European Journal of Obstetrics & Gynecology and Reproductive Biology: X 4 (2019) 100049

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology: X

journal homepage: www.elsevier.com/locate/eurox

Impact of letrozole supplementation during ovarian stimulation for fertility preservation in breast cancer patients

Charlotte Sonigo[a,b], Nathalie Sermondade[c], Jéremy Calvo[d], Julie Benard[d], Christophe Sifer[c], Michaël Grynberg[a,d,e,f,*]

[a] Department of Reproductive Medicine and Fertility Preservation, Hôpital Antoine Béclère, 157, rue de la Porte de Trivaux, 92140 Clamart, France
[b] Inserm U1185, Univ Paris-Sud, Université Paris Saclay, Le Kremlin Bicêtre, 94276, France
[c] Department of Cytogenetic and Reproductive Biology, Hôpital Jean Verdier, Avenue du 14 Juillet, 93140 Bondy, France
[d] Department of Reproductive Medicine and Fertility Preservation, Hôpital Jean Verdier, Avenue du 14 Juillet, 93140, Bondy, France
[e] Univ Paris-Sud, Université Paris Saclay, Le Kremlin Bicêtre, 94276, France
[f] Unité Inserm U1133, Université Paris-Diderot, 75013 Paris, France

ARTICLE INFO

Article history:
Received 5 March 2019
Received in revised form 9 May 2019
Accepted 10 May 2019
Available online 11 May 2019

Keywords:
Controlled ovarian stimulation
Breast cancer
Letrozole
Fertility preservation

ABSTRACT

Objectives: Oocyte and/or embryo vitrification after controlled ovarian stimulation (COS) represents the most established method of fertility preservation (FP) before cancer treatment. However, traditional COS regimens are associated with supraphysiologic serum estradiol and are therefore not recommended in estrogen-sensitive diseases such as breast cancer (BC). To protect the patients from the potential deleterious effects of elevated estrogen levels during COS for FP, protocols using aromatase inhibitors (letrozole) were developed. The present study aims at investigating whether COS with letrozole supplementation (COSTLES) modifies ovarian response in BC patients.

Study design: One hundred and seventy-seven BC patients candidates for FP using oocyte and/or embryo vitrification following COS referred to our center between July 2013 and December 2016 were included in this retrospective case-control study. 94 patients underwent COSTLES while 83 had standard GnRH antagonist protocol. The number of oocytes retrieved, oocyte maturation rates, number of oocytes vitrified and follicle responsiveness to FSH assessed by the Follicular Output Rate (FORT) were assessed.

Results: Women in both groups were comparable in terms of age and ovarian reserve tests leading to a similar number of oocyte recovered (13.1 ± 10.0 vs. 12.2 ± 8.0 oocytes, respectively, *NS*). However, oocyte maturation rates were significantly lower in COSTLES compared to standard protocol (64.9 ± 22.8 vs. $77.4 \pm 19.3\%$, $p < 0.001$). As a result, the number of mature oocyte vitrified was lower in COSTLES group (7.8 ± 5.3 vs. 10.3 ± 8.5 oocytes, $p < 0.001$ respectively)

Conclusion: Despite similar response to exogenous FSH, BC patients having undergone COSTLES show reduced oocyte maturation rates in comparison with those having received standard stimulation regimen.

© 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Breast cancer (BC) represents one of the most frequent malignancy diagnosed in women of reproductive age [1]. Recent advances in diagnostic and therapeutic strategies have significantly improved BC prognosis [1]. However, most of cases will require systemic gonadotoxic chemotherapy, and sometimes anti-hormonal therapy that will preclude any pregnancy during the course of treatment. Therefore, these women have an increased risk of destruction of their follicular stockpile, as a result of both gonadotoxic therapy and the natural ovarian aging occurring during the treatment period, resulting in a dramatic reduction of the fertility potential [2]. The question of fertility preservation (FP) in young cancer patients has become a major issue in the care-personalized path. Indeed, many FP techniques have been developed to enable cancer survivors to improve their possibility of becoming genetic parents after healing [3]. Despite improvements in ovarian tissue cryopreservation, the vitrification of fertilized or unfertilized oocytes recovered after controlled ovarian stimulation (COS) before cancer therapy still represents the most established and efficient method for preserving female fertility [3]. However, traditional COS regimens induce a 10–20-fold increase in

* Corresponding author.
E-mail address: michael.grynberg@aphp.fr (M. Grynberg).

http://dx.doi.org/10.1016/j.eurox.2019.100049
2590-1613/© 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

serum estradiol (E_2) levels [4], which might have a detrimental effect on hormonal-sensitive diseases such as BC. Therefore, specific protocols have been developed, in order to combine multiple follicular growth throughout exogenous FSH administration, while limiting the effect of hyper-estradiolemia or maintaining serum E_2 levels within the normal ranges [5]. Hence, COS with anti-aromatase (AI) supplementation [6] is now largely used for BC patients seeking FP [7]. Nevertheless, few data have compared, in BC patients, the results obtained with conventional GnRH antagonist protocols and controlled ovarian stimulation with letrozole supplementation (COSTLES) [8,9]. It is conceivable that variations in steroid concentrations within the follicle induced by AI administration may impact the response to COS in comparison with conventional GnRH antagonist protocols using only exogenous FSH. Therefore, the present investigation aims at evaluating COS outcomes in BC patients, candidates for oocyte vitrification after COSTLES or conventional GnRH antagonist protocols without AI.

Materials and methods

Patients

One hundred and seventy-seven BC patients, 20–40 years of age, undergoing COS for oocyte vitrification between July 2013 and December 2016, were included in this retrospective case-control study. All of them met the following inclusion criteria: (i) regular menstrual cycles lasting between 25 and 35 days; (ii) both ovaries present, deprived of morphological abnormalities and adequately visualized in transvaginal ultrasound scans; (iii) body mass index (BMI) <30 kg/m^2; (iv) informed consent signed.

Women included between July 2013 and September 2014 received COS with conventional GnRH antagonist protocol without letrozole supplementation (conventional antagonist protocol group). From September 2014 onwards, COSTLES (COSTLES group) was systematically applied, after informed consent.

The present investigation was approved by our local institutional review board (CLEA 2016−028).

Controlled ovarian stimulation protocols

In both groups, ovarian stimulation was performed using GnRH antagonist protocol and administration of recombinant FSH (recFSH) (Follitropin alpha; Gonal-F®, Merck-Serono Pharmaceuticals, France). Exogenous FSH therapy was initiated at a dosage ranging from 200 to 450 IU/day, S.C, calculated from patient's age, BMI, serum anti-Müllerian hormone (AMH) levels and antral follicle count (AFC).

All patients were diagnosed with BC and underwent tumorectomy or mastectomy before starting the FP process using COS. Moreover, oncologist agreement for COS was obtained systematically.

Random-start protocols were specifically performed according to the phase of the menstrual cycle [10]. Follicular phase was defined by serum progesterone levels <1.0 ng/ml and absence of antral follicle >12 mm in diameter on ultrasound scan. In these situations, recFSH was administered for at least 5 days at initial dosage. From the 6th day of recFSH therapy onwards, daily recFSH doses were adjusted according to serum E2 levels and/or the number of growing follicles. GnRH antagonist (Ganirelix, Orgalutran® 0.25 mg, S.C, MSD Pharmaceuticals, France) was initiated to prevent premature LH surge at approximately day 6 of gonadotropin stimulation. Luteal phase was defined by serum progesterone levels >3.0 ng/mL. In these patients, recFSH was administered in combination with GnRH antagonists for 5 days and further adjusted according to estradiol levels and/or the number of growing follicles.

When COSTLES was applied, AI intakes (letrozole, Femara, Novartis Pharma, 5 mg/day orally) started on the same day as recFSH and stopped on the day of ovulation triggering (dOT).

In all patients, final oocyte maturation was obtained using GnRH agonist (triptorelin 0.1 mg, Decapeptyl®, Ipsen Pharmaceuticals, 0.2 mg, S.C.) administration as soon as ≥3 preovulatory follicles (16–22 mm in diameter) were observed. Oocytes were retrieved by transvaginal ultrasound-guided aspiration, 36 h after ovulation triggering. Metaphase II oocytes (MII), confirmed by the presence of one polar body, were vitrified as previously described [11].

Ultrasound scans and hormonal measurements

On the day of oncofertility counseling (d0), a transvaginal ovarian ultrasound scan for follicle measurements as well as blood sampling for serum AMH and progesterone levels assessment were performed for each woman in order to estimate ovarian reserve and the phase of the cycle. Further, each patient underwent regular ovarian ultrasound scan and blood work for monitoring COS, until the dOT.

Ovarian ultrasound scans were performed using a 5.0–9.0 MHz multi-frequency transvaginal probe (Voluson 730 Expert®, General Electric Medical Systems, Paris, France). All follicles measuring 3–22 mm in mean diameter (mean of two orthogonal diameters) in each ovary were counted. Only antral follicles <8 mm were considered for AFC at d0 and follicles between 16 and 22 mm on dOT were considered for pre-ovulatory follicle count (PFC). To optimize the reliability of ovarian follicular assessment, the ultrasound scanner was equipped with a tissue harmonic imaging system, which allowed improved image resolution and adequate recognition of follicular borders.

Calculation of follicular OutPut rate

The Follicular OutPut Rate (FORT) represented a methodological attempt for discriminating, among the cohort of small antral follicles, those that were the most FSH-responsive [12]. The FORT was calculated by the ratio between the PFC on dOT x 100/AFC at d0. The choice of considering only 16–22 mm follicles for the calculation of FORT was used in previous investigations.

Statistical analysis

The measure of central tendency used was the mean and the measure of variability was the standard deviation (SD). Differences between COSTLES and control groups were evaluated with Student's *t*-test or Mann-Whitney-Wilcoxon, when appropriate. A p value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 177 women with BC were evaluated for fertility preservation before adjuvant chemotherapy. Among them, 94 (53.1%) underwent COSTLES for oocyte cryopreservation. The remaining 83 (46.9%) patients received conventional GnRH antagonist protocol without AI supplementation. One hundred thirty-three (75.1%) tumors showed expression of estrogen and/or progesterone receptors, while 44 (24.8%) tumors were triple-negative. The majority of BC (97.1%) was classified T1 or T2 according to TNM classification. Distribution was similar between both groups.

Overall, patients in the COSTLES or conventional protocol groups were comparable in terms of age and markers of the ovarian follicular status assessed by AFC and AMH (Table 1).

COS characteristics and outcomes

As expected, serum E_2 levels on dOT were significantly lower in COSTLES group. The mean number of eggs recovered as well as FORT values did not differ between COSTLES and conventional antagonist protocol groups. Interestingly, oocyte maturation rates ((MII/oocytes recovered) X 100) were altered in COSTLES group in comparison with conventional antagonist protocol group (64.9 ± 22.8 vs. 77.4 ± 19.3%, respectively, $p < 0.001$) leading to a significantly decreased number of MII oocytes (7.8 ± 5.3 vs. 10.3 ± 8.5 oocytes, respectively, $p < 0.001$) (Table 2).

Discussion

The present investigation aimed to analyze whether letrozole supplementation to conventional GnRH antagonist protocol impacts COS outcomes in BC candidates for FP. Since AIs inhibit androgens conversion to estrogens [13], the resulting variations in these steroid concentrations within the follicle after letrozole administration [14] might influence the ovarian response to recombinant FSH and/or oocyte quality. The central finding of our study is the AIs-related alteration in oocyte maturation rates, leading to a lower number of matured eggs cryopreserved when compared with conventional GnRH antagonist protocol. However, others cycle characteristics, such as the duration of ovarian stimulation, total amount of gonadotropins or follicles responsiveness to exogenous FSH (assessed by the FORT) were similar between COSTLES and conventional antagonist protocol groups.

Letrozole is a potent and highly selective third-generation AI that competitively inhibits the activity of the aromatase, an enzyme of the cytochrome P-450 super family and the product of the CYP19 gene. The AI-induced reduction in estrogen production and circulating E_2, account for the use of these molecules as adjuvant hormonal treatment in advanced-stage postmenopausal BC [15]. Moreover, AIs have been used successfully to induce ovulation in women with polycystic ovary syndrome [16]. More recently, letrozole has been used to suppress E_2 production in women with BC undergoing COS before chemotherapy [6,17]. This strategy of ovarian stimulation enables a follicular maturation while maintaining serum E_2 levels close to the normal ranges [5,18]. Therefore, COSTLES protocol now represents the preferred option for most of oncofertility specialists in case of estrogen-sensitive diseases [7,19], even though robust data to support an actual oncologic risk related to conventional stimulation protocol is lacking [20].

COSTLES was first proposed by Oktay et al., in a prospective non randomized trial aiming to evaluate different COS protocols for BC candidates for FP [5]. This preliminary study reported a better oocyte yield with the letrozole-gonadotropin protocol when compared with Tamoxifen-alone and Tamoxifen-gonadotropin. However, only 11 patients underwent COSTLES protocol [5]. Following these encouraging results, the same team conducted a retrospective study comparing the efficacy of letrozole supplementation to exogenous gonadotropin in 47 BC patients with a standard long IVF protocol performed in 56 non-cancer infertile women [6]. Results were similar between both groups. Nevertheless, the study design implied important biases, in particular in terms of populations (BC vs. infertile patients) and protocols used (antagonist + letrozole vs. long protocol without letrozole), limiting the interpretation of the data. More recent investigations comparing standard antagonist and COSTLES among patients included in a FP program, reported conflicting results [8,9,21–24]. Domingo et al., found a significantly lower oocyte yield in patients with hormone-dependent cancers having undergone COSTLES when compared with those with non-hormone-dependent cancers or with age matched infertile women [23]. They explained their results by a possible detrimental impact of the oncologic status. However, a direct effect of the COSTLES protocol itself might also be at play. Other authors failed to find any difference in COS outcomes between COSTLES for BC patients and standard antagonist protocols used in non-estrogen sensitive diseases [22], but the small sample size may limit the interpretation of these results. In addition, COSTLES in BC patients is associated with more mature oocytes retrieved and lower E_2 levels in comparison with conventional antagonist protocol used for elective oocyte cryopreservation [21].

Since a specific impact of the type of malignancy on COS outcomes cannot be excluded [25], further studies investigated the results of protocols using or not letrozole in a homogenous population of BC patients [8]. Revelli et al., reported a 40% lower number of mature oocytes in women having undergone COSTLES. However, the use of hMG instead of recFSH as well as the lower starting dose in the COSTLES group may be confounders. More recently, Quinn et al., compared COS outcomes between women with recent BC diagnosis and women seeking elective FP [9]. Overall, BC status did not impact the results of ovarian stimulation. In a sub analysis, these authors evaluated COS characteristics in BC patients according to letrozole supplementation in all women with HD tumors. Apart from lower E_2 peak levels on the day of ovulation triggering in women having received letrozole, all stimulation characteristics and outcomes remained comparable. Interestingly, letrozole use was associated with decreased oocyte maturity rates (MII/total oocytes retrieved) in comparison with standard protocols for elective FP even though mature oocyte yields (MII/AFC) were comparable. However, the excellent mature oocyte rate, near 100% in each group is extremely surprising and makes the results difficult to interpret and to generalize. Moreover, the lack of comparison between baseline characteristics among BC patients having received letrozole or not, as well as different triggering criteria in COSTLES do not allow to draw reliable conclusions on the potential effects of AIs on ovarian stimulation outcomes.

The present investigation was conducted to compare COSTLES and conventional GnRH antagonist protocols in a homogenous cohort of young women, all suffering from BC. Letrozole was

Table 1
Patients' characteristics.

	Conventional antagonist protocol n = 83	COSTLES n = 94	*p*
Age (years) [a]	33.6 ± 3.3	33.5 ± 4.5	*0.8*
BMI (kg/m2) [a]	23.5 ± 4.4	22.1 ± 3.8	*0.03*
No of antral follicle on d0 (n) [a]	19.2 ± 13.0	19.5 ± 12.3	*0.9*
Serum Anti-Müllerian hormone levels (ng/ml) [a]	3.0 ± 3.1	2.7 ± 3.2	*0.5*

SD: standard deviation.
[a] mean ± SD.

Table 2
COS characteristics and outcomes.

	Conventional antagonist protocol n = 83	COSTLES n = 94	*p*
Random start (%)	41.5 %	47%	*0.6*
Starting dose of gonadodropins (IU)[a]	287.5 ± 93.2	301 ± 99.0	*0.3*
Total dose of gonadotropins (IU)[a]	2970 ± 1368	3168 ± 1784	*0.4*
Duration of stimulation (days)[a]	10.2 ± 2.0	10.0 ± 2.2	*0.6*
Serum E_2 levels on dOT (pg/ml)[a]	1651 ± 1235	427 ± 332	*<0.0001*
No of follicles ≥ 16 mm on dOT	5.7 ± 3.9	5.4 ± 3.7	*0.5*
No of follicles 12 – 15 mm on dOT	6.5 ± 5.5	5.8 ± 4.6	*0.3*
No of oocytes recovered (n)[a]	13.1 ± 10.0	12.2 ± 8.3	*0.5*
No of metaphase II oocytes (n) [a]	10.3 ± 8.5	7.8 ± 5.3	*<0.001*
Maturity rate (%)	77.4 ± 19.3	64.9 ± 22.8	*<0.001*
FORT* (%)[a]	34.7 ± 20.6	33.4 ± 25.4	*0.7*

SD: standard deviation.
FORT: follicular output rate: No of Follicles > 16 mm on dOT x 100 / No of antral follicles on d0.
Maturation rate: MII/oocytes retrieved.
dOT: day of triggering.
[a] Mean ± SD.

administrated or not regardless the hormonal status. The two populations showed comparable baseline characteristics and criteria for ovulation triggering were similar in both groups. As a result, the lower oocyte maturation rates observed after COSTLES, and the subsequent reduced number of mature eggs cryopreserved may be exclusively explained by letrozole use. Such a letrozole-induced effect during COS has already been hypothesized [6,8,9]. Therefore, Oktay et al., suggested to delay ovulation triggering in COSTLES protocols when follicles reach at least 20 mm in diameter instead of 18 mm with standard protocols [6]. Nevertheless, recent series failed to observe improved oocyte maturation rates when these new criteria were applied [8,9].

Actually, there is a lack of data regarding the competence of oocytes recovered after COSTLES. Oktay et al., published preliminary reassuring results in 33 women, showing comparable pregnancy rates to those expected in a non-cancer patients undergoing IVF [26]. Very recently, Cobo et al., found similar oocyte survival and live birth rates after FP performed using either conventional antagonist protocol or antagonist with letrozole protocol [27]. However, our findings regarding the reduced number of oocytes vitrified following COSTLES may represent an important concern. Similar results were previously reported by Revelli et al. [8] and more recently by Cobo et al. [27]. Indeed, the number of frozen oocytes remains a crucial issue in women seeking FP since it is directly correlated with the chances of live birth [27,28]. Nevertheless, the theoretic safety of COSTLES protocol, confirmed by an absence of increased recurrence risk in BC during the 5 years after diagnosis [29], account for its frequent use worldwide in candidates for FP in BC patients [7].

Conclusion

The present findings indicate that COSTLES protocol may be associated with decreased oocyte maturation rates when compared with conventional antagonist protocol. As a result, the final number of mature oocyte vitrified is reduced, which might limit the future chances of live birth. The reason for such an effect remains unclear but the low intrafollicular estradiol levels might be at play. Evidence indicates that the use of letrozole during ovarian stimulation is safe. However, data are lacking to consider standard antagonist protocol unsafe, even in patients suffering from estrogen-sensitive tumors. Further investigations are needed to better understand the potential effect of AIs administration during ovarian stimulation and confirm the competence of oocytes vitrified following COSTLES protocol.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Disclosure of interests

The authors have no conflict of interest to declare.

Ethics approval

This retrospective was approved by the local ethic committee: CLEA-2016-028

References

[1] DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics. CA Cancer J Clin 2011;61:409–18, doi:http://dx.doi.org/10.3322/caac.20134 n.d..
[2] Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol Off J Am Soc Clin Oncol 2006;24:2917–31, doi:http://dx.doi.org/10.1200/JCO.2006.06.5888.
[3] Practice Committee of American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril 2013;100:1214–23, doi:http://dx.doi.org/10.1016/j.fertnstert.2013.08.012.
[4] Cahill DJ, Wardle PG, Harlow CR, Hunt LP, Hull MG. Expected contribution to serum oestradiol from individual ovarian follicles in unstimulated cycles. Hum Reprod Oxf Engl 2000;15:1909–12.
[5] Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. J Clin Oncol Off J Am Soc Clin Oncol 2005;23:4347–53, doi:http://dx.doi.org/10.1200/JCO.2005.05.037.
[6] Oktay K, Hourvitz A, Sahin G, Oktem O, Safro B, Cil A, et al. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. J Clin Endocrinol Metab 2006;91:3885–90, doi:http://dx.doi.org/10.1210/jc.2006-0962.
[7] Reynolds KA, Grindler NM, Rhee JS, Cooper AR, Ratts VS, Carson KR, et al. Variability in the practice of fertility preservation for patients with cancer. PLoS One 2015;10:e0127335, doi:http://dx.doi.org/10.1371/journal.pone.0127335.
[8] Revelli A, Porcu E, Levi Setti PE, Delle Piane L, Merlo DF, Anserini P. Is letrozole needed for controlled ovarian stimulation in patients with estrogen receptor-positive breast cancer? Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol 2013;29:993–6, doi:http://dx.doi.org/10.3109/09513590.2013.819083.
[9] Quinn MM, Cakmak H, Letourneau JM, Cedars MI, Rosen MP. Response to ovarian stimulation is not impacted by a breast cancer diagnosis. Hum Reprod Oxf Engl 2017, doi:http://dx.doi.org/10.1093/humrep/dew355.
[10] Cakmak H, Katz A, Cedars MI, Rosen MP. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. Fertil Steril 2013;100:1673–80, doi:http://dx.doi.org/10.1016/j.fertnstert.2013.07.1992.
[11] Cobo A, Garcia-Velasco JA, Domingo J, Remohí J, Pellicer A. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? Fertil Steril 2013;99:1485–95, doi:http://dx.doi.org/10.1016/j.fertnstert.2013.02.050.

[12] Genro VK, Grynberg M, Scheffer JB, Roux I, Frydman R, Fanchin R. Serum anti-Müllerian hormone levels are negatively related to Follicular Output RaTe (FORT) in normo-cycling women undergoing controlled ovarian hyperstimulation. Hum Reprod Oxf Engl 2011;26:671–7, doi:http://dx.doi.org/10.1093/humrep/deq361.
[13] Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med 2003;348:2431–42, doi:http://dx.doi.org/10.1056/NEJMra023246.
[14] Hu Y, Cortvrindt R, Smitz J. Effects of aromatase inhibition on in vitro follicle and oocyte development analyzed by early preantral mouse follicle culture. Mol Reprod Dev 2002;61:549–59, doi:http://dx.doi.org/10.1002/mrd.10107.
[15] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet Lond Engl 2015;386:1341–52, doi:http://dx.doi.org/10.1016/S0140-6736(15)61074-1.
[16] Wang R, Kim BV, van Wely M, Johnson NP, Costello MF, Zhang H, et al. Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis. BMJ 2017;356:j138.
[17] Azim AA, Costantini-Ferrando M, Lostritto K, Oktay K. Relative potencies of anastrozole and letrozole to suppress estradiol in breast cancer patients undergoing ovarian stimulation before in vitro fertilization. J Clin Endocrinol Metab 2007;92:2197–200, doi:http://dx.doi.org/10.1210/jc.2007-0247.
[18] Garcia-Velasco JA, Moreno L, Pacheco A, Guillén A, Duque L, Requena A, et al. The aromatase inhibitor letrozole increases the concentration of intraovarian androgens and improves in vitro fertilization outcome in low responder patients: a pilot study. Fertil Steril 2005;84:82–7, doi:http://dx.doi.org/10.1016/j.fertnstert.2005.01.117.
[19] Lambertini M, Di Maio M, Pagani O, Curigliano G, Poggio F, Del Mastro L, et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients. Breast Edinb Scotl 2018;42:41–9, doi:http://dx.doi.org/10.1016/j.breast.2018.08.099.
[20] Dahhan T, Balkenende E, van Wely M, Linn S, Goddijn M. Tamoxifen or letrozole versus standard methods for women with estrogen-receptor positive breast cancer undergoing oocyte or embryo cryopreservation in assisted reproduction. Cochrane Database Syst Rev 2013CD010240, doi:http://dx.doi.org/10.1002/14651858.CD010240.pub2.
[21] Pereira N, Hancock K, Cordeiro CN, Lekovich JP, Schattman GL, Rosenwaks Z. Comparison of ovarian stimulation response in patients with breast cancer undergoing ovarian stimulation with letrozole and gonadotropins to patients undergoing ovarian stimulation with gonadotropins alone for elective cryopreservation of oocytes. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol 2016;32:823–6, doi:http://dx.doi.org/10.1080/09513590.2016.1177013.
[22] Checa Vizcaíno MA, Corchado AR, Cuadri MESI, Comadran MG, Brassesco M, Carreras R. The effects of letrozole on ovarian stimulation for fertility preservation in cancer-affected women. Reprod Biomed Online 2012;24:606–10, doi:http://dx.doi.org/10.1016/j.rbmo.2012.02.020.
[23] Domingo J, Guillén V, Ayllón Y, Martínez M, Muñoz E, Pellicer A, et al. Ovarian response to controlled ovarian hyperstimulation in cancer patients is diminished even before oncological treatment. Fertil Steril 2012;97:930–4, doi:http://dx.doi.org/10.1016/j.fertnstert.2012.01.093.
[24] Goldrat O, Gervy C, Englert Y, Delbaere A, Demeestere I. Progesterone levels in letrozole associated controlled ovarian stimulation for fertility preservation in breast cancer patients. Hum Reprod Oxf Engl 2015;30:2184–9, doi:http://dx.doi.org/10.1093/humrep/dev155.
[25] Pal L, Leykin L, Schifren JL, Isaacson KB, Chang YC, Nikruil N, et al. Malignancy may adversely influence the quality and behaviour of oocytes. Hum Reprod Oxf Engl 1998;13:1837–40.
[26] Oktay K, Turan V, Bedoschi G, Pacheco FS, Moy F. Fertility preservation success subsequent to concurrent aromatase inhibitor treatment and ovarian stimulation in women with breast cancer. J Clin Oncol Off J Am Soc Clin Oncol 2015;33:2424–9, doi:http://dx.doi.org/10.1200/JCO.2014.59.3723.
[27] Cobo A, García-Velasco J, Domingo J, Pellicer A, Remohí J. Elective and Onco-fertility preservation: factors related to IVF outcomes. Hum Reprod Oxf Engl 2018;33:2222–31, doi:http://dx.doi.org/10.1093/humrep/dey321.
[28] Cobo A, García-Velasco JA, Coello A, Domingo J, Pellicer A, Remohí J. Oocyte vitrification as an efficient option for elective fertility preservation. Fertil Steril 2016;105:755–64, doi:http://dx.doi.org/10.1016/j.fertnstert.2015.11.027 e8.
[29] Kim J, Turan V, Oktay K. Long-term safety of letrozole and gonadotropin stimulation for fertility preservation in women with breast cancer. J Clin Endocrinol Metab 2016;101:1364–71, doi:http://dx.doi.org/10.1210/jc.2015-3878.