Chapter 7
Mitigating the Risk: The Role of Ovarian Transposition and Medical Suppression

Jaime M. Knopman and Nicole Noyes

Introduction

During the past 25 years, advances in reproductive medicine have led to the development of novel techniques that give cancer patients who are facing impending sterility an opportunity to bear biological offspring. However, the availability and expense of some fertility preservation methods have limited their universality and, therefore, patient access. By contrast, ovarian transposition prior to radiation therapy and treatment with gonadotropin-releasing hormone agonists (GnRHa) coincident with gonadotoxic chemotherapy are relatively simple and inexpensive techniques that are readily available. Despite their accessibility, variable success rates have limited their widespread acceptance. In this chapter, we present up-to-date information on these two potential fertility preservation options.

Ovarian Transposition (OT)

OT, otherwise known as *oophoropexy,* was introduced as a fertility preservation measure approximately 50 years ago [1]. Physicians theorized that moving the ovaries outside of the radiation field would significantly reduce radiation exposure to the organs and therefore minimize the resulting decrease in ovarian reserve [2, 3]. Prior studies have demonstrated that radiation doses less than 1.5 Gy administered to the ovary do not significantly impair its biologic function, whereas higher doses are associated with varying degrees of ovarian compromise, inversely dependent on the age at time of exposure ([4, 5]; see also Chap. 1 in this volume). Research has established

J.M. Knopman, M.D. • N. Noyes, M.D. (✉)
Division of Reproductive Endocrinology, New York University School of Medicine,
164 East 72 Street, Apt 15C, New York, NY 10021, USA
e-mail: jamie.knopman@nyumc.org; nicole.noyes@nuymc.org

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that doses of 30 Gy administered to patients younger than 26 years of age, 20 Gy to patients 26–40 years of age, and 5–6 Gy to patients over the age of 40 years most often cause complete and permanent ovarian failure [5–7]. Radiation doses commonly used to treat pelvic tumors routinely exceed these thresholds, placing women with these diagnoses at considerable reproductive risk as a result of their treatment.

Although first described exclusively in conjunction with radical open surgery for the treatment of cervical cancer [1], OT is now offered in a variety of clinical settings involving suitable reproductive-age candidates who require pelvic irradiation. The procedure is relatively simple to perform (Fig. 7.1); the utero-ovarian ligament(s) and peritoneum adjacent to the infundibulopelvic ligament(s) are incised, affording mobilization of the ovary so as to allow movement outside the radiation field and attachment to a remote peritoneal surface. Depending on the desired location, transection of the fallopian tube may be necessary to mobilize the ovary. Generally, one or two clips are placed on the transposed ovary(ies) to facilitate easy recognition in future radiographic studies. Common placement choices for the transposed ovaries include lateral locations within the pelvis, the paracolic gutters, and anterior to the psoas muscles (Fig. 7.2) [8]. Ideally, the ovary(ies) should be placed ≥3 cm from the border of the primary radiation field. Due to surgical advancements, OT no longer requires major exploratory surgery and can be effectively performed using a minimally invasive approach (laparoscopy or robot-assisted) when clinically appropriate [9–12]. Recently, a novel laparoscopic modification was described whereby a Prolene suture on a straight needle is passed through a 2-mm abdominal incision over the site where ovarian placement is desired, allowing the surgeon to attach the ovary(ies) to the anterior abdominal wall and secure the suture knot subcutaneously [13]. This approach affords easy release of the ovary back to a pelvic location once radiotherapy has been completed simply by cutting the stitch just under the skin's surface while the patient is under local anesthesia. Though this is an interesting approach, it is not clear whether returning the ovaries back to the pelvis is important for future fertility, as the majority of pregnancies achieved posttreatment have occurred without ovarian relocation. Surgical complications from OT are uncommon and primarily include bleeding, postoperative pelvic discomfort (occasionally requiring premature replacement of the organ back into the pelvis) [14], ischemia, and, though rare, occult metastasis of the ovary (in cases of cervical adenocarcinoma) [15, 16].

While the cumulative number of OT procedures performed annually is unknown, data suggest that the incidence is rising. This increase is most likely due to fertility preservation awareness as well as an improvement in cervical cancer detection [17], with more than 40% of cases now occurring in reproductive-age patients. Certainly, the most common indication for OT is cervical malignancy, with up to two-thirds of OT procedures being performed for this reason [18]. Confounding the rise in cervical cancer diagnoses is the staggering increase in the age at first birth for women around the world, which now globally approaches 28 years [19]. Therefore, a large number of women who are diagnosed with cervical cancer will not have initiated (or completed) childbearing, thereby making OT and other fertility preservation measures integral to treatment plans involving malignancy. Other reproductive-age neoplasms amenable to OT include rectal, vulva, vaginal, smooth muscle, and central

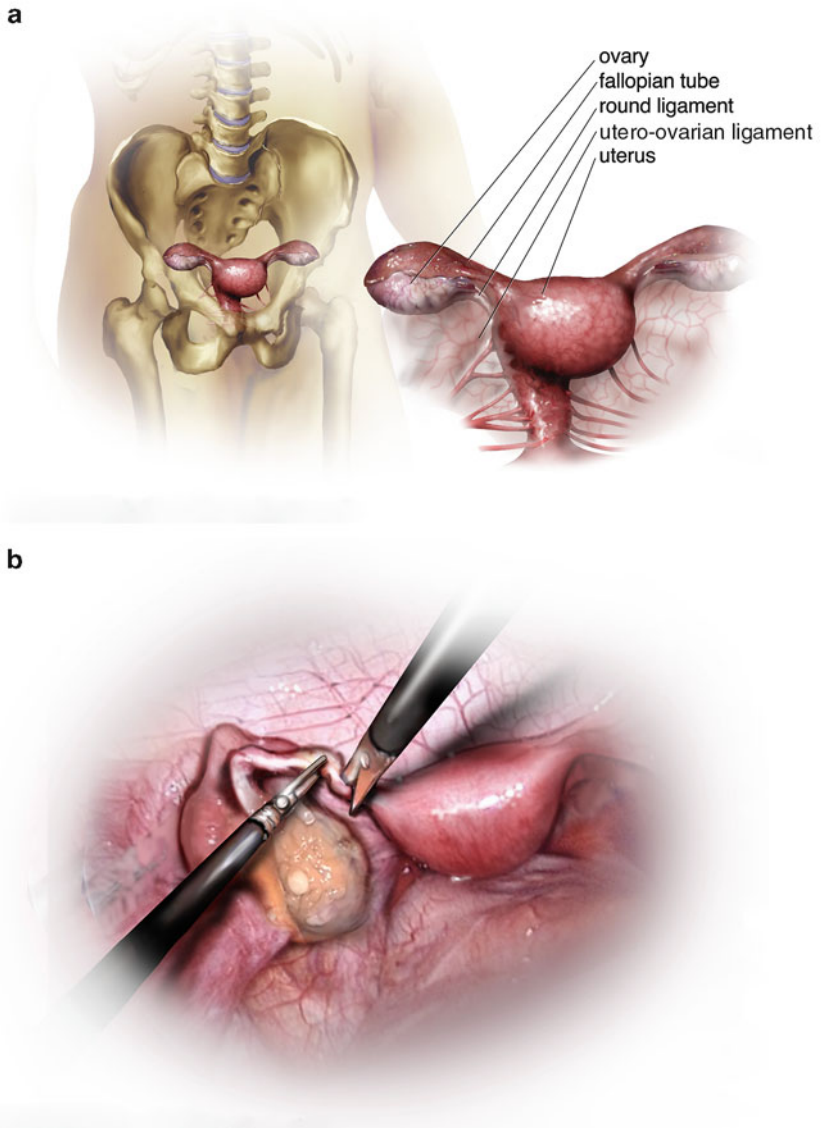

Fig. 7.1 Ovarian transposition technique. (**a**) Schematic of the female pelvis showing reproductive organs in their normal anatomic positions. To perform OT, (**b**) the ovary is first detached from the uterus at the level of the utero-ovarian ligament, and the peritoneum adjacent to the infundibulopelvic ligament is also released. Depending on the final desired ovarian location, transection of the fallopian tube may be necessary to allow for adequate mobilization. (**c**) The ovary is mobilized and then (**d**) attached to a peritoneal surface remote from the primary radiation exposure field

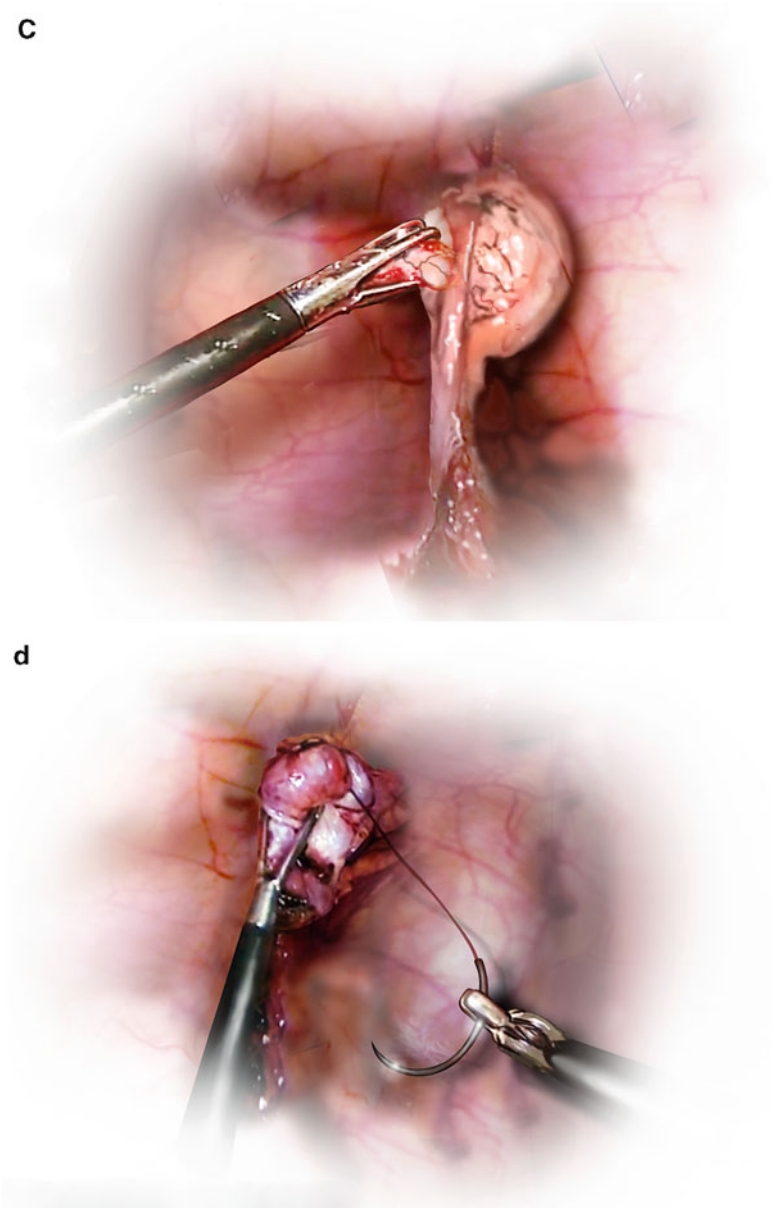

Fig. 7.1 (continued)

nervous system (CNS) tumors, as well as Hodgkin lymphomas requiring radiation therapy. For example, in the Western world, colorectal cancer is the most common malignancy of the gastrointestinal tract, with 3–6% of cases diagnosed before the age of 40 years (and nearly half of these in women) [20].

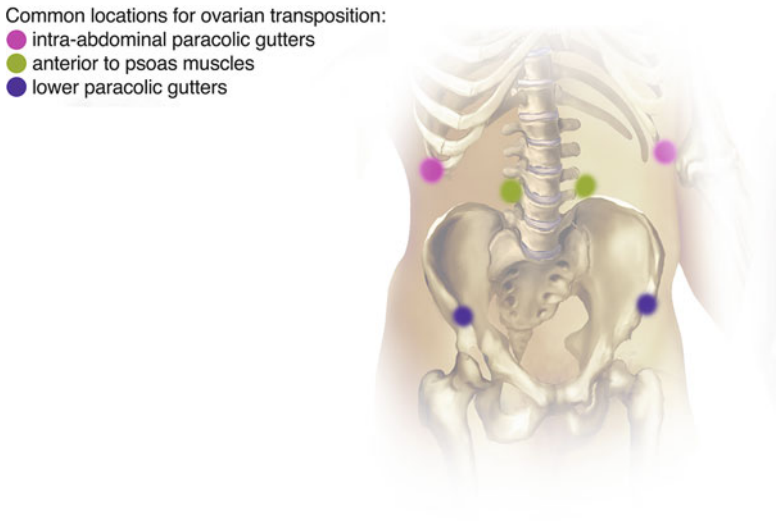

Fig. 7.2 Schematic of the common locations to which the transposed ovaries are attached: the lower paracolic gutters (*purple dots*), anterior to the psoas muscles (*green dots*), and, less commonly, higher up in the intra-abdominal paracolic gutters (*pink dots*)

Selecting appropriate candidates for OT can be difficult. Although the maintenance of ovarian endocrine function is important for a myriad of both mental and physical health reasons, performing OT as an exclusive means to retain reproductive potential is more complicated, particularly in light of the technology's reported inconsistent success. If the OT surgical technique requires that the fallopian tube be cut or damaged, patients should be counseled that in vitro fertilization (IVF) may be required to achieve pregnancy in the future. In addition, when identifying patients for this procedure, it is important to consider whether or not the uterus will be contained within the radiation field (vaginal, cervical, and colorectal cases), as high radiation exposure (14–30 Gy) has been shown to significantly impair uterine function [21]. For example, colorectal cancer treatment routinely requires 45–50 Gy (over 5–6 weeks); this dosage results in not only complete ovarian failure but also significant endometrial damage, making future implantation highly unlikely. Nonetheless, radiation effects on the uterus can be unpredictable, as isolated case reports have described successful pregnancies following high-dose radiotherapy with OT [22]. Patients receiving high-dose uterine radiation must be counseled that any future pregnancy may require the use of a gestational carrier, even if ovarian function can be preserved with OT. This additional hurdle may dissuade some patients from pursuing parenthood after malignancy. The possibility of third-party reproduction should be discussed with cancer patients prior to performing any fertility preservation procedure.

Reduction of Ovarian Failure with OT

Numerous investigators have reported on the impact of OT prior to radiation treatment with varying results [5, 9, 12, 15, 23–26]. Overall, studies demonstrate that OT can reduce the rate of radiation exposure to the ovary by approximately 50–90%. However, studies are difficult to compare because of the heterogeneity of patient characteristics, diagnoses, and surgical approaches. Feeney et al. reported on 122 women who underwent OT; 28 (21%) received postoperative radiation therapy. Despite OT, 50% of patients receiving postoperative radiotherapy experienced early menopause (RR 17.3; 95% CI 5.4–56.1) [15]. Al-Badawi et al. reported on 23 patients (15 cervical, 4 rectal, 3 Ewing sarcomas, and 1 Hodgkin lymphoma) who underwent laparoscopic OT and reported that 65% maintained their ovarian function; unfortunately, the "functional" follicle-stimulating hormone (FSH) level used in this trial was ≤25 IU/L, a value far above that judged to indicate fertility in clinical practice [12]. Cutillo et al. evaluated ovarian function defined as the return of menses in four vaginal cancer patients treated with OT followed by radiotherapy; all were noted to menstruate "regularly" posttreatment [25]. Alternatively, Clough et al. evaluated 20 women (mean age 32.8 ± 6.2 years) who underwent laparoscopic OT for three different neoplasms (17 cervical, 1 CNS, and 2 Hodgkin lymphoma) whose ovaries had received a maximum radiation dosage of 2.2 (mean 1.55) Gy; these authors reported no consequent menopause in women under the age of 40 years [9]. In addition, Gareer et al. reported successful maintenance of ovarian function in 11 of 15 cancer patients (10 rectal, 5 Hodgkin lymphoma) who had been treated using the subcutaneous Prolene-stitch OT method described above [27]. Unfortunately, the primary endpoint studied in these trials was exclusively menstrual function (pregnancy and live birth were not evaluated). While the maintenance of menses does suggest that some ovarian function *has* been retained, this measure does not provide information regarding a woman's reproductive potential and future fertility. In fact, the general consensus among gynecologic oncologists is that the success of OT in maintaining ovarian function falls somewhere between 30% and 50%. Thus, while OT can be advertised as a means to preserve menstrual function, it is difficult to wholeheartedly recommend this modality as a fertility preservation measure.

Success of OT in Preserving Fertility

For those women who do conceive after OT, reported obstetrical data are only somewhat reassuring, with varying results in terms of pregnancy outcomes after the procedure has been performed. Morice et al. reported on 37 young women (mean age 20.7 ± 5.7 years) managed with OT and uterine preservation prior to pelvic irradiation [27]. Diagnoses included clear-cell adenocarcinoma of the vagina/cervix ($n = 27$), ovarian dysgerminoma ($n = 9$), and soft-tissue sarcoma ($n = 1$). Success

rates varied significantly by tumor type/location, with only 15% of clear-cell patients—as opposed to 80% of dysgerminoma/soft-tissue tumor patients—achieving pregnancy. Though at first glance this disparity is striking, the difference can be ascribed to the radiation dosage required to achieve a cure. For example, in clear-cell tumors, the radiation dosage required is high, thereby subjecting even transposed ovaries to significant exposure; in addition, with the uterus located within the radiation field, this organ also suffers significant functional impairment. Interestingly, 67% of the pregnancies that were achieved did not require relocation of the ovary back into the pelvis, albeit 17% required IVF.

Practical Application of OT

Recent literature has suggested that OT is an underutilized fertility preservation measure [18]; a study from the Seoul National University Hospital demonstrated that of 2,524 women who received pelvic irradiation, 108 women (12–40 years of age) would have been candidates for OT. However, of these, only 31 (28.7%; 29 cervical and 2 rectal cases) had undergone OT before pelvic irradiation. Other fertility preservation experts question the benefit of OT and recommend that women pursue alternative fertility preservation options (such as oocyte or embryo cryopreservation) in the setting of malignancy requiring radiation treatment.

Designing an appropriate treatment plan that includes fertility preservation requires an open dialogue between the treating surgical/medical oncologist(s) as well as the reproductive endocrinologist (see also Chaps. 12 and 13 in this volume). Constant communication and thoughtful consideration by all parties will ensure that the correct and most appropriate fertility preservation measure(s) is selected that also addresses patient preference and condition. In fact, a combined approach is often required (including oocyte and/or embryo and/or tissue cryopreservation) to achieve optimal results. For example, in our experience, patients with either cervical or colorectal cancer who will require postoperative radiation therapy achieve the best fertility preservation results when they undergo preoperative oocyte and/or embryo cryopreservation, with or without OT. If OT is to be performed in conjunction with oocyte and/or embryo cryopreservation, we recommend OT be completed *after* the oocyte harvest; otherwise, an abdominal (versus the routine transvaginal) approach to ovum pick-up is usually necessary, which is more challenging and may yield fewer oocytes. Although the decision to perform OT often needs to be made at the time of exploratory surgery, particularly in cervical cancer cases, obtaining a preoperative (and sometimes additionally intraoperative) reproductive endocrinology consult is prudent to ensure that all feasible fertility preservation options are made available to the patient. In summary, regardless of cancer diagnoses, a multidisciplinary approach fueled by constant provider and patient communication affords the patient with the greatest chance for successful future parenthood (this topic is discussed in depth in Chap. 11 of this volume).

Medical Suppression as a Means to Prevent Fertility Loss

GnRHa have been advocated as a simple and expedient means to suppress and thereby preserve ovarian function in patients undergoing chemotherapy. Impending ovarian damage is theoretically halted by administration of GnRHa because these agents are known to inhibit endogenous pituitary gonadotropin secretion, which places the ovaries in a quiescent "prepubertal" state. Several additional hypotheses as to how GnRHa preserve ovarian function have recently been proposed; however, validation of such hypotheses in human studies has been variable [28]. Furthermore, data demonstrating a protective effect on ovarian function are somewhat inconsistent, and so acceptance of this modality by practitioners as a means to maintain fertility is not universal.

History of Medical Suppression

The administration of GnRHa to preserve fertility was first proposed by Glode in the early 1980s [29]. Although practitioners had previously prescribed these drugs to female cancer patients undergoing chemotherapy, their purpose was primarily to prevent heavy menses and resultant anemia. Glode demonstrated in a murine model that an agonistic analogue of GnRH appeared to protect male mice from the gonadal damage inflicted by the chemotherapeutic agent, cyclophosphamide. Subsequent studies performed in rats corroborated Glode's findings and demonstrated that GnRHa inhibited chemotherapy-induced ovarian follicular depletion [30]. Previous work had confirmed that prepubertal children were less susceptible to gonadal damage inflicted by chemotherapy [31–33]. These data, combined with evidence that dividing cells are more sensitive to chemotherapeutic agents than those at rest, suggested that the quiescent primordial follicles may be more resilient to gonadotoxic therapies than dividing cells in activated, growing follicles. Thus, hypothetically, GnRHa were imparting a protective effect on the ovaries by halting the recruitment of primordial follicles into the growing follicle pool [34, 35]. Further animal research demonstrated that gonadal damage was minimized after GnRHa by three additional mechanisms: a decrease in utero-ovarian perfusion that resulted in a lower total cumulative exposure of the ovaries to chemotherapeutic agents, activation of GnRH receptors that led to a decrease in cellular apoptosis, and upregulation of the anti-apoptotic molecule sphingosine-1-phosphate (S1P) [30, 35–41]. However, despite findings that GnRHa acted via these mechanisms in animals to curtail ovarian damage, data from human studies have remained variable [41–46]. It is not clear why reproducing such results in humans has been met with varying degrees of success; however, some speculate that it is because the human ovary has fewer GnRH receptors and thus may not exhibit the same response as the rat or mouse ovary [34, 35, 47]. In addition, because primordial follicles do not possess receptors for FSH or luteinizing hormone (LH), the transition from primordial to preantral follicle appears gonadotropin independent, questioning the hypothesis that suppression

of FSH and LH by GnRHa administration has any ability to lower the cytotoxic effects of chemotherapy. Whatever the explanation, inconsistent results have colored the opinions of practitioners and limited the application of GnRHa as a fertility preservation approach for cancer patients.

Oral Contraceptive Pills (OCPs)

OCPs have been proposed as an alternative means to preserve fertility in women undergoing chemotherapy. The OCP mechanism of action is theorized to be similar to that of GnRHa; OCPs inhibit the secretion of FSH and LH from the pituitary, inducing a prepubertal hypogonadal endocrine milieu [28]. Thus, theoretically, the number of ovarian follicle cells entering the active cell cycle is reduced, and ovarian function is preserved. Similar to the results demonstrated with GnRHa cotreatment, some investigators have shown that the quiescent ovary appears to better tolerate chemotherapy, though overall, the data to support the efficacy of OCP in inhibiting gonadal damage during chemotherapy administration are limited and inconsistent [44, 48, 49]. Like GnRHa, continuous usage of OCP during the course of chemotherapy does have the advantage of decreasing menstrual flow, an important consideration in the setting of anemia, thrombocytopenia, or pancytopenia. Certainly, other than daily administration, side effects associated with OCP are much fewer and better tolerated than those of GnRHa, the latter of which causes a simulated (and quite undesirable) pseudomenopausal state.

Clinical Studies on Medical Suppression

There is a dearth of prospective randomized controlled trials (RCTs) in human subjects that have assessed the efficacy and safety of GnRHa cotreatment in the setting of gonadotoxic chemotherapy to achieve fertility preservation [44, 45]. In those studies that have been reported in the literature, the cancer types, patient ages, treatment protocols, chemotherapeutic agents, and endpoints vary widely. In the majority of trials, the study endpoint was not the ability to conceive but rather the return of spontaneous menses, thereby limiting the applicability of the resultant data for patients desiring fertility preservation (i.e., menses does not equal reproductive potential). Although observational studies have more consistently demonstrated a protective effect from GnRHa cotreatment on ovarian function, unfortunately, the endpoint in these reports has almost exclusively been resumption of menses [50–52]. While some have also measured and assessed hormonal levels in an attempt to quantify ovarian reserve, testing was often performed at random and was thus not altogether useful, or the chosen value to represent “good” ovarian function (e.g., serum FSH levels greater than 24 pg/ml and even up to 40 pg/ml) exceeded that used clinically to positively predict a woman’s capacity for biologic conception.

Similarly, documenting ovulation only as a study endpoint does not guarantee or even portend a future pregnancy, as we know women in their mid-to late 40s most often ovulate but are sterile due to the poor quality of their remaining oocytes.

A recent meta-analysis by Bedaiwy reviewed six RCTs; in all of the studies, analyzed subjects were randomized to receive either chemotherapy alone or chemotherapy plus GnRHa [45]. The incidence of spontaneous menstruation and ovulation was found to be significantly higher in those women who received GnRHa cotreatment (OR 3.46; 95% CI, 1.13–10.57 and OR 5.70; 95% CI, 2.29–14.20), although data for the latter outcome came from only two reports [42, 43]. Only three of the trials reviewed the incidence of spontaneous pregnancy following chemotherapy with GnRHa cotreatment [42, 46, 53]. Analysis of these results showed no statistically significant difference between those patients who had received GnRHa cotreatment and those who did not (OR 0.26; 95% CI, 0.003–2.52).

Although the results from this meta-analysis were encouraging with regard to the impact of GnRHa on maintenance of ovarian function, when the included trials were analyzed individually, serious design flaws were noted that call into question the utility of the overall meta-analysis results. For example, the largest trial included 80 patients (40 in each study arm) for up to 8 months following treatment [43]; the small sample size and short follow-up period invited criticism, not only for this trial but also for others that have demonstrated a beneficial effect for GnRHa cotreatment. Furthermore, in this trial, although the investigators demonstrated a significant difference in the number of women who achieved spontaneous ovulation (69.2% versus 25.6%, respectively), there were concerns about the study protocol—specifically, that accurate randomization seemed improbable after reviewing patient characteristics—that cast doubt on the accuracy and reproducibility of the authors' results [43]. In addition, the investigators did not account for the potential protective effects of tamoxifen therapy on the hormonal status of the study groups.

The largest RCT included in the meta-analysis that utilized pregnancy as an endpoint studied 60 patients (30 in each study arm) [46]. Two pregnancies were achieved in total (one in each study arm), suggesting that GnRHa cotreatment had no beneficial effect on fertility. The investigators of the RCT recently released their final efficacy analysis and not only noted no difference in pregnancy rates between the two study arms but also found no significant difference in the resumption of menses and time to restoration of menses. Moreover, in their discussion, the authors revealed two clinically relevant confounding factors in their trial that could have exaggerated any beneficial effect noted with GnRHa: (1) the patients in the GnRHa group tended to be younger, and (2) the number of chemotherapy cycles administered was lower. Although one observational study [52] did report eight pregnancies in 10 women who received GnRHa cotreatment and were attempting pregnancy, the lack of a comparison group limits the conclusions that can be drawn from these data. In addition, the patients in the study were significantly younger (mean age 34 years) than those in other studies, suggesting that the reassuring results might simply be a function of patient age rather than a protective effect of GnRHa cotreatment.

Ben-Aharon et al. also recently published a comprehensive meta-analysis of studies of GnRHa for fertility preservation in women with cancer [44]. These

authors evaluated 12 comparative clinical trials and concluded that while GnRHa cotreatment reduced amenorrhea rates (RR 0.26, 95% CI 0.14–0.49), this advantage was only found in observational studies and not in RCTs. Furthermore, biomarkers for ovarian reserve were noted to be similar in both arms of their analysis.

Overall, data suggest that the coadministration of GnRHa in the face of gonadotoxic chemotherapy *may* preserve ovarian hormonal function and the ability to achieve spontaneous ovulation. However, it appears that oocyte quality and quantity are likely still diminished despite GnRHa therapy, accounting for the lack of benefit with respect to pregnancy. While longer-term follow-up and larger RCTs might provide additional support for the use of GnRHa as a means to fertility preservation, there is currently insufficient evidence that these agents preserve fertility.

Prepubertal girls present a unique challenge in terms of fertility preservation in that ovarian stimulation cannot be performed prior to menarche. Thus, commonly employed modalities, such as embryo and/or oocyte cryopreservation, are not an option for these individuals. A shortage of viable fertility preservation options has led some practitioners to advocate for the use of GnRHa cotreatment; however, the lack of reliable data [54] demonstrating a positive effect of GnRHa treatment on future fertility makes it difficult to support this approach in prepubertal girls.

Recommendations at Present

Currently, the most compelling indication for the use of GnRHa/OCP cotreatment in reproductive-age women undergoing chemotherapy is to significantly reduce (or discontinue) menstrual bleeding, specifically in the presence of chemotherapy-induced thrombocytopenia and/or anemia. The use of medical suppression for fertility preservation remains debatable. While some studies have demonstrated a significantly higher return to spontaneous menses and ovulation in patients receiving GnRHa cotreatment, they have not been able to consistently demonstrate an improvement in pregnancy rates. Maintenance of ovarian hormonal function is important and should be recognized, but the appropriate primary endpoint for patients electing fertility preservation should be successful pregnancy. Therefore, until data demonstrating a significant improvement in pregnancy outcomes for women receiving GnRHa is produced, GnRHa cotreatment with chemotherapy as an exclusive means to preserve fertility should be recommended with caution.

Conclusions

Advances in assisted reproductive technology, specifically fertility preservation techniques, have revolutionized the options available to patients afflicted with cancer at a time before they have had the opportunity to bear children. Although the past decade has been marked with success and innovation, the potential for further

developments is vast. Collaboration between disciplines, specifically oncologists and reproductive endocrinologists (in cooperation with reproductive biologists), is essential to the continued progress of fertility preservation technology. Furthermore, multidisciplinary efforts will diminish knowledge deficiencies and ensure that all potential fertility preservation candidates are provided with the opportunity to achieve a family. This topic is discussed in greater detail in Chaps. 12, 13 and 14 of this volume.

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References

1. McCall M, Keaty E, Thompson J. Conservation of ovarian tissue in the treatment of the carcinoma of the cervix with radical surgery. Am J Obstet Gynecol. 1958;75:590–600.
2. Nahhas W, et al. Lateral ovarian transposition: ovarian relocation in patients with Hodgkin's disease. Obstet Gynecol. 1971;38:785–8.
3. Baker J, et al. Preservation of ovarian function in patients requiring radiotherapy for paraaortic and pelvic Hodgkin's disease. Lancet. 1972;1:1307–8.
4. Stillman R, Schinfeld J, Schiff I. Ovarian failure in long-term survivors of childhood malignancy. Am J Obstet Gynecol. 1981;139:62–6.
5. Wo J, Viswanathan A. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys. 2009;5:1304–12.
6. Donnez J, Bassil S. Indications for cryopreservation of ovarian tissue. Hum Reprod Update. 1998;4:248–59.
7. Lushbaugh C, Casarett G. The effects of gonadal irradiation in clinical radiation therapy: a review. Cancer. 1976;37 Suppl 2:1111–25.
8. Sella T, Mironov S, Hricak H. Imaging of transposed ovaries in patients with cervical cancer. Am J Roentgenol. 2005;184:1602–10.
9. Clough K, et al. Laparoscopic unilateral ovarian transposition prior to irradiation: prospective study of 20 cases. Cancer. 1996;77:2638–45.
10. Barwijuk A, Jankowska S, Paplicki A. Laparoscopic anterolateral ovarian transposition before irradiation of chordoma. Acta Obstet Gynecol Scand. 2005;84:822–3.
11. Gareer W, et al. Preservation of ovarian germinal follicles by temporary laparoscopic ovarian transposition in teen-aged girls undergoing craniospinal irradiation for radiosensitive CNS tumors. Taiwan J Obstet Gynecol. 2008;47:300–4.
12. Al-Badawi I, et al. Laparoscopic ovarian transposition before pelvic irradiation. Int J Gynecol Cancer. 2010;20:1082–6.
13. Gareer W, Gad Z, Gareer H. Needle oophoropexy: a new simple technique for ovarian transposition prior to pelvic irradiation. Surg Endosc. 2007;25:2241–6.
14. Anderson B, et al. Ovarian transposition in cervical cancer. Gynecol Oncol. 1993;49:206–14.
15. Feeney D, et al. The fate of the ovaries after radical hysterectomy and ovarian transposition. Gynecol Oncol. 1995;56:3–7.
16. Gershenson D. Fertility-sparing surgery for malignancies in women. J Natl Cancer Inst Monogr. 2005;34:43–7.
17. SEER Cervical Cancer Statistics Review. http://seer.cancer.gov/csr/1975_2008/browse_csr.php?section=5&page=sect_05_zfig.03.html. Accessed 24 Jun 2011.

18. Han S-S, et al. Underuse of ovarian transposition in reproductive-aged cancer patients treated by primary or adjuvant pelvic irradiation. J Obstet Gynaecol Res. 2011;37:825–9.
19. Organization for Economic Cooperation and Development. Chart SF2.3A: Mean age of women at the birth of first child. 2008. http://www.oecd.org/dataoecd/62/49/41919586.pdf. Accessed 21 Jun 2011.
20. O'Connell J, et al. Do young colon cancer patients have worse outcome? SEER data. World J Surg. 2004;28:558–62.
21. Critchley H, et al. Abdominal irradiation in childhood; the potential for pregnancy. Br J Obstet Gynaecol. 1992;99:392–4.
22. Kurt M, et al. Successful spontaneous pregnancy in a patient with rectal carcinoma treated with pelvic radiotherapy and concurrent chemotherapy; the unique role of laparoscopic lateral ovary transposition. Eur J Gynaecol Oncol. 2007;28:408–10.
23. Ray G, et al. Oophoropexy: a means of preserving ovarian function following pelvic megavoltage radiotherapy for Hodgkin's disease. Radiology. 1970;96:175–80.
24. Haie-Meder C, et al. Radiotherapy after ovarian transposition: ovarian function and fertility preservation. Int J Radiat Oncol Biol Phys. 1993;25:419–24.
25. Cutillo G, et al. Conservative treatment of reproductive and sexual function in young woman with squamous carcinoma of the vagina. Gynecol Oncol. 2006;103:234–7.
26. Gareer W, Gad Z, Gareer H. Needle oophoropexy: a new simple technique for ovarian transposition prior to pelvic irradiation. Surg Endosc. 2011;25:2241–6.
27. Morice P, et al. Fertility results after ovarian transposition for pelvic malignancies treated by pelvic malignancies treated y external irradiation or brachytherapy. Hum Reprod. 1998;13:660–3.
28. Blumenfeld Z, von Wolff M. GnRH-analogues and oral contraceptives for fertility preservation in women during chemotherapy. Hum Reprod Update. 2008;14:543–52.
29. Glode LM, Robinson J, Gould SF. Protection from cyclophosphamide induced testicular damage with an analogue of gonadotropin-releasing hormone. Lancet. 1981;1:1132–4.
30. Kitajima Y, et al. Hyperstimulation and a gonadotropin-releasing hormone agonist modulate ovarian vascular permeability by altering expression of the tight junction protein claudin-5. Endocrinology. 2006;147:694–9.
31. Sutcliffe SB. Cytotoxic chemotherapy and gonadal function in patients with Hodgkin's disease: facts and thoughts. JAMA. 1979;242:1898–9.
32. Ortin TT, Shoshlak CA, Donaldson SS. Gonadal status and reproductive function following treatment of Hodgkin's disease in childhood: the Stanford experience. Int J Radiat Oncol Biol Phys. 1990;19:873–80.
33. Wallace WH, et al. Ovarian function following the treatment of childhood acute lymphoblastic leukemia. Med Pediatr Oncol. 1993;21:333–9.
34. Lobo RA. Potential options for preservation of fertility in women. N Engl J Med. 2005;353:64–73.
35. Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embryo, oocytes or ovaries. Oncologist. 2007;12:1044–54.
36. Saitta A, et al. Randomized, double-blind, placebo-controlled study on effects of raloxifene and hormone replacement therapy on plasma no concentrations, endothelin-1 levels, and endothelium-dependent vasodilation in postmenopausal women. Arterioscler Thromb Vasc Biol. 2001;21:1512–9.
37. Grudker C, Emons G. Role of gonadotropin-releasing hormone (GnRH) in ovarian cancer. Reprod Biol Endocrinol. 2003;1:65–71.
38. Imai A, et al. Direct protection by a gonadotropin-releasing hormone analog from doxorubicin-induced granulosa cell damage. Gynecol Obstet Invest. 2007;63:102–6.
39. Perez GI, et al. Apoptosis associated signaling pathways are required for chemotherapy-mediated female germ cell destruction. Nat Med. 1997;3:1228–32.
40. Morita Y, et al. Targeted expression of Bcl-2 in mouse oocytes inhibits ovarian follicle atresia and prevents spontaneous and chemotherapy-induced oocyte apoptosis in vitro. Mol Endocrinol. 1999;13:841–50.

41. Morita Y, et al. Oocyte apoptosis is suppressed by disruption of the acid sphingomyelinase gene or by sphingosine-1-phosphate therapy. Nat Med. 2000;6:1109–14.
42. Waxman JH, et al. Failure to preserve fertility in patients with Hodgkin's disease. Cancer Chemother Pharmacol. 1987;19:159–62.
43. Badawy A, et al. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. Fertil Steril. 2009;91:694–7.
44. Ben-Aharon I, et al. Pharmacological intervention for fertility preservation during chemotherapy: a systematic review and meta-analysis. Breast Cancer Res Treat. 2010;122:803–11.
45. Bedaiwy M, et al. Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: a systemic review and meta-analysis. Fertil Steril. 2011;95:906–14.
46. Gerber B, et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy. The GBG 37 ZORO study. J Clin Oncol. 2010;29:2334–41.
47. Lutchman Singh K, Davies M, Chatterjee R. Fertility in female cancer survivors: pathophysiology, preservation and the role of ovarian reserve testing. Hum Reprod Update. 2005;11:69–89.
48. Chapman RM, Sutcliffe SB. Protection of ovarian function by oral contraceptives in women receiving chemotherapy for Hodgkin's disease. Blood. 1981;58:849–51.
49. Longhi A, et al. Effect of oral contraceptive on ovarian function in young females undergoing neoadjuvant chemotherapy treatment for osteosarcoma. Oncol Rep. 2003;10:151–5.
50. Recchia F, et al. Gonadotropin-releasing hormone analogues added to adjuvant chemotherapy protect ovarian function and improve clinical outcomes in young women with early breast carcinoma. Cancer. 2006;106:514–23.
51. Del Mastro L, et al. Prevention of chemotherapy-induced menopause by temporary ovarian suppression with goserelin in young, early breast cancer patients. Ann Oncol. 2006;17:74–8.
52. Urruticoechea A, et al. Ovarian protection with goserelin during adjuvant chemotherapy for pre-menopausal women with early breast cancer (EBC). Breast Cancer Res Treat. 2008;110:411–6.
53. Giuseppe L, et al. Ovarian function after cancer treatment in young women affected by Hodgkin disease (HD). Hematology. 2007;12:141–7.
54. Pereyra Pacheco B, et al. Use of GnRH analogues for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: a preliminary report. Gynecol Oncol. 2001;81:391–7.