ASSESSING THE UPDATED ANESTHESIA PROTOCOLS FOR PATIENTS UNDERGOING FERTILITY PRESERVATION PROCEDURES LIKE OOCYTE RETRIEVAL AND OVARIAN TRANSPOSITION BEFORE CANCER TREATMENT

ABSTRACT

The preservation of fertility is a highly important consideration for patients undergoing cancer treatment, especially those requiring procedures such as egg retrieval or ovarian transplantation. These procedures pose unique challenges because they require anesthesia protocols that ensure patient safety while preserving fertility. Recent advances in anesthesia techniques offer promising opportunities to optimize the outcomes of fertility-sparing procedures. The conventional anesthesia approaches for fertility preservation procedures include general anesthesia, which has risks and may not be the best option for all patients, especially those with underlying medical conditions. However, in recent years, there has been a shift toward alternative anesthesia methods, such as opting for regional anesthesia techniques such as spinal anesthesia and epidural anesthesia, and monitored anesthesia (MAC). These approaches have benefits such as reduced systemic impact, reduced recovery time, and improved postoperative pain management. Egg retrieval is an important step in preserving fertility for female cancer patients. Modern anesthesia protocols, particularly the use of regional techniques such as transvaginal ultrasound-guided paracervical blocks and spinal anesthesia, have been shown to improve patient comfort and safety during the procedure. Studies have reported comparable oocyte retrieval rates and fertilization outcomes between patients who underwent oocyte retrieval

under local and general anesthesia. Additionally, local anesthesia techniques are associated with lower rates of postoperative complications and shorter hospital stays. This literature review aims to assess the effectiveness of modern anesthesia protocols in promoting successful fertility preservation in patients undergoing oocyte retrieval and ovarian transposition before cancer treatment. It will help reflect on the pros and cons that make these updated techniques an excellent choice to be utilized in such challenging situations.

Keywords: reproductive ages, fertility, fertility preservation, ovarian reserve, oocyte preservation, uterine transplantation.

INTRODUCTION

The treatments for oncological diseases are known to have a potential impact on a patient's fertility, and a variety of factors influence the magnitude of this impact. (1)

According to current research, factors such as the patient's age at the start of treatment, treatment duration, severity, and type play an important role in determining the degree of fertility impairment. Although cancer primarily affects older adults, it can also affect children, adolescents, and young adults. (2)

In particular, survival rates are highest for individuals between the ages of 15 and 44 years, with 5-year survival rates ranging from 60% to 82%, depending on factors such as age, location of the tumor, and the country's healthcare system. (3)

The cancer incidence reported by India's National Cancer Registry shows an alarming trend, with an expected annual increase from about 980,000 cases in 2010 to 1.14 million cases in 2020. (4)Given these statistics, the concept of fertility preservation has received considerable attention. Fertility preservation involves strategies aimed at preserving an individual's or couple's fertility and allowing them to start a family at a later date if desired. The term "cancer infertility" or "oncofertility" specifically refers to the maintenance of fertility in cancer patients.(5)

Importantly, it is becoming increasingly important to incorporate fertility preservation considerations into the comprehensive care of cancer patients. Advances in cancer treatment, particularly treatments that target the genital tract, including some cancers, such as endometrial cancer and testicular cancer, have led to improved treatment efficacy, longer survival rates, and significant advances in infertility treatment. (6)As a result, healthcare providers are being forced to prioritize discussions of fertility preservation options alongside cancer treatment strategies to optimize the overall well-being and quality of life of these individuals. (7)

THE IMPACT OF CANCER ON THE FERTILITY STATUS OF MALES AND FEMALES

The negative effects of cancer treatment on ovarian function are a major concern for young patients. Direct radiation damage within a radiation field affects all female reproductive organs, but scattered radiation can cause damage even when shielding measures are taken.(8)

Chemotherapy and radiation are toxic to the ovaries and have been shown to increase the risk of early menopause, ovarian endocrine disorders, infertility, and premature ovarian failure (POF). (9)The degree of reduction in ovarian reserve depends on factors such as the age of the patient, the specific chemotherapy drug used (alkylating agents being the most risky ones), and the duration of treatment.(10)

Radiotherapy poses the risk of damaging both fertility and hormone production, and radiation has a particularly negative effect on eggs. Radiation to the hypothalamus, pituitary gland, and pelvis, alone or in combination with alkylating drugs, has been associated with acute ovarian failure and early menopause. (11)

In particular, exposure to radiation doses of 20–30 Gy (Gy) or whole-body radiation of 15 Gy can cause ovarian dysfunction. (12)Low doses, such as less than 6 Gy for adult women, less than 10 Gy for post-pubertal women, and less than 15 Gy for pre-pubertal women, pose a significant risk of infertility throughout the pelvis or abdomen. Of particular concern is the increased sensitivity of the gonads to radiation during the pre-pubertal stage, where even minimal exposure can cause significant oocyte loss.(13)

Considering that fertility decline in young women with cancer is multifactorial, including cancer treatment, older age, and underlying reproductive disorders, maintaining egg quantity and quality is critical to fertilization and embryonic development. It has emerged as an important consideration for successful development. (14)

Therefore, egg preservation strategies, whether implemented before, during, or after cancer treatment, are of paramount importance to reduce the negative effects on fertility and improve future parenting prospects for these individuals. (15)

Similarly, in male cancer patients, impaired sperm transport may be caused by impaired sperm production or decreased spermatogonial stem cell numbers. Both radiotherapy and anticancer drugs can have negative effects on spermatogonia, and increased sensitivity is observed during the differentiation stage.(16) However, late-stage germ cells exhibit greater resistance to cell-killing effects, allowing continued sperm production despite the initial decrease in spermatogonia after cancer treatment.(17)

PROPOSED TECHNIQUES FOR THE PRESERVATION OF FERTILITY IN FEMALE PATIENTS BEFORE CANCER SURGERY

Among the several methods that are proposed for the preservation of fertility in female cancer patients, a few commonly proposed ones have been overviewed as under.

Oocyte retrieval for freezing, in vitro fertilization (IVF) of the retrieved eggs, and subsequent cryopreservation of the embryos represent an established approach that relies on the availability of a male partner or sperm donor for fertilization. (18)

Embryo cryopreservation based on the total number and quality of frozen embryos has a high success rate and is therefore a viable option for fertility preservation. (19)In particular, in patients with certain malignancies such as low- and intermediate-risk Hodgkin's lymphoma and low-grade sarcomas, the possibility of cryopreservation of embryos, if oncological treatment can be postponed for oocyte stimulation cycles, should be taken into account. Challenges associated with this process include the need for a reliable male partner, legal considerations regarding embryo processing, and the duration of ovarian stimulation.(20)

Another approach, ovarian tissue cryopreservation (OTC), freezes ovarian tissue containing primordial follicles, eliminating the need for ovarian stimulation.(21) This technique is usually performed laparoscopically and preserves the ovarian cortex in a frozen state outside the body. OTC is particularly attractive for fertility preservation, especially in prepubertal cancer patients, and is recognized as a standard of care by the American Society of Reproductive Medicine. Transplanted ovarian tissue can be reimplanted orthotopically within the pelvis or ectopically outside the pelvis, providing flexibility in treatment options.(19)

Additionally, ovarian transposition or ovariopexy represents a method of protecting the ovary from radiation exposure by removing it from the radiation field. However, the effectiveness of this approach depends on the radiation distribution, and patients must be informed of its limitations and potential risks, including the possibility of ovarian remigration.(22)

CHOICE OF ANESTHESIA AND THEIR PROPOSED UPDATED PROTOCOLS FOR FERTILIZATION PRESERVATION TECHNIQUES

The Enhanced Recovery After Surgery (ERAS) guidelines provide valuable insight into the perioperative care of gynecological/oncology patients. The ERAS approach focuses on preoperative, intraoperative, and postoperative interventions and aims to reduce mortality, complications, and length of hospital stay, thereby preventing readmissions.(23)

However, certain clinical scenarios pose challenges to anesthesia management during fertility-sparing surgery and require a tailored approach within ERAS. Notable challenges include laparoscopy in patients with high BMI, fluid management in early stage 1C epithelial ovarian cancer, and anesthesia management in uterine transplantation.(24)High BMI (>25 kg/m2) significantly increases the risk of developing endometrial cancer worldwide, posing challenges to surgical treatment. (25)

Surgeons increasingly encounter patients with high BMI who are at increased risk of morbidity and mortality. Considerations in the perioperative care of patients with high BMI include difficult airway management, pre-existing respiratory complications affecting intraoperative ventilation, postoperative respiratory complications, difficulty in venous access, and drug handling and administration.(26) These include changes in volume, pressure ulcer risk, and increased venous thromboembolism risk. In particular, increased BMI correlates with the risk of converting from laparoscopic to open surgery, leading to surgical complications such as wound infection, postoperative pain, and prolonged hospital stay.(27)

In women undergoing radical debulking of stage 1C epithelial ovarian cancer, fluid management is critical due to associated paraneoplastic syndromes and complex medical symptoms. Some of these patients who still have the potential to become pregnant may prioritize fertility preservation and need to optimize their physiological status preoperatively to reduce surgical complications.(28)

Women with advanced ovarian cancer often suffer from several preoperative problems, such as ascites, anemia, and malnutrition. Corrective measures, such as blood and iron transfusions for anemia and nutritional support for hypoalbuminemia, are an important part of preoperative care. Intraoperative fluid management poses additional complications, further complicated by factors such as anesthetic-induced hypotension, positive pressure ventilation, and local anesthesia-induced venous dilatation.(29)

Patients with ascites are at increased risk as a large amount of extracellular fluid can be expected to be lost during surgery. Targeted fluid therapy to maintain true blood volume using inotropes and intravenous fluids is important. (30)

Achieving intraoperative normovolemia is associated with fewer surgical complications, shorter hospital stays, and avoidance of ileus. During major abdominal surgery, extended hemodynamic monitoring is recommended to facilitate fluid resuscitation, especially when significant blood loss or systemic inflammatory response is anticipated. (31)

Intravenous fluids should be adjusted to optimize cardiac performance while avoiding fluid overload. Vasopressors are used to maintain mean arterial pressure after intravascular volume normalizes. Regular arterial blood gas analysis provides valuable insight into oxygenation, ventilation, anion gap, and lactate levels and guides further fluid management. (32)

In cases of electrolyte imbalance and excessive protein loss, albumin infusion (20%) may be considered to correct these issues. Furthermore, patients with ascites are at increased risk of renal hypoperfusion and hypothermia and require careful monitoring and aggressive treatment.(33)

Additionally, up to 50% of ovarian cancer patients may require blood transfusions during or postoperatively, highlighting the importance of strategies to minimize intraoperative blood loss. There is evidence that a single dose of tranexamic acid can effectively reduce intraoperative blood loss without increasing the risk of thromboembolic events.(34)

The utilization of living donors in uterine transplantation offers distinct advantages, notably the ability to conduct comprehensive preoperative assessments. However, this approach is not without risks, primarily stemming from the surgical procedure itself. Analysis of data from the initial 45 uterine transplantation cases reveals that living donors have a mean age of 45.4 years. Notably, the retrieval surgery for living donors resembles a radical hysterectomy, a procedure typically performed on much older patients (median age 65 years) undergoing debulking for ovarian malignancies. (35)

Hence, it is important to note that women undergoing uterine transplantation are significantly younger, typically with reduced pre-anesthetic medical comorbidities. This is further ensured through strict inclusion criteria, including a BMI < 30, ASA physical status 1, and absence of renal pathology.(36)

However, challenges associated with living donors persist, particularly concerning cold ischemic time, defined as the duration between organ retrieval and subsequent implantation. Minimizing cold ischemic time is crucial, as prolonged durations are associated with ischemic-reperfusion injury, acute and chronic allograft dysfunction, and systemic inflammation. (15)

Notably, 29% of uterine transplantation patients have required emergency hysterectomy, with a majority of cases attributed to complications of graft thrombosis. Nonetheless, superior transplant outcomes are observed among living donors, likely due to shorter cold ischemic times compared to deceased donors, highlighting the importance of timely transplantation.(37)

CONCLUSION

Anesthesia protocols for ovarian reserve management are essential in ensuring the safety and efficacy of medical procedures involving ovarian manipulation. Through comprehensive preoperative assessment and tailored anesthesia regimens, medical professionals aim to minimize potential risks while optimizing patient outcomes. These protocols comprise careful consideration of factors such as patient age, medical history, surgical complexity, and the desired reproductive goals. By employing appropriate anesthesia techniques, monitoring vital signs, and mitigating intraoperative complications, healthcare providers can contribute to preserving ovarian function and fertility potential. Despite the inherent risks associated with surgery, meticulous preoperative assessments and adherence to strict donor selection criteria in uterine transplantation can help mitigate potential complications. Challenges such as cold ischemic time underscore the importance of timely transplantation and ongoing advancements in surgical techniques. While living donor transplantation offers advantages over deceased donor procedures, ongoing research, and clinical experience will continue to refine protocols and improve outcomes. With careful consideration of risks and benefits, uterine transplantation holds the potential to revolutionize fertility treatment for women with absolute uterine factor infertility.

REFERENCES

1. Yi M, Li T, Niu M, Luo S, Chu Q, Wu K. Epidemiological trends of women’s cancers from 1990 to 2019 at the global, regional, and national levels: a population-based study. Biomark Res. 2021 Jul 7;9:55.

2. Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, et al. The global burden of women’s cancers: an unmet grand challenge in global health. Lancet Lond Engl. 2017 Feb 25;389(10071):847–60.

3. Sheikhalipour Z, Ghahramanian A, Fateh A, Ghiahi R, Onyeka TC. Quality of Life in Women with Cancer and Its Influencing Factors. J Caring Sci. 2019 Mar 1;8(1):9–15.

4. Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. Indian J Med Res. 2022;156(4–5):598–607.

5. Jensen JR, Morbeck DE, Coddington CC. Fertility Preservation. Mayo Clin Proc. 2011 Jan;86(1):45–9.

6. González C, Boada M, Devesa M, Veiga A. Concise Review: Fertility Preservation: An Update. Stem Cells Transl Med. 2012 Sep;1(9):668–72.

7. Peterson AM, Singh M. Fertility Preservation in Benign and Malignant Conditions. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Apr 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK576435/

8. Pinelli S, Basile S. Fertility Preservation: Current and Future Perspectives for Oncologic Patients at Risk for Iatrogenic Premature Ovarian Insufficiency. BioMed Res Int. 2018 Jul 11;2018:6465903.

9. Chen H, Liu C, Zhu S, Li S, Zhang Q, Song L, et al. The Therapeutic Effect of Stem Cells on Chemotherapy-Induced Premature Ovarian Failure. Curr Mol Med. 2021 Aug 5;21(5):376–84.

10. Mauri D, Gazouli I, Zarkavelis G, Papadaki A, Mavroeidis L, Gkoura S, et al. Chemotherapy Associated Ovarian Failure. Front Endocrinol. 2020 Dec 8;11:572388.

11. Wo JY, Viswanathan AN. The Impact of Radiotherapy on Fertility, Pregnancy, and Neonatal Outcomes of Female Cancer Patients. Int J Radiat Oncol Biol Phys. 2009 Apr 1;73(5):1304–12.

12. Marci R, Mallozzi M, Di Benedetto L, Schimberni M, Mossa S, Soave I, et al. Radiations and female fertility. Reprod Biol Endocrinol RBE. 2018 Dec 16;16:112.

13. Gao W, Liang JX, Yan Q. Exposure to radiation therapy is associated with female reproductive health among childhood cancer survivors: a meta-analysis study. J Assist Reprod Genet. 2015 Aug;32(8):1179–86.

14. Himpe J, Lammerant S, Van den Bergh L, Lapeire L, De Roo C. The Impact of Systemic Oncological Treatments on the Fertility of Adolescents and Young Adults—A Systematic Review. Life. 2023 May 18;13(5):1209.

15. Waimey KE, Smith BM, Confino R, Jeruss JS, Pavone ME. Understanding Fertility in Young Female Cancer Patients. J Womens Health. 2015 Oct 1;24(10):812–8.

16. Dohle GR. Male infertility in cancer patients: Review of the literature. Int J Urol Off J Jpn Urol Assoc. 2010 Apr;17(4):327–31.

17. Yumura Y, Takeshima T, Komeya M, Karibe J, Kuroda S, Saito T. Long-Term Fertility Function Sequelae in Young Male Cancer Survivors. World J Mens Health. 2023 Apr;41(2):255–71.

18. Rose BI. Approaches to oocyte retrieval for advanced reproductive technology cycles planning to utilize in vitro maturation: a review of the many choices to be made. J Assist Reprod Genet. 2014 Nov;31(11):1409–19.

19. Estudillo E, Jiménez A, Bustamante-Nieves PE, Palacios-Reyes C, Velasco I, López-Ornelas A. Cryopreservation of Gametes and Embryos and Their Molecular Changes. Int J Mol Sci. 2021 Oct 8;22(19):10864.

20. Konc J, Kanyó K, Kriston R, Somoskői B, Cseh S. Cryopreservation of embryos and oocytes in human assisted reproduction. BioMed Res Int. 2014;2014:307268.

21. Prasath EB. Ovarian tissue cryopreservation: An update. J Hum Reprod Sci. 2008;1(2):50–5.

22. Rivas Leonel EC, Lucci CM, Amorim CA. Cryopreservation of Human Ovarian Tissue: A Review. Transfus Med Hemotherapy. 2019 Jun;46(3):173–81.

23. Santiago AE, Filho AL da S, Cândido EB, Ribeiro PA, Silva JCR e, Primo WQSP, et al. Perioperative management in gynecological surgery based on the ERAS program. RBGO Gynecol Obstet. 2022 Feb 25;44(2):202–10.

24. Slavchev S, Yordanov A. Enhanced Recovery After Surgery (ERAS) protocol in minimally invasive gynecological surgery: a review of the literature. Pol Przegl Chir. 2022 Aug 12;95(3):1–5.

25. Peng J, Dong R, Jiao J, Liu M, Zhang X, Bu H, et al. Enhanced Recovery After Surgery Impact on the Systemic Inflammatory Response of Patients Following Gynecological Oncology Surgery: A Prospective Randomized Study. Cancer Manag Res. 2021 Jun 1;13:4383–92.

26. Bajsová S, Klát J. ERAS protocol in gynecologic oncology. Ceska Gynekol. 2019;84(5):376–85.

27. Bisch SP, Nelson G. Outcomes of Enhanced Recovery after Surgery (ERAS) in Gynecologic Oncology: A Review. Curr Oncol. 2022 Jan 28;29(2):631–40.

28. Morosan M, Popham P. Anaesthesia for gynaecological oncological surgery. Contin Educ Anaesth Crit Care Pain. 2014 Apr 1;14(2):63–8.

29. Savant SS, Sriramkumar S, O'Hagan HM. The Role of Inflammation and Inflammatory Mediators in the Development, Progression, Metastasis, and Chemoresistance of Epithelial Ovarian Cancer. Cancers. 2018 Jul 30;10(8):251.

30. Szender JB, Emmons T, Belliotti S, Dickson D, Khan A, Morrell K, et al. Impact of ascites volume on clinical outcomes in ovarian cancer: A cohort study. Gynecol Oncol. 2017 Sep;146(3):491–7.

31. Cybulska P, Goss C, Tew WP, Parameswaran R, Sonoda Y. Indications for and complications of transfusion and the management of gynecologic malignancies. Gynecol Oncol. 2017 Aug;146(2):416–26.

32. Laky B, Janda M, Bauer J, Vavra C, Cleghorn G, Obermair A. Malnutrition among gynaecological cancer patients. Eur J Clin Nutr. 2007 May;61(5):642–6.

33. Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A, Meyer LA, et al. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2019 May;29(4):651–68.

34. Carter J, Rowland K, Chi D, Brown C, Abu-Rustum N, Castiel M, et al. Gynecologic cancer treatment and the impact of cancer-related infertility. Gynecol Oncol. 2005 Apr 1;97(1):90–5.

35. Lundin ES, Johansson T, Zachrisson H, Leandersson U, Bäckman F, Falknäs L, et al. Single-dose tranexamic acid in advanced ovarian cancer surgery reduces blood loss and transfusions: double-blind placebo-controlled randomized multicenter study. Acta Obstet Gynecol Scand. 2014 Apr;93(4):335–44.

36. Di Donato V, Kontopantelis E, Aletti G, Casorelli A, Piacenti I, Bogani G, et al. Trends in Mortality After Primary Cytoreductive Surgery for Ovarian Cancer: A Systematic Review and Metaregression of Randomized Clinical Trials and Observational Studies. Ann Surg Oncol. 2017 Jun;24(6):1688–97.

37. Kasaven LS, Jones BP, Keays R, Saso S. Anaesthetic considerations for fertility-sparing surgery and uterine transplantation. Anaesthesia. 2021 Apr;76 Suppl 4:46–55.