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Review
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Breast cancer and ovulation induction

Meme kanseri ve ovulasyon indüksiyonu

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Abstract

Breast cancer is the most common malignancy of women at reproductive age. Nowadays, with increasing early diagnosis, survival rate is higher, which is why the number of patients wanting to get pregnant are on the rise. Fertility preservation, ovulation induction, the safety of these interventions and pregnancy results are discussed in this review.

Keywords: Breast cancer, Ovulation induction, Infertility

Öz

Meme kanseri, üreme çağındaki kadınların en sık görülen malignitesidir. Günümüzde meme kanseri erken teşhis edilir ve hastaların sağkalım oranı yüksektir. Bu nedenle hamile kalmak isteyen hastalar çok yaygındır. Bu derlemede doğurganlığın korunması, ovulasyon indüksiyonu ve indikiyonun güvenliği ve gebelik sonuçları tartışılmıştır.

Anahtar kelimeler: Meme kanseri, Ovulasyon indüksiyonu, İnfertilite

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Introduction

Breast cancer is the most common malignancy of women at reproductive age. According to data published by WHO, it constitutes 25% of all cancers [1]. In Europe, the incidence of breast cancer is 30/100,000 for women in the premenopausal period. Regarding the estimations, invasive breast cancer will emerge in one of each 202 women before the age of 39 in the USA [2].One-fifth of these women are diagnosed before the age of 45 and the 5-year survival rate increased up to 91.0% in 2007, while it was 74.6% between 1975 and 1979 [3]. The majority of women with breast cancer have to undergo chemotherapy, which is life-saving, but has negative effects on ovarian reserve. The American Society of Clinical Oncology recommended the early introduction of certain alternatives at the beginning of chemotherapy to preserve fertility in young women [4]. Regarding women who want to get pregnant in the future, referral to a specialist gynecologist just after the diagnosis will minimize the time between diagnosis and the initiation of chemotherapy and increase the potential of fertility preservation. The duration of these interventions is 2-3 weeks. The fertility preservation procedures may be implemented between surgery and chemotherapy.

Fertility preservation methods in women with breast cancer

Breast cancer patients usually undergo an adjuvant hormone therapy for 5 years. Pregnancy is contraindicated during neoadjuvant therapy. At the time appropriate for pregnancy, the ovarian reserve may be insufficient for a natural conception. Therefore, clinicians should refer to some techniques to preserve the fertility in women who plan to have a child in the future, before anti-cancer treatment impairs fertility.

There are several alternatives for fertility preservation: Vitrification of oocytes, embryo freezing, ovarian tissue freezing, and in vitro maturation of oocytes. The latter two, which are less common in daily practice, are still considered as experimental methods. The cryopreservation of embryos is the most common. In recent years, vitrification of oocytes became gradually popular. The cryopreservation of oocytes and embryos is usually implemented after the controlled ovarian hyperstimulation (KOH). The cryopreserved embryos and oocytes may be stored for years without any negative effect on their viability. A higher rate of the frozen embryos survives during the freeze-thaw process compared to the unfertilized oocytes (50%-70% vs >90%). In an experienced center, the live birth rate in patients, who received frozen oocyte for IVF, is 21%, while the same rate is approx. 60% for IVF cycles containing fresh oocytes [5].

KOH is not recommended after the initiation of chemotherapy. The response to the stimulation and the quality of the harvested oocytes decline with each chemotherapy session. It may cause double helix breaks in the DNA in human oocytes. Therefore, a waiting period of 6 months is recommended before pregnancy for women who undergo chemotherapy. During this 6-month waiting period, the follicles with DNA damage are eliminated from the primordial follicles [6].

Oocyte freezing - Matured Oocytes

Cryopreservation of matured oocytes is an alternative for women, who do not have a partner for IVF and do not prefer the donor sperms. Unlike the embryos and sperms, oocyte cryopreservation is a rather difficult technique, as the oocytes contain less water and consequently, they are more sensitive to injury related to the development of ice crystals. Meiotic fibers, cellular skeleton, cortical granules, and zona pellucida are particularly sensitive to freezing [5].

Cryopreservation of ovarian tissue

Women with BRCA positivity and hereditary breast-ovarian cancer syndrome are not suitable for cryopreservation of the ovarian tissue for later transplantation of it because of the risk of the development of ovarian cancer. However, in the future, storage of frozen-thawed ovarian tissue band will may be possible to obtain the oocyte maturation and IVF implementation [6].

Treatment with GnRH agonists

In women who are not suitable for cryopreservation procedures (because of timing, specific reasons related to cancer or other patient problems), some clinicians prefer GnRH (Gonadotropin-Releasing Hormone) agonist therapy to preserve the ovarian function. GnRH agonists are not recommended as the first-line therapy in fertility preservation, as it was demonstrated that they are not superior to the embryo or oocyte freezing [7]. The protective mechanism of GnRH agonists on fertility is not fully elucidated yet. Nevertheless, patients should be informed that this treatment method may provide a limited benefit to fertility preservation. The GnRH agonists suppress the ovarian function and therefore ovaries may be relatively less affected by the toxic effects of chemotherapy. However, follicles are exposed to the toxic agents, which damage DNA, even though the ovarian hormone production is inhibited. As the primordial follicles do not express gonadotropin receptors, it is not known how the treatment with GnRH agonists will increase the survival of the cells [8].

The GnRH agonists are mainly used for the relief of the metrorrhagia. The evaluation of the efficacy of the GnRH treatment on fertility preservation is rather difficult, as most of the studies focused on this topic are not based on reliable criteria. The levels of the anti-Müllerian hormone (AMH) and antral follicle counts (AFC) are established markers of the ovarian reserve. In studies focused on AMH and AFC, it was reported that GnRH agonists were not effective in the preservation of the ovarian reserve. Long-term analyses showed that GnRH did not preserve the ovarian reserve or fertility [9].

Data related to the effects of the suppression of the ovarian function by GnRH agonists on fertility in women undergoing chemotherapy are conflicting and methodological errors limit the interpretation as mentioned above.

The primordial follicles, which constitute the ovarian reserve, do not have receptors for FSH or GnRH agonists. Therefore, they are not able to respond to any hormonal manipulation [7].

Alternatives for women who cannot undergo KOH

In breast cancer patients with large mass lesion and rapid progress, neoadjuvant chemotherapy is initiated before the surgery just after the diagnosis. If KOH is not applicable due to the timing and safety reasons, the harvest of the immature oocytes may be an alternative. Under emergency conditions, after the harvest of the oocyte in the luteal phase (instead of in

vivo conventional maturation), in vitro maturation (IVM) and preservation with embryo freezing (IVF) may be an alternative.

In fact, fertility preservation is a complex process, as breast cancer is often sensitive to estrogen and supra-physiological estradiol, which is produced during KOH, may induce the proliferation of the cancer cells. Standard KOH protocols significantly increase estrogen concentrations. The mean estradiol level, which has a peak of 300pg/ml during a natural cycle, may increase up to 456-6957pg/ml during KOH [10]. This is a concern in women with breast cancer, as many breast cancers contain estrogen receptor positive (ER+) cells, which may be affected negatively from the supra-physiological estradiol levels related to ovarian stimulation. Even breast cancer, which is diagnosed as estrogen receptor negative (ER-), may be sensitive to estrogen particularly if exposed to high estrogen levels. Therefore, the exposure to estrogen should be minimized during KOH in this patient group.

Studies showed that endogenous and exogenous estrogen might play a key role in the pathogenesis of breast cancer. However, none of these studies supported the hypothesis, which suggested that short-term exposure to exogenous estrogen may impair the prognosis in breast cancer [11].

Standard KOH protocols may be changed to decrease the potential damage related to the increased estradiol levels.

Neither cancer cells, nor healthy cells in the breast respond to the gonadotropins (FSH, LH). On the other hand, exposure to estrogen induces the proliferation in cancer cells in ER (+) patients depending on the dosage. Besides, as estradiol stimulates angiogenesis, which is critical for the tumor neovascularization, may induce the proliferation of the breast cancer cells. Its long-term usage stimulates the production of insulin-like growth factor 1, which is mitogenic on breast cancer cells [12].

A more conservative approach to women with breast cancer to decrease the temporarily elevated estrogen concentrations during KOH will minimize the potential risks. The complications related to KOH in women with breast cancer is not limited to women with ER (+) malignancy. The tumor cells may be classified as “estrogen receptor negative” if less than 10% of the cells stained positive for the estrogen receptor and these cells may be clinically important. The receptor heterogeneity leads to the overlooking ER (+) cells and approximately 15%-20% of the reports may contain false-negative results. Breast cancer is a heterogeneous and complex disease with different responses to the hormonal stimuli and clinical applications depending on the gene mutation in the cell receptors and the diverse methylation pattern.

In women with ER (+) breast cancer, there is strong evidence that minimizing the estrogen exposure may decrease the recurrence and the cancer-related mortality. Two agents, which are widely used for this purpose, are receptor modulators such as aromatase inhibitors and selective estrogen-binding tamoxifen (TMX), which inhibit the catalytic conversion of androstenedione to estrone and of estradiol to testosterone [13].

Aromatase inhibitors

The aromatase inhibitors (e.g. letrozole) are used in breast cancer patients for the in vitro fertilization (IVF) and the ovarian stimulation in combination with gonadotropins. The maximum estradiol levels close to the levels observed in natural cycles are the advantage of the ovarian stimulation with the aromatase inhibitors. A protocol consisting of letrozole and follicle stimulation hormone (FSH) combination is used for the ovarian stimulation in most of the women with breast cancer undergoing IVF for the embryo or oocyte cryopreservation. This combination causes low estradiol levels and enables high oocyte harvesting. Theoretically, these agents have a good safety profile. It was observed that letrozole cycles cause a more significant decline in estradiol levels compared to anastrozole [14].

Studies showed that letrozole administration together with the FSH stimulation provided comparable cycle periods, number of harvested embryos and rates of conception and decreased the need for gonadotropins by 44% (a retrospective, controlled study focused on women in similar age group, who underwent IVF due to the tubal reasons). Although letrozole may be used in doses of 0.1-10mg/day, the usual daily dose is between 2.5mg and 5mg. It was recommended that estrogen levels should be checked in every examination and letrozole dose be increased to 10mg if estrogen levels follow a high course [15].

Safety - The safety of the letrozole

FSH protocol is investigated with a prospective clinical study. In this study, 79 of 215 women with breast cancer received letrozole and FSH during KOH and the remaining 136 patients were in the control group.

Although the time between breast surgery and chemotherapy was longer (mean: 34 or 45 days) among women who underwent IVF compared to those who did not, the risk of recurrence was 0.56 in those who have received IVF treatment (95% CI: 0.17-1.9). There was no significant difference between the groups with respect to survival rate. The same investigators conducted another study to evaluate the safety and applicability of two sequential stimulation cycles in patients with breast cancer. In two cycles compared to one cycle, more oocytes (16 vs 9) and more embryos (6.4 vs 3.7) were harvested without a significant prolongation of the time between surgery and chemotherapy (64 days vs 58 days). The recurrence rates in the groups were comparable after a 59-month follow-up period [16].

Pregnancy Rates In a study which was conducted on 131 breast cancer patients (≤stage 3), who underwent ovarian stimulation with letrozole for fertility preservation and 33 infertility cases, the comparison of the data did not show any difference between the groups considering the live birth rates. Reddy et al found similar results in their study [17,18].

Tamoxifen (TMX)

TMX which is a selective estrogen receptor modulator and has an anti-estrogenic effect on the breast tissue is as effective as the clomiphene citrate in the anovulatory infertility treatment. Therefore, it seems to be useful in breast cancer patients. The safety and efficacy of TMX were demonstrated in prospective studies, in which the breast cancer patients treated with TMX were compared with control groups consisting of breast cancer patients with a natural IVF cycle [19].

In patients stimulated with TMX, less cycle cancellation occurred (1/15 vs 4/9) and more mature oocytes (1.6±0.3 vs 0.7±0.2) and embryos (1.6±0.3 vs 0.6±0.2) were harvested. While embryo was harvested in all 12 patients who underwent

KOH with TMX, embryo harvesting was successful only in 3 ut oof 5 patients who underwent natural cycle IVF [20].

As TMX acts on estrogen receptors instead of inhibiting estrogen production, TMX treatment does not decrease estrogen levels during KOH. Therefore, peak estradiol levels were higher in the TMX group compared to the control group. However, it was observed that the rates of the cancer recurrence did not increase after a 2-year follow-up. Studies are reporting that the rate of cancer recurrence did not increase for 10 years after TMX administration for KOH in the conventional IVF cycle [19].

The efficacy of the letrozole-FSH protocol for KOH was demonstrated with a prospective study, in which letrozole/low-dose FSH (LetFSH-IVF), TMX/low-dose FSH (TMX FSH-IVF) and only TMX (TMX-IVF) were compared [19]. LetFSH-IVF provided the highest embryo yield (LetFSH-IVF: 5.3±0.8; TMX FSH-IVF: 3.8±0.8 and TMX-IVF: 1.3±0.2) and the lowest estradiol levels (LetFSH-IVF: 380±57; TMX-IVF: 419±39 and TMX FSH-IVF: 1182±271pg/mL) [21].

The KOH process in patients with gene 1 (BRCA) mutation among infertile cases with breast cancer exhibits different features. The low response to KOH (3% vs 33%) and low oocyte development (7 vs 12) are additional concerns in carriers of BRCA 1 compared to BRCA-negative patients [22].

A wide range of studies showed that carriers of BRCA mutation go through menopause earlier than BRCA-negative patients. It was demonstrated that the serum levels of anti-Müllerian hormone (AMH) were decreased and BRCA 1-mutant mice had less primordial follicles at birth [23].

In the carriers of BRCA mutation, the mechanism of the decreased ovarian reserve was explained with the deficiency of DNA repair in the BRCA-mutant oocytes, which makes them more sensitive to the genotoxic stress such as oxygen radicals and chemotherapy. In a cross-sectional study that was conducted on approx. 700 women, serum levels of AMH were found 25% lower in the carriers of BRCA mutation compared to BRCA-negative subjects. Taking these accumulating data into consideration, it may be suggested that the carriers of BRCA mutation are more defenseless against the gonadotoxic effects of the cancer treatments [24].

Typically, there is a gap of 4-6 weeks between breast cancer surgery and the initiation of chemotherapy. Although the oocytes can be harvested during a natural cycle, the yield is very low. The interval of 4-6 weeks is sufficient for the completion of one KOH and oocyte harvesting cycle. An early application to the endocrinologist may even give time for two cycles and more oocytes may be harvested for cryopreservation [25].

Although several different protocols were already introduced, protocols containing gonadotropin antagonists are usually preferred. As the treatment with a gonadotropin antagonist started on the 21st day of the previous cycle causes prolonged downregulation, timing problems emerge and therefore, is not much preferred. The antagonist agents may be started in the luteal phase of the previous cycle and thus the resorption of the corpus luteum is accelerated and synchronized follicle development can be achieved during the menstruation period [26]. This method is one of the treatment options preferred for the estrogen receptor-positive breast cancer patients [27]. If 3mg cetrorelix is administered in the mid-luteal phase, the menstruation occurs in a couple of days and KOS might be implemented without wasting time in cancer patients [28].

In the conventional ovarian stimulation protocols, starting induction in the early stage of the follicular phase is the rule. A standard approach was developed based on the opinion that better clinical results could be achieved with this principle. However, as the first day of the next cycle should be waited for this approach, the treatment may be delayed. Some ovarian stimulation protocols with random start were developed for cases, in which the onset of the next menstruation cannot be waited [29].

Studies showed that mostly 2 follicle development waves occurred between two ovulation cycles (3 waves in 30% of patients) and it was reported that oocyte harvesting could be performed twice or thrice during this interval [30].

If a suitable follicular development wave is achieved thanks to this process, random ovulation induction forms can be implemented as a late follicular and luteal ovulation induction in the same cycle except for the classical ovulation induction. Depending on the same principle, more than one ovulation induction in both follicular and luteal phases can be carried out in the same cycle [31,32].

Accordingly, the suggestion that the majority of the oocytes, which are harvested during the luteal phase are atretic, is disputable.

The late follicular phase is defined as the 7th day of the menstrual cycle when the 13-mm dominant follicle appears and the progesterone level is under 2ng/ml. In patients in this phase, who have a timing problem, KOH is started without antagonist agents if the follicle is smaller than 12mm and continued until the spontaneous LH peak, while the follicle size is <12mm. After the LH peak, the gonadotropin stimulation is started and GnRH antagonist is administered after the secondary cohort becomes >13 mm to inhibit the premature LH peak, or hCG is administered. GnRH administration is also an option for ovulation. After 2-3 days, the ovarian stimulation is started in the luteal phase.

If the ovulation already occurred or induced or the patient is in the luteal phase, a conventional protocol with a gonadotropin antagonist can be started. In this process, induction must be continued with FSH without including LH to support corpus luteum, which is luteolyzed due to the effects of the antagonist agent. The inductions implemented in the late follicular phase and luteal phase last approx. 2 days longer than the conventional approaches and lead to the usage of more gonadotropin [33]. Contrary to general belief, the presence of corpus luteum in the luteal phase or increased progesterone do not have any negative effect on follicular development. Harvesting oocytes at independent times in the same cycle supports the physiological changes defined in the ovarian physiology.

The most common protocol, which is used to stimulate patients with breast cancer, consists of 5mg oral letrozole administered after the 2nd or 3rd day. The ideal doses of the follicle stimulation hormone (FSH) are <13 IU/l with an estradiol level <60pg/ml. After a 2-day treatment, recombinant FSH (rFSH) (150-300IU/day) is added to the letrozole treatment. If the serum estradiol concentration exceeds 250pg/ml or the size

of the follicle exceeds 13mm, a GnRH antagonist is started to prevent a premature peak of LH. The follicular growth is monitored until the diameters of at least two follicles reach 20mg and ovulation is triggered with a GnRH antagonist. The comparison of the GnRH antagonists with hCG for triggering capacity showed that the GnRH antagonists cause a greater and faster decrease of the estradiol level without decreasing the number of the oocytes.

The induction protocol started with letrozole is implemented along with the addition of rFSH and triggering of the ovulation with the GnRH antagonists (e.g. triptorelin) independent from the molecular phenotype of breast cancer. In letrozole cycles, ovarian stimulation can be initiated randomly within the cycle without making concession on the fertilization rates. Similar IVF success rates were reported for the stimulations started in the 2nd day and 15th day of the cycle [34].

Ovulation induction protocols in patients with estrogen receptor positive breast cancer

Time constraints

The chemotherapeutic agents used in the treatment of breast cancer are gonadotoxic. As these agents are administered just after the diagnosis, there will be usually no time for the ovarian stimulation and harvesting oocytes, which requires generally 2-3 weeks.

The oncologists do not recommend the delay of KOH. Therefore, it is normal to start with the stimulation in the 2nd-3rd days of the menstrual cycle. The strategy may change according to the timing of the cycle. If the cycle is in the early proliferative phase and the dominant follicles are not dominant yet, stimulation can be initiated even though the patient is not on the 2nd or 3rd day of the cycle. If the cycle is in the late phase and the diameter of the dominant follicle exceeds 18mm, direct oocyte harvesting and vitrification can be carried out. Afterwards, a GnRH antagonist is administered for 5 days. If the diameter of the dominant follicle is smaller than 18mm, it can be stimulated with minimum FSH doses until the diameter reaches 18mm. Then a GnRH antagonist is given for 5 days [35].

If the ultrasonographic examination and blood progesterone levels indicate that the patient is in the secretory phase, a GnRH antagonist is administered for 4-5 days and then stimulation be started. The goals of the GnRH antagonist administration are to keep estradiol levels under 60pg/ml and not to delay the treatment until a new physiological cycle starts. Single or double trigger protocols with hCG and GnRH analogs are used for the harvesting of mature oocytes from the small antral follicles in patients with an insufficient response. In breast cancer patients, the use of a GnRH agonist trigger during KOH enables a rapid decline in the estradiol concentrations after the oocyte harvesting. Likewise, the risk of hyperstimulation is decreased with this method. Besides, more oocytes are harvested without decreasing pregnancy or live birth rates. The decreased pregnancy and live birth rates which are reported in the fresh cycles during the administration of a GnRH agonist trigger are not encountered in the “cryo cycles” or donor cycles, and this is believed to have occurred secondary to the endometrial receptor defects. As cryopreservation is usually used for fertility preservation, the decrease in the pregnancy rates seen during the cycles triggered by the GnRH agonist is not relevant [36].

Approximately 70%-80% of breast cancers are androgen receptor positive (AR+). As the aromatase inhibitors prevent the conversion of androgens to estrogens, the androgen levels may increase during the letrozole treatment. It is not elucidated yet whether the androgenic effects have proliferative or anti-proliferative effects on the breast cancer cells [37].

The androgen receptor may inhibit the ER activity in breast cancer cell proliferation induced by estradiol and the increased androgen concentrations during KOH depending on the letrozole treatment does not seem to have harmful effects [38].

Response to KOH cycles in breast cancer

Cancer is related to catabolism and insufficient nutrition. Several patients lose so much weight, that the fertilization capacity is impaired depending on the negative effects of the weight loss on the hypothalamus-hypophysis axis. Furthermore, the emergence of psychological stress increases the levels of prolactin and endogenous opioids. Therefore, the disease may affect the ovarian response even before chemotherapy and radiotherapy. Anderson et al. showed in their study that AMH levels, which were measured before chemotherapy in cancer patients, were lower than the healthy women in the same age group. Moreover, the number of antral follicles was fewer in women with cancer compared to the healthy control group in the same age group [39]. A recently published meta-analysis showed that women with cancer, who underwent KOH, produced fewer oocytes compared to healthy women in the same age. In this analysis, gonadotropins were higher and the stimulation duration was longer in the cancer group [40].

The recurrence rate of breast cancer reaches its peak level in the 18th month and 5th year after surgery. This rate declines within the next 15 years. Considering these data, KOH was related always to some concern in breast cancer patients. These concerns were aggravated with the addition of the teratogenicity risk [41].

Taking the limited data in the studies into consideration, we are still not able to come to a definitive conclusion about the safety of KOH with TMX. TMX has a similar chemical structure to diethylstilbestrol and it may have teratogenic effects if administered during pregnancy. However, if it is used for the ovulation induction before pregnancy, there is no place for concerns related to the teratogenicity [42]. TMX is approved for ovulation induction in some countries. The exposure of the embryo to drugs is different from the exposure of the oocytes to drugs during the ovulation induction. The increase of the risks of malformation and cardiac anomalies in 150 infants after the ovulation induction with letrozole raised some concerns about the safety of this method and the manufacturer of this drug included certain warnings related to the usage of letrozole before menopause in the leaflet. All these findings were not published in a peer-reviewed journal because of the methodological limitations and inappropriate demographic reports.

The medical differences between the treatment and control groups and lack of information about pregnancy termination in the control groups are the main limitations of

these studies. The results of a more comprehensive study (n=2707 females) did not support an increased risk for the fetus during the letrozole treatment [43].

Even Novartis, which is the responsible manufacturer of letrozole (Femara), does not recommend the usage of letrozole as an inducer. In a brand new retrospective study, natural cycles (n=3136) were compared with IVF cycles (KOH with letrozole; n=7921) (1.5% natural cycle, 1.9% letrozole cycle; *P*=0.52). It was found out that there was no significant increase in the rate of major congenital anomalies in women treated with letrozole [44].

In a study conducted with 911 neonates, the rates of major and minor congenital malformation were comparable between the women who became pregnant after letrozole or clomiphene citrate treatment [45].

Regarding the concerns related to recurrence, the aromatase inhibitors are superior to TMX in the prevention of the breast cancer recurrence [46]. Studies showed that letrozole administration during KOH decreased estrogen levels without any significant effect on oocytes. Letrozole suppresses the estrogen levels during KOH cycles better than anastrozole, which is another aromatase inhibitor [47].

However, the following findings should also be kept in mind: In the largest study focused on the KOH with letrozole (n=120 breast cancer patients), patients were followed for 5 years [48].

In another study focused on the recurrence, the participants followed for 272-600 days after KOH and no difference was found between the KOH patients and non-KOH patients for breast cancer recurrence [49].

Conclusion

Studies related to KOH, which is used for fertility preservation in breast cancer patients, still exhibit an observational value. The study sample sizes are limited and the follow-up periods are relatively short. It is easy to imagine the difficulties of a randomized controlled design in this patient population. The available data show that KOH implemented with letrozole does not significantly impair the prognosis in breast cancer patients. Besides, this treatment decreases the estradiol concentration without decreasing the number of oocytes and impairing the quality of oocytes. Likewise, it cannot be suggested that KOH cycles either with letrozole or with TMX may cause teratogenic effects.

Further studies with a long-term design and larger sample sizes are needed for more definitive conclusions on the safety of KOH in patients diagnosed with breast cancer.

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