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Editorial

Impact of Breast Cancer Treatment on Ovarian Function and Fertility

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Introduction

Breast cancer is the most frequent malignancy among women of reproductive age. Approximately 13% of all breast cancer cases are diagnosed in women younger than 45 years of age [1]. Prevalence of breast cancer is rising among younger women due to changed lifestyle. With the advances in the field of therapeutic modalities in terms of chemotherapy, hormonal therapy, radiotherapy and surgical interventions for breast cancer, long term prognosis of patients diagnosed with early stage breast cancer is excellent. But improved life expectancy for the reproductive-age group of women has raised the problems of fertility preservation because of chemotherapy-induced amenorrhea. Aggressive chemotherapy causes infertility or premature ovarian failure due to destruction ovarian reserve [2]. In comparison with young women, older women have higher incidence of ovarian failure because of large primordial follicle reserve among young women declines with age [3]. Most of the young patients diagnosed with the breast cancer have significant anxiety and lack of information about the reproductive issues and fertility related concerns significantly affect their quality of life.

Impact of chemotherapy on ovarian reserve

Adjuvant chemotherapy has an impact on the fertility and ovarian function depending on the age of the patients and cumulative dose and type of specific cytotoxic drugs administered. Chemotherapeutic agents affect ovarian function by different mechanisms like loss of primordial follicles, atrophy of the ovary, oocyte apoptosis, ovarian vascular injury and stromal fibrosis leading to loss of ovarian reserve. Also, chemotherapeutic agents may hamper the endocrine ovarian function that impairs the production of sex hormones like testosterone and estrogen [4]. But exact mechanism of chemotherapy induced ovarian failure has not been fully understood. Patients may have regular menstrual cycles during or after chemotherapy cycles. But still there may be ovarian failure because of follicular depletion due to rapid ovarian aging [5].

With alkylating agents like cyclophosphamide, there is well-documented significantly greatest risk of ovarian failure compared to all chemotherapeutic agents. Classic cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimen, incidence of amenorrhea has been reported 61% among women less than 40 years and 95% in patients aged more than 40 years [6]. With Anthracycline based regimens, lower incidence (34%) of amenorrhea has been reported [7]. With regard to taxanes, no significant findings were observed, while trastuzumab did not have detrimental effects on fertility. The effects of different chemotherapeutic agents on the ovary may be reversible and temporary [8]. Its immediate effects are cessation of menses that may be reversible and generally observed among young women, while in long term effects irreversible premature menopause may be experienced especially among older women [9].

Fertility preservation is an important but mostly neglected decision-making but critical factor during management of breast cancer particularly among young patients. Anticancer cytotoxic agents cause may cause ovarian dysfunction that can present as oligomenorrhea, transient amenorrhea and early menopause leading to infertility [10]. Incidence of chemotherapy-associated amenorrhea varies widely because of differences in the definition of amenorrhea, menopause and variations in age distribution, drug regimens and duration of follow up [11]. But some researchers documented improved prognosis among breast cancer patients with amenorrhea induced after administration of chemotherapy or gonadotropin releasing hormone therapy [12]. Premature ovarian failure after adjuvant chemotherapy in women with early breast cancer has been observed to be associated with osteoporosis and rapid bone loss. Age and pretreatment serum anti-Mullerian hormone (AMH), which indirectly reflect the oocyte or primordial follicle pool, are the reliable indicators of ovarian reserve. AMH is a glycoprotein produced by granulosa cells of the ovary is a promising tool to assess ovarian reserve. It is preferred endocrine marker being a non-invasive and relatively stable indicator across menstrual cycle. Its level may change during and after chemotherapy and shows recovery after the treatment, as chemotherapy-induced amenorrhea is a reversible phenomenon. In some studies, long-term effects on the levels of AMH are documented. Numerous ovarian reserve tests, either biochemical or biophysical have been described in literature in context with the fertility [13]. But data pertaining to indicators of ovarian reserve in chemotherapy receiving breast cancer patients is limited and inconclusive.

Fertility preservation options

Number of options like cryopreservation of the embryos, oocyte and ovarian tissue, assisted reproduction and simultaneous administration of analogues of LH-RH during chemotherapy are available for fertility preservation in cancer patients. Most effective option is embryo cryopreservation as the human embryo is resistant to damage caused by cryopreservation. In the United Kingdom, OPTION trial tested effect of administration of gonadotropin releasing hormone (GnRH) agonist on the risk of chemotherapy induced premature ovarian insufficiency among early breast cancer women. The study reported reduced prevalence of amenorrhea among women less than 40 years of age [14]. But its long-term results about fertility are yet under evaluation. According to the American Society of Clinical Oncology, there are insufficient evidences for safety and efficacy of GnRH analogues and other methods of ovarian suppression for fertility preservation [15]. Aromatase inhibitors are also under evaluation for ovarian stimulation in patients with breast and endometrial cancer. Most promising way of fertility preservation is the cryopreservation of ovarian tissue. Primordial follicles harboring in ovarian cortex are resistant to cryoinjury. But it also has several restrictions and risk of reimplantation of primary tumor, malignant transformation and the risks of procedure itself [2].

Conclusion

Effect of chemotherapy on fertility is gaining growing importance among young breast cancer survivors. Breast cancer patients receiving different chemotherapy regimens must be counseled for probability of chemotherapy induce ovarian failure and infertility especially among patients in reproductive age group. Baseline assessment of ovarian reserve among premenopausal women who will need gonadotoxic chemotherapy is an essential step before initiation of the treatment. If young patients wish to plan pregnancy after treatment of breast cancer, issues of fertility preservation and its options should be discussed with the patients. Chemotherapy regimens adversely affect the ovaries. Preservation of ovarian function and fertility is a major and critical quality of life issue during management of the disease with chemotherapy at reproductive age and may cause psychological problems. To address the complex and challenging problem of infertility, careful analysis by oncologists and fertility specialists is mandatory. Large prospective studies are needed in future to identify and validate the markers of ovarian reserve and methods of fertility preservation among young breast cancer survivors treated with different chemotherapy regimens.

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