Major Depression in Breast Cancer Patients with Ovarian Function Suppression: A Cross-Sectional Study Comparing Ovarian Ablation and Gonadotropin-Releasing Hormone Agonists

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Abstract

Purpose: We examined whether there were differences in major depression outcomes and independent risk factors associated with gonadotropin-releasing hormone agonists (GnRHa) and ovarian ablation (OA) in premenopausal breast cancer patients.

Methods: Premenopausal breast cancer patients from seven hospitals who received OFS participated in the study between June 2019 and June 2020. The independent variable was the type of ovarian suppression, categorized as either OA (n = 174) or GnRHa (n = 389). Major depression was evaluated using the Patient Health Questionnaire (PHQ-9), and the Female Sexual Function Index questionnaire was used to assess sexual function.

Results: A total of 563 patients completed the surveys. The mean PHQ-9 sum score was slightly lower in the GnRHa cohort than in the OA cohort (11.4 ± 5.7 vs. 12.8 ± 5.8, P = 0.079). There were significantly fewer patients with major depression (PHQ-9 ≥ 15) in the GnRHa cohort (31.1% vs. 40.2%, P = 0.025). Further, the duration of OFS was closely correlated with major depression, indicating a time-dependent trend [duration of OFS > 2 years vs. duration of OFS ≤ 2 years: Exp (B) = 1.651, P = 0.031]. Sexual dysfunction was negatively correlated with major depression [sexual dysfunction vs. normal: Exp (B) = 0.769, P = 0.046].

Conclusions: This is the first study to demonstrate that GnRHa results in more favorable depression outcomes than OA. Moreover, most patients preferred alternatives to their OFS treatment. These findings can contribute to improving and alleviating the adverse effects of OFS.

Backgroud

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths among women worldwide. In China, there has been a marked increase in the breast cancer incidence among younger women [DeSantis CE et al 2019]. An increasing number of premenopausal Chinese patients aged 45–55 years are being diagnosed with breast cancer, and approximately 6% of patients diagnosed with breast cancer are below 40 years of age [Fan L et al 2014]. In recent decades, extended adjuvant endocrine therapy, entailing ovarian function suppression (OFS) has been administered to premenopausal breast cancer patients, with beneficial results for the hormone receptor (HR) -positive population [Yeo W et al 2019]. However, few studies have compared the impacts of OFS on major depression using either ovarian ablation (OA) or gonadotropin releasing-hormone agonists (GnRHa).

OFS, which can eliminate or reduce ovarian estrogen production, was the first endocrine therapy to be investigated for use in premenopausal breast cancer patients. Initially, OFS was achieved through surgical bilateral oophorectomy or ovarian irradiation [Metwally IH et al 2019,Nourmoussavi M et al 2017]. However, more recently, GnRHa (also known as luteinizing hormone-releasing hormone agonists) has been used to achieve this outcome [Regan MM et al 2019,Sa-Nguanraksa D et al 2019]. Real-world

use of ovarian irradiation for OFS has been limited in China. Consequently, only patients undergoing surgical bilateral oophorectomy and/or receiving GnRHa were enlisted in this comparative study.

It is now well established that the effect of OFS in reducing the risk of breast cancer relapse or distant metastases is similar to that of the older cyclophosphamide, methotrexate, and fluorouracil regimen [Recchia F et al 2015]. The findings of the Suppression of Ovarian Function Trial (SOFT) indicated that when combined with tamoxifen, OFS had greater benefits for premenopausal women aged <35 years with a high risk of relapse and that a combination of OFS with exemestane increased this benefit [Francis PA et al 2015, 2018, Pagani O et al 2019]. There is an urgent need to explore the use of GnRHa for OFS for protecting ovarian function and improving fertility outcomes following the adverse effects of chemotherapy [Blumenfeld Z 2019]. Moreover, it is important for clinicians to help patients to understand and protect their ovarian function prior to receiving chemotherapy [Senkus E et al 2014, Allaway H C M et al 2017].

A comprehensive analysis of the SOFT results revealed that OFS combined with GnRHa has a similar effect to OA but with clear advantages for premenopausal women [Park YH et al 2019, Huerta-Reyes M et al 2019, Silvestris E et al 2020]. First, GnRHa has reversible effects and can be discontinued if the patient experiences intolerable symptoms. Thus, GnRHa may be preferred over permanent OA entailing bilateral oophorectomy or ovarian irradiation. All OFS techniques contribute to premature ovarian failure, which has significant consequences, including infertility, sexual dysfunction, and vasomotor symptoms [Stuursma A et al 2018, Hsieh AH et al 2016]. However, to date, there has been little discussion of emotional disorders, such as major depression or sexual dysfunction, associated with the deployment of different OFS strategies. This study examined whether GnRHa is superior to OA in terms of the incidence of major depression in premenopausal patients with breast cancer.

Methods

Participants

We conducted an anonymous, cross-sectional study between July 2019 and June 2020 at seven hospitals across China. Eligible patients had either undergone OA (bilateral oophorectomy) or were undergoing medical OFS, treatment with GnRHa entailed monthly doses of 3.6 mg of goserelin acetate (Zoladex, AstraZeneca) or leuprorelin acetate (Leuplin, Takeda) administered as a monthly dose of 3.75 mg or an intramuscular injection of 11.25 mg once every three months.

Included criteria and exclusion criteria

Patients were invited to complete the Breast Cancer Survivorship Ovarian Function Suppression Survey (OFS-Q5), an online questionnaire that included the Patient Health Questionnaire 9 (PHQ-9), which is an instrument for screening depression, and the Female Sexual Function Index (FSFI) questionnaire. The validity and reliability of the Chinese versions of these questionnaires have been previously demonstrated [Lan B et al 2020, Zhang C et al 2017, Xia J et al 2019]. The study was anonymized to improve the

participation rate and accuracy of the responses. Participants fitting the following criteria were included in our study: (1) a clear diagnosis of breast cancer (tissue or cell diagnosis), (2) age >18 years, and (3) recipient of OFS via surgical bilateral oophorectomy or GnRHa. The exclusion criteria were as follows: (1) refusal to provide informed consent, (2) inability to understand the questionnaires, and (3) undergoing ovarian irradiation. Written informed consent was obtained from each participant, and the study protocols were reviewed and approved by the ethics committee of the Cancer Hospital of China Medical University (protocol RB no. 20190545). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Questionnaire and data gathering

The questionnaire was divided into four sections. The first section comprised mostly items for obtaining the respondents' demographic and clinical characteristics, the second section recorded OFS information, and the following two sections respectively evaluated major depression and sexual function in both cohorts. Two assistants were trained to develop a knowledge base and communication skills related to OFS and breast cancer. The first assistant explained and confirmed the information, step by step, with the patients, and the second assistant reconfirmed the responses via telephone 3–10 days after the survey's implementation. The questionnaire was in Chinese, which was the respondents' native language.

Depression questionnaire

As previously noted, PHQ-9 questionnaire, each of the nine items was assigned a score of 0–3, and the scores were then summed to obtain the final score. The following PHQ-9 score ranges have been recommended for determining levels of depression: 0–7: none and/or mild, 8–14: moderate, 15–19: moderate to severe, and 20–27: severe. Lower scores indicate better emotional functioning, whereas a sum score of ≥15 indicates major depression.

Sexual function questionnaire

Sexual function was quantified using the FSFI questionnaire, which is a 19-item survey instrument that specifically assesses six sexual functioning domains (FSFI-1: desire, FSFI-2: arousal, FSFI-3: lubrication, FSFI-4: orgasm, FSFI-5: satisfaction, and FSFI-6: pain).

Statistical methods

Data analysis was performed using the IBM SPSS Statistics for Windows, version 23.0 software package (IBM Corp., Armonk, N.Y., USA). Fisher's exact test was used for categorical data. Differences in age and OFS duration were analyzed using unpaired *t*-tests. The means of the PHQ-9 total scores, FSFI total

scores, and FSFI sub-scores were subjected to nonparametric Mann–Whitney *U* tests to determine whether the data were normally distributed. *P* values < 0.05 indicated statistical significance.

Results

Patient characteristics

As shown in Figure 1, the final sample of patients with complete demographic characteristics and PHQ-9/FSFI scores comprised 563 individuals. Of these patients, 174 had undergone OA and 389 were being given GnRHa for OFA. Table 1 lists the main characteristics of the GnRHa and OA cohorts. The patients' median ages in the OA and GnRHa cohorts were 46.0 and 43.0 years, respectively.

Table 1 shows that the time lapse from the commencement of ovarian suppression was significantly longer in the OA cohort than in the GnRHa cohort (30.3 ± 31.2 months vs. 22.8 ± 22.2 months, *P* = 0.009). The majority of respondents had low annual incomes (77.0%), had estrogen receptor or progesterone receptor positive breast cancers (97.2%), and were human epidermal growth factor receptor-2 (HER2)-negative (76.1%). In addition, 59.2% of the patients in the GnRHa cohort were educated up to or above college level, whereas the corresponding percentage for the OA cohort was only 42.4%. Strikingly, patients receiving GnRHa favored breast-conserving surgery (26.0% vs. 16.7%, *P* = 0.015).

Major depression in the GnRHa and OA cohorts

The results shown in Table 2 reveal that the mean PHQ-9 sum score for the GnRHa cohort was lower than that for the OA cohort (11.4 ± 5.7 vs. 12.8 ± 5.8, *P* = 0.079). According to the treatment algorithm for depression, 36.2% (63/174), 28.2% (49/174), and 12.6% (22/174) of the patients in the OA cohort were respectively categorized in the moderate, major, and severe depression groups. Notably, there were significantly fewer patients with major depression (PHQ-9 ≥ 15) in the GnRHa cohort than in the OA cohort. A positive correlation was found between major depression and OA, and the absolute difference was approximately 9.1 percentage points (31.1% vs. 40.2%, *P* = 0.025). Item-level responses indicated that 15 of the 174 patients who underwent OA and 30 of the 389 patients taking GnRHa experienced suicidal ideation, which is considered a symptom of major depression, but this difference was not statistically significant (8.6% vs. 7.7%, *P* = 0.713).

Sexual dysfunction in the GnRHa and OA cohorts

As shown in Table 3, patients receiving GnRHa had lower mean and median FSFI scores than patients who had undergone OA (mean: 17.8 ± 8.7 vs. 19.3 ± 8.5, *P* = 0.205; median: 17.8 vs. 19.6). The results for sexual dysfunction, which was defined as FSFI < 23, revealed that there was strong evidence of GnRHa-induced sexual dysfunction; 61.5% of OA patients met the criteria for sexual dysfunction compared with 72.2% of patients receiving GnRHa (*P* = 0.011). According to the data shown in Fig. 2, patients receiving

GnRHa had slightly lower scores for most of the FSFI sub-scores compared with the scores of patients who had undergone OA. However, their scores for items in the pain section were significantly lower (FSFI-6 scores: mean ± SD: 3.3 ± 2.2 vs. 2.5 ± 2.2, $P = 0.007$), and there were also significant differences in scores for the item on lubrication (FSFI-3 scores: mean ± SD: 3.5 ± 2.5 vs. 2.9 ± 2.6, $P = 0.048$).

Independent risk factors for major depression in patients with OFS

Strikingly, the data in Table 4 show that type of ovarian suppression was an independent risk factor for major depression in the univariate and multivariate analyses (OA vs. GnRHa: Exp (B) = 2.483 [95% CI: 1.056–6.450], $P = 0.026$). As noted above, patients receiving GnRHa favored breast-conserving surgery (26.0% vs. 16.7%, $P = 0.015$). However, an examination of the data presented in Table 3 showed that the type of surgery was not an independent risk factor for major depression in the multivariate analysis. Further analysis revealed that the duration of OFS was closely correlated with major depression, and there was a marked time-dependent trend (a duration of OFS > 2 years vs. a duration of OFS ≤ 2 years: Exp (B) = 1.651 [95% CI: 1.071–2.518], $P = 0.031$). Sexual dysfunction was negatively correlated with major depression (sexual dysfunction vs. normal: Exp (B) = 0.769 [95% CI: 0.523–0.996], $P = 0.046$). Large-sample studies are required for further investigations of the correlation between sexual dysfunction and major depression.

Alternative to OFS treatment

In the final part of the questionnaire, respondents were asked, “Would you choose to change to another kind of OFS; for example, would you choose OA instead of GnRHa or vice versa?” Surprisingly, the majority of the respondents in both cohorts viewed this change positively. Approximately both more than half of the patients opted to change the type of OFS (GnRHa: 62.7% vs. OA: 60.8%). Because concerns regarding costs could affect the final choice, we included the following item: “If cost was not a consideration, would you choose to change to another kind of OFS” In response to this question, the ratio of substitution showed a marked increase to 70.3% for the OA cohort, whereas the increase was not marked for the GnRHa cohort (67.1%). The majority of respondents in both cohorts may have been dissatisfied with their current OFS solution because of depression, sexual dysfunction, or an overall decreased quality of life, and the majority of participants were reluctant to receive OA because of its cost.

Discussion

We conducted a cross-sectional investigation to explore the association between depression and the type of OFS (OA or GnRHa) administered to breast cancer patients in seven hospitals. Our results demonstrated that the GnRHa cohort presented with clinically meaningful lower levels of major depression compared with the OA cohort. This is the first cross-sectional study to provide a direct

comparison of levels of serious major depression in breast cancer patients undergoing OA and GnRHa. Differing from other studies that used Common Terminology Criteria for Adverse Events (CTCAE) grades to assess the negative effects of OFS, we used PHQ-9 scores in our study. For instance, Moore et al. [2015] found that adverse effects identified in early breast cancer patients included eight cases of grade-2 emotional disorders and one case of a grade-3 emotional disorder in their OFS cohort compared with three cases of grade-2 emotional disorders in the non-OFS cohort. Major depression evaluated using the PHQ-9 questionnaire, as in our study, may offer a multidimensional perspective on emotional disorders.

Our results for major depression confirmed our hypotheses and endorsed previous findings [Lan B et al 2020, Alshehre Sallwa M et al 2020]. Young breast cancer survivors are at the greatest risk of experiencing major depression because of the potential for abrupt menopause and breast disease to occur, and the incidence of major depression among them is considerably higher than would be expected in a general cohort of the same age range. One meta-analysis of four studies covering 3,373 patients revealed that the difference in depression levels between those undergoing OFS and those not undergoing OFS was insignificant (RR: 1.28, 95% CI: 0.94–1.74, $P = 0.12$), with no significant heterogeneity among the studies ($P = 0.46$, $I^2 = 0\%$) [25]. In our investigation, we focused on major depression and its independent risk factors in women with early and metastatic breast cancer. Depression, which is linked to both the psychological aspects of social relationships and the physical effects of chemotherapy, can be overwhelming during treatment of metastatic breast cancer [Park EM et al 2018].

The administration of GnRHa to premenopausal women to reduce estrogen levels can increase vaginal dryness and dyspareunia [Maciejewska-Jeske M et al 2018]. Whereas aromatase inhibitors have similar sexual dysfunction effects, they are rarely administered to premenopausal women without OFS. Unlike OA-related sexual dysfunction issues, those associated with GnRHa may be reversible after treatment cessation. However, ovarian failure caused by OA or chemotherapy is permanent [Kuehn R et al 2019]. Our results indicated that sexual dysfunction was more common and serious among women in the GnRHa cohort than those in the OA cohort regardless of the duration of the OFS. Notably, the respondents' mean age within the GnRHa cohort was lower than that of respondents in the OA cohort. (47.4 years), indicating that more women in the OA cohort than in the GnRHa may have reached menopause. Studies on cancer care have reported low sexual desire in young survivors, who are more likely to be distressed by alterations to their appearance than are older women [Robinson PJ et al 2017]. The observed inconsistencies may therefore be attributed to the unequal age distribution within our cohorts and, specifically, spontaneous age-related decline in sexual desire. Previous studies have suggested that the association between tamoxifen and sexual dysfunction remains controversial in premenopausal patients [Gandhi C et al 2019, Stabile C et al 2017Hummel SB et al 2017, Soldera SV et al 2018].

Limitations of the study We found significant associations between GnRHa treatment and a lower incidence of major depression as well as a higher degree of sexual dysfunction in breast cancer patients. However, there were inherent limitations in the cross-sectional design of the study, as indicated below.

First, because the survey was anonymized, all treatment information was based on patient recall and could not be re-checked for accuracy using medical records. Therefore, the reporting may not have been sufficiently accurate for making reliable evaluations based on the patients' responses to the questionnaires alone. A fully prospective evaluation may provide additional information and limit recall bias.

Second, the cross-sectional design constrains us from drawing cause-and-effect conclusions regarding major depression and sexual dysfunction. While the reliability and validity of the Chinese versions of the three questionnaires have previously been confirmed [Lan B et al 2020, Zhang C et al 2017, Xia J et al 2019, Tong J et al 2020, Li L et al 2019], we cannot ignore the possibility of social bias given the methods used to deliver the questionnaire and retrieve the responses. Two assistants confirmed the responses with the patients face to face and by telephone in an attempt to reduce the possibility of bias. Additionally, we were unable to evaluate the presence or absence of sufficient ovarian suppression in the GnRHa cohort in our study. Whether or not insufficient ovarian suppression affects major depression, sexual dysfunction, and the quality of life of patients thus remains unclear. Nevertheless, in spite of its exploratory nature, this study offers some insights into the management of the individual adverse effects of OFS.

Conclusion

We highlight a greater incidence of major depression in patients who had undergone OA than in those receiving medically administered GnRHa. This finding indicates that medical GnRHa is a simple, reversible, and preferable therapy for OFS in patients with breast cancer. Further research that examines the links between major depression and OFS more closely is evidently needed. Moreover, studies should highlight the adverse effects of OFS in premenopausal breast cancer patients. Further, the routine application of a personalized approach seems to be warranted.

Abbreviations

CTCAE: Common Terminology Criteria for Adverse Events, FSFI: Female Sexual Function Index, GnRHa: gonadotropin-releasing hormone agonists, OA:ovarian ablation, OFS: ovarian function suppression, PHQ-9:Patient Health Questionnaire 9, SOFT: Suppression of Ovarian Function Trialgonadotropin-releasing hormone agonists (GnRHa) and ovarian ablation (OA)

Declaration

Consent for publication

Not applicable.

Availability of data and materials

We would not share the data and material used in this manuscript, because we need them for further research.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

XZ, and TS: Conceived and designed the experiments. JX, LC, LM, LN, JH performed the survey. JJ and JX analyzed the datas. JX wrote the draft of paper. All authors read and approved the final manuscript and submission of this manuscript.

Ethics Approval and Consent to Participate

This study was conducted in full conformance with the International Conference for Harmonization (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. A written informed consent was obtained from each participant and the study protocols were reviewed and proved by the Ethic Committee of Cancer Hospital of China Medical University (protocol number RB #20190545). All participants provided written informed consent.

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Not Applicable

References

Allaway HCM, Chizen DR, Adams GP, et al. (2017) Effects of a single 20 mg dose of letrozole on ovarian function post dominant follicle selection: An exploratory randomized controlled trial. J Ovarian Res 10:6. http://doi.org/10.1186/s13048-017-0303-x

Alshehre SM, Duffy S, Jones G, et al. (2020) A prospective, single-centre, single-arm, open label study of the long term use of a gonadotropin releasing hormone agonist (Triptorelin SR, 11.25 mg) in combination with Tibolone add-back therapy in the management of chronic cyclical pelvic pain. Reprod Biol Endocrinol 18:28. http://doi.org/10.1186/s12958-020-00586-z

Blumenfeld Z (2019) Fertility preservation using GnRH agonists: Rationale, possible mechanisms, and explanation of controversy. Clin Med Insights Reprod Health 13:1179558119870163. http://doi.org/10.1177/1179558119870163

Bober SL, Fine E, Recklitis CJ (2020) Sexual health and rehabilitation after ovarian suppression treatment (SHARE-OS): A clinical intervention for young breast cancer survivors. J Cancer Surviv 14:26-30. http://doi.org/10.1007/s11764-019-00800-x

Davis SR, Robinson PJ, Jane F, et al. (2018) Intravaginal testosterone improves sexual satisfaction and vaginal symptoms associated with aromatase inhibitors. J Clin Endocrinol Metab 103:4146-4154. http://doi.org/10.1210/jc.2018-01345

DeSantis CE, Ma J, Gaudet MM, et al. (2019) Breast cancer statistics, 2019. CA Cancer J Clin 69:438-451. https://doi.org/10.3322/caac.21583

Fan L, Strasser-Weippl K, Li JJ, et al. (2014) Breast cancer in China. Lancet Oncol 15(7):e279-e289. https://doi.org/10.1016/S1470-2045(13)70567-9

Flynn KE, Reese JB, Jeffrey D, et al. (2012) Patient experiences with communication about sex during and after treatment for cancer. Psychooncology 21:594-601. http://doi: 10.1002/pon.1947

Francis PA, Pagani O, Fleming GF, et al. (2018) SOFT and TEXT Investigators and the International Breast Cancer Study Group. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med 379(2):122-137. http://doi.org/10.1056/NEJMoa1803164

Francis PA, Regan MM, Fleming GF, et al. (2015) SOFT Investigators; International Breast Cancer Study Group. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 372:436-446. http://doi.org/10.1056/NEJMoa1412379

Fugger G, Dold M, Bartova L, et al. (2019) Major depression and comorbid diabetes -Findings from the European Group for the Study of Resistant Depression. Prog Neuropsychopharmacol Biol Psychiatry 94:109638. http://doi.org/10.1016/j.pnpbp.2019.109638

Gandhi C, Butler E, Pesek S, et al. (2019) Sexual dysfunction in breast cancer survivors: Is it surgical modality or adjuvant therapy? Am J Clin Oncol 42:500-506. http://doi.org/10.1097/COC.0000000000000552

Hsieh AH, Kichenadasse G, Vatandoust S, et al. (2016) Goserelin toxicities and preferences for ovarian suppression method in pre-menopausal women with breast cancer. Intern Med J 46:1153-1159. http://doi.org/10.1111/imj.1316

Huerta-Reyes M, Maya-Núñez G, Pérez-Solis MA, et al. (2019) Treatment of breast cancer with gonadotropin-releasing hormone analogs. Front Oncol 9:943. http://doi.org/10.3389/fonc.2019.00943

Hummel SB, Hahn DEE, van Lankveld JJDM, et al. (2017) Factors associated with specific diagnostic and Statistical Manual of Mental Disorders, Fourth Edition sexual dysfunctions in breast cancer survivors: A study of patients and their partners. J Sex Med 14:1248-1259. http://doi.org/10.1016/j.jsxm.2017.08.004

Kuehn R, Casaubon J, Raker C, et al. (2019) Sexual dysfunction in survivorship; the impact of menopause and endocrine therapy. Ann Surg Oncol 26:3159-3165. http://doi.org/10.1245/s10434-019-07552-z

Lan B, Jiang S, Li T, et al. (2020) Depression, anxiety, and their associated factors among Chinese early breast cancer in women under 35 years of age: A cross sectional study. Curr Probl Cancer 100558. http://doi.org/10.1016/j.currproblcancer.2020.100558

Li L, Yang B, Li H, et al. (2019) Chinese multicentre prospective registry of breast cancer patient-reported outcome-reconstruction and oncoplastic cohort (PRO-ROC): A study protocol. BMJ Open 9(12):e032945. http://doi.org/10.1136/bmjopen-2019-032945

Maciejewska-Jeske M, Szeliga A, Męczekalski B (2018) Consequences of premature ovarian insufficiency on women's sexual health. Prz Menopauzalny. 17(3):127-130. http://doi.org/10.5114/pm.2018.78557

Mahmoud R, Wainwright SR, Chaiton JA, et al. (2016) Ovarian hormones, but not fluoxetine, impart resilience within a chronic unpredictable stress model in middle-aged female rats. Neuropharmacology 107:278-293. http://doi.org/10.1016/j.neuropharm.2016.01.033

Metwally IH, Hamdy O, Elbalka SS, et al. (2019) Oophorectomy as a hormonal ablation therapy in metastatic and recurrent breast cancer: Current indications and results. Indian J Surg Oncol 10:542-546. http://doi.org/10.1007/s13193-019-00938-1

Moore HC, Unger JM, Phillips KA, et al., POEMS/S0230 Investigators (2015) Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Me 372:923-932. http://doi.org/10.1056/NEJMoa1413204

Nguyen TV, Reuter JM, Gaikwad NW, et al. (2017) The steroid metabolome in women with premenstrual dysphoric disorder during GnRH agonist-induced ovarian suppression: Effects of estradiol and progesterone addback. Transl Psychiatry 7(8):e1193. http://doi.org/10.1038/tp.2017.146

Nourmoussavi M, Pansegrau G, Popesku J, et al. (2017) Ovarian ablation for premenopausal breast cancer: A review of treatment considerations and the impact of premature menopause. Cancer Treat Rev 55:26-35. http://doi.org/10.1016/j.ctrv.2017.02.005

Pagani O, Francis PA, Fleming GF, et al. SOFT and TEXT Investigators and International Breast Cancer Study Group (2019) Absolute improvements in freedom from distant recurrence to tailor adjuvant endocrine therapies for premenopausal women: Results from TEXT and SOFT. J Clin Oncol 38:1293-1303.http://doi.org/10.1200/JCO.18.01967

Park EM, Gelber S, Rosenberg SM, et al. (2018) Anxiety and depression in young women with metastatic breast cancer: A cross-sectional study. Psychosomatics 59:251-258. http://doi.org/10.1016/j.psym.2018.01.007

Park YH, Kim TY, Kim GM, et al.; Korean Cancer Study Group (KCSG). (2019) Palbociclib plus exemestane with gonadotropin-releasing hormone agonist versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (KCSG-BR15-10): A multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 20:1750-1759. http://doi.org/10.1016/S1470-2045(19)30565-0

Pooley AE, Benjamin RC, Sreedhar S, et al. (2018) Sex differences in the traumatic stress response: The role of adult gonadal hormones. Biol Sex Differ 9(1):32. http://doi.org/10.1186/s13293-018-0192-8

Recchia F, Candeloro G, Rosselli M, et al. (2015) Adjuvant ovarian suppression, high-dose chemotherapy and immunotherapy for premenopausal patients with high-risk breast cancer. Anticancer Res; 35:6847-6853.Regan MM, Fleming GF, Walley B, et al. (2019) Adjuvant systemic treatment of premenopausal women with hormone receptor-positive early breast cancer: Lights and shadows. J Clin Oncol 37(11):862-866. http://doi.org/10.1200/JCO.18.02433

Robinson PJ, Bell RJ, Christakis MK, et al. (2017) Aromatase inhibitors are associated with low sexual desire causing distress and fecal incontinence in women: An observational study. J Sex Med 14:1566-1574. http://doi.org/10.1016/j.jsxm.2017.09.018

Sa-Nguanraksa D, Krisorakun T, Pongthong W, et al. (2019) Survival outcome of combined GnRH agonist and tamoxifen is comparable to that of sequential adriamycin and cyclophosphamide chemotherapy plus tamoxifen in premenopausal patients with early breast cancer. Mol Clin Oncol 11:517-522. http://doi.org/10.3892/mco.2019.1913

Senkus E, Gomez H, Dirix L, et al. (2014) Attitudes of young patients with breast cancer toward fertility loss related to adjuvant systemic therapies. EORTC study 10002 BIG 3-98. Psycho-Oncology; 23(2):173-182. http://doi.org/10.1002/pon.3384

Silvestris E, Dellino M, Cafforio P, et al. (2020) Breast cancer: An update on treatment-related infertility. J Cancer Res Clin Oncol 146:647-657. http://doi.org/10.1007/s00432-020-03136-7

Soldera SV, Ennis M, Lohmann AE, et al. (2018) Sexual health in long-term breast cancer survivors. Breast Cancer Res Treat 172:159-166. http://doi.org/10.1007/s10549-018-4894-8

Stabile C, Goldfarb S, Baser RE, et al. (2017) Sexual health needs and educational intervention preferences for women with cancer. Breast Cancer Res Treat 165:77-84. http://doi.org/10.1007/s10549-017-4305-6

Stuursma A, van Driel CMG, Wessels NJ, et al. (2018) Severity and duration of menopausal symptoms after risk-reducing salpingo-oophorectomy. Maturitas 111:69-76. http://doi.org/10.1016/j.maturitas.2018.01.012

Tong J, Zhang C, Zhang L, et al. (2020) Analysis of low sexual desire in Chinese women: A national population-based epidemiological survey in mainland China. Sex Health 17:61-68. http://doi.org/10.1071/SH19097

Xia J, Tang Z, Wu P, et al. (2019) Use of item response theory to develop a shortened version of the EORTC QLQ-BR23 scales. Sci Rep 9:1764. http://doi.org/10.1038/s41598-018-37965-x

Yeo W, Ueno T, Lin C, et al. (2019) Treating HR+/HER2—breast cancer in premenopausal Asian women: Asian breast cancer cooperative group 2019 consensus and position on ovarian suppression. Breast Cancer Res Treat. 177:549-559. https://doi.org/10.1007/s10549-019-05318-5.

Zhang C, Cui L, Zhang L, et al. (2017) Sexual activity and function assessment in middle-aged Chinese women using the female sexual function index. Menopause 24:669-676. http://doi.org/10.1097/GME.0000000000000812

Zhang P, Li CZ, Jiao GM, et al. (2017) Effects of ovarian ablation or suppression in premenopausal breast cancer: A meta-analysis of randomized controlled trials. Eur J Surg Oncol 43:1161-1172. http://doi.org/10.1016/j.ejso.2016.11.011

Zhang Y, Chen Y, Ma L (2018) Depression and cardiovascular disease in elderly: Current understanding. J Clin Neurosci. 47:1-5. http://doi.org/10.1016/j.jocn.2017.09.022

Tables

Table 1 Baseline social demographics and clinical characteristics in breast cancer patients with ovarian function suppression

Characteristics	Total	Ovarian Ablation OA	GnRH agonist GnRHa	P Value
N	563	174	389	
Age, years				
Median	44	46	43	
Range	22-63	31-61	22-63	
Mean (SD)	42.7 ± 7.8	45.2 ± 7.0	41.6 ± 7.8	0.013
Duration of OFS Mean (SD), months	25.1 ± 25.4	30.3 ± 31.2	22.8 ± 22.2	0.009
Educational level				0.0002
High school or below	268	103	165	
College or above	295	71	224	
Annual income (RMB)				0.360
≤ 50,000	398	126	272	
> 50,000	165	48	117	
Smoking habit				0.439
Never or little	548	168	380	
Mostly	15	6	9	
Alcohol drinking habit				0.271
Never or little	556	170	386	
Mostly	7	4	3	
Co-morbidity				0.077
Diabetes/Hypertension	51	22	29	
None	522	162	360	
Type of Surgery				0.015
Mastectomy	433	145	288	
Breast-conserving	130	29	101	

TNM staging				
I-III	400	110	290	0.006
IV	163	64	99	
Hormone Receptor Status				0.0004
ER or PR Positive	526	153	373	
ER and PR Negative	37	21	16	
HER2 Status				0.262
Positive	130	35	95	
Negative	433	139	294	

Table 2 Depression (PHQ-9) by the type of ovarian function suppression in patients with breast cancer

	Ovarian function suppression		
	Ovarian Ablation (OA) n, (%)	GnRH agonist (GnRHa) n, (%)	*P* value
Total	174	389	
PHQ-9 scores Median (IQR)	13 (8.0-17.0)	11 (7.0-16.0)	
PHQ-9 scores Range	1-24	0-25	
PHQ-9 scores Mean (SD)	12.8 ± 5.8	11.4 ± 5.7	0.079
PHQ-9 scores subgroups			
None or mild (0-7), n(%)	40 (23.0)	101 (26.0)	
Moderate (8-14), n(%)	63 (36.2)	167 (42.9)	
Major (15-19), n(%)	49 (28.2)	87 (22.4)	
Severe (20-27), n(%)	22 (12.6)	34 (8.7)	
Major Depression (PHQ≥15), n(%)	71 (40.2)	121 (31.1)	0.025
Suicidal ideation, n(%)	15 (8.6)	30 (7.7)	0.713

PHQ-9, Patient Health Questionnaire - 9 items; SE, standard errors; IQR, interquartile range (25^{th}, 75^{th} percentiles).

Table 3 Sexual function by the type of ovarian function suppression in patients with breast cancer

	Ovarian function suppression		
	Ovarian Ablation (OA) N=174	GnRH agonist (GnRHa) N=389	*P* value
FSFI total scores			
Mean (SD)	19.3 ± 8.5	17.8 ± 8.7	0.205
Median (IQR)	19.6(13.0-26.7)	17.8(12.2-24.3)	
Range	2-34	2-34	
Sexual dysfunction (FSFI<23), n(%)	107 (61.5)	281 (72.2)	0.011

FSFI, female sexual function index; SE, standard errors; IQR, interquartile range (25^{th}, 75^{th} percentiles).

Table 4 The associated factors on major depression (PHQ-9, scores <15 vs ≥15) by logistic regression in patients with breast cancer

Characteristics	Univariate			Multivariate		
	OR	95%CI	P value	OR	95%CI	P value
Age, years						
≤ 45	1					
> 45	1.392	0.924-2.095	0.113			
Educational level						
High school or below	1					
College or above	0.773	0.522-1.145	0.199			
Annual income (RMB)						
≤ 50,000	1					
> 50,000	0.883	0.577-1.351	0.565			
TNM staging						
I- III	1					
IV	1.233	0.641-2.373	0.530			
Type of Surgery						
Breast-conserving	1					
Mastectomy	2.079	1.338-3.230	0.001	1.459	0.951-3.630	0.058
HER2 Status						
Negative	1					
Positive	0.734	0.420-1.283	0.278			
Endocrine Therapy						
AI	1					
TAM	1.030	0.655-1.619	0.898			
Type of OFS						
GnRH agonist	1					
Ovarian Ablation	1.910	1.006-2.518	0.043	2.483	1.056-6.450	0.026
OFS Time						
≤ 2 years	1					
> 2 years	1.555	1.010-1.568	0.037	1.651	1.071-2.518	0.031

Sexual dysfunction						
No	1					
Yes	0.689	0.516-0.916	0.029	0.769	0.523-0.996	0.046

Figures

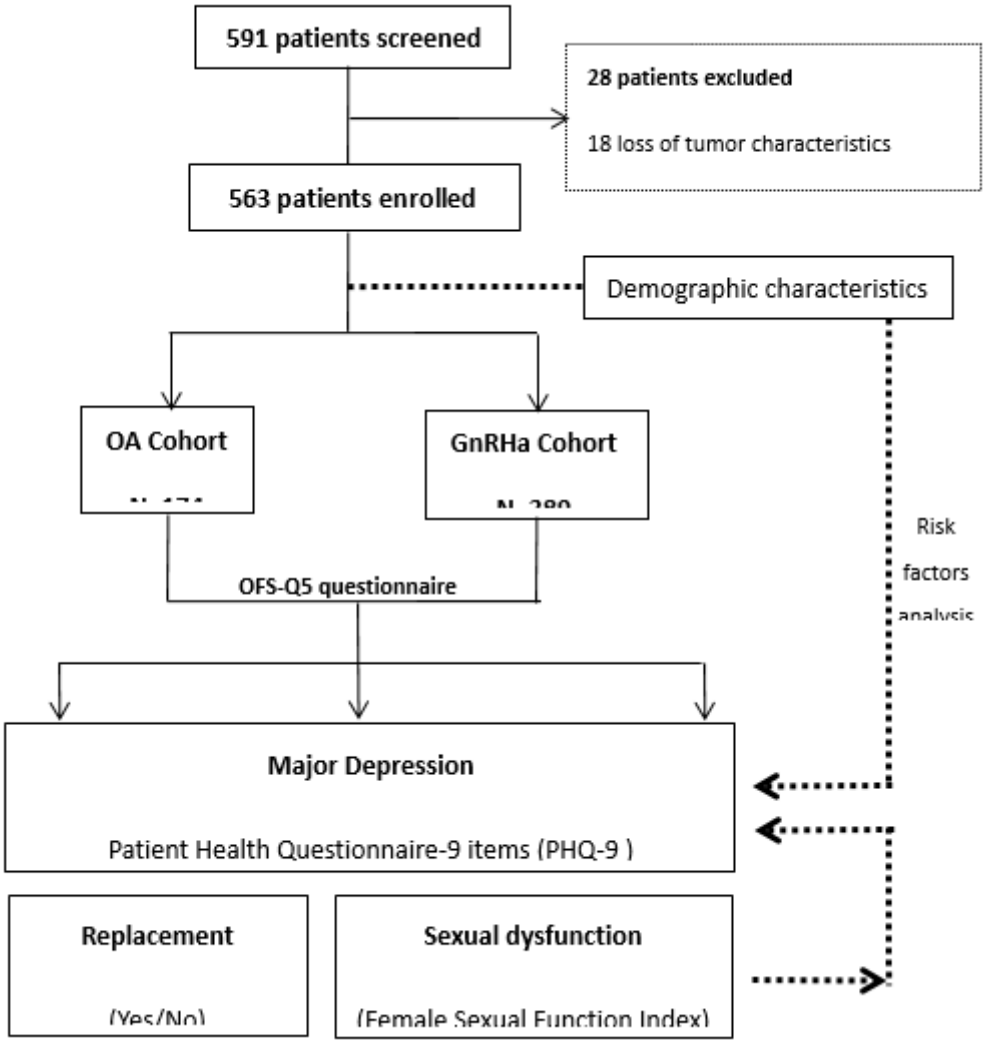

Figure 1

Patients disposition in our study

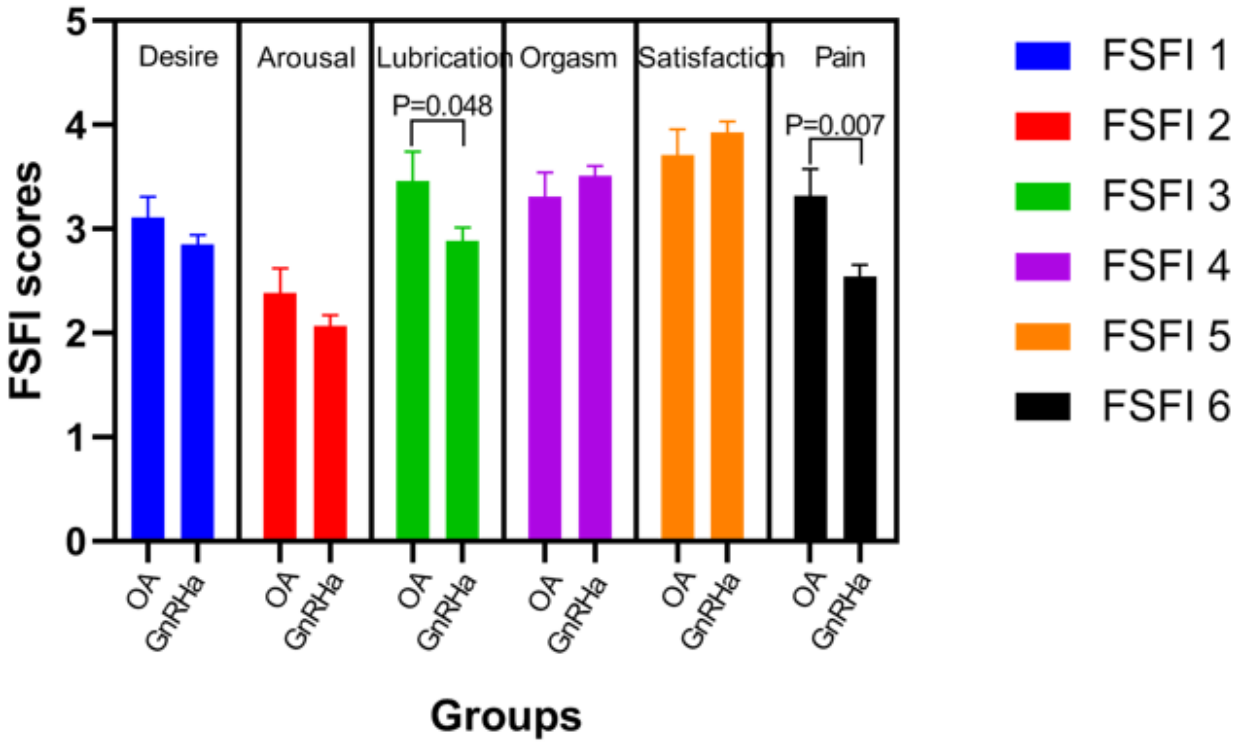

Figure 2

Sexual function sub-items between medicine GnRHa and ovarian ablation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FSFIScoringAppendix.pdf
- PHQ91.pdf