes. Oocytes were first frozen and thawed to achieve a live birth in 1989.2 Quickly the potential to preserve fertility in the face of gonadotoxic treatments was recognized, but oocyte quality and fertilization rates were initially concerning.3 The experimental label was not removed by ASRM until 2012 after significantly increased cryopreservation survival rates were obtained following improvements in vitrification as opposed to prior slow freezing protocols. Now, it is time for our clinical communities to become aware of and utilize available and effective pathways for fertility preservation. In an era defined by the recognition of gender and racial inequities, we challenge the reproductive healthcare community to create safe and equitable fertility preservation care systems that ensure the opportunity to pursue a family after treatment with gonadotoxic medications, radiation therapy, or surgical excision.

After patients have fought to survive cancer or other major disease, the inability to get pregnant and deliver a baby can seem like the ultimate betrayal by their own bodies. Cancer survivors have a relative risk of infertility of 1.30–1.48 compared to their age-matched cohort.4,5 In many Scandinavian countries, fertility preservation is free of charge to all individuals at risk of sterility due to medical or surgical treatment. From 1998 to 2018, 73% of adult women who received counseling proceeded with ovarian stimulation and 27% of those survivors returned to utilize fertility services.6 This return rate was consistent across patients with benign and malignant conditions.6 In a US cohort, Dolmans et al.7 showed a true come-back rate of 23%. This return rate to utilize cryopreserved oocytes is sufficient to recommend consideration of oocyte cryopreservation in almost all individuals who are about to undergo potentially gonadotoxic treatment.

**Objective**

We reviewed the literature on safe management of fertility preservation through oocyte and embryo cryopreservation to facilitate decision-making, appropriate patient-selection, and treatment planning. The important management issues are addressed such as: expectations for cycle yield, impact on disease progression, protocol strategies, and adjuvants that enhance safety and success.

**Methods**

**Search and selection strategy**

A systematic literature search was conducted in PubMed, Embase, and Ovid MEDLINE from their establishment through June 2021. No language restriction was imposed. The following search terms were used: (oocyte OR embryo) AND (cryopreservation OR fertility preservation) AND (cancer OR chemotherapy) AND (stimulation). The International Prospective Register of Systematic Reviews guidelines were followed (identification number CRD42021251821). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were employed. Ethical approval by an institutional review board (IRB) and informed consent was not required for this systematic review. No financial support was provided. Figure 1 provides an overview of the literature search and selection process.

Data published only as abstracts in conference proceedings were reviewed, and attempts were made to contact authors for full details; the data were included if these details were made available. All peer-reviewed, published studies meeting the inclusion criteria for the primary outcomes of evaluating outcomes of stimulation and cryopreservation of embryos or oocytes prior to gonadotoxic treatment in female patients ages 14–45 years were evaluated in full-text form for inclusion. Studies were excluded if they focused on ovarian tissue cryopreservation, did not include novel data, or if the full text was not available. Two authors independently reviewed all citations and their abstracts to assess appropriate studies to be included. Conflicts were then reviewed with a third reviewer to achieve consensus.

Bias was assessed in all included randomized control trials and cohort studies. The Cochrane Risk of Bias 2 assessment tool and the Newcastle–Ottawa Scale were used, respectively.5 The scoring is noted in Table 3 of the supplemental materials.

**Results**

The objective was to complete a systematic review of the fertility preservation process and opportunities to enhance safety and yield. In total, 62 studies met inclusion criteria, plus an additional 20 expert opinions or reviews contributed to the subsequent synthesis reported in this article.

**Barriers to seeking safe fertility preservation**

**Expected ovarian stimulation outcomes.** Many providers still share a perception of poor cycle outcomes in the setting of medically indicated fertility preservation. The first technical barrier has been oocyte survival following cryopreservation and subsequent pregnancy rate. However, growing evidence demonstrates a comparable live birth rate with vitrified oocytes compared to fresh oocytes.9
Biologic concerns remain regarding malignancy and disease and the subsequent "detrimental impact on the quality and behavior of oocytes."3,10 Multiple studies have now demonstrated that fertility preservation cycles in the setting of planned gonadotoxic therapy have resulted in oocyte yield consistent with an age-matched infertility cohort as well as people undergoing planned oocyte cryopreservation.11–14 This does not guarantee that all patients will have adequate ovarian response to fulfill their family planning desires. Cohort data do show that when adjusted for age and body mass index (BMI), people with systemic cancer may have a lower antral follicle count and require higher doses of stimulatory medications.15 Part of a successful fertility preservation consultation is a tailored discussion regarding realistic expectations of both ovarian stimulation and post-chemotherapy ovarian reserve using markers like anti-mullerian hormone (AMH), antral follicle count and age to predict outcomes.16–18

Retrospective cohort data suggest a mean number of oocytes collected as 8.2 per cycle, with 6.1 of those being mature oocytes for fertilization or cryopreservation.19 Furthermore, utilization of a cutoff of 1.2 ng/mL for AMH predicted a high likelihood of retrieval of 4 or greater oocytes following stimulation.20 Finally, AMH values can help predict post-chemotherapy ovarian reserve and function.21 Women diagnosed with early breast cancer who maintained regular menses following completion of chemotherapy had an average AMH of 2.5 ± 0.4 ng/mL compared to 0.7 ± 0.1 ng/mL for those who did not (p < 0.0001). All women in this cohort with a pretreatment AMH less than 1.9 ng/mL became amenorrheic during treatment.22

Sometimes patients or the medical team may need to prioritize the first round of chemotherapy or pelvic surgery over fertility preservation. In these situations, subsequent oocyte yield will be lower, but many patients will still have a successful round of cryopreservation following a first round of chemotherapy.23 Consideration should be given to stimulation for preservation as soon as possible in patients despite ongoing treatment, as AMH decreases and follicle-stimulating hormone (FSH) increases at 1, 6, 12, 24, and 36 months following chemotherapy.24,25 Providers may find the American Society for Clinical Oncology (ASCO) recommendations on fertility preservation and risk of permanent amenorrhea helpful when counseling patients.26

Risk of delay in treatment, disease progression, or complication. When battling against the threat of mortality from cancer or the life-altering morbidity of lupus, vasculitis, or endometriosis, patients and care teams may have their focus...
absorbed by short-term disease treatment to the detriment of future survivorship goals. Physicians can provide objective counseling regarding future family opportunities following fertility preservation in conjunction with cancer or other treatment. Minimal, if any, delay in treatment is required for oocyte cryopreservation.

If rapid referral occurs during ongoing oncologic evaluation, cancer can be fully evaluated while fertility preservation is discussed, coverage sought, and medications obtained. The mean duration of ovarian stimulation is only 11 days. Breast cancer is the most common malignancy to affect reproductive age females, and data have demonstrated that a delay of up to 12 weeks between surgery and chemotherapy has no effect on survival or recurrence.28,29

The need for early consideration for fertility preservation goes beyond malignancy and the many indications are reviewed in Table 1. Autoimmune conditions can have worse fertility outcomes and gonadotoxic treatment-dependent side effects, so affected individuals can also benefit from early referral for consultation. Patients with endometriosis are another group at risk for infertility and have the additional risk of diminished ovarian reserve following surgery, with more surgeries increasing the risk of their being poor responders to ovarian stimulation.31–34

Oncologists, infertility specialists, and patients alike worry about the risk of disease progression later. Cohort studies continue to add to the body of literature showing that patients who undergo ovarian stimulation show no increased risk of death or recurrence compared to those who chose not to pursue stimulation.39,48,53,66,72 This remains true even in hormone sensitive cancer when appropriate protocols are utilized.39 Furthermore, if patients do plan pregnancy after completion of their therapy, these survivors should be reassured that these pregnancies do not affect long-term survival and recurrence risk.40,56,58 Of note, therapies like radiation may still affect uterine competence during pregnancy, particularly if exposure occurs around or before the time of puberty.57

The concern regarding the likelihood of complications of fertility preservation can seem like a black box given the relative lack of familiarity with ovarian stimulation outside of the fertility community. The most common side effects of ovarian stimulation include local pain and bruising; gastrointestinal changes including nausea, diarrhea and

| Table 1. Conditions associated with increased risk of infertility due to diminished ovarian reserve and/or early menopause. |
|---------------------------------------------------------------|
| **Mild increased risk** | **Moderate increased risk** | **Severe increased risk** | **Planned surgical menopause** |
| Endometriosis | Endometriosis with endometrioma | Endometriosis with history of multiple pelvic surgeries or multiple endometriomas | Bilateral salpingo-oophorectomy |
| Unilateral salpingo-oophorectomy due to other benign disease | Planned trachelectomy | Ovarian cancer with any stage beyond 1A | Advanced stage cervical, endometrial, and ovarian cancer |
| Stage 1A ovarian cancer | Planned chemotherapy with BEP, paclitaxel, docetaxel, cisplatin, anthracyclines, or carboplatin | Planned chemotherapy with high-dose alkylating agents or procarbazine | Gender-affirming surgery in transmasculine/trans male people |
| Planned chemotherapy with non-alkylating agents | Planned chemotherapy with cyclophosphamide with cumulative dose of 5 g/m² or less in women age 30–40 years | Planned chemotherapy with cyclophosphamide with cumulative dose of 5 g/m² in women age >40 years or dose of >7.5 g/m² in all women | |
| Planned chemotherapy with low-dose cyclophosphamide in women age <30 | Abdominal or pelvic radiation with ovaries outside of planned radiation field | Whole body irradiation or pelvic radiation with ovaries within radiation field | |
| Planned gender-affirming hormonal therapy in transmasculine/trans male people | Systemic lupus erythematosus | Autoimmune oophoritis | |
| Nephritis not requiring chemotherapy | Vasculitis | Addison’s disease | |
| Autoimmune disorder diagnosis | Type I diabetes | Turner syndrome | |
| Type II diabetes | Nephritis requiring chemotherapy treatment | Galactosemia | |
| Recurrent pregnancy loss | Fragile X pre-mutation carrier | Carrier of other autosomal disorders associated with ovarian failure | |
| BRCA 1 and 2 carriers | First degree relative with menopause prior to 40 | Age 40+ years, compared to women <35 | |
| Age 35–37 years, compared to women <35 | Age 37–40 years, compared to women <35 | Age 40+ years, compared to women <35 | |

BEP= bleomycin, etoposide, platinum; BRCA= breast cancer gene.
constipation; hormonal symptoms to include mood swings, fatigue, breast tenderness, hot flashes and bloating; and finally, pelvic fullness and pain.

More serious but uncommon complications include ovarian hyperstimulation syndrome (OHSS) and thromboembolism which in current practice occur in 1%–5% and 0.19% of stimulation cycles, respectively.\textsuperscript{70,73} OHSS is characterized by increasing fluid shifts due to vascular permeability and leakage into the extravascular space; this can lead to accumulation of fluid in the abdomen (ascites) and in severe cases lead to pleural effusions, respiratory complications, and even acute renal injury. Planned cryopreservation cycles reduce the risk of OHSS by avoiding subsequent exposure to endogenous human chorionic gonadotropin (HCG) which occurs with a developing pregnancy.\textsuperscript{67} This can be reduced even further through utilization of a gonadotropin-releasing hormone (GnRH) agonist to trigger final oocyte maturation instead of HCG.\textsuperscript{38}

Thromboembolisms are known to be increased in oncologic conditions at baseline and should be considered during the elevated estrogenic, hypercoagulable state associated with ovarian stimulation. The annual rate of thromboembolism during oncologic treatment ranges from 0.9% in breast cancer, to 3.7% in Hodgkin’s and non-Hodgkin’s lymphoma, and 4.2% in ovarian cancer.\textsuperscript{67} By avoiding OHSS, this risk is likely decreased, but no trials currently exist to guide fertility preservation-specific prophylaxis.\textsuperscript{67} ASCO guidelines do not routinely recommend antithrombotic prophylaxis for outpatient procedures.\textsuperscript{26,74}

From a different perspective, De Groot et al.\textsuperscript{75} found that controlled ovarian stimulation prior to chemotherapy in breast cancer patients not only demonstrated no increase in grade II/IV side effects but may have a protective effect for mucositis and constipation. Table 2 offers a summative review of the most common questions and current interpretation of the available literature.

### Current stimulation strategies
Traditional ovarian stimulation protocols start stimulation shortly after initiation of menses which allows for synchronization of natural follicular recruitment with medication-driven oocyte stimulation. While the broad range of options for stimulation is beyond the scope of this review, we will focus on stimulation strategies that do not await natural menses and utilize the precious resource of time in these medically motivated patients. These options are also reviewed in Figure 2.

**Random start.** Random start stimulation strategies advocate for immediate initiation of stimulation medications utilizing letrozole 2.5 mg/day and recombinant FSH 150–300 IU/day or human menopausal gonadotropins (HMG) 150–225 IU/day with early start of GnRH antagonist dependent on baseline ultrasound and cycle
through to oocyte trigger. HMG at a low dose of 150 IU/day continued for 4 days, and clomiphene citrate is continued citrate 25 mg/day and letrozole 2.5 mg/day. Letrozole is first stage of stimulation on cycle day 3 with clomiphene retrieval.

measuring antagonist was added on identification of a follicle binant luteinizing hormone (LH) 150 IU/day. GnRHulation on cycle day 2 with FSH 300 IU/day and recom-

with estradiol 4 mg/day with initiation of injectable stim-

the identical protocol was started 5 days after oocyte trigger and rapid luteolysis. Repeat stimulation utilizing cohort. When that occurs, GnRH agonist was utilized for

of a mature cohort is achieved, and final oocyte maturation is triggered with a GnRH agonist and ibuprofen 600 mg. Stimulation is quickly started again the day following oocyte retrieval with HMG 225 IU/day and letrozole 2.5 mg/day. Letrozole is continued through identification of a 12-mm follicle. Medroxyprogesterone acetate 10 mg was added on stimulation day 12 through oocyte retrieval to prevent premature onset of menses. Finally, GnRH agonist and ibuprofen 600 mg was employed for cycle-completing oocyte-maturation trigger. Table 4 maps out key safety concerns and mitigation strategies.

Luteal phase. Luteal phase stimulation specifically denotes ovarian stimulation in the luteal phase of the menses, in other words, 1–3 days following ovulation. This protocol can be the random start protocol as listed above, or an alternate as described by Chen et al. This strategy includes a combination of letrozole 2.5 mg/day and HMG 225 IU/ day. A non-androgenic progestin in the form of medroxy-

Dual stimulation. Dual stimulation was developed to enhance oocyte yield in patients with poor ovarian stimulation, this condition may also describe older patients with a medical indication for cryopreservation. The two published versions of the protocol have moderate differences, but both allow for stimulation and retrieval in the follicular and luteal phases of the cycle to enhance total oocyte yield and may be started at a wide range of points within the cycle.

Vaiarelli and colleagues recommend luteal priming with estradiol 4 mg/day with initiation of injectable stimulation on cycle day 2 with FSH 300 IU/day and recom-

Kuang and colleagues instead advocated for a mild first stage of stimulation on cycle day 3 with clomiphene citrate 25 mg/day and letrozole 2.5 mg/day. Letrozole is continued for 4 days, and clomiphene citrate is continued through to oocyte trigger. HMG at a low dose of 150 IU/day is started on cycle day 6 and continued every other day until a mature cohort is achieved, and final oocyte maturation is triggered with a GnRH agonist and ibuprofen 600 mg. Stimulation is quickly started again the day following oocyte retrieval with HMG 225 IU/day and letrozole 2.5 mg/day. Letrozole is continued through identification of a 12-mm follicle. Medroxyprogesterone acetate 10 mg was added on stimulation day 12 through oocyte retrieval to prevent premature onset of menses. Finally, GnRH agonist and ibuprofen 600 mg was employed for cycle-completing oocyte-maturation trigger. Table 4 maps out key safety concerns and mitigation strategies.

Adjuvants that may enhance safety and outcomes

Letrozole. Letrozole, an aromatase inhibitor, is commonly used in medical therapy for breast cancer. Its utility in ovarian stimulation results from both the increase in follicular recruitment along with the decreased peak estradiol level seen during cycles in which it is used. Initial cohort studies attempted stimulation with letrozole from cycle start compared to tamoxifen. The letrozole cohort had both significantly enhanced oocyte yield compared to control or tamoxifen stimulation (7.8 ± 0.9 compared to 2 ± 0.3 and 6 ± 1, respectively) and lower estradiol levels (380 ± 57 pg/mL compared to 419 ± 39 pg/mL and 1182 ± 271 pg/mL, respectively). Follow-on studies have demonstrated appropriate pregnancy and live birth rates. This has led to utilization of letrozole not only in estrogen-receptor sensitive cancers but also in other conditions that might be aggravated by a hyper-estrogenic state such as autoimmune diseases and preservation prior to gender-affirming therapy.

GnRH agonists. Previously mentioned in stimulation strategies, an injection of GnRH agonist for final oocyte maturation was initially explored to enhance safety in patients at high risk of OHSS. The brief flare and rapid luteolysis greatly reduces the occurrence of moderate to severe OHSS in a high responder cohort, particularly when appropriate caution in stimulation dosing is exercised, no
Table 3. Risk of bias assessment.

Assessment of randomized control trials via risk-of-bias tool for randomized trials (RoB 2)

| Author            | Year | Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Risk of Bias Judgment |
|-------------------|------|----------|----------|----------|----------|----------|-----------------------|
| Prapas            | 2017 | Low      | Low      | Low      | Low      | Some     | Low risk of bias      |
| Xu                | 2018 | Some     | Low      | Some     | Some     | Some     | Some concerns         |

Assessment of cohort studies via Newcastle–Ottawa Scale (7 or greater considered good quality)

| Author            | Year | Selection | Comparability | Outcome | Overall score |
|-------------------|------|-----------|---------------|---------|---------------|
| Adeleye           | 2018 | 1 1 1 1 2 | 1 1 1 9      |
| Anderson          | 2011 | 1 1 1 1 1 | 1 1 1 8      |
| Anderson et al.   | 1999 | 1 0 1 2 2 | 1 1 1 8      |
| Azim had to       | 2008 | 1 1 1 2 2 | 1 1 1 9      |
| Azim              | 2013 | 1 1 1 2 2 | 1 1 1 9      |
| Barton            | 2013 | 1 1 1 2 2 | 1 1 1 9      |
| Bastu             | 2014 | 1 1 0 2 2 | 1 1 1 8      |
| Blumenfeld        | 2002 | 1 1 1 1 2 | 1 1 1 8      |
| Boumpas           | 1993 | 1 0 1 1 1 | 1 1 1 7      |
| Carter            | 2010 | 1 1 1 1 1 | 1 1 1 8      |
| Cavagna           | 2017 | 1 0 1 2 2 | 1 1 1 8      |
| Checa             | 2015 | 1 1 1 2 2 | 1 1 1 9      |
| Checa             | 2012 | 1 1 1 1 1 | 1 1 1 8      |
| Chehra            | 2019 | 1 1 1 2 2 | 1 1 1 9      |
| Ciccarone         | 2020 | 1 1 1 2 2 | 1 1 1 8      |
| Clowse            | 2011 | 1 1 1 1 1 | 1 1 1 8      |
| Cobo              | 2020 | 1 1 1 1 1 | 1 1 1 8      |
| Cold              | 2005 | 1 1 1 2 2 | 1 1 1 9      |
| Courbiere         | 2014 | 1 1 1 1 1 | 1 1 1 8      |
| Courbiere         | 2013 | 1 0 1 1 1 | 1 1 1 7      |
| Devesa            | 2014 | 1 1 1 1 1 | 1 1 0 7      |
| Dolinko           | 2018 | 1 1 1 2 2 | 1 1 1 9      |
| Dolmans           | 2015 | 1 1 1 1 1 | 1 1 1 8      |
| Dolmans           | 2005 | 1 0 1 2 2 | 1 1 1 9      |
| Domingo           | 2016 | 1 1 1 2 2 | 1 1 0 8      |
| Elizur            | 2008 | 1 0 1 1 1 | 1 1 1 7      |
| Grifo             | 2010 | 1 1 1 2 2 | 1 1 0 8      |
| Henes             | 2012 | 1 1 1 2 2 | 0 1 0 7      |
| Henes             | 2012 | 1 1 1 2 2 | 0 1 0 7      |
| Henes             | 2011 | 1 1 1 2 2 | 0 1 0 7      |
| Kim               | 2016 | 1 1 1 2 2 | 1 1 1 9      |
| Knopman           | 2009 | 1 1 1 1 1 | 1 1 1 8      |
| Kuang             | 2014 | 1 0 1 2 2 | 1 1 1 8      |
| Kuang             | 2015 | 1 1 1 1 1 | 1 1 1 8      |
| Lambertini et al. | 2018 | 1 1 1 2 2 | 1 1 1 9      |
| Lambertini        | 2020 | 1 1 1 2 2 | 1 1 1 9      |
| Lee               | 2010 | 1 1 1 1 1 | 1 1 1 8      |

(Continued)
Table 4. Mapping out the safety strategies.

| Possible risks for oocyte stimulation in fertility preservation | Key points | Applicable sources |
|---------------------------------------------------------------|------------|--------------------|
| Delay in treatment                                            | "Most cycles can be completed within 14 days; the mean is 11 days of stimulation. "The introduction of multiple cycle options has added to the flexibility of the start time. | 13, 28 |
| Worsening of diagnosis                                        | "Patients who undergo ovarian stimulation show no increased risk of death, shorter disease-free survival, or recurrence. "Post-treatment pregnancies also do not affect survival or recurrence risk. "Aromatase inhibitors can keep peak estradiol levels within physiological levels | 36–40, 41–43, 52, 59, 60 |
| Ovarian hyperstimulation syndrome (OHSS)                      | "Rates are low and can be enhanced with liberal use of: GnRH agonist triggers, cabergoline, and delay of long-acting GnRH agonist until at least a week after retrieval. | 45, 48, 62, 63, 64, 65, 70 |
| Venous thromboembolism (VTE)                                 | "There is currently no evidence to suggest a higher rate of VTE during stimulation compared to the baseline of having a cancer diagnosis. At this time, routine prophylaxis is not recommended. | 27, 47, 49 |
| Poor oocyte yield                                              | "The number of oocytes collected is similar to an age-matched infertility control. "Appropriate consultation will need to discuss expectations and medication dosing based on age and a limited evaluation. | 12–15, 17–19 |
HCG is added, and no fresh transfer is planned. Furthermore, in a breast cancer preservation cohort, a GnRH agonist led to a more rapid drop in estradiol post trigger while enhancing the number of mature oocytes retrieved. Collaborating physicians should also be cautioned not to administer long-acting GnRH agonist in the 1–2 weeks following retrieval as this may create a prolonged cascade of stimulation. The GnRH agonist utilized in individual protocols may vary by country and professional preference. The literature supports the use of leuprolide acetate 1 mg, triptorelin pamoate 0.2 mg, or buserelin acetate 1 mg. Another option, if GnRH agonist trigger is not available or recommended, is consideration of a double dose (a.m. and p.m. administration) of GnRH antagonist the day prior to HCG trigger.

**Dopamine agonists.** The recent review by Tang et al. reports that dopamine agonists have been shown in 16 randomized control trials to decrease the risk of moderate to severe OHSS. Cabergoline, quinagolide, and bromocriptine have all been shown effective, but may increase the risk of other adverse gastrointestinal side effects. As these medications are widely available and not employed until the decision to move forward with final oocyte-maturation trigger, they can be considered for a last layer of protection for at risk patients.

**Antithrombotic prophylaxis.** As reviewed previously, routine use of antithrombotics, such as low molecular weight heparin, is not recommended routinely with ovarian stimulation or in outpatient care in oncologic conditions. The best prophylaxis is likely avoidance of OHSS. However, if significant concern arises, antithrombotics may be considered for windowing around the time of retrieval.

**Progestins.** Progestins may be used to prime a patient prior to cycle start, to suppress ovulation, or may simply be left in place due to the presence of a previously placed intrauterine device (IUD).

Endogenous progesterone is utilized in luteal stimulation to prevent loss of the follicular cohort prior to retrieval. Progestin-primed ovary stimulation extends this into follicular stimulation with the use of daily medroxyprogesterone acetate 10 mg starting on cycle day 3. This cost-effective option has been utilized in overweight, obese, and polycystic ovarian syndrome patients to good effect. It may be an excellent adjunct in patients with endometrial hyperplasia or cancer. An ongoing trial is underway to compare the effectiveness for prevention of premature LH surges even in a cohort of poor responders.

IUDs have grown in popularity due to their effectiveness both as a contraceptive as well as control of heavy menstrual bleeding. If noted prior to fertility preservation, IUDs should be left in place as they do not affect cycle performance in women undergoing ovarian stimulation.

**Other supplements.** Poor quality evidence exists for use of over-the-counter supplements to improve oocyte yield or quality. Some limited trial data showed improvement in oocyte number, fertilization, and high-quality embryos in low-prognosis young women with 60 days of treatment with coenzyme Q10. However, the short timeframe for treatment in fertility preservation likely minimizes any possible benefit.

Low-dose aspirin has become a common part of the obstetric armamentarium. A recent meta-analysis concluded that its use may improve clinical pregnancy rate, but that current data did not show its use affected oocyte yield, fertilization rates or live birth.

**Discussion**

The medical community has had increasing recognition of the importance of the loss of fertility that often occurs in addition to the morbidity caused by malignancies, autoimmune disease, metabolic and genetic disorders, and other medical conditions that are gonadotoxic in their course or their treatment. However, fertility preservation services have been deployed unevenly and generally insufficiently. Our results echo the opinions of multiple medical organizations including but not limited to ESHRE, ASRM, ACOG, and FIGO that fertility preservation can be safely used in most patients and should be made available for these women.

In patients with gynecologic cancer, 77% express clinically significant levels of distress in relation to loss of fertility or impaired fertility. This despair is echoed in young patients across the diagnostic spectrum. Success in treating cancer has created a new focus on the quality of life after cancer, and therefore, a demand for quality fertility preservation care.

At this time, evidence is largely limited to cohort studies. These are often limited in number of participants and heterogeneity of diagnosis and baseline characteristics. Trials in the general infertility population do offer insight to safer strategies. However, the wider the utilization of fertility preservation, the greater we can voluntarily enroll patients in studies to clarify these areas of ambiguity.

This need for fertility preservation services extends beyond the oncologic community to individuals affected with other diseases notorious for their systemic inflammatory effects and associated gonadotoxic treatments. Vasculitis, lupus, and nephritis all disproportionately affect reproductive age females and place them at higher risk of menstrual irregularity and fertility failure. Medical pre-disposition and risk should be identified, and patients supported and treated. Societal barriers need to be overcome. Insurance coverage of fertility preservation services varies widely by country and state of residence. The financial burden associated with gamete preservation for oocytes compared to sperm reflect the complexity but also serve as
another example of a “pink tax” that discriminates against women, especially with respect to reproductive healthcare.

In the face of potential mortality for their patients, we hope this review helps treating physicians reach safely across medical subspecialties to think not only of their patient’s survival, but also to the life and family choices that most of them desire, and that are every individual’s right.

Author contribution(s)
Meghan CH Ozcan: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft.
Victoria Snegovskikh: Conceptualization; Data curation; Writing – review & editing.
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References
1. ESHRE Guideline Group on Female Fertility Preservation, Anderson RA, Amant F, et al. ESHRE guideline: female fertility preservation. Hum Reprod Open 2020; 2020(4): hoaa052.
2. Chen C. Pregnancy after human oocyte cryopreservation. Lancet 1986; 1(8486): 884–886.
3. Pal L, Leykin L, Schifren JL, et al. Malignancy may adversely influence the quality and behaviour of oocytes. Hum Reprod 1998; 13(7): 1837–1840.
4. Barton SE, Najita JS, Ginsburg ES, et al. Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol 2013; 14(9): 873–881.
5. Velez MP, Richardson H, Baxter NN, et al. Risk of infertility in female adolescents and young adults with cancer: a population-based cohort study. Hum Reprod 2021; 36(7): 1981–1988.
6. Rodriguez-Wallberg KA, Marklund A, Lundberg F, et al. A prospective study of women and girls undergoing fertility preservation due to oncologic and non-oncologic indications in Sweden–Trends in patients’ choices and benefit of the chosen methods after long-term follow up. Acta Obstet Gynecol Scand 2019; 98(5): 604–615.
7. Dolmans MM, Hollanders De Ouderaen S, Demyyle D, et al. Utilization rates and results of long-term embryo cryopreservation before gonadotoxic treatment. J Assist Reprod Genet 2015; 32(8): 1233–1237.
8. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: 14898.
9. Grifo JA and Noyes N. Delivery rate using cryopreserved oocytes is comparable to conventional in vitro fertilization using fresh oocytes: potential fertility preservation for female cancer patients. Fertil Steril 2010; 93(2): 391–396.
10. Gerber B, Dieterich M, Müller H, et al. Controversies in preservation of ovary function and fertility in patients with breast cancer. Breast Cancer Res Treat 2008; 108(1): 1–7.
11. Knopman JM, Noyes N, Talebian S, et al. Women with cancer undergoing ART for fertility preservation: a cohort study of their response to exogenous gonadotropins. Fertil Steril 2009; 91(4 Suppl.): 1476–1478.
12. Robertson AD, Missmer SA and Ginsburg ES. Embryo yield after in vitro fertilization in women undergoing embryo banking for fertility preservation before chemotherapy. Fertil Steril 2011; 95(2): 588–591.
13. Devesa M, Martinez F, Coroleu B, et al. Ovarian response to controlled ovarian hyperstimulation in women with cancer is as expected according to an age-specific nomogram. J Assist Reprod Genet 2014; 31(5): 583–588.
14. Moraes CC, Marinho VFW, Campos ALM, et al. Oocyte cryopreservation for future fertility: comparison of ovarian response between cancer and non-cancer patients. JBRA Assist Reprod 2019; 23(2): 91–98.
15. Dolinko AV, Farland LV, Missmer SA, et al. Responses to fertility treatment among patients with cancer: a retrospective cohort study. Fertil Res Pract 2018; 4: 3.
16. Lee S, Ozkavukcu S, Heytens E, et al. Value of early referral to fertility preservation in young women with breast cancer. J Clin Oncol 2010; 28(31): 4683–4686.
17. Naasan M, Harrity C, Rajab H, et al. Patients with cancer at the margins of reproductive age had reduced levels of anti-Müllerian hormone compared with patients experiencing infertility. Int J Gynaecol Obstet 2016; 133(2): 226–229.
18. Domingo J and García-Velasco JA. Oocyte cryopreservation for fertility preservation in women with cancer. Curr Opin Endocrinol Diabetes Obes 2016; 23(6): 465–469.
19. Courbiere B and Decanter C. [Practical clinical aspects of oocyte vitrification for fertility preservation]. Gynecol Obstet Fertil 2014; 42(9): 653–656.
20. Lee S, Ozkavukcu S, Heytens E, et al. Anti-Müllerian hormone and antral follicle count as predictors for embryo/oocyte cryopreservation cycle outcomes in breast cancer patients stimulated with letrozole and follicle stimulating hormone. J Assist Reprod Genet 2011; 28(7): 651–656.
21. Anderson RA and Cameron DA. Pretreatment serum anti-Müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J Clin Endocrinol Metab 2011; 96(5): 1336–1343.
22. Alexander VM, Martin CE, Schelble AP, et al. Ovarian stimulation for fertility preservation in women with cancer: a systematic review and meta-analysis comparing random and conventional starts. J Gynecol Obstet Hum Reprod 2021; 50(8): 102080.
23. Dolmans MM, Demyline D, Martinez-Madrid B, et al. Efficacy of in vitro fertilization after chemotherapy. *Fertil Steril* 2005; 83(4): 897–901.

24. Ciccarone M, Hohaus S, Pulsoni A, et al. Preliminary results of a counselling programme for fertility preservation in female cancer patients: the experience of the GEMME DORMIENTI network. *Eur J Cancer Care* 2020; 29(1): e13174.

25. Blumenfeld Z, Dann E, Avivi I, et al. Fertility after treatment for Hodgkin’s disease. *Ann Oncol* 2002; 13(Suppl. 1): 138–147.

26. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006; 24(18): 2917–2931.

27. Courbiere B, Decanter C, Bringer-Deutsch S, et al. Emergency IVF for embryo freezing to preserve female fertility: a French multicentre cohort study. *Hum Reprod* 2013; 28(9): 2381–2388.

28. Lohrisch C, Paltiel C, Gelmon K, et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* 2006; 24(30): 4888–4894.

29. Cold S, Düring M, Ewertz M, et al. Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG). *Br J Cancer* 2005; 93(6): 627–632.

30. Elizur SE, Chian RC, Pineau CA, et al. Fertility preservation treatment for young women with autoimmune diseases facing treatment with gonadotoxic agents. *Rheumatology* 2008; 47(10): 1506–1509.

31. Tamauchi S, Kajiyama H, Osuka S, et al. Reduced response to controlled ovarian stimulation after radical trachelectomy: a pitfall of fertility-sparing surgery for cervical cancer. *Int J Gynaecol Obstet* 2021; 154: 162–168.

32. Donnez J and Dolmans MM. Fertility preservation in men and women: where are we in 2021? Are we rising to the challenge? *Fertil Steril* 2021; 115: 1089–1090.

33. Bastu E, Yasa C, Dural O, et al. Comparison of ovulation induction protocols after endometrioma resection. *J SLS* 2014; 18(3): e2014.00128.

34. Cobo A, Giles J, Paolelli S, et al. Oocyte vitrification for fertility preservation in women with endometriosis: an observational study. *Fertil Steril* 2020; 113(4): 836–844.

35. Christ J, Herndon CN and Yu B. Severe ovarian hyperstimulation syndrome associated with long-acting GnRH agonist in oncology patients. *J Assist Reprod Genet* 2021; 38(3): 751–756.

36. Tang H, Mourad S, Zhai S-D, et al. Dopamine agonists for preventing ovarian hyperstimulation syndrome. *Cochrane Database Syst Rev* 2016; 11: CD008605.

37. Prapas Y, Ravanos K, Petousis S, et al. GnRH antagonist administered twice the day before hCG trigger combined with a step-down protocol may prevent OHSS in IVF/ICSI antagonist cycles at risk for OHSS without affecting the reproductive outcomes: a prospective randomized control trial. *J Assist Reprod Genet* 2017; 34(11): 1537–1545.

38. Anderson RA, Kinniburgh D and Baird DT. Preliminary experience of the use of a gonadotropin-releasing hormone antagonist in ovulation induction/in-vitro fertilization prior to cancer treatment. *Hum Reprod* 1999; 14(10): 2665–2668.

39. Kim J, Turan V and Oktay K. Long-term safety of letrozole and gonadotropin stimulation for fertility preservation in women with breast cancer. *J Clin Endocrinol Metab* 2016; 101(4): 1364–1371.

40. Lambertini M, Kroman N, Ameye L, et al. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. *J Natl Cancer Inst* 2018; 110(4): 426–429.

41. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion. *Fertil Steril* 2018; 110(3): 380–386.

42. Wang L, Yin M, Liu Y, et al. Effect of frozen embryo transfer and progesterin-primed ovary stimulation on IVF outcomes in women with high body mass index. *Sci Rep* 2017; 7(1): 7447.

43. Oktay K, Turan V, Bedoschi G, et al. Fertility preservation success subsequent to concurrent aromatase inhibitor treatment and ovarian stimulation in women with breast cancer. *J Clin Oncol* 2015; 33(22): 2424–2429.

44. Qin N, Chen Q, Hong Q, et al. Flexibility in starting ovarian stimulation at different phases of the menstrual cycle for treatment of infertile women with the use of in vitro fertilization or intracytoplasmic sperm injection. *Fertil Steril* 2016; 106(2): 334–341.e1.

45. Vaiarelli A, Cimadomo D, Conforti A, et al. Luteal phase after conventional stimulation in the same ovarian cycle might improve the management of poor responder patients fulfilling the Bologna criteria: a case series. *Fertil Steril* 2020; 113(1): 121–130.

46. Checa MA, Brassesco M, Sastre M, et al. Random-start GnRH antagonist for emergency fertility preservation: a self-controlled trial. *Int J Womens Health* 2015; 7: 219–225.

47. Wang Y, Kuang Y, Chen Q, et al. Gonadotropin-releasing hormone antagonist versus progester in the prevention of premature luteinising hormone surges in poor responders undergoing in vitro fertilisation treatment: study protocol for a randomised controlled trial. *Trials* 2018; 19(1): 455.

48. Vukovic P, Kasum M, Raguz J, et al. Fertility preservation in young women with early-stage breast cancer. *Acta Clinica Croatica* 2019; 58(1): 147–156.

49. Carter J, Chi DS, Brown CL, et al. Cancer-related infertility and gonadotropin stimulation for fertility preservation in women facing treatment with gonadotoxic agents. *Br J Cancer* 2018; 109(6): 627–632.

50. Adelaye AJ, Aghajanova L, Kao C-N, et al. Impact of the long-acting progesterone levonorgestrel-releasing intrauterine device on controlled ovarian stimulation outcomes. *J Assist Reprod Genet* 2021; 38(3): 751–756.

51. Xu Y, Nisenblat V, Lu C, et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. *Reprod Biol Endocrinol* 2018; 16(1): 29.

52. Wang L, Huang X, Li X, et al. Efficacy evaluation of low-dose aspirin in IVF/ICSI patients evidence from 13 RCTs: a systematic review and meta-analysis. *Medicine* 2017; 96(37): e7720.

53. Letourneau JM, Wald K, Sinha N, et al. Fertility preservation before breast cancer treatment appears unlikely to
affect disease-free survival at a median follow-up of 43 months after fertility-preservation consultation. *Cancer* 2020; 126(3): 487–495.

54. Vaiarelli A, Cimadomo D, Alviggi E, et al. The euploid blastocysts obtained after luteal phase stimulation show the same clinical, obstetric and perinatal outcomes as follicular phase stimulation-derived ones: a multicenter study. *Human Reprod* 2020; 35(11): 2598–2608.

55. Tanus S, Turki R, Cohen Y, et al. Reproductive outcomes after a single dose of gonadotropin-releasing hormone agonist compared with human chorionic gonadotropin for the induction of final oocyte maturation in hyper-responder women aged 35–40 years. *Fertil Steril* 2017; 107(6): 1323–1328.

56. Lambertini M, Hamy AS, Zingarello A, et al. Pregnancy after breast cancer in patients with germline BRCA mutations. *J Clin Oncol* 2020; 38(26): 3012–3023.

57. Griffiths MJ, Winship AL and Hutt KJ. Do cancer therapies damage the uterus and compromise fertility? *Hum Reprod Update* 2020; 26(2): 161–173.

58. Azim HA Jr, Kroman N, Paesmans M, et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol* 2013; 31(1): 73–79.

59. Checa Vizzaino MA, Corchado AR, Cuadri ME, et al. The effects of letrozole on ovarian stimulation for fertility preservation in cancer-affected women. *Reprod Biomed Online* 2012; 24(6): 606–610.

60. Henry L and Mocanu E. Preserving fertility before cancer treatment, 2019, https://www.figo.org/news/preserving-fertility-cancer-treatment

61. Sönmez M, Türkçuoğlu I, Coşkun U, et al. Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles. *Fertil Steril* 2011; 95(6): 2125.e9–2125.e11.

62. Kuang Y, Chen Q, Hong Q, et al. Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol). *Reprod Biomed Online* 2014; 29(6): 684–691.

63. Cavagna F, Pontes A, Cavagna M, et al. A specific controlled ovarian stimulation (COS) protocol for fertility preservation in women with breast cancer undergoing neoadjuvant chemotherapy. *Contemp Oncol* 2017; 21(4): 290–294.

64. Oktay K, Buyuk E, Libertella N, et al. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. *J Clin Oncol* 2015; 23(19): 4347–4353.

65. Oktay K, Türkçuoğlu I and Rodriguez-Wallberg KA. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. *Reprod Biomed Online* 2010; 20(6): 783–788.

66. Azim AA, Costantini-Ferrando M and Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. *J Clin Oncol* 2008; 26(16): 2630–2635.

67. Somigliana E, Peccatori FA, Filippi F, et al. Risk of thrombosis in women with malignancies undergoing ovarian stimulation for fertility preservation. *Hum Reprod Update* 2014; 20(6): 944–951.

68. Manzanares MA, Gómez-Palomares JL, Ricciarelli E, et al. Triggering ovulation with gonadotropin-releasing hormone agonist in in vitro fertilization patients with polycystic ovaries does not cause ovarian hyperstimulation syndrome despite very high estradiol levels. *Fertil Steril* 2010; 93(4): 1215–1219.

69. Chen H, Wang Y, Lyu Q, et al. Comparison of live-birth defects after luteal-phase ovarian stimulation vs. conventional ovarian stimulation for in vitro fertilization and vitrified embryo transfer cycles. *Fertil Steril* 2015; 103(5): 1194–1201.

70. Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. *Fertil Steril* 2016; 106(7): 1634–1647.

71. Kuang Y, Chen Q, Fu Y, et al. Medroxyprogesterone acetate is an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. *Fertil Steril* 2015; 104(1): 62–70.

72. Rodriguez-Wallberg KA, Eloranta S, Krawiec K, et al. Safety of fertility preservation in breast cancer patients in a register-based matched cohort study. *Breast Cancer Res Treat* 2018; 167(3): 761–769.

73. Velthuis E, Hubbard J, Longobardi S, et al. The frequency of ovarian hyperstimulation syndrome and thromboembolism with originator recombinant human follicitropin alfa (GONAL-f) for medically assisted reproduction: a systematic review. *Adv Ther* 2020; 37(12): 4831–4847.

74. Key NS, Bohlke K and Falanga A. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update summary. *J Oncol Pract* 2019; 15(12): 661–664.

75. De Groot S, Louwé LA, Ramautar A, et al. Effects of controlled ovarian stimulation on toxicity of TAC chemotherapy in early breast cancer patients. *Cancer Manage Res* 2018; 10: 3931–3935.

76. Iorio GG, Rovetto MY, Conforti A, et al. Severe ovarian hyperstimulation syndrome: a prospective controlled comparison of final oocyte maturation in hyper-responder women aged 35–40 years. *Fertil Steril* 2017; 107(6): 1323–1328.

77. Barmat LI, Chantilis SJ, Hurst BS, et al. A randomized prospective trial comparing gonadotropin-releasing hormone (GnRH) antagonist/recombinant follicle-stimulating hormone (rFSH) versus GnRH-agonist/rFSH in women pretreated with oral contraceptives before in vitro fertilization. *Fertil Steril* 2005; 83(2): 321–330.

78. Reddy J, Turan V, Bedoschi G, et al. Triggering final oocyte maturation with gonadotropin-releasing hormone agonist (GnRHα) versus human chorionic gonadotropin (hCG) in breast cancer patients undergoing fertility preservation: an extended experience. *J Assist Reprod Genet* 2014; 31(7): 927–932.

79. ACOG Committee Opinion No. 747: gynecologic issues in children and adolescent cancer patients and survivors. *Obstet Gynecol* 2018; 132(2): e67–e77.
80. Clowse ME, Copland SC, Hsieh TC, et al. Ovarian reserve diminished by oral cyclophosphamide therapy for granulomatosis with polyangiitis (Wegener’s). *Arthritis Care Res* 2011; 63(12): 1777–1781.

81. Henes JC, Henes M, Von Wolff M, et al. Fertility preservation in women with vasculitis: experiences from the FertiPROTEKT network. *Clin Exp Rheumatol* 2012; 30(1 Suppl. 70): S53–S56.

82. Henes M, Henes JC, Neunhoeffer E, et al. Fertility preservation methods in young women with systemic lupus erythematosus prior to cytotoxic therapy: experiences from the FertiPROTEKT network. *Lupus* 2012; 21(9): 953–958.

83. Henes M, Henes JC, Schmalzing M, et al. [Fertility preservation for young patients with autoimmune diseases and the need for cytotoxic treatment. Clinical experiences from interdisciplinary consultation]. *Z Rheumatol* 2011; 70(2): 146–153.

84. Boumpas DT, Vaughan EM, Yarboro CH, et al. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. *Ann Intern Med* 1993; 119(5): 366–369.

85. McDermott EM. Incidence of ovarian failure in systemic lupus erythematosus after treatment with pulse cyclophosphamide. *Ann Rheum Dis* 1996; 55(4): 224–229.