reproductive organs as much as possible for subsequent fertility. Reports are generally limited in size and lack randomized controls. However, they reveal no obvious increased risk of disease recurrence in women treated with fertility sparing approaches. For example, in the two largest published series of 212 women with malignant ovarian germ cell tumors, fertility-sparing surgery with or without chemotherapy did not appear to substantially affect the risk of recurrence compared with historical controls.[124,125]

Other considerations of fertility preservation options in females. The possibility that fertility preservation interventions and/or subsequent pregnancy may increase the risk of cancer recurrence has been most concerning in breast cancer and the gynecologic malignancies. To date, the effect of subsequent pregnancy after breast cancer on prognosis has not been studied prospectively.[126] Several case-control and retrospective cohort studies have not shown a decrement in survival or an increase in risk of recurrence with pregnancy.[127-133] While these data are reassuring, the studies are all limited by significant biases, and concerns remain for some women and their physicians.[20,134] Since breast, endometrial, and ovarian cancer cells have been shown to express GnRH receptors, a GnRH agonist could affect cancer cell proliferation or apoptosis.[135] However, GnRH agonists have also been used as treatments for hormone receptor-positive premenopausal breast tumors, and combined trials of GnRH agonists and chemotherapy are underway.[136] In women with hormone receptor–positive breast cancer who undergo successful fertility preservation treatments, continued menstrual cycling after chemotherapy could theoretically increase relapse rates by interfering with one proposed mechanism of action (ovarian suppression) of adjuvant therapy.[137]

There is concern that instrumentation of the pelvis to perform fertility preservation maneuvers can result in local spread of disease. In one case report, a woman with cervical adenocarcinoma developed an abdominal wall metastasis at the site of trocar insertion for laparoscopy done for ovarian transposition for fertility preservation.[138] It is unclear how often this occurs however.

IV. What Is the Role of the Oncologist in Advising Patients About Fertility Preservation Options?

Discuss infertility as a potential risk of therapy. As with the other potential complications of cancer treatment, oncologists have a responsibility to inform patients about the risks that their cancer treatment will permanently impair fertility. Yet, recent surveys of male and female cancer survivors of reproductive age concur that at least half have no memory of a discussion of fertility at the time of their treatment disposition.[19,20,23,139] The few studies of oncologists' practices of discussing infertility confirm patients' reports. In clinical practice many oncologists do not mention even proven techniques such as sperm banking.[48,140,141] Even when patients do recall infertility discussions, many are dissatisfied with the quality and amount of information provided.[27,141,142] Almost all these studies rely on retrospective self-reports from either oncologists or cancer survivors, and the role of recall bias cannot be ascertained. Patients who participate in survey research are usually self-selected, affluent, well-educated, Caucasians.[19,20] Furthermore, the participation rates by physicians have been very low, often under 33%, so that it is unclear whether the results are generalizable.[48,141]

Studies document many reasons why oncologists do not discuss infertility with the frequency that they discuss other treatment related complications such as neutropenia and cardiopulmonary toxicity. Physicians may be prioritizing discussions about immediate or potentially life-threatening complications instead of discussing infertility. Data regarding the risks of infertility with various chemotherapy regimens are poor or nonexistent. Some physicians do not recognize the importance of fertility to cancer survivors[143] or believe that the cost of fertility preservation interventions is prohibitive. For example, 51% of oncologists in a United States study believed that most men could not afford to bank sperm because of out-of-pocket costs.[141] However, oncologists overestimated these costs[48] and their deterrent effect; in a companion survey of young men, only 7% cited financial reasons for not banking sperm.[19] Oncologists are also less likely to refer patients for sperm banking if the cancer prognosis is poor[141,144] or they believe that patients would not be interested for other reasons. Physicians' emotional discomfort with discussing fertility issues may also play a role[141] along with lack of knowledge and time. While the Panel recommends discussion about risks of treatment-induced infertility at the earliest possible opportunity, the Panel recognizes that raising this issue at the first encounter or at the time of diagnosis may not always be practical or wise. Clinician judgment should be employed in the timing of raising this issue, with the goal of discussion and referral at the earliest possible opportunity.

While professional organizations such as the American Society for Reproductive Medicine and patient advocacy organizations such as Fertile Hope,[145] Lance Armstrong Foundation/Livestrong, and the Susan G. Komen Breast Cancer Foundation do provide patient information, patients may not be aware of these resources and able to access information in a timely fashion when confronted with a new diagnosis of cancer. In addition, a physician's recommendation is a very strong predictor of whether a man banks sperm, almost as influential as the patient's desire for children in the future.[19,146] This finding is reminiscent of the important influence of physician recommendations in promoting smoking cessation and cancer screening[147,148] and suggests that physician encouragement affects patient interest in fertility preservation options. An algorithm for triaging fertility preservation referrals is presented in Figure 1, and suggested talking points are illustrated in Table 3. Ideally, after referral, the decision about who is an appropriate candidate to attempt specific fertility preservation techniques could be rendered by a team including a medical oncologist, reproductive endocrinologist, and a psychosocial provider, all guided by written protocols which can be shared with patients.[149] Patients, and parents of minors, should not be provided with unrealistic expectations about their cancer prognoses, the success rates of fertility preservation interventions or the cost of attempting to preserve fertility, and the option of declining fertility preservation interventions should also be discussed. Potential legal issues, such as ownership of embryos and reproductive tissue in the event of a patient's death, divorce or incapacity, should also be discussed by the reproductive specialist.

Answer basic questions about whether fertility preservation options decrease the chance of successful cancer treatment, increase the risk of maternal or perinatal complications, or compromise the health of offspring. Specific risks of fertility preservation options are discussed above in the sections on male and female considerations. Although studies are generally small and either not prospective or have short follow-up, there is no evidence that currently used fertility preservation options directly compromise the success of cancer therapy. There may of course be individual considerations, such as if chemotherapy is delayed to give time to pursue fertility preservation options or in the case of hormonally sensitive tumors.

There have been many published reports regarding parental outcome after interventions to spare fertility through cancer treatment and/or pregnancy following cancer. However, available studies are generally limited to case reports and small series. The few larger studies addressing these issues have generally been comprised of heterogeneous patient populations, retrospective in nature, with relatively short-term follow-up, and lacking randomized controls. Available data are reassuring, however, in that there is no clear increased risk to a survivor's health from available interventions to preserve fertility or from subsequent pregnancy, beyond that of normal populations with similar comorbidities.

In light of the long-term organ toxicity that may result from cancer and cancer therapy, pregnancy after cancer treatment may be complicated by an increased risk of organ impairment, especially of the heart, lungs, and uterus. For example, there is evidence that pregnancy may increase the risk of worsening cardiac ejection fraction in women treated with doxorubicin for childhood cancer,[150] and uterine or total-body irradiation appears to increase the risk of miscarriage, prematurity and low birth weight.[151-154] While several studies have revealed no evidence that use of cryopreserved sperm regardless of mode of extraction or fertilization technique has a detrimental effect on perinatal health of offspring or mother, the available data regarding the effects of female fertility sparing interventions on maternal or fetal perinatal health are limited. The major risk that has been recognized appears to be an increased risk of cervical incompetence, miscarriage, prematurity and low birth weight in women with lower gynecologic malignancies who have undergone conservative surgery such as trachelectomy for fertility preservation,[122,155-157] and the health risks associated with a higher rate of multiple births after assisted reproductive technology. Short and long-term follow-up following fertility sparing interventions for women with cancer is warranted. At the present time, in light of concerns, women with a history of cancer and cancer treatment should be considered high risk for perinatal complications and would be prudent to seek specialized perinatal care.

Aside from hereditary genetic syndromes, however, there is scant evidence that a history of cancer, cancer therapy, or fertility interventions increases the risk of problems in the progeny. Available studies including large registry studies have revealed no increased risk of genetic abnormalities, birth defects, or cancers, aside from hereditary syndromes, in the children of cancer survivors.[72,152,158-161] Data regarding the effects of interventions to spare parental fertility on the health of the progeny are limited to case reports and small series with relatively short follow-up. At present, there does not appear to be a clear detrimental effect from any of the available fertility sparing interventions. However, patients should be encouraged to participate in registries and clinical studies as available to define further the safety of fertility preservation interventions and strategies.

As needed, refer patients to reproductive specialists and psychosocial providers. Oncologists should refer interested and appropriate patients to reproductive specialists as soon as possible. Some methods of fertility preservation in females require timing with the menstrual cycle, so expeditious referrals are suggested to avoid missing opportunities. As long as the oncologist presents the options in enough detail for the patient to decide whether to seek a consultation, the detailed counseling could be done by an infertility specialist. However, oncologists' input will still be invaluable to help guide patients as they think about how to prioritize fertility preservation in the context of their cancer treatment plan. When referring patients, oncologists should remember that many methods are still investigational. Ethical guidelines published by the American Society for Reproductive Medicine states that fertility preservation involving oocyte, ovarian and testicular harvesting for freezing should be performed only in specialized centers working with IRB-approved consents.[162] In addition, the experience of the infertility specialist in working with cancer patients should also be considered.

One option the oncologist should routinely offer is a referral for psychological counseling when a man or woman has moderate to severe distress about potential infertility. Research on infertility patients has shown that structured, cognitive-behavioral counseling can reduce anxiety and depression.[163-165] The American Society for Reproductive Medicine has both a Fertility Preservation Special Interest Group (http://www.asrm.org/Professionals/PG-SIG-Affiliated_Soc/fpsig/fpsig_index.html) and a Mental Health Professional Group (http://www.asrm.org/Professionals/PG-SIG-Affiliated_Soc/MHPG/index.html).

Previous Consensus Statements

Consensus statements have also been developed by some professional societies, including the British Fertility Society (http://www.britishfertilitysociety.org.uk/practicepolicy/documents/fccpaper.pdf),[166] the European Society of Human Reproduction and Embryology (ESHRE) Task Force (http://www.eshre.com), and the American Society for Reproductive Medicine.[162,167] The Panel has evaluated the Guidelines produced by reproductive specialist societies and found them to be consistent with the ASCO guidelines.

Interpretive Summary

Fertility preservation is often possible in people undergoing treatment for cancer. Broader application of fertility preservation methods is limited by several factors: lack of knowledge about the risk of infertility with current cancer treatments, failure to discuss and consider options before treatment, lack of insurance coverage for most procedures with consequent high out of pocket costs, and the investigational status of many fertility preservation methods. The Panel recommends that oncologists discuss at the earliest opportunity the possibility of infertility as a risk of cancer treatment, recognizing that in many cases, adequate data are not available to provide accurate predictions for any one individual. For patients at risk for infertility who are interested in evaluating their options for fertility preservation, referral to appropriate specialists as early as possible is recommended. People attempting fertility preservation in the context of cancer treatment are encouraged to enroll in clinical trials that will advance the state of knowledge. Figure 1 and Table 3 provide additional guidance to oncologists in initial discussions. Supplementary materials available for public use such as a summary of guidelines, slide set, and patient information may be found on ASCO's Web site (http://www.asco.org).

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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ERRATA

The June 20, 2006, ASCO special article by Lee et al entitled, "American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients" (J Clin Oncol 24:2917-2931, 2006) contained an error. In Table 1, the dosage for busulfan was given as 600 mg/kg, while it should have been 600 mg/m^2. This was due to a misprint in the original textbook where the data were taken.

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2006.11.904

The November 1, 2006, article by Harvey et al entitled, "Phase III Trial Comparing Three Doses of Docetaxel for Second-Line Treatment of Advanced Breast Cancer" (J Clin Oncol 24:4963-4970, 2006) contained an error.

In the Introduction section, the third sentence of the first paragraph was given as:

"Phase III trials showed higher response rates with second-line single-agent docetaxel compared with doxorubicin (47.8% *v* 33.3%, respectively; $P = .008$),[3] mitomycin plus vinblastine (30.0% *v* 11.6%, respectively; $P < .0001$),[4] or methotrexate plus fluorouracil (42% *v* 21%, respectively; $P < .001$)[5] but not compared with fluorouracil plus vinorelbine (38.9% *v* 43.0%, respectively; $P = .69$)[6] and paclitaxel (25.0% *v* 32.0%, respectively; $P = .1$).[7]"

While it should have read:

"Phase III trials showed higher response rates with second-line single-agent docetaxel compared with doxorubicin (47.8% *v* 33.3%, respectively; $P = .008$),[3] mitomycin plus vinblastine (30.0% *v* 11.6%, respectively; $P < .0001$),[4] or methotrexate plus fluorouracil (42% *v* 21%, respectively; $P < .001$)[5] but not compared with fluorouracil plus vinorelbine (**43.0% *v* 38.9%**, respectively; $P = .69$)[6] and paclitaxel (**32.0% *v* 25.0%**, respectively; $P = .1$).[7]"

The online version has been corrected in departure from the print.

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FERTILITY PRESERVATION

Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer

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Abstract Fertility issues should be addressed to all patients in reproductive age before cancer treatment. In men, cryopreservation of sperm should be offered to all cancer patients in reproductive age regardless of the risk of gonadal failure. In women, the recommendation of fertility preservation should be individualized based on multiple factors such as the urgency of treatment, the age of the patient, the marital status, the regimen and dosage of cancer treatment.

Keywords Fertility preservation · Cancer · Lymphoma · Leukemia · Breast cancer · Chemotherapy · Ovarian tissue cryopreservation · Oocyte cryopreservation · Primary ovarian insufficiency · Cancer survival · Gonadal failure · GnRH agonist · Fertility

Fertility issues should be addressed to all patients in reproductive age before cancer treatment. In cases where the

Capsule The ISFP Practice committee developed recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer.

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patient is a minor, it is recommended to obtain assent from a patient in addition to signed consent from the parents. In men, cryopreservation of sperm should be offered to all cancer patients in reproductive age regardless of the risk of gonadal failure. In women, the recommendation of fertility preservation should be individualized based on multiple factors such as the urgency of treatment, the age of the patient, the marital status, the regimen and dosage of cancer treatment. If the risk of gonadal failure is very low (such as ABVD), fertility preservation may not be required. On the other hand, the patient who undergoes hematopoietic stem cell transplant (HSCT) should strongly consider fertility preservation. In principle, embryo cryopreservation or oocyte cryopresevtion is recommended as a fertility preservation option, if there is enough time for ovarian stimulation before initiation of cancer therapy. If cancer treatment cannot be delayed or ovarian stimulation is contraindicated, ovarian tissue cryopreservation should be the first option of fertility preservation.

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Incidence and survival (cited from http://seer.cancer.gov)

1) Lymphoma

Hodgkin lymphoma (HL): It is estimated that 4,010 women are newly diagnosed with HL in 2011. Among those, approximately 1,760 are under age 34. Approximately, 12.3 % were under age 20, 32 % between 20–34, and 15.8 % between 35–44. (2004–2008). The overall 5-year relative survival for 2001–2007 was 84 %. Currently, 5-year relative survival for women under age 49 is 90-95 %.

Non Hodgkin lymphoma (NHL): It is estimated that 30,300 women are diagnosed with NHL in 2011. Among those, approximately 1,670 are under age 34. Approximately 1.7 % were diagnosed under age 20, 3.8 % between 20–34, and 6.8 % between 35 and 44. The overall 5-year relative survival for 2001–2007 was 67 %. Currently, 5-year relative survival for women under age 49 is 80-85 %.

2) Leukemia

Acute lymphocytic leukemia (ALL): It is estimated that 2,410 women are newly diagnosed with ALL in 2011. Among those, approximately 1,750 are under age 34. Approximately, 60.3 % were under age 20, 10.3 % between 20–34, and 5.9 % between 35–44. (2004–2008). The overall 5-year relative survival for 2001–2007 was 64 %.

Chronic lymphocytic leukemia (CLL): The incidence is about 6,000/year, but it is very rare disease in women with age under 34 (0.3 %). The overall 5-year relative survival for 2001–2007 was 78 %.

Acute myeloid leukemia (AML): It is estimated that 6,120 women are diagnosed with AML in 2011. Among those, approximately 810 are under age 34. Approximately, 6.1 % were under age 20, 6.6 % between 20–34, and 6.6 % between 35–44. (2004–2008). The overall 5-year relative survival for 2001–2007 was 23 %.

Chronic myeloid leukemia (CML): It is estimated that 2,150 women are newly diagnosed with HL in 2011. Among those, approximately 220 are under age 34. Approximately, 2.6 % were under age 20, 7.7 % between 20–34, and 9.9 % between 35–44. (2004–2008). The overall 5-year relative survival for 2001–2007 was 57 %.

3) Breast Cancer

It is estimated that 230,480 women are newly diagnosed with breast cancer in 2011. Among those, approximately 11,000 are under age 40. From 2004–2008, 0 % were diagnosed under age 20, 1.9 % between 20–34, and

10.2 % between 35–44. The overall 5-year relative survival is approximately 90 %. In US there are approximately 2.6 million women alive with a history of breast cancer.

Treatment and its effects on gonadal function

1) Lymphoma

Chemotherapy induced gonadal dysfunction depends on the age at first treatment and the treatment protocols. The risk of gonadal dysfunction after cancer treatment is low in pediatric population. NHL patients treated with chemotherapy (except HSCT) have very low risk of developing primary ovarian insufficiency (POI). Here are the common treatment regimens for HL and NHL.

HL

ABVD (adriamycin, bleomycin, vinblastine, dacarbazine): POI rates are less than 10 % in the reproductive age; *BEACOPP* (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, predisone): POI rates are around 50 % in those under 30 years; *MOPP* (chlormethamine, oncovine: procarbazine, prednisone): POI rates are 20- 50 % in women in reproductive age; *HSCT*: POI rates are 70-100 %, post-treatment parenthood rates are as low as 3-8 % [1].

NHL

CHOP (cyclophosphamide, doxorubicin, vincristine, predisone): POI rates are around 5 %, pregnancy rates after treatment are 50 % [2]; *Hyper-CVAD* (cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, methotrexate): POI rates are 14 %, pregnancy rates after treatment are 43 % [3]; *HSCT*: POI rates are 70-100 % [1].

2) Leukemia

The risk of infertility in patients with ALL or AML (unless treated with HSCT) is very low as contemporary treatment protocols entails lower doses of alkylating agents or are devoid of alkylating agents. CML can be treated with tyrosin kinase inhibitors such as imatinib or rituximab. Tyrosin kinase inhibitors may not impair fertility in humans, but there is insufficient data on these medications on reproductive potential. Of note, tyrosin kinases are important for follicle growth and development.

3) Breast cancer

Adjuvant chemotherapy after surgery or neo-adjuvant chemotherapy before surgery has an important role in breast cancer treatment, as it is likely to reduce the risk of recurrence and death from breast cancer by a relative factor of 50 % or more [4]. The primary factors affecting chemotherapy induced gonadotoxicity are age of the patient, and dose and number of cycles of the alkylating agent received. For example, the risk of amenorrhea after six cycle of *CMF* (cyclophosphamide, methotrexate, fluorouracil) or four cycyles of *AC* (anthracycline, cyclophosphamide) is 33 %, on the other hand, 50-65 % of patients will experience amenorrhea after treatment with six cycles of *FEC* (fluorouracil, epirubicin, cyclophosphamide), or *FAC* (fluorouracil, doxorubicin, cyclophosphamide), or four cycles of *AC* followed by four of *docetaxel* [4].

Recommendations for fertility preservation

All patients who desire to preserve fertility should be counseled and informed about currently available fertility preservation options by fertility specialists. Recommendations should be individualized and should not violate the ethical principles. In general, fertility preservation before cancer treatment is strongly recommended if the chance of losing fertility is over 30 % with cancer therapy. In pediatric patients, the risk of gonadal failure with chemotherapy is very low in the absence of HSCT.

1) Lymphoma

Post-pubertal male: Cryopreservation of spermatozoa. GnRHa co-treatment is not recommended in male.

Pre-pubertal male: No good option. Cryopreservation of testicular tissue may be available in some centers as a strictly experimental procedure.

Post-pubertal female: Cryopreservation of embryos or cryopreservation of oocytes is recommended if cancer treatment can be delayed. However, immediate treatment is required in most of lymphoma patients and thus cryopreservation of ovarian tissue should be considered as a fertility preservation option. Alternatively, immature oocyte retrieval followed by IVM and cryopreservation of oocytes or embryos can be considered. The protective effect of GnRHa is questionable and controversial. However, GnRHa co-treatment can be considered for female patients undergoing chemotherapy (not for HSCT) if there is no other option.

Pre-pubertal female: Ovarian tissue cryopreservation, if the risk of ovarian failure after cancer treatment is high enough to justify the procedure.

2) Leukemia

Post-pubertal male: cryopreservation of spermatozoa.

Pre-pubertal male: no currently available option.

Post-pubertal female: No ideal option to date. However, cryopreservation of ovarian tissue should be considered before HSCT. Any harvested tissue from leukemia patients should not be used for auto-transplantation because of high risk of cancer cell reintroduction. Alternatively, immature

oocyte retrieval followed by IVM and cryopreservation of oocytes or embryos can be considered.

Pre-pubertal female: Ovarian tissue cryopreservation before HSCT. Any harvested tissue from leukemia patients should not be used for auto-transplantation because of high risk of cancer cell reintroduction. In the absence of HSCT, fertility preservation before chemotherapy is not necessary.

3) Breast cancer

It is recommended that fertility preservation consultation is arranged at the time of initial diagnosis. In many cases, young breast cancer patients require adjuvant chemotherapy after surgery (mastectomy or lumpectomy). The best time for fertility preservation is after surgery and before adjuvant therapy. Cryopreservation of embryos or cryopreservation of oocytes is recommended as a fertility preservation option before chemotherapy. As cryopreservation of embryos or oocytes requires controlled ovarian stimulation (COS), the risk of increased peak estradiol levels with COS in breast cancer patients (especially with ER+tumor) should be discussed before the procedure. The COS strategy using tamoxifen or letrozole in conjunction with gonadotropin may be safer for women with ER+tumor. For women who require urgent cancer treatment such as neo-adjuvant chemotherapy, cryopreservation of ovarian tissue should be considered. Alternatively, immature oocyte retrieval followed by IVM and cryopreservation of oocytes or embryos can be considered.

(Addendum)

Criteria for ovarian tissue banking (by S. Samuel Kim)

1) Age: under 37 years (may be individualized based on the status of ovarian reserve)
2) Ovarian function: premenopausal by FSH, antral follicle count (AFC) or AMH
3) Communication with oncologists: cancer treatment plan, prognosis
4) When embryo freezing or oocyte freezing is not indicated: delaying cancer treatment is not acceptable, hormonal stimulation is not permitted, ART is not allowed.
5) Prepubertal girls who do not have any other options
6) High risk for POF (when significant loss of ovarian follicles is anticipated with cancer therapy)
7) Informed consent from adult patients
8) Informed consent from parents/guardians as well as informed assent from minors, if the patient is less than 18 years
9) Physically and mentally healthy enough for surgery
10) Desires to have a child in the future (preferably before the age 50)
11) Thorough patient counseling: currently available fertility preservation options including embryo and oocyte cryopreservation, how to use cryobanked ovarian tissue for fertility restoration
12) Should understand experimental nature and potential risks of cancer cell transmission.

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FERTILITY PRESERVATION

Fertility preservation in young women with breast cancer

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on behalf of ISFP Practice Committee**

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Abstract When a young woman is diagnosed with breast cancer, there is often a sense of urgency by the patient and her providers to initiate treatment. This article provides guidelines for incorporating the discussion of fertility preservation with newly diagnosed young women with breast cancer.

Keywords Fertility preservation · Breast cancer · Chemotherapy · Cancer · Survivorship · Oocyte cryopreservation · Embryo cryopreservation · Ovarian tissue cryopreservation · Ovarian stimulation · Infertility

Capsule Guidelines for Fertility Preservation in young women with breast cancer.

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Background

Breast cancer is the most common cancer in women with over 230,000 new diagnosis of invasive breast cancer per year in the United States [1]. With more than 5–7 % of new breast cancers diagnosed under age 40 [2, 3], we have a growing need to develop best practices for addressing fertility preservation in this population of young women. As a result of early detection and targeted therapies, many of these women will survive, resulting in the need to educate patients and providers about the late and long-term effects of cancer and its treatment including issues related to fertility.

It has previously been reported that female cancer survivors routinely do not receive counseling about fertility preservation prior to initiating their cancer treatment and this has resulted in many experiencing long-term regret and worse overall quality of life [4].

The challenge is incorporating this discussion into an already intense, complicated and emotional time for young woman newly diagnosed with breast cancer. In 2006, the American Society of Clinical Oncology (ASCO) [5] published recommendations on fertility preservation and included this statement, "As part of education and informed consent prior to cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists". However, it was subsequently reported that fertility preservation is not a priority for oncologists [6]. This may be due to a lack of awareness on options for fertility preservation, access to resources and fertility specialists, and insurance reimbursement concerns.

With professional recommendations from ASCO, the American Society of Reproductive Medicine, the International Society for Fertility Preservation, web-based resources, and

Table 1 Methods for fertility preservation in young women with breast cancer

Method	Description
Embryo Cryopreservation	ovarian stimulation, harvesting eggs, in vitro fertilization, and freezing of embryos
Oocyte Cryopreservation	ovarian stimulation, harvesting eggs, and freezing of mature eggs
Ovarian Tissue Cryopreservation	harvesting ovarian tissue surgically, freezing of ovarian tissue
Ovarian Suppression with GnRHa	administration of GnRHa

publications highlighting research and practice guidelines, there are now tools available for improving access to education and resources.

What are the goals of fertility preservation?

It is important to understand even if cyclic menses resumes, fertility may be compromised post treatment. Therefore, it is essential for patients to receive education on topics related to methods for preserving fertility, based on many factors including age, ovarian reserve, treatment, time, and partner availability. Part of the informed decision making process for newly diagnosed patients include the late and long-term side effects of their recommended treatment and impact on fertility and options for preservation (Table 1) should be a standard part of that discussion.

Recent publications have highlighted the incorporation of fertility preservation into practice for young women newly diagnosed with breast cancer. These algorithms demonstrate the need for informed decision making from the time of diagnosis depending on breast cancer subtype and treatment regimen [7], adequate ovarian reserve [8], adequate time prior to initiating treatment and access to self or donor egg and partner or donor sperm [9], along with the patient's age, prognosis, the toxicity of the treatment regimen recommended, and taking into account the patient's individual choice to undergo fertility preservation [10]. These algorithms provide a useful reference for busy oncologists and their treatment team. In addition, consultation post-adjuvant treatment may also be an opportunity for young women with breast cancer to discuss their potential ovarian reserve and should be considered in women who did not undergo pre-treatment consultation. Figures 1 and 2 highlight the incorporation of discussions around fertility preservation at the time of diagnosis or in post-treatment care.

When to refer the patient?

In an ideal situation, a fertility specialist should counsel women at the time of a cancer diagnosis. If a woman is considering future fertility, an immediate referral to a fertility specialist should be made prior to the initiation of cancer treatment. Ovarian stimulation for 2–3 weeks is usually required for oocyte cryopreservation and embryo cryopreservation. For women who require immediate cancer treatment (such as those who require neo-adjuvant chemotherapy) or those who are not good candidates for ovarian stimulation, ovarian tissue cryopreservation may be an option. The best time for fertility preservation is after surgery and before adjuvant chemotherapy.

Fig. 1 Young women with breast cancer at the time of diagnosis

Fig. 2 Young women with breast cancer post-treatment

What to consider for fertility preservation?

The rate of ovarian failure following breast cancer treatment is dependent on multiple factors including the age of the patient, ovarian reserve, dosage and type of chemotherapy, and number of cycles of chemotherapy, and ranges from 18–61 %. For example, if the age of the patients is over 37y/o with a low ovarian reserve, the chance of preserving fertility is low. In that case, the risk/benefit ratio may not favor fertility preservation. As a rule of thumb, ovarian tissue cryopreservation is recommended if the patient requires immediate chemotherapy or has rapidly growing estrogen dependent tumor. Otherwise, embryo cryopreservation (for those who have a partner) or oocyte cryopreservation should be considered as the first line of strategy. The risk of controlled ovarian stimulation in breast cancer patients (especially ER+) is unknown. Although short-term exposure to high concentrations of estrogen may not have adverse effects on tumor growth, it is recommended to avoid excess exposure to high concentrations of estrogen during ovarian stimulation in breast cancer patients. To minimize this potential risk with super-physiological levels of serum estrogen used with controlled ovarian stimulation, it is sensible to use modified gonadotropin protocol in combination with letrozole or tamoxifen.

Implications for clinical practice

Fertility preservation is one area in which cancer service providers need to focus on developing more formal methods to inform young women with breast cancer about the impact of cancer on fertility and options for fertility preservation. Access to quality patient education, stream-lined referrals to fertility experts, and providing continuing staff education can be the initial steps in providing this level of care to young women with breast cancer. In addition, many cancer care providers have access to cancer survivorship resources, including navigators, who are well suited to facilitate education and access to resources for many community and academic cancer care practice settings. One of the challenges in educating patients on fertility preservation is the lack of adequate community resources for a timely referral. Therefore, this requires an established relationship with a fertility clinic to ensure timely consultation with young women with breast cancer interested in fertility preservation. This means not waiting weeks or months for an appointment, but scheduling within a few days. Establishing this type of network will facilitate a more efficient process and will prevent unnecessary treatment delays.

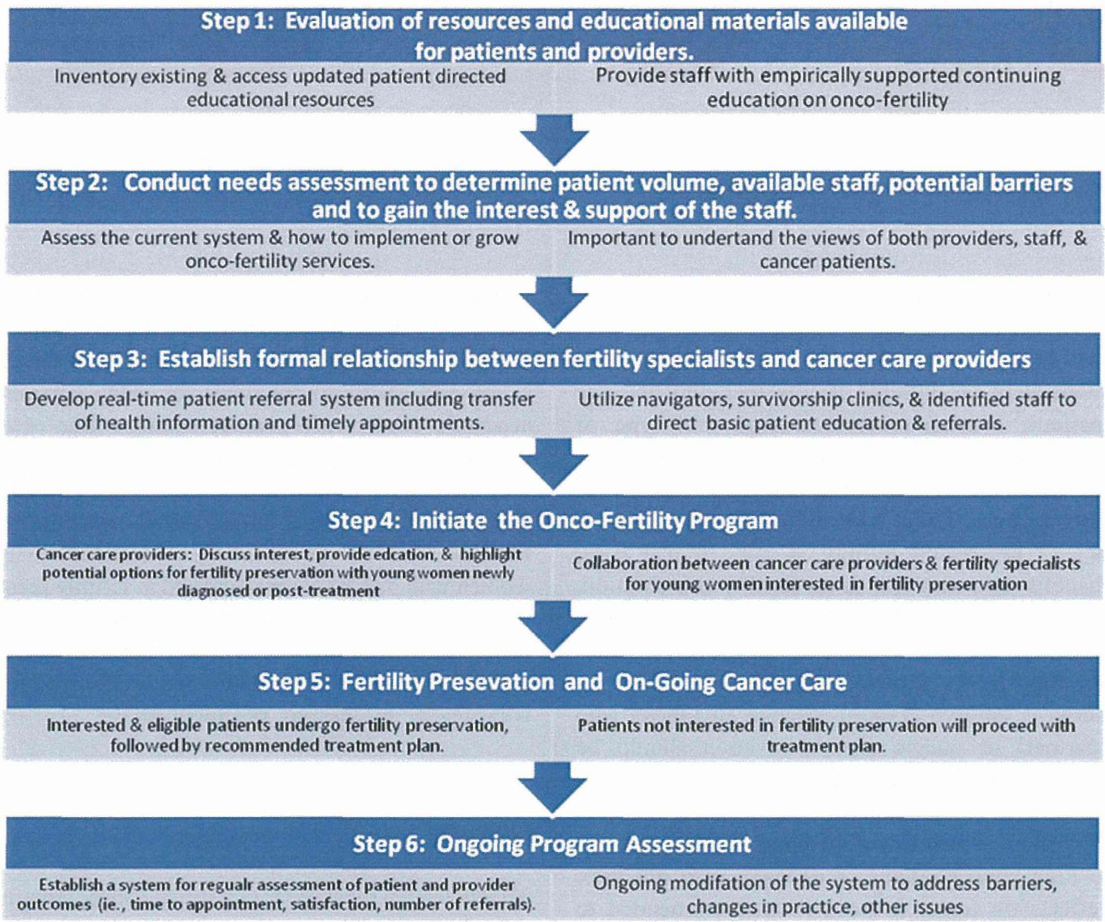
Summary

Young women diagnosed with breast cancer require a multidisciplinary approach to treatment planning, which includes access to information and resources to address fertility. Informed decision making regarding treatment options includes understanding the late and long-term effects of treatment and loss of fertility along with options for maintaining fertility should be a standard part of the discussion. The development of stream-lined referrals to qualified reproductive specialists is key to this process working due the sense of urgency by both the providers and patients to initiate the treatment process.

Understanding the needs of young women with breast cancer, making practice adjustments, and establishing relationships between oncology and reproductive specialists will make this process more efficient. Utilizing breast cancer survivorship programs and patient navigators may also help facilitate access to fertility preservation services and improve the experience of both patients and providers.

Addendum

Fertility Preservation: Recommendations for Program Development and Patient Directed Care



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GYNECOLOGIC ONCOLOGY

Fertility preservation in women—a practical guide to preservation techniques and therapeutic strategies in breast cancer, Hodgkin's lymphoma and borderline ovarian tumours by the fertility preservation network FertiPROTEKT

Michael von Wolff · Markus Montag · Ralf Dittrich · Dominik Denschlag · Frank Nawroth · Barbara Lawrenz

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Abstract
Purpose Fertility preservation methods are playing an increasing role in women up to the age of 40 years because of rising survival rates in those affected by cancer. However, balanced practical recommendations concerning all relevant fertility preservation, to support doctors in counselling and treating patients, are still rare.
Methods These recommendations were prepared by the network FertiPROTEKT (http://www.fertiprotect.eu), a collaboration of around 70 centres in Germany, Switzerland and Austria. The recommendations were developed by specialists in reproductive medicine, reproductive biology and oncology, which gave a comprehensive overview of all named techniques as well as their benefits and risks. Furthermore, practice-orientated recommendations for the individual use of fertility preservation methods for various indications such as breast cancer, Hodgkin's lymphoma and borderline ovarian tumours are given.
Results Various options such as ovarian stimulation and cryopreservation of unfertilised or fertilised oocytes, cryopreservation and transplantation of ovarian tissue, GnRH-agonist administration and transposition of the ovaries can be offered. All the techniques can be performed alone or in combination within a maximum of 2 weeks with low risk and different success rates.
Conclusions Fertility preservation in women has become an option with realistic chances to become pregnant after cytotoxic therapies. The information provided allows a well balanced and realistic counselling and treatment.

Keywords Cancer · Fertility preservation · Oocytes · Ovarian tissue · Cryopreservation · GnRH agonists

In the name of all members of the network FertiPROTEKT.

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Introduction

Increasing survival rates in patients affected by oncological disease and advances in reproductive medicine have led to the development and increasing use of various fertility preservation techniques. Over the last few years, several techniques have been particularly favoured despite insufficient data and others have not been recommended. Meanwhile however, improving data and optimisation of the available techniques have allowed a realistic portrayal of the efficacy and risks of the most commonly used methods as well as recommendations for the use of the techniques alone or in combination. Many recommendations can be found in the literature on fertility protection; however, there is no current publication which objectively considers all the established techniques [1, 2]. Furthermore,

most work focuses only on the techniques as such or on their relevance in various disease states without considering both aspects and connecting them with one another. Recommendations from the FertiPROTEKT Network [3], described below, were formulated for clinical practice in such a way that not only the techniques are objectively represented, but also recommendations for their use in clinical practice for the commonest oncological diseases are also given. The recommendations, developed by specialists in reproductive medicine and reproductive biologists as well as oncologists, avoid a detailed listing of all the underlying work, and rather summarise their key messages and reinforce them with information from current publications or review articles. This concept allows a comprehensive and practice-orientated description of a complex topic and an application for specialists in reproductive medicine and oncologists.

The general recommendations for the counselling on and use of fertility preservation methods are presented first in the following review (Fig. 1), followed by the techniques, a description of their efficacy and risks, and finally a discussion of their use in breast cancer, Hodgkin's lymphoma and borderline ovarian tumours (Tables 1, 2, 3 and 4).

General recommendations

- All women between the ages of ca. 14 and 40 years who receive chemotherapy which could lead to a significant chance of disruption to their ovarian function should be counselled by a doctor trained in reproductive medicine on fertility preservation methods, in agreement with the responsible oncologists.
- All applicable methods should be included in the counselling.
- All counselling and treatments, including complications which occur, should be documented in the records.
- Performing fertility preservation techniques, i.e. due to the postponement of a cytotoxic therapy, must not affect the efficacy of the oncological regimen.

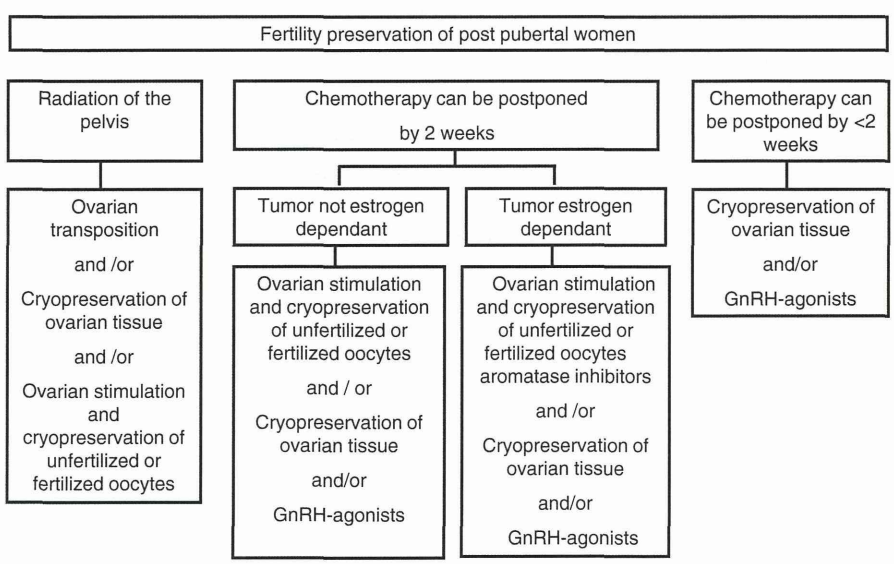

Fig. 1 Simplified regimen for the use of fertility preservation procedures. It should be noted that the choice of method also depends on the patient's age, their prognosis, the toxicity of the chemotherapy and the individual wishes of the patient and their partner

Table 1 Breast cancer: chemotherapy-associated amenorrhoea rate (A = doxorubicin; C = cyclophosphamide; E = epirubicin; F = 5-fluorouraci; M = methotrexate (modified according to [39])

Age (years)	Chemotherapy	Rate of amenorrhoea (%)
>40	6 × CMF, 6 × FEC, 6 × FAC	> 80 (High risk)
<40	High-dose EC	
30–39	6 × CMF, 6 × FEC, 6 × FAC	20–80 (Moderate risk)
>40	4 × AC	
<30	6 × CMF, 6 × FEC, 6 × FAC	<20 (Low risk)
<40	4 × AC	

Insufficient data: taxanes, monoclonal antibodies, avastin® (bevacizumab), lapatinib, herceptin® (trastuzumab) and gemzar® (gemcitabine)

Table 2 Breast cancer: fertility preservation procedures depending on hormone receptor status and oncological treatment plan in women with a medium to high risk of amenorrhoea

	Adjuvant situation (fertility preservation after surgery and before chemotherapy)		Neoadjuvant situation (fertility preservation before chemotherapy and before surgery)	
	Hormone receptor negative	Hormone receptor positive	Hormone receptor negative	Hormone receptor positive
Hormonal stimulation and cryopreservation of unfertilised and fertilised oocytes	+	(+) (± combination with letrozole)	(+) (± combination with letrozole)	–
Cryopreservation of ovarian tissue	+	+	+	+
Combination of hormonal stimulation and cryopreservation of oocytes and ovarian tissue	+	(+) (± combination with letrozole)	(+) (± combination with letrozole)	–
GnRH-agonists	+	(–)	+	(–)

Table 3 Hodgkin's lymphoma—Chemotherapy-associated amenorrhoea rate (A = adriamycin; B = bleomycin; C = cyclophosphamide; E = etoposide; O = oncovin; P = procarbazine and prednisone V = vinblastine) modified according to [40])

Age (years)	Chemotherapy	Rate of amenorrhoea (%)
≥30	2 × ABVD (HD 7, arm B)	0
<30		5.6
≥30	2 × COPP/ABVD (HD 8)	12.2
<30		3.5
≥30	4 × COPP/ABVD (HD 9 A)	53.3
<30		23.5
≥30	8 × BEACOPP (HD 9, arm B)	42.1
<30		11.8
≥30	8 BEACOPP escalated (HD 9, Arm C)	70.4
<30		40.4

Fertility protection techniques

Ovarian stimulation and cryopreservation of unfertilised and fertilised oocytes

Indications and requirements

- Postmenarchal women up to the age of 40 years with a sufficient ovarian reserve, who receive chemotherapy or another treatment which could lead to a significant chance of premature ovarian insufficiency or loss of ovarian function
- The time until the start of chemotherapy is at least 2 weeks

Description of ovarian stimulation

- Starting stimulation during menstruation: perform a classic GnRH-antagonist protocol, as this is associated with a lower risk of ovarian hyperstimulation syndrome (OHSS) [4]
- Starting stimulation in other cycle phases: GnRH-antagonist immediately and simultaneously start administering recombinant follicle stimulating hormone (FSH) [5]
- Induction of ovulation in the case of impending OHSS with triptorelin 0.2 mg [6]
- In the case of estrogen-dependent tumours, stimulation can be combined with letrozole 5 mg daily [7], which is administered at the same time as the gonadotrophin.

Description of cryopreservation of fertilised and unfertilised oocytes

To reduce the risk of fertilisation failure, intracytoplasmic sperm injection (ICSI) should be considered, with only justifiable exceptions, and independent of the spermiogram.

Unfertilised oocytes are preserved by slow freezing or vitrification. According to the current data, vitrification appears to be more effective [8, 9]. Cryopreservation of unfertilised oocytes by vitrification should only be performed when internal controls have shown that there is technique proficiency.

Success rates

On average, 11.6 oocytes from 205 follicle punctures were collected in the FertiPROTEKT Network (STD: ±7.7; 25% quartile: $n = 6$; 75% quartile: $n = 15$). The fertilisation

Table 4 Hodgkin's lymphoma: Fertility preservation procedures for the chemotherapy regimens currently performed by the German Hodgkin's Society [36]

	ABVD	BEACOPP	BEACOPP escalated
Hormonal stimulation and cryopreservation of unfertilised and fertilised oocytes	−	+	+
Cryopreservation of ovarian tissue	−	+	+
Combination of hormonal stimulation and cryopreservation of oocytes and ovarian tissue	−	+	+
GnRH-agonists	(+)	+	+

rate was 61.3%. If fertilisation was carried out on all oocytes, the following number of fertilised oocytes resulted in each age group: 18–25 years; 8.5 oocytes, 26–30 years; 7.3 oocytes, 31–35 years; 6.1 oocytes, 36–40 years; 5.1 oocytes [10, 11].

After cryopreservation of unfertilised oocytes, each thawed, surviving egg cell had an implantation potential of 6–8%. This applies to vitrification as well as to the new and adapted slow egg freezing protocols [9].

Risks

Significant risks are ovarian hyperstimulation syndrome (OHSS) or the collection of immature oocytes with a low fertilisation potential. According to the complication records from FertiPROTEKT from 205 follicle punctures performed, no oocytes could be preserved in three cases. Significant overstimulation did not occur [11].

Cryopreservation of ovarian tissue

Indications and requirements

- Girls and women up to the age of ca. 35–37 years and with an age-appropriate ovarian reserve who receive chemotherapy or another treatment which could lead to a significant chance of premature ovarian insufficiency
- With oncological disease: exclusion of ovarian metastases using appropriate diagnostic imaging
- Exclusion of an oncological disease which is associated with a high risk of ovarian metastases (haematological neoplasias, metastatic breast cancer, ovarian cancer, etc.)
- The time until the start of chemotherapy is at least 3 days
- Low risk intubation of the patient and surgery is possible (caution: mediastinal tumours in patients with Hodgkin's lymphoma)

Description

Removal of ovarian tissue: removal of the ovarian tissue is performed laparoscopically where possible. The amount of tissue removed depends on the expected probability of losing all egg cells. Histological examination of a reference biopsy (to exclude tumour cells, proof of follicle presence) is necessary.

Transport from operating theatre to laboratory: rapid transport of the removed tissue is performed in transport medium on ice. However, transport from the place of removal to the tissue bank is also possible over a longer period of time (<20 h) [12, 13].

Cryopreservation: the most efficient method of cryopreservation is currently the slow freezing technique [14]. Testing the effectiveness of the freezing method is recommended, for example by transplanting thawed tissue into immunodeficient mice.

Retransplantation: orthotopical transplantation has—according to the current literature—the greatest chance of success [15]. It is still unclear which exact site should be used for the transplant, whether a spontaneous pregnancy or IVF should be given priority and how the patient should be treated after the transplant. The transplantation should in most cases be performed 2 years after the end of treatment at the earliest, in agreement with the responsible oncologists, when the risk of relapse has significantly decreased.

Success rates

Fourteen births have been reported up to now. Spontaneous pregnancies occurred as well as pregnancies after IVF treatment. Successful teams [16] have achieved a pregnancy rate of ca. 30% per transplantation up to now, although the birth rate is lower. However, other teams report lower success rates, so it can be assumed that the success depends on the correct indication for cryopreservation, the age of the patient, the freezing technique and the transplantation technique.

A maximum age limit of ca. 35–37 years is recommended for the cryopreservation of ovarian tissue [15].

Risks

One surgical revision after laparoscopic tissue removal from of a total of 500 laparoscopies has been documented

in the FertiPROTEKT Network records [11]. A further risk is the retransplantation of tumour tissue. Up to now, metastases have been described in a cryoconserved specimen from a patient with Hodgkin's lymphoma [17], however not with breast cancer [18].

The risk of a remetastasis after retransplantation is unforeseeable in patients with haematological neoplasias or a high risk of ovarian metastasis [19], therefore this should not be performed at the present time.

GnRH-Agonists (GnRHa)

Indication

- Postmenarchal women up to the age of 40 years, who receive chemotherapy or another treatment which could lead to a significant chance of premature ovarian insufficiency.

As a definitive proof of efficacy is not yet available, other techniques should also be considered in addition to drug treatment.

Description—GnRHa

After an initial gonadotrophin release (flare-up effect), GnRHa bring about a downregulation of the GnRH receptor, followed by hypogonadism. Further possible protective mechanisms on the gonads are under discussion [20].

The flare-up effect of the GnRHa takes about 1 week; they should therefore be administered at least 1 week before the start of chemotherapy. If the flare-up needs to be reduced, a GnRH-antagonist can be administered once a day for 6 days at the same time as the GnRHa depot injection [21]. Whether the fertility preserving effect of GnRHa can thereby be improved has yet to be proven.

The effect of the GnRHa should continue for at least 1–2 weeks after the last chemotherapy cycle.

Success rates of GnRHa

Twelve studies carried out between 1966 and 2008 showed that out of 234 patients who received chemotherapy, 59% of cases had premature ovarian failure (POF) versus 9% after a combination of chemotherapy with a GnRHa ($n = 345$) [22]. A summary of nine studies (1980–2008) confirmed these results with a POF rate of 55.5 versus 11.1% ($n = 189$ vs. $n = 225$) [20].

In 2009 and 2010, three meta-analyses were published addressing the co-treatment GnRHa during chemotherapy to reduce ovarian damage (23–25). Clowse et al. [23] and Ben-Aharon et al. [24] included 8, 16 studies, respectively, including those with retrospective controls. Clowse revealed that GnRHa are effective in preserving ovarian function (RR 1.68) and Ben-Aharon revealed that GnRHa are effective in reducing amenorrhoea (RR 0.26). Bedaiwy et al. [25] only included prospective randomized studies ($n = 7$) with 173 patients receiving GnRHa and 167 control patients. They calculated an odds ratio of 3.5 favouring the use of GnRHa.

On the whole, the evidence that GnRHa have a protective effect on the ovaries is becoming more established. Nevertheless, the final conformation is still awaited.

Risks

One possible side effect of GnRH analogues is menopausal symptoms. These symptoms are delayed, but are also possible with chemotherapy alone. Treatment with GnRHa for over 6 months leads to a loss of bone mass [26]. In case of severe symptoms and in case of long term use (>6 month), add-back therapies, using low estrogen dosages, can be considered. However, data concerning the influence of add-back therapies on the fertility preserving action of GnRHa are not available.

There is a theoretical risk of reducing the efficacy of chemotherapy when using GnRHa in a patient with estrogen receptor positive breast cancer, but there is no conclusive evidence for or against this hypothesis. As the data is unclear, GnRHa should not be used where estrogen receptor positive disease is present, or should only be used after a careful risk/benefit analysis.

Combination of the techniques

Fertility preservation procedures can be combined to increase their efficacy (Fig. 2).

Ovarian tissue can be removed laparoscopically and ovarian stimulation can be started ca. 1–2 days later [27]. The theoretical chance of pregnancy is almost doubled with this combination. Use of the luteal phase stimulation protocol is recommended if the stimulation is stared after the fifth day of the cycle [5]. Additional administration of an aromatase inhibitor should be considered if breast cancer is present [7]. Short acting GnRHa are used for ovulation induction [6], which can be combined with a GnRHa depot. Chemotherapy can be started 1–2 days after follicle aspiration.

Starting chemotherapy before recovery of the ovaries after stimulation did not lead to more damage to the ovaries in an animal study [28].

Transposition of the ovaries

Indications

- Radiotherapy to the pelvis, which would lead to a significant chance of premature ovarian insufficiency.