THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (November–December 2014) 64(6):381–387
DOI 10.1007/s13224-014-0626-0

INVITED REVIEW ARTICLE

Fertility Preservation in Reproductive Age Women with Cancer

Kovacs Peter

Received: 27 August 2014 / Accepted: 22 September 2014 / Published online: 30 October 2014

About the Author

Peter Kovacs has graduated from the Albert Szent-Gyorgyi School of Medicine in Szeged, Hungary and then completed his OB/GYN and Reproductive Endocrinology and Infertility training at the Albert Einstein College of Medicine in New York. Subsequently, he was invited to join the largest Hungarian IVF Center, Kaali Institute, and in 2008 was promoted to become the medical director. In 2005, he earned a PhD degree for studies regarding the reproductive effects of diabetes. His current research interest is focused on stimulation protocols, predictors of IVF outcome, and the clinical benefits of time-lapse embryo monitoring. He has published 40 peer-reviewed papers and several book chapters; he was the co-editor of the first Hungarian textbook on infertility evaluation and treatment

Abstract Cancer may be detected at any age and could affect children, and reproductive age women as well. In recent years, cancer treatment has become less destructive and more specific. As a result, survival rates and quality of life following successful treatment have continuously improved. Cancer treatment typically involves surgery, chemo- or radiation therapy, or the combinations of these. These interventions often adversely affect the function of the reproductive organs. Chemo- and radiation therapy are known to be gonadotoxic. Survivors of oncologic therapy are typically rendered infertile primarily due to the loss of ovarian function. There are, however, several medical, surgical, and assisted reproductive technology options that could be and should be offered to those diagnosed with cancer and wish to maintain their fertility. Embryo cryopreservation has been available for decades and has been successfully applied for fertility preservation in women diagnosed with cancer. Recent advances in cryobiology have increased the efficacy of not just embryo but even oocyte and ovarian tissue freezing–thawing. Oocyte vitrification just like embryo cryopreservation requires the use of stimulation but does not require the patient to be in a stable relationship or accept the use of donor sperm. Ovarian tissue cryopreservation does not require stimulation and, following successful transplantation, provides the patient with the most eggs but is currently still considered experimental. This paper summarizes the various fertility-sparing medical, surgical and assisted reproductive technology options. It reviews the current status of embryo, oocyte, and ovarian tissue cryopreservation and discusses their risks and benefits.

Keywords Cancer · Fertility preservation · Cryopreservation · Oocyte vitrification · Embryo vitrification · Ovarian tissue cryopreservation

Kovacs P. (✉)
Kaali Institute, IVF Center, Istenhegyi ut 54/a, Budapest 1125, Hungary
e-mail: peterkovacs1970@hotmail.com

Introduction

In 2014, 810,320 new cases of cancers are predicted to occur among women in the US. In about one third of them, the patient will not survive the disease. While the majority of cancers occur later in life, certain cancers are typical among children and young adults, and other types of cancers that are more common at an advanced age can also be diagnosed in reproductive age women. Breast cancer is the most commonly found malignancy among women followed by lung, colorectal, uterine, and thyroid cancer. In the 20–39 year-old group, breast cancer, cervical cancer, leukemia, and colorectal and central nervous system cancers are the five leading causes of cancer death [1].

Cancer therapy usually requires the combination of surgery and chemo- and/or radiation therapy. Such treatment will typically result in sterility as both radiation and chemotherapy are toxic to the germ cells and destroy the latter [2].

Cancer treatment, however, has become more specific, effective, and less destructive, resulting in improved survival and better quality of life following completion of therapy [1]. Following successful treatment, reproductive age women who wish to become pregnant often face the problem of infertility though primarily due to the loss of follicles. Their desire to have a family needs to be addressed prior to initiation of therapy as there are numerous surgical, medical, and assisted reproductive technology (ART) options that could be offered, and these could help them start a family in the future. This paper reviews the currently available surgical, medical, and ART options that could be offered to reproductive age women with the diagnosis of cancer who wish to maintain their fertility.

Discussion

Surgical Options

Gynecologic cancers (e.g., cervical, uterine, ovarian cancer) initially are typically managed by surgery. Cervical cancer is mainly associated with human papilloma virus infection, and routine screening can pick up precancerous lesions as well as early cancer [3]. While the standard of care for early-stage cervical cancer is radical hysterectomy with post- or pre-operative radiation and chemotherapy, disease localized to the cervix (up to stage IIb) can be managed by conservative surgery. Radical trachelectomy involves the removal of the cervix, upper vagina, parametrium, and proper lymph node sampling but retains the uterine corpus [4, 5]. In well-selected cases, the survival rate is similar to that achieved following radical hysterectomy. Spontaneous conceptions as well as pregnancies through ART have been reported following this approach [6]. Due to the lack of cervix, these pregnancies are complicated by a higher risk of miscarriage and preterm delivery, and the incidence of low birth weight is increased as well. It is important to minimize the risk of multiple pregnancies for fear of preterm delivery.

Radiation therapy in the abdominal area may be required in cases of cervical cancer, lymphoma, etc. Radiation destroys the ovarian follicles in a dose-dependent manner and, when used in doses in excess of 800 cGy, ovarian failure likely develops [7]. However, when the radiation does not directly reach the ovaries, the destructive effect is reduced as well. Therefore, by placing the ovaries out of the field of direct radiation, the ovarian function can be salvaged. Laparoscopic transposition of the ovaries out of the field of direct radiation results in close to 90 % maintenance of ovarian activity in women less than the age of 40 [8]. Transposition of the ovaries 3 or more cm out of the field of radiation will give best results [9].

Ovarian cancer is typically diagnosed at an advanced stage (stage III–IV). Proper staging involves the removal of the uterus, both adnexa, lymph nodes, omentum, any involved area, and pelvic washings. Unilateral oophorectomy or the use of chemo-, radiation therapy alone can be considered for early-stage disease (1 A–C) and less-aggressive histologic types (germ cell tumors, borderline tumors). Conservative surgery has even been explored for early-stage epithelial ovarian cancer as well [10–12].

While surgery plays a crucial role in the proper diagnosis and treatment of cancers of the female reproductive organs, in well-selected cases following proper counseling, a less radical approach can be offered without compromising long-term outcome. These options should be discussed with the patient who wishes to have children later on.

Medical Options

In reproductive age women, endometrial cancer is typically induced by prolonged unopposed estrogen exposure (e.g., chronic anovulation) resulting in uncontrolled proliferation. While definitive therapy involves the removal of the uterus, when the diagnosis is made at an early-stage (well-differentiated cancer localized to the endometrium), medical therapy using high dose progesterone can be considered [13, 14]. Usually medroxyprogesterone-acetate or megestrol-acetate is used over at least a 3–6-month period. There are no clear guidelines on the appropriate dose or duration of the treatment, however. It is also not clear how (by ultrasound, hysteroscopy, or repeat biopsies) these patients should be followed and for how long. According to a recent meta-analysis, remission can be achieved in a

majority of the cases (rarely beyond the first year though), but one has to consider the possibility of recurrence as well (recurrence rates continuously increase up to 2 years). Medroxyprogesterone-acetate seems to be associated with the best results [15].

Chemotherapy may be gonadotoxic, and could result in gonadal failure. The impact depends on the agent used (alkylating agents are the most gonadotoxic), duration of exposure, patient's age, and ovarian reserve at the initiation of therapy [16]. It is believed that, by suppressing ovarian activity by gonadotropin-releasing hormone (GnRh) analogue and rendering it inactive, the toxic exposure could be limited. Promising results have been published with the use of GnRh analogues prior to and during chemotherapy though not all reports confirm the protective effect [17, 18]. A meta-analysis of six randomized trials by Bedaiwy and colleagues reported higher rate of spontaneous cycle and ovulation recurrence in GnRh agonist-cotreated patients but found no significant benefit when pregnancy rates were compared [19]. Considering the potential side effects of long-term GnRH agonist therapy (vasomotor symptoms, bone loss) and the lack of definitive supportive evidence, its routine use is currently not recommended for the preservation of fertility among those undergoing chemotherapy [20].

These surgical and medical options can be offered only to selected cancer patients. The use of conservative methods should only be offered following proper counseling and ensuring the patient's understanding that she does take an often unknown risk with the less-aggressive treatments. Recent improvements in the field of ART, especially in the field of cryopreservation, have opened up safer alternative ways to maintain fertility to those diagnosed with cancer during the reproductive years.

Assisted Reproductive Technology—Embryo Cryopreservation

Embryo cryopreservation, the most well-established method of fertility preservation, has an over-three-decade history [21]. This option can be offered to those who are either in a stable relationship or accept the use of donated sperm. Embryo cryopreservation requires the patient to undergo a full IVF cycle involving ovarian stimulation. In some cases, however, the patient cannot afford to delay oncologic treatment, and therefore, IVF is not considered an option. In other cases, the use of stimulation may have an adverse impact on the prognosis of cancer therapy (hormone sensitive tumors, e.g., breast cancer). Embryo cryopreservation is not an option for prepubertal girls.

There are several cryopreservation protocols in use: computer-controlled slow-freezing and vitrification (conventional or ultra-rapid). Nowadays, vitrification is increasingly replacing slow-freezing. Embryo cryopreservation requires the use of cryoprotectants (e.g., 1,2-propanediol [PROH], dimethyl-sulfoxide [DMSO] or glycerin). The concentration of the cryoprotectant and the cooling rate differ between these methods. Embryos then can be stored for many years in plastic straws in liquid nitrogen containers [22].

Following successful cancer therapy, embryos can be transferred in a natural, stimulated, or artificial cycle. Frozen-thawed embryos can also be transferred into a surrogate mother; so this is an option for those who have to have their uteri removed during the management of cancer or for those who are not allowed to become pregnant due to fear of cancer recurrence.

Success with cryopreservation depends on the method of cryopreservation, developmental stage, and quality of embryo [22].

A disadvantage of embryo cryopreservation for the patient expecting to start cancer therapy is the need for ovarian stimulation. This traditionally is started with the onset of menses. Waiting for the menstruation and then the delay due to the stimulation and retrieval may compromise the outcome of cancer therapy. Several groups have reported successful stimulation: retrieval of mature oocytes with random start stimulation (even luteal phase start) using the combination of letrozole and gonadotropins in patients undergoing stimulation for fertility preservation [23, 24].

While stimulation increases the efficacy of IVF, it also leads to endocrine changes that could be undesirable in case of hormone-sensitive tumors, primarily in the case of breast cancer. Several alternative stimulation protocols using anti-estrogens (tamoxifen), aromatase inhibitors (letrozole), or their combination with gonadotropins were assessed and were shown not to compromise the oncologic outcome [25, 26].

Embryo cryopreservation is an effective method of fertility preservation when the use of stimulation is not contraindicated, when there is time to carry the IVF procedure out, and for those who have a partner or accept donor sperm use. Those who do not meet these criteria may elect to have oocytes or ovarian tissue frozen.

Assisted Reproductive Technology—Oocyte Cryopreservation

The first birth with the use of frozen-thawed oocyte was reported in 1986 [27]. Despite this early success, it took a long-time before oocyte cryopreservation became an accepted method of fertility preservation [28]. Intracellular ice crystal formation that could injure the spindle apparatus, low survival rate, suboptimal fertilization, and disappointing pregnancy rates were the initial problems that had

to be addressed. Recent developments, especially the introduction of vitrification, however, have led to significant improvements.

An Italian study analyzed egg-freezing efficacy (slow-freezing/vitrification combined) in a non-oncologic setting and found less-optimal embryo development, lower implantation, and pregnancy rates when the use of frozen oocytes was compared with fresh oocytes [29]. Vitrification of oocytes is now replacing slow-freezing; however. Smith et al. compared outcome with slow-freezing versus vitrification in a randomized trial. Vitrified oocytes were more likely to survive the warming (81 vs 67 %), the embryos obtained had better cleavage rate, and their transfer resulted in a higher clinical pregnancy rate (38 vs 13 %) [30]. A study by Almodin et al. found a survival rate of 84.9 % among vitrified oocytes. Fertilization rate and clinical outcome were similar to those achieved with fresh eggs [31]. Another longitudinal cohort study of 486 cycles reported a survival rate of 84.7 % after thawing vitrified oocytes. Three quarters fertilized normally and close to half of the fertilized eggs turned into top-quality embryos. A close to 30 % pregnancy rate per transfer was achieved [32]. A different study involving egg donation reported even higher (90 %) survival rate, and the fertilization, embryo development, implantation, and pregnancy rates were comparable to that achieved with freshly retrieved eggs [33]. A 2011 meta-analysis compared treatment outcome with fresh, vitrified, and slow-frozen oocytes based on the results of five studies. Fertilization and cleavage rates, the availability of top-quality embryos, and clinical pregnancy rates were comparable with fresh and vitrified oocytes. Vitrification was superior for all these parameters over slow-freezing [34]. When a different approach was used to evaluate the efficacy of fertility treatment with frozen versus fresh oocytes, Goldman and colleagues found no difference in the live birth rate/oocyte (fresh: 4.25 vs frozen: 2.7 %). The live birth rate per transfer did not differ either [35].

Besides the efficacy, it is equally important to establish the safety of mature oocyte cryopreservation before it can be routinely offered. Pietro et al. studied the biomolecular quality of vitrified oocytes. They compared eight genes involved in embryo development and the transcriptome and found no differences between the fresh and vitrified oocytes [36]. In a report based on over 900 births following the use of frozen-thawed oocytes by Noyes et al. a congenital anomaly rate of 1.3 % was found which is not different from the rate observed in natural conceptions [37]. Levi Setti and colleagues compared clinical and neonatal outcomes with the use of the freshly collected and frozen-thawed sibling oocytes in a group of 855 women. The rate of fetal anomalies was similar between the two groups, but the risk of miscarriage was higher with frozen oocytes (26.9 vs 17.6 %). The risk of major anomalies did not differ between the two groups. While there was no difference in the mean gestational age at delivery, the mean birth weight was lower in both singleton and twin pregnancies in the group where fresh eggs were used [38].

Immature oocytes can be collected both in the follicular and luteal phases. Subsequently, they can be matured in vitro, and then can be cryopreserved and stored for later use. This may be an alternative to mature oocyte cryopreservation in those cases when the use of stimulation is absolutely contraindicated or when there is no time to use even random start stimulation. The need for in vitro maturation, however, does limit the efficacy of this approach [39].

Most of the experience with mature oocyte cryopreservation is reported by IVF centers with large donor egg programs. These eggs are produced by young, fertile women and are expected to be of excellent quality. Even in these cases, close to 20 eggs are needed to achieve a live birth as reported by Goldman et al. [35]. Infertile women or women with cancer may not have such good quality eggs and may therefore have inferior outcome with oocyte cryopreservation. This has to be part of the counseling prior to offering this method. It will be important to collect data on the use of mature oocyte cryopreservation among survivors of cancer therapy, who subsequently undergo ART using their previously cryopreserved oocytes.

Assisted Reproductive Technology—Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation is an emerging alternative to oocyte/embryo freezing for fertility preservation. Ovarian tissue can be collected at anytime in the cycle, it does not require the patient to be in a stable relationship or to accept the use donated sperm, and there is no need for stimulation prior to the removal ovarian tissue. This is the only option that can be offered to prepubertal girls. Those patients who need to undergo abdominal surgical procedure as part of the staging or treatment of their cancer may choose this procedure, as ovarian cortical pieces or the whole ovary can be removed at the time of the procedure. Successful grafting of the tissue not just preserves fertility but restores hormone production as well, and therefore these patients will not suffer from the long-term effects of hypoestrogenism. At this stage, however, ovarian tissue cryopreservation is still considered experimental [40].

The follicles are located in the ovarian cortex, and follicle density declines with age. Ovarian tissue cryopreservation is not recommended to women with advanced reproductive age or low ovarian reserve prior to cortical biopsy since the graft is unlikely to work if we consider the loss during freezing–thawing and transplantation. Most

centers apply an upper age limit (35–38 years) for this procedure [41].

Typically, several cortical pieces (<1 cm) of 1–2-mm thickness are harvested and cryopreserved. Slow-freezing and vitrification can both be considered [42–44]. The thawed cortical pieces can then be transplanted in the original site (orthotopic) or at a distant location (heterotopic). Orthotopic transplantation may be done on to the medulla of the remaining or contralateral ovary or into peritoneal pockets at the ovarian fossa [41]. Orthotopic transplantation has the benefit of enabling the patient to have a spontaneous pregnancy. Heterotopic (e.g., forearm) transplantation has the benefit of easier access to the grafted tissue.

The grafted tissue usually regains its activity within 3–6 months [43]. The life-span of the grafted tissue depends on the follicle density at cryopreservation, the damage induced by the cryopreservation-thawing, the surgical technique, and the duration of ischemia before proper neovascularization develops. In order for the graft to regain its activity, proper blood supply through neovascularization has to be established. The longer it takes to establish blood supply the greater the damage in the follicle pool is. Mechanical injury inducing inflammation and angiogenesis at the transplantation site, the administration of anti-oxidants, and the use of neoangiogenic growth factors have been evaluated to promote neoangiogenesis with more, or less, success [44]. In carefully selected, managed cases, the graft could maintain its activity for at least 4–5 years [41, 42]. In 2013, Donnez and colleagues reported on clinical outcomes after ovarian tissue reimplantation based on 60 cases. In close to 90 % of the cases, ovarian activity was successfully restored. Twenty percent of the women conceived successfully upon return of ovarian activity [45].

One, however, also has to consider the possibility of reintroducing cancer cells at the time of reimplantation. This is especially necessary concerning with cancers that may infiltrate the ovary (hematologic cancers) or tend to metastasize to the ovaries. Histological evaluation, immunohistochemistry, and PCR analysis should be done on the tissue prior to transplantation to minimize the transmission risk [46]. Based on these concerns, ovarian tissue should not be transplanted in the case of hematologic malignancy, ovarian cancer, or cancers that metastasize to the ovary [40].

The transfer of the entire ovarian cortex or an intact whole ovary will leave the patient with more follicles than with smaller cortical strips. Successful procedures have been reported with fresh and frozen tissue transfer between monozygotic twins [41]. In these cases, the ovary is removed with a vascular pedicle, the cortex is trimmed down to <1-mm thickness, and is then grafted onto a denuded ovarian medulla of the recipient. It is important to maintain perfect hemostasis, to use very thin sutures and to continuously irrigate the graft. Follicle loss may result from poor neovascularization, poor surgical technique resulting in ischemia, and due to cryoinjury in case cryopreserved tissue is used. In the nine fresh transfer cases described by Silber et al. ovarian function returned in 2–4 months, and in six cases, the graft was still working after 3–4 years. Six patients gave birth to eight babies in the follow-up period [47]. Donnez and coauthors reported successful ovarian cortical transplantation between non-identical sisters. The graft regained its activity by a bit over 3 months. This patient eventually successfully conceived through IVF and gave birth to a healthy newborn [48].

Hilders et al. have reported successful whole ovary autotransplantation to the upper arm (heterotopic) in a young patient requiring surgery and radiation therapy for cervical cancer. Vascular connection was established, and the autotransplanted ovary regained its activity [49]. In 2008, Silber and colleagues published a report on the fresh transfer of a whole ovary with a vascular pedicle between identical twins. Three months after the transplantation, the recipient experienced her first menstruation, and a year later, she successfully conceived [50].

There are still challenges to be met with the cryopreservation of a whole ovary. It is hard to achieve even diffusion of the cryoprotectant in the entire ovary. In addition, the ovary–vascular pedicle complex has to survive the freezing–thawing. Successful procedures have been carried out in various animal models already, but the human protocols require further refinements [44].

Research has already begun with regard to in vitro tissue culture. This approach would not require tissue transplantation and could eliminate the risk of malignant cell reimplantation. It also would not require the use of assisted reproduction in case pregnancy could not be achieved spontaneously. The process is limited by the complex and changing nutritional needs of the developing follicles from the primordial stage to the preovulatory stage, ischemia, and inability to properly monitor follicle development [46]. An alternative to tissue culture and maturation could be isolated follicle culture in two- and three-dimensional culture systems with subsequent in vitro fertilization and embryo transfer. These techniques are under development currently [46].

Assisted Reproductive Technology—Donor Egg, Donated Embryos Use, Surrogacy

Those patients who did not have a chance to undergo embryo, oocyte, or ovarian tissue cryopreservation prior to the initiation of cancer treatment but had undergone successful treatment and are left with severely reduced ovarian

function or lack of ovarian function could choose to undergo assisted reproduction using donated eggs or embryos. Those patients who had to have the uteri removed during the procedure but were having adequate ovarian function left may choose to undergo assisted reproduction involving a surrogate mother. The regulation of these procedures differs from country to country and may not be available to all.

Conclusions

Cancer can be cured with increasing efficacy. As the oncologic protocols improve, the treatments become less radical, and patients in increasing numbers survive the treatment and can live with proper quality of life. Chemo- and radiation therapy are both gonadotoxic though, and therefore, many of the survivors become infertile due to loss of ovarian activity. Oncologic care requires a multidisciplinary approach, and the involvement of a fertility specialist is important as the fertility needs of the survivors have to be addressed. There are various surgical and medical options that one can consider. The improvements in the field of ART now make it possible for both reproductive age and prepubertal patients to maintain fertility even if they are not in an established relationship. Future refinements of these protocols and the currently available experimental technologies should further increase the efficacy and safety of these procedures and should make fertility preservation available to even a still wider population of patients diagnosed with cancer.

Conflict of Interest Peter Kovacs declares that he has no conflict of interest.

References

1. Siegel R, Ma J, Zou Z, et al. Cancer Statistics, 2014. CA Cancer J Clin. 2014;64:9–29.
2. Barber HR. The effect of cancer and its therapy upon fertility. Int J Fertil. 1981;26:250–9.
3. Sankaranarayanan R, Gaffikin L, Jacob M et al. A critical assessment of screening methods for cervical neoplasia. Int J Gynaecol Obstet. 2005;89:S4–12.
4. Plante M, Renaud MC, Hoskins IA, et al. Vaginal radical trachelectomy: a valuable fertility-preserving option in the management of early-stage cervical cancer. A series of 50 pregnancies and review of the literature. Gynecol Oncol. 2005;98:3–10.
5. Ungar L, Palfalvi L, Hogg R, et al. Abdominal radical trachelectomy: a fertility-preserving option for women with early cervical cancer. BJOG. 2005;112:366–9.
6. Palfalvi L, Ungar L, Boyle DCM, et al. Announcement of healthy baby boy born following abdominal radical trachelectomy. Int J Gynecol Cancer. 2003;13:249.
7. Damewood MD, Grochow LB. Prospects for fertility after chemotherapy or radiation for neoplastic disease. Fertil Steril. 1986;45:443–59.
8. Bisharah M, Tulandi T. Laparoscopic preservation of ovarian function: an underused procedure. Am J Obstet Gynecol. 2003;188:367–70.
9. Bidzinski M, Lemieszczuk B, Zielinski J. Evaluation of the hormonal function and features of the ultrasound picture of transposed ovary in cervical cancer patients after surgery and pelvic irradiation. Eur J Gynaecol Oncol. 1993;14Suppl:77–80.
10. Gershenson DM, Miller AM, Champion VL, et al. Gynecologic oncology group. Reproductive and sexual function after platinum-based chemotherapy in long-term ovarian germ cell tumor survivors: a gynecologic oncology group study. J Clin Oncol. 2007;25:2792–7.
11. Schilder JM, Thompson AM, DePriest PD, et al. Outcome of reproductive age women with stage IA or IC invasive epithelial ovarian cancer treated with fertility-sparing therapy. Gynecol Oncol. 2002;87:1–7.
12. Tinelli FG, Tinelli R, La Grotta F, et al. Pregnancy outcome and recurrence after conservative laparoscopic surgery for borderline ovarian tumors. Acta Obstet Gynecol Scand. 2007;86:81–7.
13. Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under the age 40. Obstet Gynecol. 1997;90:434–40.
14. Yamazawa K, Hirai M, Fujito A, et al. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. Hum Reprod. 2007;22:1953–8.
15. Koskas M, Uzan J, Luton D, et al. Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. Fertil Steril. 2014;101:785–94.
16. Posada MN, Kolp L, Garcia JE. Fertility options for female cancer patients: facts and fiction. Fertil Steril. 2001;75:647–53.
17. Blumenfeld Z, Avivi I, Eckman A, et al. Gonadotropin-releasing hormone agonist decreases chemotherapy-induced gonadotoxicity and premature ovarian failure in young female patients with Hodgkin lymphoma. Fertil Steril. 2008;89:166–73.
18. Elgindy EA, El-Haieg DO, Khorshid OM, et al. Gonadotrophin suppression to prevent chemotherapy-induced ovarian damage. Obstet Gynecol. 2013;121:78–86.
19. Bedaiwy MA, Abou-Setta AM, Desai N, et al. Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: a systematic review and meta-analysis. Fertil Steril. 2011;95:906–14.
20. Loren AW, Mangu PB, Beck LN, et al. American sociaty of clinical oncology. Fertility preservation for patients with cancer: Americal society of clinical oncology practice guideline update. J Clin Oncol. 2013;31:2500–10.
21. Trounson A, Mohr L. Human pregnancy following cryopreservation, thawing and transfer of an eight-cell embryo. Nature. 1983;305:707–9.
22. Abdel Hafez FF, Desai N, Abou-Setta AM, et al. Slow freezing, vitrification and ultra-rapid freezing of human embryos: a systematic review and meta-analysis. Reprod Biomed Online. 2010;20:209–22.
23. Kuang Y, Hong Q, Chen Q, et al. Luteal-phase ovarian stimulation is feasible for producing competent oocytes in women undergoing in vitro fertilization/intracytoplasmic sperm injection treatment, with optimal pregnancy outcomes in frozen-thawed embryo transfer cycles. Fertil Steril. 2014;101:105–11.
24. Cakmak H, Katz A, Cedars MI, et al. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. Fertil Steril. 2013;100:1673–80.

25. Oktay K, Buyuk E, Libertella M, 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. 2005;23:4347–53.
26. Azim AA, Costantini-Ferrando M, 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;26:2630–5.
27. Chen C. Pregnancy after human oocyte cryopreservation. Lancet. 1986;1:884–6.
28. The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2013;99:37–43.
29. Scaravelli G, Vigiliano V, Mayorga JM, et al. Analysis of oocyte cryopreservation in assisted reproduction: the Italian National Register data from 2005 to 2007. Reprod Biomed Online. 2010;21:496–500.
30. Smith GD, Serafini PC, Fioravanti J, et al. Prospective randomized comparison of huan oocyte cryopreservation with slow-freezing or vitrification. Fertil Steril. 2010;94:2088–95.
31. Almodin CG, Minguetti-Camara VC, Paixao CL, et al. Embryo development and gestation using fresh and vitrified oocytes. Hum Reprod. 2010;25:1192–8.
32. Rienzi L, Cobo A, Paffoni A, et al. Consistent and predictable delivery rates after oocyte vitrification: an observational longitudinal cohort multicentric study. Hum Reprod. 2012;27:1606–12.
33. Cobo A, Remohi J, Chang CC, et al. Oocyte cryopreservation for donor egg banking. Reprod Biomed Online. 2011;23:341–6.
34. Cobo A, Diaz C. Clinical application of oocyte vitrification: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2011;96:277–85.
35. Goldman KN, Noyes NL, Knopman JM, et al. Oocyte efficiency: does live birth rate differ when analyzing cryopreserved and fresh oocytes on a per-oocyte basis? Fertil Steril. 2013;100:712–7.
36. Di Pietro C, Vento M, Guglielmino MR, et al. Molecular profiling of human oocytes after vitrification strongly suggests that they are biologically comparable with freshly isolated gametes. Fertil Steril. 2010;94:2804–7.
37. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babied born with no apparent increase in congenital anomalies. Reprod Biomed Online. 2009;18:769–76.
38. Levi Setti PE, Albani E, Morenghi E, et al. Comparative analysis of fetal and neonatal outcomes of pregnancies from fresh and cryopreserved/thawed oocytes in the same group of patients. Fertil Steril. 2013;100:396–401.
39. Chian RC, Uzelac PS, Nargund G. In vitro maturation of immature oocytes for fertility preservation. Fertil Steril. 2013;99:1173–81.
40. The Practice Committee of the American Society for Reproductive Medicine. Ovarian tissue cryopreservation: a committee opinion. Fertil Steril. 2014;101:1237–43.
41. Donnez J, Dolemans MM. Fertility preservation in women. Nat Rev Endocrinol. 2013;9:735–49.
42. Oktay K, Oktem O. Ovarian cryopreservation and transplantation for fertility preservation for medical indications: report of an ongoing experience. Fertil Steril. 2010;93:762–8.
43. Oktay K, Economos K, Kan M, et al. Endocrine function and oocyte retrieval after autologous transplantation of ovarian cortical strips to the forearm. JAMA. 2001;286:1490–3.
44. Bedaiwy MA, Falcone T. Whole ovary transplantation. Clin Obstet Gynecol. 2010;53:797–803.
45. Donnez J, Dolmans MM, Pellicier A, et al. Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. Fertil Steril. 2013;99:1503–13.
46. Salama M, Winkler K, Murach KF, et al. Female fertility loss and preservation: threats and opportunities. Ann Oncol. 2013;24:598–608.
47. Silber S, Kagawa N, Kuwayama M, et al. Duration of fertility after fresh and frozen ovary transplantation. Fertil Steril. 2010;94:2191–6.
48. Donnez J, Squifflet J, Pirard C, et al. Live birth after allografting of ovarian cortex between genetically non-identical sisters. Hum Reprod. 2011;26:1384–8.
49. Hilders CG, Baranski AG, Peters L, et al. Successful human ovarian autotransplantation to the upper arm. Cancer. 2004;101:2771–8.
50. Silber SJ, Grudzinskas G, Gosden RG. Successful pregnancy after microsurgical transplantation of an intact ovary. N Engl J Med. 2008;359:2617–8.