

Recent advances for improving fertility in gynaecological cancer patients

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Abstract. – 15% of cancers affecting women are of gynaecologic origin, thereby most of them affect fertility of the women who are in reproductive age indirectly by their treatment protocols including chemotherapy, radiotherapy, etc. Chances of getting pregnant is the crucial point of concern in these patients as pathological state of these women potentially limits chances of giving birth to new born. However, current advances in our understanding of these diseases, along with improved multimodality treatments, allow for consideration of fertility options.

So, the present review shall enlighten technological advancements available including robotic surgical procedures, fertility preservation innovations and other latest developments in the area for improvising fertility options in gynaecological cancer patients.

Key Words:

Gynaecological cancer, Infertility, Robotic surgery, Zinc.

Introduction

Cancers that invade female reproductive systems viz. ovaries, fallopian tubes, uterus, vagina, cervix and the associated organs are all collectively bunched under solitary term called gynaecological cancer¹. Furthermore, 80% of above cancers are reported in the developing countries². The nomenclature of gynaecological cancer is also classified on the basis of reproductive organ affected thereby leading to different gynaecological cancer types. Gynaecological cancers that are widely reported include ovarian cancer as it begins in ovaries; cervical cancer affects tissues of the cervix and endometrial cancer that originate from the lining of the uterus or womb. On the other hand, rare types of gynaecological cancers include cancer in fallopian tubes called fallopian tube cancer; vulvar cancer that represents cancer

of external female genitals and vaginal cancer which exists in the canal that leads from a woman's cervix to the vulva.

Gynaecological cancer is the result of multiple causing factors including viruses, gene mutations and hormone imbalance. Infection with human papilloma virus leads to cervical cancer³. On the other hand, gene mutations of BRCA1 or BRCA2 have been reported to cause ovarian cancer^{4,5}. Also, hormonal conditions such as polycystic ovary syndrome and endometriosis are associated with ovarian cancer, but the link is not completely confirmed. Excessive exposure to the hormone estrogen results in development of endometrial cancer⁶. Obesity is another causative factor leading to endometrial cancer in 40% of cases⁷. So, gynaecological cancer is a result of multiple causes and a lot of research is being focused to help woman fight this life threatening disorder. However, besides this in order to cure above pathological state many therapeutic procedures are in use that include chemotherapy, radiation therapy, surgical interventions, target specific immune-therapies and stem cell therapy. The major point of concern here is that these therapeutic advances provide some relief from the growing disease but are associated with many side effects. One of the major side effects of these therapies is inability of a woman to become pregnant. Cancer, or more often cancer treatments, interfere with some part of the in-vivo physiological process and affect woman's ability to have children⁸. The present review shall put light on this area of woman cancer. Also, latest alternatives being explored worldwide to prevent infertility in these women with gynaecological cancers will be discussed.

Therapeutic Procedures and Fertility

Fertility is often compromised for life in women with gynaecological cancer⁹. Most com-

mon and first line of treatment when woman diagnosed with gynaecological cancer is chemotherapy. It involves use of toxic chemicals and the widely used chemo-therapeutic drugs in use include cisplatin, carboplatin, doxorubicin, etc.¹⁰. These can cause instant death in cancer cells. On the other hand, woman has fixed number of eggs stored in their ovarian sacs right from their birth. So, these chemo-therapeutic drugs have major flaw pertaining to their lack of specificity. In other words, they don't target cancer cells specifically, instead nearby normal cells also become target of chemotherapy^{11,12}. In gynaecological cancers, these normal cells include ovarian sacs enclosing eggs inside. Damage to ovarian sacs means permanent damage to eggs and that in turn result in infertility as woman is unable to make new eggs because they are fixed in number right from birth.

Radiation treatments involve use of high-energy radiations to destroy cancer cells¹³. These rays can also damage a woman's ovaries. For a woman getting radiation therapy to the abdomen (belly) or pelvis, the amount of radiation absorbed by the ovaries will determine if she becomes infertile. High doses can destroy some or all of the eggs in the ovaries and might result in infertility or early menopause. Even if the radiation is not aimed right at the ovaries, the rays can bounce around inside the body and might still damage the ovaries. Furthermore, when the radiation is directed inside the vagina, the ovaries absorb a high dose of radiation resulting in direct damage to ovarian sacs. Moreover, radiation to the uterus can cause scarring, which restricts flexibility and blood flow to the uterus¹⁴. These problems can limit the growth and expansion of the uterus during pregnancy, and increase the risk of miscarriage, low-birth weight infants, and premature births. On other hand, radiation can result in infertility indirectly when radiation is targeted towards brain. In these cases, radiation targeted towards brain affects the pituitary gland which normally signals the ovaries to make hormones. So, any damage to pituitary gland can interfere with natural process of ovulation which ultimately results in infertility. The radiation therapy is used in the form ¹³¹I which has ability to cause instant damage to cancer cells due to its high linear energy transfer (LET).

Highly specific anti cancer drugs are the latest drugs that collectively termed under targeted therapy¹⁵. Targeted therapy exploits antibody-antigen specificity to target cancer cells specifi-

cally. For example, drug rituximab is basically a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells¹⁶. It destroys B cells that are present in excessive numbers in cancer cells. As compared to chemotherapeutic drugs, targeted therapy has fewer reports with regard to infertility in woman undergoing treatment. However, Bevacizumab (Avastin®) is one such exception in targeted therapies that has been reported to cause ovarian failure resulting permanent infertility¹⁷. Further, in latest stem cell/bone-marrow transplant therapy, patient is often exposed to high doses of chemo and sometimes radiation to the whole body before the transplant. This permanently stops a woman's ovaries from releasing eggs.

Women affected by gynaecological cancer, sometimes advised to get hysterectomy for the survival as there is risk of malignancy and spread to other organs. A hysterectomy is surgery to remove the affected organ like uterus (womb) or ovary. Once the uterus is removed, a woman cannot carry a child. The surgical removal of ovaries is called an *oophorectomy*. Without ovaries, a woman can't get pregnant because she no longer has any eggs. Sometimes surgery can result in scarring in the fallopian tubes. These scars ultimately block the tubes and prevent eggs from fusing with the sperm and hence cause infertility.

Robotic Surgical Intervention-A Ray of Hope

Technological advancement in any field helps to enhance efficiency, reduce time and provide better results. Similarly, in the recent past technological advancements in the form of robotic support to the gynaecology oncologists/surgeons have really proved to be a great asset to the patients especially with regard to fertility and other associated complications. Conventional surgical operations are usually associated with various limitations like lack of depth perception, two-dimensional optics, camera instability, limited range of motion, and steep learning curves. So, this lack of precision makes the surgical procedure less specific and leads to removal of normal tissues including ovarian sacs that ultimately causes infertility. On the other hand, with robotic assistance improved three-dimensional stereoscopic vision is possible for better clarity of affected area. Robotic assistance also enhances dexterity of the surgeons as well as moderate had tremors during surgery. Moreover, it improvises

surgical precision to great extent. All these collectively contribute towards fast, less invasive surgical intervention as less invasive is now the standard care for both benign as well as malignant tumors^{18,19}. Moreover, many recent observations have confirmed the efficacy of robotic approach in varied gynaecological cancers including endometrial cancer, ovarian cancer and cervical cancer^{20,21}. Moreover, other complications like blood loss and spread of infection were also significantly less in robotic assisted surgeries as compared to conventional ones²².

To retain fertility during gynaecological cancer treatment, alternative therapies have been initiated long back in the form of vaginal radical trachelectomy using the Dargent technique ovarian cancer patients and was successful in retaining fertility in 70% of cases^{23,24}. However, the above procedure was highly complex and involved mobilization of ureter. So, a whole lot of complications were involved in radical trachelectomy. On the other hand, preamble of robotic assistance offered greater efficiency and made the procedure simpler as well as more precise. With robotic assistance, more than 85% cases showed fertility preservation upon arrival of robotic assistance confirming its expediency²⁵.

Moreover, with its less invasive nature, it also helps to reduce recurrent ovarian cancer cases²⁶. The only drawback of robotic assistance is the cost factor as it is highly expensive for both the hospitals to have this facility followed by training as well as running cost. Also, patients get affected by steep hike in the cost of anti-cancer treatment with robotic assistance.

Computer Assisted Surgery

Computer assisted surgical intervention is another latest technological advancement in the field of surgical procedures against gynaecological cancers²⁷. With the advanced technological interventions with computer assistance it is now possible for the surgeons to preserve ovarian follicles during surgical operation during gynaecological cancer to preserve fertility. In simple words, computer assisted surgery can be described as computer-assisted laparoscopy combined with intuitive operative environment of open surgery with the minimal invasiveness of laparoscopy. Moreover, the utilization of computer technology allows prevention of swivel effect caused by the passage of instruments through the fixed point of the anterior abdominal wall. Also, studies in recent past confirmed that

computer-assisted laparoscopy helped inexperienced users to complete complex laparoscopic tasks with less training, greater efficiency, and reduced operator workload compared with conventional laparoscopy^{28,29}.

Trace Element Supplementation and Fertility

Trace elements, no doubt play an essential role in maintenance of adequate physiological homeostatic balance for proper growth as well as fitness of the organism³⁰. Although, they are required to be taken in minute quantities but their deficiency can affect enzymatic reactions, respiratory system, molecular physiology, immune functionalities, reproduction and overall optimum health of the individual. Zinc is the trace element whose deficiency can lead to cancer including colon, lung, pancreatic and gynecological cancers. Studies, in recent past have also proved the anti-cancer properties of zinc in the experimental models of cancers³¹. On the other hand, besides its anti-cancer properties, it also contributes towards reproductive health of females. During menses and follicular phase, normal women show increased plasma Zn levels which start receding during the ovulation and luteal phases³². Plasma Zn concentrations are high during menses and the follicular phase, and then decline during the ovulation and luteal phases. This change in Zn concentration is connected to hormonal changes and plasma albumen variations. Lowered serum Zn levels are related to risk factors during pregnancy, and labor complications. However, supplementation with Zn results in fewer complications³³. Virgin female mice fed on a Zn-deficient diet demonstrated a reduced and shrunken corpus luteum, lack of pre ovulatory Graafian follicles, and a fragmented zona pellucida and vitelline membrane which suggested termination of oogenesis and ovulation³⁴. So, supplementation of zinc to the patients undergoing cancer treatment can help them to fight against the state of infertility. It is the only single option available that is preventive in nature and can help human race to prevent themselves from the deadly pathological state as well as depressing situation of infertility later on.

Surgical Preservation of Fertility

As discussed earlier that some advanced cancer stages only allow surgery as an option for the survival of the patient during gynaecological cancer. Further, more this surgery sometimes in-

volves certain parts of the reproductive system can cause infertility. So, in recent years to overcome this problem selective surgery technique is in use that helps to treat against cancer as well as allow the patient to preserve its fertility. For example, in some women with early stage ovarian or cervical cancer, the surgeon will try to save one ovary, if possible, to preserve eggs, which might still allow a woman to become pregnant. Keeping at least one ovary also preserves the hormones that prevent menopause symptoms like hot flashes and vaginal dryness. Some women with small cervical cancers can have a surgery called a *trachelectomy*, which removes the cervix but leaves the uterus behind so a woman can carry a pregnancy.

Conclusions

It is clear from the above discussion that scientific community is working on various avenues for the better management of fertility concerns in gynecological patients. However, more studies are required in the area for the further betterment of women suffering from this pathological state.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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