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GNRH AGONIST FOR CHEMOTHERAPY CAUSED PREMATURE OVARIAN INSUFFICIENCY IN YOUNG CANCER PATIENTS (META ANALAYSIS)

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ABSTRACT

Premature ovarian insufficiency indicated as the loss of ovarian follicles before the age of 40, is considered one of the most concerning long-term adverse effects of chemotherapy for cancer patients of reproductive age. Premature ovarian insufficiency is illustrated by primary amenorrhea (lack of menarche) and secondary amenorrhea (missed periods for month or longer). Symptoms of premature ovarian insufficiency include: low estradiol levels (measured once every four weeks), not being able to conceive or have periods for four months or more, hypoestrogenism, and elevated blood GnRH values, especially follicle-stimulating hormone and luteinizing hormone (>4 weeks apart) in the menopause range. Ovarian cancer is categorized as the development of cellular growth in the ovaries. The cells can get into healthy biological tissue, destroy it completely and quickly multiply there. Chemotherapy has high toxicity level to cause insufficiency of ovaries and the menopause. Utilizing gonadotropin-releasing hormone (GnRH) can result in safe and protective ovarian stimulation.GnRH analogues primarily replicate the pre-pubertal hormonal milieu by decreasing gonadotropin levels. GnRH-II can increase gonadotropin secretion (in vivo) by interacting with hGnRHR-I. The fact that hGnRH-I, hGnRH-II, and hGnRHR-I are expressed in tissues of mammary cancer supports the use of these molecules as BC therapeutic targets. A noteworthy distinction (statistically), the RR and CI are as follows: 95% CI=1.2-1.5, RR=1.3 and P=0.003. This shows that chemotherapy administered along with GnRHa may significantly speed up the restoration of menstrual function. GnRHa considerably accelerated the recovery of menstrual cycle. It decreases the velocity to recover the menstrual function and abridged the frequency of premature ovarian failure (POF). There is no effect on the possibility of being pregnant, endurance from tumor and general stability rates. However, not every woman with premature ovarian failure has a significant lack of menstruation or ovarian function. Ovarian function naturally changes with age, a process known as early menopause or menopause, which affects most women once they reach their forties. Menopause, the outcome of aging ovaries that eventually cease to produce eggs, often occurs between the ages of 50 and 55. Women of reproductive age who want to have children may struggle to accept a premature ovarian insufficiency (POI) diagnosis. Reproductive ambulatory care, such as fertility problems and birth controls, must be addressed as part of a comprehensive interdisciplinary treatment method of infertility and other reproductive issues. Unfortunately, to date, there is no curative therapy for premature ovarian insufficiency, while addressing the underlying causes may be able to reverse the illness and prevent further damage to the ovaries. In addition, 10 percent of women diagnosed with premature ovarian insufficiency go on to conceive a child without treatment. Some women may have what is known as "unexpected recovery" of premature ovarian insufficiency, in which their ovarian function returns to normal, fertility becomes fully recovered, and they are able to conceive regularly again. There is a great deal of potential in the future to learn more about the root cause of preterm ovarian failure, major health concerns related to premature ovarian insufficiency in the future will be a relevant research issue.

KEYWORDS: Premature ovarian insufficiency, GnRH agonists, ovarian preservation, Chemoprotection, chemotherapy.

INTRODUCTION

Ovarian toxicity is a significant adverse effect of chemotherapy in young cancer patients. Numerous symptoms, including temporary or persistent amenorrhea, infertility, and early menopause, can indicate ovarian injury. There is also a long-term risk of early ovarian failure for the continuation of menstruation in women who can recommence their fertility signs (Del Mastro et al., 2014). Menopausal symptoms, a higher risk of cardiovascular illnesses, osteoporosis, sexual dysfunction, and infertility are just a few of the adverse effects of POF on health. The main international recommendations state that embryo/oocyte cryopreservation is the industry standard practise for preserving fertility in young cancer patients. However, these methods simply retain fertility without preventing POF and associated side effects; they actually do not protect the entire ovarian function from the gonadotoxicity of anticancer medicines (Conte & Del Mastro, 2017). For female patients with some malignant and other non-malignant illnesses, chemotherapy has considerably improved prognosis. But ovarian toxicity is a side effect of this medication. The usage of agonists and antagonists of gonadotropin-releasing hormone (GnRH) analogues may have a protective effect on the ovaries. GnRH analogues work primarily by suppressing gonadotropin levels to mimic the pre-pubertal hormonal environment. This prevents primordial follicles from maturing, which reduces the amount of follicles that are more susceptible to chemotherapy (Chen, Xiao, Li, Cui, & Huang, 2019). Among them, the toxic effects of chemotherapy are valuable in the case of women of age 15-30-year females. The fact is that it accelerates early menopause and ovarian insufficiency (POI). It increases the possibility of a diversity of unconstructive strength impacts like symptoms of menopause, dysfunctionality of sexual hormones, joint diseases and cardiac disorders. Neurological functions are also disabled (Leonard et al., 2017). The development of POF, which can lead to either temporary or chronic amenorrhea, is a potential adverse reaction of chemotherapy in pre-menopausal female. Patients still run the danger of going through early menopause even if normal menses return or are present after chemotherapy since cytotoxic therapy has damaged their ovarian reserve (Poggio, Levaggi, & Lambertini, 2016). Recent findings from the SOFT (Suppression of Ovarian Function Trial) research reveals that pre-menopausal women with breast cancer who were successfully in regaining fertility after undergoing chemotherapy and received adjuvant endocrine therapy for five years had outstanding survival outcomes (Del Mastro et al., 2016). Review of the research reveals that insufficient ovaries are mostly seen in the women who are already suffered with mammary gland's cancer. Chemical structures of agonists for human gonadotropin receptors (I, II) are given in the table 01.

Table 01: A short list of highly studied and preferable agonists for the deterrence of chemotherapy effects in women having POI.

Agonists of GnRHa and GnRHa-II	Clinical uses	References
Goserelin	In the treatment of breast and prostate cancer, suppress the production of sex hormones (testosterone and estrogen)	(Wang, Pei, Hu, Jia, & Wang, 2021)
Gonadorelin	Women with lack of regular ovulation and menstruation periods due to a lack of GnRH release from the hypothalamus Gland can use this medication to cause ovulation (the release of an egg from the ovary).	(Barrett, Barrett, Dhar, & Birch, 2021)
Triptorelin	It treats early stage breast cancer in premenopausal women	(Venturelli, Guaitoli, Omarini, & Moscetti, 2018)
Buserelin	Buserelin stimulates the pituitary glands gonadotrophin-releasing hormone receptor (GnRHR). Estrogen secretion is inhibited	(Namavar, Ghalavandi, & Bahmanpour, 2020)

In recent years, lutenizing hormone-releasing hormone analogues (LHRHa) have become a viable option for temporary ovarian suppression during chemotherapy in order to maintain both gonadal function and fertility. Although multiple randomised clinical trials have shown that provisional ovarian repression with LHRHa is a useful method for lowering the risk of treatment-related POF, its usage as a regular therapy is still up for dispute (Conte & Del Mastro, 2017). Goserelin was found to be particularly effective in lowering the risk of POI among women under the age of 40 who were receiving chemotherapy for early breast cancer. The extent of ovarian defense also appears to be limited, and it is necessary to assess the clinical importance for fertility and long-term avoidance of consequences connected to oestrogen shortage (Leonard et al., 2017). For premenopausal women with breast cancer patients who are applicant for chemotherapy treatment and focused in maintaining their follicular activity, chemotherapy with GnRHa (goserelin) may be regarded a viable alternative, it also in improves the chance of conceiving after treatment ends (Cui & Phillips, 2019). A hypothalamic hormone called GnRH-I was initially discovered in the hypothalamus of pigs. Hormones such as this are released pulsatile into the hypophyseal portal circulation by GnRH neurons in the hypothalamus, where they act predominantly on the anterior pituitary. When it binds to the receptor in gonadotropic cells, the hGnRHR-I then it activates enzymes that produce pituitary gonadotropic hormones, such as follicle-stimulating hormone (FSH),

and luteinizing hormone (LH). When hGnRH-II binds to hGnRHR-I, it induces gonadotropin secretion (in vivo). There is evidence that human Gn regulating hormone (I, II) and the receptors (I, II) are uttered in cancers, most probably in the breast cancer. This supports the use of these molecules as molecular targets for the therapy of BC. The biopsy of tissues (primary human cancer) showed the presence of binding sites for gonadotropin receptor I in the cytoplasm. Its ratio was about 64%. Same is the case in neoplastic disease (malignant), which is about 50% in ratio(Huerta-Reyes et al., 2019).

MATERIALS AND METHODS

We looked for published articles in internet sources, such as PubMed, Google Scholar, SciHub, Springer, and thesis works, to find all the publications that documented that, in adjuvant chemotherapy for breast cancer, GnRH agonists protect the ovary.

Inclusion and exclusion criteria

- The following are the requirements for inclusion in the meta-analysis: The patient population consisted of premenopausal women who had been diagnosed with breast cancer by pathology and whose fundamental characteristics had been meticulously described. The strategy included the use of GnRH agonists with chemotherapy, allowing for comparisons to be drawn between those individuals and those who got just chemotherapy. Both the chemotherapeutic treatment and the usage of GnRH agonists were unrestricted. This study has to be conducted using a randomised controlled clinical trial. Where there were more than different intervention groups in a trial, each valid ranking method was considered separately. Exclusion criteria for the meta-analysis included the following:
- Women with advanced cancer stages would be included in the study.
- Controlled trials without randomization;
- Abstract trials without relevant data or outcomes required to be measured. This is shown in figure 01.

Quality assessment

Utilizing the adjusted Jadad scale, which previously stated, the eleven studies validity was assessed. The mean modified Jadad scale score after analysing each study was 6, with a standard deviation of 0.3. Seven randomised controlled studies (RCTs) altogether were included. Appropriate random processes or strict execution of allocation concealment were considered to have minimal bias risk in selection bias. Uncertain risk was assigned to insufficient strategies (for instance, when only the term "random" was mentioned). High risk was assigned to non-implementation or non-random processes. It was determined that there was a high danger that a lack of blinding could affect the results in performance bias and detection bias. On the other hand, reliable blinding techniques were deemed to have low risk. The risk of inaccurate reporting was minimal when the procedure of study was unavailable but all predetermined findings were provided. Uncertain danger was defined as issues that the study did not address and insufficient information in biases like attrition, reporting, and other bias.

A modified Jadad scale was used to evaluate the quality of methods. A gain of 0-1 meant the quality was poor, while a score of 2-4 meant the quality was excellent.

Statistical analysis

The author used Cochrane Collaboration Review Manager, version 5.3 (RevMan 5.3), for statistical analyses. Standard mean difference (SMD) was used to synthesize constant statistics. It is mentioned as mean (M) and standard deviation (SD). 95% confidence intervals were provided for each effect size (Cl). Firstly, this research hunt for and investigate the sources of heterogeneity. It was decided which subgroups would receive surgical treatment and which would receive treatment without surgery. By contrasting the earlier meta-analyses with fresh meta-analyses carried out after eliminating one RCT at a time, sensitivity assessments were carried out. The clinical randomised controlled trial evaluation suggested by the Cochrane system evaluator handbook was followed in conducting the risk assessment. It is shown in figure 02.

RESULTS

Study selection

Electronic databases were searched, yielding 240 records in total. There were no more records found in other sources. 33 records were left after 17 duplicate records were removed using the EndNote X8 programme. After reviewing the titles and abstracts, a total of 3 records were eliminated. 16 studies were further removed from the 40 full-text papers that were evaluated for eligibility due to the following factors: duplicate data (n = 4), failure to assemble assemblage necessities (n = 45), insufficient information on the hormonal outcomes (n = 10), and other reasons (n = 4). In the end, 7 RCTs in total were included in the meta-analysis. This is shown in table 02.

Table 02: Randomization and study selection.

Study	Randomization	Analysis method described	Dropouts	Total
(Huerta-Reyes et al., 2019)	1	2	0	3
(Leonard et al., 2017)	0	1	1	2
(Cui & Phillips, 2019)	2	1	0	3
(Venturelli et al., 2018)	1	0	0	1

(Wang et al., 2021)	0	1	0	1
(Namavar et al., 2020)	1	2	1	4
(Lu et al., 2021)	1	0	0	1

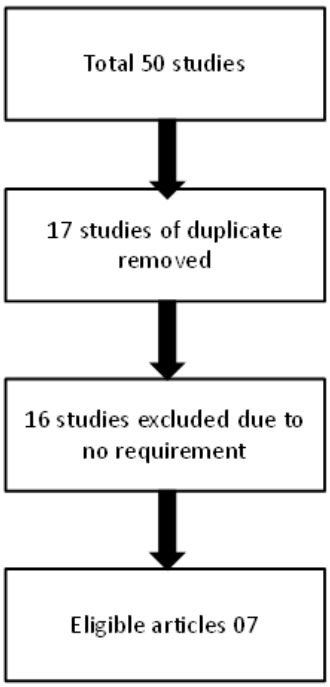

Figure 01: Exclusion and inclusion criteria.

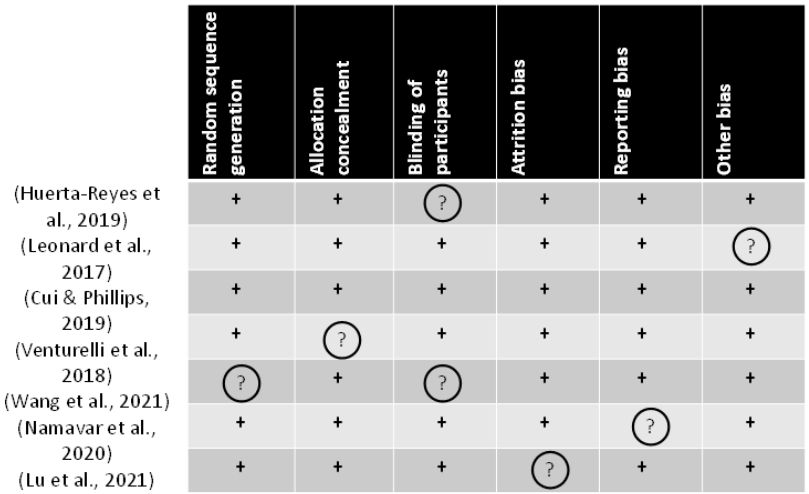

Figure 02: Assessment by using Cochrane system.

META ANALYSIS RESULTS

Seven references offered the proof that neither the GnRHa nor the control groups showed a significant impact on the rate of menstrual function recovery when menstrual function recovery was compared. The menstrual functions of 43 of 55 control patients had returned to normal. This study showed an absolute risk ratio of 1.29, with a 95% confidence interval of 1.09-1.54, and a statistically significant difference of P0.004. Menstrual function may be greatly enhanced by chemotherapy combined with GnRHa. Since the aggregation of the points of the overturned focus scheme was fewer regular, publication bias might have occurred since some undesirable outcomes might not have been reported as presented in 03.

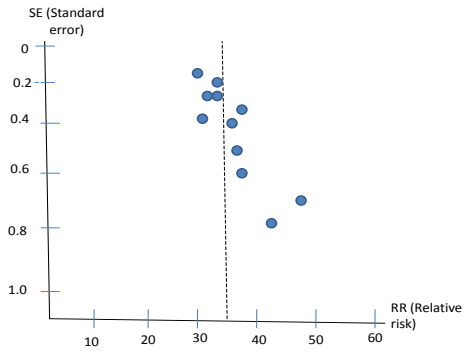

Figure 03: Meta analysis plot for the effect of GnRH agonists on menstrual recovery rate.

DISCUSSION

According to the findings of the current meta-analysis, GnRHa may help chemotherapy patients' menstrual functions recover more quickly and have fewer cases of POF. It may also lessen the damage that chemotherapy-induced toxicity causes to their ovarian function. The impact of GnRHa on the healing properties of chemotherapy medicines has also been examined in earlier investigations. The study found no interaction between GnRHa and chemotherapy when used as adjuvant therapy for cancer patients. The current meta-analysis showed that When analyzing the durable tumor-free endurance speed and the overall survival rate of patients, GnRHa had no consequence on long lasting chemotherapy.

Chemotherapy can damage the ovaries in a number of ways, including 1) amenorrhea, 2) irreversible ovarian dysfunction, and 3) infertility. This compromises the well being of diseased persons and the quality of life of them. Chemical medicines mostly fall into three categories that can harm ovarian function. Numerous studies have been done on the defensive belongings of agonist (GnRHa) upon functions of women ovary. Gonadotropin can be inhibited by the combination of GnRHa and its receptor, which also prevents the release of LH and FSH. Ovarian protection is explained by a number of mechanisms. It has been established that gonadotropins are necessary for the expression of messenger RNA capable of expressing the hormone receptors (for FSH and lutein) in primordial follicles, which are necessary for the maturation and expansion of these follicles. According to a number of studies, cell apoptosis is what causes chemotherapy-induced harm to female reproductive and endocrine systems. Sphingosine-1-phosphate (S-1-P), a gonadal protective chemical that can stop reproductive cell death or damage to follicles, can be secreted more frequently when GnRHa is present. The current study had a few drawbacks. First, differing definitions of POF and noticeably varying following up of references of the study could have an impact on the findings of this investigation. Second, eight references showed that there were pregnancies in the GnRHa and control groups. Contraception use after chemotherapy stopped and during follow-up, however, was not mentioned. As a result, it was challenging to assess how chemotherapy and GnRHa affected prolificacy. A tiny sample size is mounted according to the 7 researches which showed the long term survival of patients without tumor. This might have produced inaccurate results. Additionally, there was a general variability across the 7 clinical randomised controlled studies that were considered, and the variations in illness, treatment, follow-up period, and POF classification may have had an impact on the outcomes. A In order to establish the preventive benefits of GnRHa against chemotherapy-induced ovarian damage, larger sample sizes, longer summarized periods, and well-made clinical randomized controlled trials are required. In conclusion, According to this meta-analysis, GnRHa may reduce the amount of deterioration in ovarian function associated with chemotherapy. Menstrual function recovery and POF incidence were greatly accelerated by GnRHa, but it did not affect pregnancy rates, tumor-free survival rates, or overall survival rates.

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