Abstract. The protective effects of gonadotropin-releasing hormone agonist (GnRHa) against ovarian chemotherapy induced-toxicity have not completely been demonstrated and the impact of chemotherapy on ovarian dysfunction remains unclear. The present meta-analysis aimed to evaluate the efficiency of GnRHa and to determine whether GnRHa could influence the long-term survival rate of patients with cancer. A total of 12 clinical randomized controlled trials were included, consisting of 1,413 patients who were divided into the GnRHa group (n=705) and the control group (n=708). The meta-analysis revealed that GnRHa may significantly improve the menstrual function recovery rate in patients who received chemotherapy \[RR=1.29, 95\% \text{ confidence interval (CI)}=1.09-1.54, P=0.004\] and reduce the rate of premature ovarian failure \[RR=0.47, 95\% \text{ CI}=0.31-0.71, P=0.0004\]. However, it had no effect on the pregnancy rate \[RR=1.40, 95\% \text{ CI}=0.98-1.98, P=0.06\], on the rate of disease-free survival and overall survival of patients (disease-free survival rate: \[RR=1.04, 95\% \text{ CI}=0.95-1.13, P=0.40\]; overall survival rate: \[RR=1.02, 95\% \text{ CI}=0.90-1.16, P=0.72\]). In conclusion, GnRHa may reduce chemotherapy-induced ovarian dysfunction without compromising or influencing the therapeutic effects of chemotherapy.

Introduction

Chemotherapy is a widely used tumor treatment; however, it can cause various degrees of ovarian dysfunction, which can be irreversible. It is therefore important to protect ovaries during chemotherapy to avoid compromising pregnancy rate, considering the gradual improvement of women's survival following chemotherapy.

In 1985, Ataya et al (1) demonstrated that long-acting gonadotropin releasing hormone (GnRH) agonist (GnRHa) significantly protects rat ovaries against cyclophosphamide-induced toxicity. Blumenfeld and Eckman (2) performed a prospective clinical study on fertile women undergoing chemotherapy, and reported similar results. However, subsequent clinical studies have revealed different results and opposite conclusions (3,4). At present, reports on the protective effects of GnRHa on ovarian function and whether it alters chemotherapeutic efficiency are lacking.

In the present meta-analysis, clinical randomized controlled trials of premenopausal women using GnRHa to protect ovarian function during chemotherapy were systematically retrieved and collected. Menstrual function recovery rate, premature ovarian failure rate and pregnancy rate were analyzed. In addition, the influence of GnRHa on long-term survival rate was evaluated. This work may provide an effective strategy to protect ovarian function in premenopausal women undergoing chemotherapy.

Materials and methods

Strategy for retrieving literature. By the end of December 2017, the following key words were used in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Embase database (https://www.eMBASE.com/) and Cochrane library (https://www.cochranelibrary.com/advanced-search/search-manager) to retrieve and collect clinical randomized controlled trials in which GnRHa was administered to premenopausal women undergoing chemotherapy: ‘GnRH agonist’, ‘GnRH analog’, ‘chemotherapy’, ‘ovarian damage’, ‘ovarian suppression’, ‘ovarian protection’, ‘ovarian function’, ‘ovarian dysfunction’, ‘fertility’ and ‘fertility preservation’.

Literature search. The following inclusion criteria were applied in the meta-analysis: i) Premenopausal women with...
malignant tumors, systemic lupus erythematosus or other diseases requiring chemotherapy (according to characteristics including age, menstrual function history, ultrasound and hormone levels); ii) a control group with the same disease who did not receive GnRHα treatment; and iii) no limits to ethnicity or language. The following exclusion criteria were applied in the meta-analysis: i) The test design in the original reference was not rigorous and the results were not reliable; ii) the indispensable analytical data were not provided; iii) case reports; iv) patients with metastatic advanced malignant disease or malignant tumors; and v) patients who were under hormone therapy or replacement therapy 3 months prior to treatment with chemotherapy. The studies consisted of randomized controlled trials of premenopausal women undergoing treatment with GnRHα to protect ovarian function during chemotherapy.

Quality assessment and statistical analysis. Two evaluators independently conducted literature screening, risk assessment and data extraction. The risk assessment was conducted according to the clinical randomized controlled trial evaluation recommended by the Cochrane system evaluator manual 5.1 (5). RevMan 5.3 (http://ims.cochrane.org/revman/download) provided by Cochrane collaboration, was used to analyze data. The statistical heterogeneity of each result was analyzed using χ² test, and the significance level was set at P=0.1. P<0.1 was considered to indicate a statistically significant heterogeneity. F² was used to quantitatively evaluate the heterogeneity of the results. F²<25% indicated that heterogeneity may not be important, F²>50% indicated heterogeneity and F²>75% indicated high heterogeneity. When heterogeneity was small, the fixed effect model was adopted. When heterogeneity was high among the literature, the random effect model was adopted and subgroup analysis was carried out. All participants were included in the analysis, and divided into various treatment groups, including the GnRHα group (chemotherapy combined with GnRHα) and control group (chemotherapy not combined with GnRHα) according to the type of intervention. Relative risk (RR) and 95% confidence interval (CI) were calculated for the following variables: Menstrual function recovery rate, pregnancy rate, premature ovarian failure (POF) incidence, tumor-free survival rate, total survival rate.

Results

Features of the included study. A total of 492 references were retrieved and 12 references were included in the present meta-analysis following accurate selection (3,4,6-15) (Fig. 1). A total of 1,413 premenopausal patients with breast cancer or lymphoma undergoing chemotherapy were included in the selected studies. All studies selected included a comparison between the GnRHα group (705 patients) and control group (708 patients). No significant difference in baseline data between the GnRHα and control groups was observed in these 12 studies. The GnRHα drugs used were triptorelin, goserelin or leuprolide. GnRHα was used either at the beginning of chemotherapy or prior to it. Basic features of the included literature are presented in Table I. Quality assessment is shown in Fig. 2.

Meta-analysis results. With regards to the effect of GnRHα on the menstrual function recovery rate, 10 references provided evidence of menstrual function recovery in both the GnRHα and control groups. In the GnRHα group (561 patients), 429 presented menstrual function recovery. In the control group (561 patients), 335 had menstrual function recovery. The results exhibited the following RR and CI: RR=1.29, 95% CI=1.09-1.54, P=0.004, with statistically significant differences, suggesting that GnRHα may significantly improve menstrual function recovery rate (Fig. 3). The scattered points of the inverted funnel plot were less symmetrical and the aggregation was more concentrated; therefore, some publication bias may be present as certain negative results may not be published, as presented in Fig. 4.

The effects of GnRHα on POF incidence were then analyzed. Among the 12 references, nine provided evidence of POF incidence in both GnRHα and control groups. The total number of patients in the GnRHα group was 373, with 61 patients with POF, whereas the total number of patients in the control group was 377, with 135 patients with POF. The results were as follows: RR=0.47, 95% CI=0.31-0.71, P=0.0004, with statistically significant differences, suggesting that chemotherapy combined with GnRHα may significantly reduce POF incidence (Fig. 5).

The effects of GnRHα on pregnancy rate were also assessed. Eight references provided evidence of pregnancy in both the GnRHα and control groups. The total number of patients in the GnRHα group was 501, with 56 pregnant patients, whereas the total number of patients in the control group was 505, with 42 pregnant patients. The results were as follows: RR=1.40, 95% CI=0.98-1.98, P=0.06, without any statistically significant difference, suggesting that chemotherapy combined with GnRHα may have no effect on pregnancy rate (Fig. 6).
Table 1. Basic features of the literature included in the present meta-analysis.

| First author, year | Disease          | Results                                                                 | Drugs     | Dose and interval | Start time                                      | Follow-up time | (Refs.) |
|--------------------|------------------|-------------------------------------------------------------------------|-----------|-------------------|-------------------------------------------------|----------------|---------|
| Badawy, 2009       | Breast cancer    | Menstrual recovery, POF                                                | Goserelin | 3.6 mg/28 days   | 2 weeks before chemotherapy                     | 8 months       | (3)     |
| Demeestere, 2016   | Lymphoma         | POF, pregnancy, tumor-free survival, overall survival                 | Triptorelin | 3.75 mg/28 days | 2±0.51 days before chemotherapy                | GnRHa group: 5.33 years (4) |
| Elgindy, 2013      | Breast cancer    | Menstrual recovery, pregnancy                                           | Triptorelin | 3.75 mg/28 days | 10 days before chemotherapy                     | 1 year         | (6)     |
| Gerber, 2011       | Breast cancer    | Menstrual recovery, pregnancy                                           | Goserelin | 3.6 mg/28±3 days | At least 2 weeks before chemotherapy            | 2 years        | (7)     |
| Giuseppe, 2007     | Lymphoma         | Menstrual recovery, POF, pregnancy                                      | Triptorelin | Triptorelin     | Immediately after diagnosis                     | GnRHa group: 2.42±1.7 years (8) Control group: 5.93±4.47 years |
| Karimi-Zarchi, 2014| Breast cancer    | Menstrual recovery, POF, pregnancy, tumor-free survival               | Triptorelin | 3.75 mg/28 days | Same time as chemotherapy                       | 6 months       | (9)     |
| Lambertini, 2015   | Breast cancer    | Menstrual recovery, POF, pregnancy, tumor-free survival               | Triptorelin | 3.75 mg/28 days | At least 1 week before chemotherapy             | 7.3 years      | (10)    |
| Leonard, 2017      | Breast cancer    | Menstrual recovery, POF, pregnancy, overall survival                  | Goserelin | 3.6 mg/28 days  | At least 1-2 weeks before chemotherapy          | 2 years        | (11)    |
| Moore, 2015        | Breast cancer    | Menstrual recovery, POF, pregnancy, tumor-free, survival overall survival | Goserelin | 3.6 mg/28 days  | 1 week before chemotherapy                      | 5-7 years      | (12)    |
| Munster, 2012      | Breast cancer    | Menstrual recovery, POF, pregnancy, overall survival                  | Triptorelin | 3.75 mg/28-30 days | At least 7 days before chemotherapy            | GnRHa group: 4.96 years (13) Control group: 5.82 years 1 year |
| Song, 2013         | Breast cancer    | Menstrual recovery, POF                                                | Leuprolide | 3.75 mg/28 days | Before chemotherapy (if ovarian suppression was confirmed, patients started to receive chemotherapy) | 3 years        | (14)    |
| Sverrisdotti, 2009 | Breast cancer    | POF                                                                     | Goserelin | 3.6 mg/28 days  | Same time as chemotherapy                       | 3 years        | (15)    |

GnRHa, gonadotropin-releasing hormone agonist, POF, premature ovarian failure.
The effects of GnRHa on the menstrual function recovery rate, POF incidence and pregnancy rate were also determined on patients <40 years old. This subgroup analysis was conducted because the literature was heterogenous. Results revealed that GnRHa improved the menstrual function recovery rate of patients undergoing chemotherapy (RR=0.16, 95% CI=0.07-0.38, P<0.0001) and reduced POF incidence (RR=1.51, 95% CI=1.02-2.23, P=0.04), with no effect on pregnancy rate (RR=0.36, 95% CI=0.06-2.27, P=0.28; Fig. 7).

With regards to the effect of GnRHa on long-term overall survival rate, two references provided evidence of long-term survival in both the GnRHa and control groups. The total number of patients in the GnRHa group was 170, of which 158 survived, whereas the number of patients in the control group was 177, of which 158 survived. The results of the meta-analysis were as follows: RR=1.02, 95% CI=0.90-1.16, P=0.72, without any statistically significant difference, suggesting that chemotherapy combined with GnRHa may have no effect on long-term overall survival rate (Fig. 8).

Discussion

The results of the present meta-analysis revealed that GnRHa may reduce ovarian function damage caused by chemotherapy-induced toxicity, and may significantly improve the menstrual function recovery rate and reduce POF incidence in patients undergoing chemotherapy. A previous study (16) has also analyzed the influence of GnRHa on the therapeutic effects of chemotherapeutic drugs. Cuzick et al (16) performed a meta-analysis on 16 randomized controlled trials, and evaluated a total of 11,906 premenopausal women who required chemotherapy for early breast cancer. The study revealed that GnRHa as an adjuvant chemotherapy for cancer patients does not affect chemotherapy. The present meta-analysis analyzed long-term tumor-free survival rate and overall survival rate of patients, and demonstrated that GnRHa had no effect on long-term chemotherapy.

Chemotherapy can cause several collateral effects to the ovaries, resulting in damage, including irreversible ovarian dysfunction, amenorrhea and infertility, thus compromising the health and quality of life of patients. There are three main types of chemical drugs that can cause damage to ovarian function (3). The first group comprises nitrogen mustard, cyclophosphamide and other alkylating agents, which have effects on cells in any cell cycle phase; these are the most harmful drugs. The second group of chemotherapeutic drugs includes cisplatin and adriamycin, which mainly affect proliferative cells. These drugs have minor effects on the primordial follicle, do not induce ovarian damage and only result in short-term amenorrhea. The third chemotherapeutic drugs group, including the methotrexate-treated group, exerts only minor or no damage to the ovaries. Overall, the effects of chemotherapy on ovarian function are influenced by numerous factors: i) The concentration of chemotherapeutic drugs; ii) the duration of chemotherapy; iii) drug superposition; and iv) age of the patient at the beginning of chemotherapy and the type of disease.

The protective effects of GnRHa on ovarian function have been extensively studied. GnRHa can be combined with the GnRH receptor, which inhibits the secretion of lutein hormone and follicle-stimulating hormone (FSH), thus inhibiting gonadotropin. Numerous mechanisms explain ovarian protection. Primordial follicle maturation and growth depends on FSH, and it has been demonstrated that these follicles...
contain mRNA able to express FSH and lutein hormone receptors; this expression is dependent on gonadotropins (17). Furthermore, the chemical structure of GnRHa is similar to GnRH; however it has a stronger affinity to the receptors. When GnRHa is combined with the pituitary gland receptors, it can induce an increase in gonadotropin release, known...
as the flare-up effect. The number of GnRH receptors then decreases, blocking the hypothalamus-pituitary-ovarian axis and subsequently decreasing the amount of FSH released, reducing the maturity and growth of original follicles, and reducing the sensitivity of the ovaries to chemotherapy (18). Badaru et al (19) demonstrated that this inhibition is positively correlated with the dosage of GnRHa, and that the inhibitory effect of GnRHa on the hypothalamus-pituitary-ovarian axis is increased when administered at 7.5 mg/month compared with at 3.75 mg/month. Previous studies have suggested that GnRHa reduces the amount of blood flowing through the ovaries, leading to a reduced concentration of topical drugs. However, few studies are available on this subject, and the results are contradictory. Kitajima et al (20) suggested that high levels of estrogen can significantly increase ovarian hyperstimulation and ovarian blood flow in a mouse model, whereas these effects are inhibited by GnRHa, and the degree of inhibition is positively associated with GnRHa dosage. A prospective study completed by Reinsch et al (21) revealed that after 3 months of continuous use of leuprolelin acetate, the blood flow to the uterus decreases by 21% and the signal of blood flow to the ovaries disappears. Conversely, Ng et al (22) and Jarvela et al (23) discovered that there is no alteration in ovarian blood flow before or after GnRHa treatment. The

| Study or Subgroup | GnRHa Events | Control Events | Total | Weight | Risk Ratio | M.H. Fixed, 95% CI |
|-------------------|--------------|----------------|-------|--------|------------|-------------------|
| Demeester 2016    | 17           | 32             | 15    | 35     | 34.2%      | 1.24 [0.75, 2.05] |
| Elgindy 2013      | 1            | 50             | 2     | 50     | 4.8%       | 0.50 [0.05, 5.34] |
| Gerber 2011       | 1            | 30             | 1     | 30     | 2.4%       | 1.00 [0.07, 15.26]|
| Giuseppe 2007     | 0            | 14             | 2     | 15     | 5.8%       | 0.21 [0.01, 4.09] |
| Lambertini 2015   | 8            | 148            | 3     | 133    | 7.5%       | 2.40 [0.65, 8.65] |
| Leonard 2017      | 7            | 95             | 5     | 107    | 11.2%      | 1.59 [0.52, 4.90] |
| Moore 2015        | 22           | 105            | 12    | 113    | 27.6%      | 1.97 [0.03, 3.79] |
| Munster 2012      | 0            | 27             | 2     | 22     | 6.5%       | 0.16 [0.01, 3.25] |

Total (95% CI): 501 / 505 / 100.0% 1.10 [0.98, 1.98]

Total events: 56 / 42
Heterogeneity: Chi² = 6.31, df = 7 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)

Figure 6. Forest plot of meta-analysis for the effects of GnRHa on the rate of pregnancy. CI, confidence interval; GnRHa, gonadotropin-releasing hormone agonist.

| Study or Subgroup | GnRHa Events | Control Events | Total | Weight | Risk Ratio | M.H. Random, 95% CI |
|-------------------|--------------|----------------|-------|--------|------------|---------------------|
| 2.1.1 Restore menstruation | | | | | | |
| Badawy 2009       | 35           | 39             | 13    | 39     | 22.4%      | 2.69 [1.71, 4.25]   |
| Elgindy 2013      | 27           | 50             | 27    | 50     | 25.3%      | 1.00 [0.70, 1.44]   |
| Giuseppe 2007     | 14           | 14             | 8     | 15     | 22.0%      | 1.82 [1.14, 2.91]   |
| Leonard 2017      | 54           | 60             | 44    | 59     | 30.4%      | 1.21 [1.02, 1.43]   |
| Subtotal (95% CI) | 163          | 163            | 100.0%| 151    | 1.02 [0.98, 1.06] |

Total events: 130 / 92
Heterogeneity: Tau² = 0.12; Chi² = 15.48, df = 3 (P = 0.001); I² = 81%
Test for overall effect: Z = 2.06 (P = 0.04)

| Study or Subgroup | GnRHa Events | Control Events | Total | Weight | Risk Ratio | M.H. Random, 95% CI |
|-------------------|--------------|----------------|-------|--------|------------|---------------------|
| 2.1.2 POF | | | | | | |
| Badawy 2009       | 4            | 39             | 21    | 39     | 74.3%      | 0.19 [0.07, 0.50]   |
| Elgindy 2013      | 0            | 14             | 7     | 15     | 9.1%       | 0.07 [0.00, 1.14]   |
| Leonard 2017      | 1            | 39             | 6     | 30     | 16.5%      | 0.13 [0.02, 1.01]   |
| Subtotal (95% CI) | 92           | 84             | 100.0%| 0.16   | 0.07 [0.02, 0.38] |

Total events: 5 / 34
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 4.24 (P < 0.0001)

| Study or Subgroup | GnRHa Events | Control Events | Total | Weight | Risk Ratio | M.H. Random, 95% CI |
|-------------------|--------------|----------------|-------|--------|------------|---------------------|
| 2.1.3 Pregnancy  | | | | | | |
| Elgindy 2013      | 1            | 50             | 2     | 50     | 60.0%      | 0.50 [0.05, 5.34]   |
| Giuseppe 2007     | 0            | 14             | 2     | 15     | 39.1%      | 0.21 [0.01, 4.09]   |
| Subtotal (95% CI) | 64           | 65             | 100.0%| 0.36   | 0.06 [0.08, 2.27] |

Total events: 1 / 4
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.28)

Figure 7. Forest plot of meta-analysis for the effects of GnRHa on menstrual recovery rate, POF incidence and pregnancy rate in patients <40 years old. CI, confidence interval; GnRHa, gonadotropin-releasing hormone agonist, POF, premature ovarian failure.
effects of GnRHa on ovarian blood flow remain unclear and require further investigation.

There are two main types of GnRH receptors: GnRH receptor-I and GnRH receptor-II. Choi et al. (24) discovered that GnRH receptors are present in ovarian cancer cell lines, ovarian surface epithelium, preovulatory follicles and corpus luteal cells, but are not detectable in the original follicles and early sinus follicles. Imai et al. (25) reported that GnRHa acts directly on the granulosa cells, thus reducing the toxic effect of chemotherapy drugs. Recent studies (26,27) have suggested that the damage induced by chemotherapy to female reproduction and endocrine function is due to cell apoptosis. GnRHa can be used to increase secretion of the gonadal protective molecule sphingosine-1-phosphate (S-1-P), which can prevent follicle injury or reproductive cell apoptosis. It has been demonstrated that S-1-P application to patients undergoing radiotherapy reduces ovarian damage (28).

The number follicles contained in the ovaries can reach 7,000,000 in a 28-week-old fetus, after which the follicles gradually die. No new cells are produced in the ovaries, and all cells stored will eventually disappear, resulting in perimenopausal symptoms. However, a recent study (29) has presented opposite results, indicating that the ovaries contain ovarian stem cells. Johnson et al. (29) reported that rat ovaries have active germ line stem cells, which can continuously replace the immature ovarian follicles, allowing primordial follicular pool regeneration. Therefore, some researchers have hypothesized that GnRHa may preserve ovarian function by protecting the undifferentiated germ line stem cells. This hypothesis requires further investigation.

The present study had some limitations. Firstly, the 12 references included in this study had different definitions of POF and the follow-up time was markedly different, which potentially affects the results of this work. Secondly, eight references provided evidence of pregnancy in the GnRHa and control groups; however, no information was given on the use of contraception following cessation of chemotherapy and during follow-up. It was therefore difficult to evaluate the effects of chemotherapy combined with GnRHa on fertility. Thirdly, only three of the 12 references provided long-term tumor-free survival rate, which represented a small sample size that could potentially have led to a wrong conclusion. In addition, the 12 clinical randomized controlled trials included had an overall heterogeneity, and their differences in disease, chemotherapy, follow-up time and POF definition may have affected the results. A larger sample size, longer follow-up period and well-designed clinical randomized controlled trials are therefore required to further study and/or confirm the protective effects of GnRHa on ovarian damage induced by chemotherapy.

In conclusion, the present meta-analysis demonstrated that GnRHa may reduce ovarian function damage caused by chemotherapy. GnRHa significantly increased the rate of menstrual function recovery and reduced POF incidence; however, it had no effect on pregnancy rate, tumor-free survival rate and overall survival rate.

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Availability of data and materials
The analyzed datasets generated during the study are available from the corresponding author on reasonable request.
Authors' contributions

FZ and BZ designed the study and performed the literature review. YL and YW interpreted the data and wrote the manuscript. QF and LW performed the literature review, data collection and analysis, and wrote the manuscript. YC designed the study, performed data analysis and wrote the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Reference

1. Ataya KM, McKanna JA, Weintraub AM, Clark MR and LeMaire WJ: A luteinizing hormone-releasing hormone agonist for the prevention of chemotherapy-induced ovarian Bicular loss in rats. Cancer Res 35: 3653-3656, 1985.
2. Blumenfeld Z and Eckman A: Preservation of fertility and ovarian function and minimization of chemotherapy-induced gonadotoxicity in young women by GnRHa. J Nail Cancer Inst Monogr 34: 40-43, 2003.
3. Badawy A, El-Ashry M and Shabat M: Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: Prospective randomized study. Fertil Steril 91: 694-697, 2009.
4. Demeestere I, Brice P, Peccatori FA, Fantus G, Dupuis j, Vincenzo L: Ovarian function after cancer treatment in young women affected by Hodgkin disease (HD). Hematology 12: 141-147, 2007.
5. Gerber B, von Minkwitz G, Stehle H, Reimer T, Felberbaum R, Imai A, Sugiyama M, Furui T, Tamaya T and Ohno T: Direct protection by a gonadotropin-releasing hormone analog from chemotherapy for breast cancer. Natl Cancer Inst 91, 664-666, 1999.
6. Reinsch RC, Murphy AA, Morales AJ and Yen SS: The effects of GnRH depot leuprorelin. Clin Pharmacokinet 41: 485-504, 2002.
7. Badarin A, Wilson DM, Badar A, El-Ashry M and Shabat M: Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: Prospective randomized study. Fertil Steril 91: 694-697, 2009.
8. Munday PL, Wilson DM, BADarin A, El-Ashry M and Shabat M: GnRHa for the prevention of chemotherapy-induced ovarian failure. Lancet 369: 1711-1723, 2007.
9. Zheng W, Magid MS, Kramer EE and Chen YT: Follicle-stimulating hormone receptor is expressed in human ovarian surface epithelium and fallopian tube. Am J Pathol 148: 47-53, 1996.
10. Periti P, Mazzei T and Mini E: Clinical pharmacokinetics of depot leuprolin. Clin Pharmacokinet 41: 485-504, 2002.
11. 26. Morita Y and Tilly j L: Oocyte apoptosis: Like sand through an hourglass. Dev Biol 213: 1-17, 1999.
12. Reynolds T: Cell death genes may hold clues to preserving fertility after Chemotherapy. Natl Cancer Inst 91, 664-666, 1999.
13. Morita Y, Perez GJ, Paris F, Miranda SR, Ehleiter D, Haimovitz-Friedman A, Fuku Z, Xie Z, Reed JC, Schuchman EH, et al: Oocyte apoptosis is suppressed by disruption of the acid sphingomyelinase gene or by sphingosine-1-phosphate therapy. J Clin Invest 120: 1109-1114, 2006.
14. Johnson J, Canning J, Kaneko T, Pru JK and Tilly JL: Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature 428: 145-150, 2004.

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