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FERTILITY PRESERVATION

# IVF for fertility preservation in breast cancer patients—efficacy and safety issues

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**Abstract**
*Background* Potential risks on future fertility have become a dominant issue in consultation and management of newly diagnosed young cancer patients. Several fertility preservation strategies are currently available. Of those, ovarian stimulation followed by IVF and embryo cryopreservation is the most established one and is especially applicable in reproductive aged breast cancer patients.
*Aim* The aim of this study is to provide a comprehensive review on ovarian stimulation and IVF for fertility preservation in newly diagnosed breast cancer patients.
*Methods* Review of relevant literature is available through PubMed and Google scholar.
*Results* The use of IVF for fertility preservation in breast cancer patients raises dilemmas regarding efficacy and safety of controlled ovarian stimulation. Among these are the suggested role of malignancy and BRCA mutation in reducing ovarian response to stimulation, strategies designated to protect against hyper-estrogenic state associated with stimulation (co-treatment with tamoxifen or letrozole), and possible adjustments to accommodate oncologic-related time constraints.
*Conclusion* Ovarian stimulation followed by IVF forms an important fertility preservation strategy for newly diagnosed young breast cancer patients, though live born rates following thawed embryo transfer in these patients are still lacking. Recent advances in controlled ovarian stimulation protocols provide practical options for some of the challenges that breast cancer patients present.

**Keywords** Breast cancer · Fertility preservation · IVF · Ovarian stimulation · Tamoxifen · BRCA

*Capsule* A comprehensive review on ovarian stimulation for fertility preservation in newly diagnosed breast cancer patients, along with a preliminary presentation of our reassuring experience with BRCA mutation carriers undergoing this procedure.

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## Introduction

Breast cancer is the most common malignancy diagnosed among reproductive aged women. In accordance with an ongoing rise in its incidence among young women [1, 2], and with the current social trend to delay motherhood until later in life, we nowadays witness an increasing number of patients who have not completed childbearing when cancer is diagnosed and who are likely to desire pregnancy once cure has been confirmed. Although previously thought to be contraindicated purely on theoretical basis, pregnancy following successfully cured breast cancer is currently not considered unsafe, including in patients with a history of hormone receptor-positive disease [3].

Reproductive-aged breast cancer patients often present with biologically aggressive disease [4, 5], and many will be treated with adjuvant cytotoxic therapy which may impair gonadal function and threaten future fertility. The commonly accepted recommendation to avoid pregnancy for a minimum of 2 years after cancer treatment is completed [6], further compromising chances for future biological child birth by pushing conception attempts into the later stages of reproductive time span. It is difficult to accurately predict one's risk for future sterility; though the occurrence of chemotherapy-induced ovarian failure can be estimated according to patient's age, type of regimen

used, and cumulative dose [7]. With reference to agents commonly used for breast cancer, alkylating agents have the greatest gonadotoxic potential. Taxans cause an intermediate ovarian damage, whereas methotrexate and 5-fluorouracil are associated with a lower toxicity risk [8–11]. The extent of anthracycline-related ovarian toxicity is controversial. According to our previous findings, it is expected to be low [10].

Fertility concerns among young cancer patients are more than legitimate and have a true role in determining quality of life in survivors [12, 13]. Current guidelines recommend an elaborate discussion on family planning matters and early referral for fertility preservation on presentation [14–16]. To reduce ovarian damage, patients can be prescribed with a GnRH analogue during chemotherapy. Though the benefit of this strategy is doubtful, a recent study has clearly found GnRH analogue to have a protective ovarian effect in hormonal receptor-negative breast cancer patients [17]. Anyhow, medical consultation usually includes active fertility preservation methods: ovarian tissue cryopreservation, in vitro maturation (IVM) of oocytes, and controlled ovarian hyperstimulation (COH) followed by oocyte/embryo banking. The latter forms an available, well-established, and most used technique. However, when performing IVF for breast cancer patients, several considerations and adjustments regarding efficacy and safety should be made.

## Ovarian response in COH cycles

Among the different fertility preservation techniques available, embryo cryopreservation is the most established approach. Pregnancy rates per thawed transferred embryo are well known, but most data are concluded from cycles performed for infertile patients. Current literature offer sparse data on definitive success rates following embryo banking for cancer patients. There are scant reports based on small series which present reassuring live born rates in cancer patients who have returned for thawed embryo transfer [18–21]. The largest series, which include 21 cancer patients, display that pregnancy and live born rates achieved per transfer of thawed embryos, do not differ between fertility preservation patients and infertile (tubal/male factor) patients [22].

Oocyte cryopreservation by means of vitrification is nowadays considered a standardized technique [23] and forms a viable option for patients with no permanent male partner. Most evidence, to date, suggest that vitrified oocytes are equivalent to fresh oocytes in terms of fertilization rates, embryo development, implantation rates, and pregnancy rates [24]. This has been repeatedly shown in oocyte recipients and in infertile patients, with a recent study also showing that normal obstetric and perinatal outcomes can be expected [25]. A large meta-analysis, however, has outlined lower ongoing pregnancy rates (>20 weeks of gestation) when warmed oocytes were in use [26], and this finding was proposed to stem from studies heterogeneity. As opposed to donors and infertile subjects, for oncologic patients, data is currently limited to several case reports and small series [27–32]. In the meantime, while information on outcomes for this population is awaited, experience drawn from infertile patients/oocyte recipients can be used when consulting cancer patients seeking fertility preservation. Experienced hands are in need to provide favorable results, and local success rates should be cautiously taken into account.

Clearly, appropriate ovarian response to stimulation with exogenous gonadotropins is a prerequisite in maximizing chances for future pregnancy. Number of collected oocytes and their quality play a major role in estimating the expected efficacy of this procedure, especially in cases where only one cycle can be performed due to time constraints. Recent exposure to chemotherapeutic agents may result in morphologic/genetic abnormalities in retrieved oocytes and in reduced ovarian response to stimulation [33, 34]. Therefore, COH is contraindicated in a patient who has recently (~6 M) been treated with chemotherapy. It has been suggested that the presence of malignancy may adversely affect performance in COH cycles, even before exposure to gonadotoxic agents. In some sense, impaired ovarian response in COH cycles may be anticipated in chemotherapy-naïve cancer patients due to a higher catabolic state resulting in elevated stress hormones and endogenous opiate production [35], but in an early staged breast cancer disease, this seems unlikely.

Table 1 presents studies that have been taken to assess ovarian performance in the face of cancer disease, in all of which breast cancer disease was a predominant diagnosis. Among these studies, only two revealed lower oocyte yield in cancer patients. Several studies described other findings pointing towards reduced IVF performance in the presence of malignancy, such as increased poor response rates [37] and reduced fertilization rates [19].

It is important to note, however, that evaluating cancer patients for their innate ovarian response may not be as straight forward as it seems. In one study [39], diminished oocyte yield was mainly observed among patients with hormonal dependent tumors, who were systematically co-treated with letrozole during stimulation in order to reduce estrogen exposure. The authors suggested that the inferior performance may be attributed to the different COH protocol in use, rather than to the neoplastic process itself. In another study, results might have been confounded by lower stimulation dose aimed to prevent ovarian hyper-stimulation syndrome (OHSS) [38]. OHSS may result in further delay in cancer treatment; hence, GnRH-a for ovulation triggering is used in high risk patients to minimize the risk of OHSS [40].

## BRCA mutation and IVF performance

In young breast cancer patients, poor IVF performance has been explained by a possible association between BRCA

**Table 1** IVF outcomes, cancer patients versus non cancer patients

| Author | Number[a] | Breast cancer patients[b] (%) | Oocytes (M2 oocytes)[c] | | 2PN | |
|---|---|---|---|---|---|---|
| | | | Cancer | Control | Cancer | Control |
| Comparable oocyte yield | | | | | | |
| Knopman et al. [36] | 26 | 10 (38 %) | 14 | 12 | NA | NA |
| Michaan et al. [20] | 22 | 12 (55 %) | 8.8 | 8.8 | 5.4 | 5 |
| Quintero et al. [37] | 50 | 28 (56 %) | 11.5 (9.6) | 13 (9.7) | 6.8 | 7.4 |
| Robertson et al. [21] | 38 | 16 (42 %) | 12 (9) | 14 (11) | 6 | 7 |
| Johnson et al. [19] | 50 | 29 (58 %) | 12.4 (9) | 11.7 (8.9) | 5.4 | 6 |
| Cardozo et al. [22] | 63 | 41 (65 %) | 12.4 | 10.9 | 6.6 | 7.1 |
| Inferior oocyte yield | | | | | | |
| Klock et al. [38] | 28 | 11 (39 %) | 10 | 13.9 | 6.62 | 8.25 |
| Domingo et al. [39] | 208 | 142 (69 %) | 10.5 (7.8) | 12.4 (9.5) | NA | NA |

[a] Number of cancer patients included in study

[b] Number and percentage of breast cancer patients included in study

[c] Mean number of oocytes collected for cancer patients/control patients. Numbers in brackets represent mean number of M2 oocytes, when available

mutation carriage and reduced reproductive competence. However, this association is very controversial, and studies show contradictory results by means of parity, age at menopause, and AMH levels (Table 2). Low performance in IVF was reported in only one small study which evaluated young breast cancer patients undergoing COH prior to cancer treatment [50]. Four of 12 BRCA1 carriers displayed poor ovarian response compared to only two of 68 non-carriers and untested patients. Carriers were also found to have a significantly reduced mean oocyte yield compared to non-carriers.

Due to high prevalence of BRCA mutations in our local population (~2.5 % in Ashkenazi Jews), and together with an increasing demand for fertility preservation among carriers diagnosed with cancer, we took a special interest in evaluating the BRCA effect on COH outcomes. In a 10-year period, 70 pre-chemotherapy breast cancer patients underwent COH for

**Table 2** Reproductive performance in BRCA mutation carriers

| Author | Number[a] | Patients diagnosis | Endpoint | Results |
|---|---|---|---|---|
| Comparable/superior reproductive performance in BRCA mutation carriers | | | | |
| Pal et al. [41] | 2245 | Breast cancer, non-cancer | Parity | NS |
| | | | Infertility | NS |
| | | | Age at first birth | NS |
| Smith et al. [42] | 181 | Non-cancer | Parity | $p$=0.01 |
| Finch et al. [43] | 908 | Non-cancer | Parity | NS |
| | | | Use of infertility drugs | NS |
| | | | Fertility problems | NS |
| Collins et al. [44] | 829 | Non-cancer | Age at menopause | NS |
| Valentini et al. [45] | 1426 | Breast cancer | Risk for amenorrhea post chemotherapy | NS |
| Michelson-cohen et al. [46] | 43 | Non-cancer | AMH Levels | NS |
| Van Tilborg et al. [47] | 1236 | Breast cancer, non-cancer | Age at menopause | NS |
| Verpoest et al. [48] | 13 | Non-cancer | IVF performance | NS |
| Diminished reproductive performance in BRCA mutation carriers | | | | |
| Rzepka-Górska et al. [49] | 39 | Breast cancer | Age at menopause | $p$<0.05 |
| Oktay et al. [50] | 12 | Breast cancer | IVF performance | $p$=0.001 |
| Lin et al. [51] | 382 | Non-cancer | Age at menopause | $P$=0.01 |
| Finch et al. [43] | 908 | Non-cancer | Age at menopause | $p$=0.001 |
| Titus et al. [52] | 24 | Breast cancer | AMH levels | $p$<0.0001 |
| Wang et al. [53] | 143 | Non-cancer | AMH levels | $P$<0.012 |

[a] Number of BRCA1/2 mutation carriers included in study

fertility preservation. Twenty of them tested positive for the BRCA mutation and 36 tested negative. In the additional 14 patients, mutation status was unknown. When patients were compared according to BRCA status, carriers and non-carriers showed no difference in stimulation characteristics. Their cycles resulted in comparable ovarian response, with similar fertilization rates and number of resultant zygotes (Table 3). Our reassuring experience with BRCA mutation carriers highlights the relevance of COH and embryo banking as a fertility preservation strategy in these patients. Altogether, when appropriate, BRCA mutation carriers can and should be offered with IVF before cancer treatment has begun.

## Estrogen exposure

Conventional ovarian stimulation protocols performed for IVF are associated with a marked elevation of estradiol, often to levels ten times higher than physiologic E2 levels. Increased circulating E2 levels may induce proliferation and dissemination of breast cancer cells, although there is no definite evidence that the short-term increase in E2 levels is detrimental.

However, some oncologists and fertility preservation practitioners discourage the use of traditional COH regimens in breast cancer patients. Until several years ago, breast cancer patients were usually offered with natural IVF cycles when fertility preservation was needed. However, natural cycles resulted in a single embryo in about 60 % of cycles [54], thus not providing the patient with real chances for a future pregnancy. To increase the amount of embryos available for cryopreservation, ovulation induction using tamoxifen/letrozole alone or in combination with low-dose FSH was introduced. These regimens resulted in an improved, yet still relatively low oocyte yield [54, 55]. In view of this limitation and along with the need to minimize the potential risk from a short-term hyper-estrogenic state, COH protocols specially designated for breast cancer patients were developed.

A commonly used such regimen involves the use of letrozole with a concomitant administration of exogenous gonadotropins. Letrozole, a competitive inhibitor of the aromatase enzyme complex, has an important role in treatment of hormonal receptor-positive metastatic and non-metastatic breast cancer patients. As a third-generation aromatase inhibitor, it avoids the conversion of androgenic substrates to their respective estrogenic products. By reducing estrogen levels, it also triggers the hypothalamic–pituitary axis to raise gonadotropin secretion. According to a suggested protocol [55], 5 mg of letrozole is started on the 2nd–3rd day of the cycle, followed by initiation of rFSH or hMG in variable doses. GnRH antagonist is used to avoid premature LH surge [56]. After oocyte retrieval, letrozole is continued until a proper decline in E2 levels is documented. This protocol is associated with peak E2 levels that are lower than those seen in conventional IVF cycles and is considered cost-effective due to a reduced gonadotropin requirement [57]. Although it was claimed to result in outcomes comparable to those seen in standard IVF cycles, oocyte maturity rate was found to be compromised. To overcome this finding, it was suggested to delay ovulation triggering until the dominant follicle reaches a greater diameter (20 mm). However, even when implementing this triggering threshold, high rate of oocyte immaturity was still described by other groups [19, 58]. Additionally, in a retrospective cohort study of 16 IVF units, a significantly lower oocyte yield in patients treated with this protocol was observed [59]. In terms of safety, although E2 reduction is clearly achieved when using letrozole, some patients still exhibit levels which are higher than those observed during a natural ovulatory cycle. In fact, some patients display very high E2 levels even when treated with letrozole, and there is no available information regarding the maximal E2 levels that are considered safe. However, based on a short-term follow-up (2 years on average) of 79 patients, this protocol is not expected to alter recurrence rates [60].

An additional regimen aiming to prevent the possible detrimental effect of increased E2 levels involves co-administration of tamoxifen during IVF stimulation. Tamoxifen is a selective estrogen receptor modulator (SERM), which acts as a competitive estrogen antagonist in breast tissue. It also blocks estrogen receptors found in the CNS, leading to attenuation of estrogenic-negative feedback and increased levels of endogenous gonadotropins. Correspondingly, in patients with active ovaries treated with tamoxifen, extremely high E2 levels are commonly observed [61]. However, tamoxifen's role in

**Table 3** Fertility preservation COH cycles for breast cancer patients, according to BRCA mutation status

| | BRCA(+) [$n$=20] | BRCA(−) [$n$=36] | $P$ |
|---|---|---|---|
| Mean age | 32.40±3.86 | 33.94±5.48 | 0.22 |
| Stimulation days | 10.54±2.37 | 9.92±1.56 | 0.23 |
| Long GnRH-agonist protocol | 52.94 % | 61.76 % | 0.56 |
| GnRH-antagonist protocol | 47.06 % | 38.24 % | 0.56 |
| Max E2 (pmol/L) | 6255±4875 | 6306±4150 | 0.97 |
| Oocytes collected | 11.50±6.63 | 11.69±7.23 | 0.92 |
| Zygotes | 8.4±6.39 | 7.19±5.21 | 0.57 |
| Fertilization rate | 70.6 % | 59.66 % | 0.11 |

prophylaxis and treatment of hormonal receptor-positive breast cancer disease is well established. It reinforces blockage of estrogen receptors found on cancerous cells and has been proven to be beneficial in patients with and without reserved ovarian function [62–65]. We have recently presented a flexible IVF protocol which incorporates tamoxifen to standard IVF regimens (GnRH-a and GnRH-antagonist). In this protocol, tamoxifen is not used for the purpose of ovarian stimulation, but rather for protection against high E2 levels during stimulation. Tamoxifen 20 mg/day is added a few days after the initiation of gonadotropins when E2 levels are rising and continued throughout the entire COH protocol (Fig. 1). No stimulation effect is attributed to tamoxifen because it is given after pituitary suppression is obtained with concomitant use of GnRH agonist or antagonist. In our prospective cohort of 70 breast cancer patients undergoing IVF for fertility preservation, tamoxifen was added for hormonal receptor-positive patients or when receptors status was yet to be known [61]. Patients who were co-treated with tamoxifen showed no decline, but rather a non-significant improvement in IVF outcomes (oocyte yield, embryos stored), and a trend towards higher E2 levels was observed. Reassuringly, such increased levels are commonly seen when tamoxifen is given as a long-term adjuvant agent, with its clear beneficial impact on prognosis. In a long follow-up (3–10 years), no increase in cancer recurrence or mortality was observed. Conveniently, and in contrast to letrozol which is not licensed as a fertility drug, tamoxifen has been commonly used for ovulation induction for many years and no special approval is needed for its use in this context.

## Timing and schedule flexibility

In standard IVF practice, stimulation is started at the early follicular phase, in the hopes to achieve an optimal synchronization with innate ovarian physiology. Stimulation with gonadotropins may take up to 14 days and is sometimes preceded by 2 weeks of pituitary downregulation with GnRH agonists. Alternatively, GnRH antagonist may be used to attain an immediate pituitary suppression, thereby allowing for a shorter time interval from admission to ovum pickup. When IVF is performed for the purpose of fertility preservation, oncologic considerations dictate the time available for ovarian stimulation. With the exception of patients necessitating neo-adjuvant therapy for whom chemotherapy is initiated within 2–3 weeks, a window of 6–8 weeks commonly exists between surgery and the start of chemotherapy. Supposedly, in an early-staged disease, this interval of time can be extended to up to 12 weeks without compromising prognosis [66, 67]. This allows a reasonable period to complete an IVF cycle, assuming that early referral is carried out. When possible, it is desirable to perform more than one cycle in order to obtain more mature oocytes and maximize chances for future pregnancy [68].

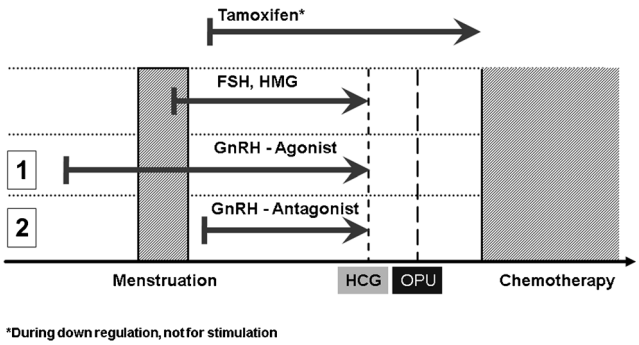


**Fig. 1** Co-administration of tamoxifen (20 mg/day) to COH protocols used for IVF in breast cancer patients. Long luteal GnRH-a (*1*), antagonist protocol (*2*)

With the aim to prevent delay in cancer treatment and allow for a more flexible schedule, non-conventional start stimulation protocols have been developed. Such protocols rely on the presence of multiple waves of follicular recruitment within a single inter-ovulatory interval and are independent of endometrial synchronization [69–71]. Initiation of ovarian stimulation during the luteal phase was originally described following induced luteolysis performed for two breast cancer patients [72]. Upon presentation, patients were started on GnRH antagonist. This resulted in regression of corpus luteum, decrease in progesterone levels, with menses following 2–4 days later. At that time, gonadotropin (HMG) administration commenced. Later on, several authors [73, 74] reported that GnRH antagonist and gonadotropins can be started at the same time, with a satisfactory ovarian response. In both studies, stimulation was done using recombinant FSH only to avoid corpus luteum maintenance by LH. However, luteolysis is not necessarily required, and follicular development may occur when high progesterone levels are present. There is therefore no definitive need for a concomitant initiation of GnRH antagonist and gonadotropins; GnRH antagonist can be started later when the follicle cohort reach 12–14 mm in order to prevent secondary LH surge [58, 75, 76], and this approach applies also for patients presenting during the late follicular phase. These protocols of random start COH and have repeatedly been shown to be as effective as standard early follicular-start protocols in terms of oocyte yield, oocyte maturity rates, and fertilization rates [58, 75, 77], with a recent study pointing on satisfactory pregnancy outcomes from thawed embryos originating from luteal phase ovarian stimulation in infertility patients [78].

## Conclusions

Breast cancer patients referred for COH for the purpose of fertility preservation represent a unique group of patients, which differ in several aspects from typical infertile patients. Recent advances in COH protocols provide practical options for some of the challenges that breast cancer

patients present. Regimens aimed to provide protection against the associated hyper-estrogenic state are increasingly being used, and flexible starting points allow adjustment to onco-therapy recommended schedules. Although some inconsistency still exists, it seems that a reasonable ovarian response can be expected in these patients. According to our clinical experience, this holds truth also for BRCA mutation carriers.

To date, there is little information on actual pregnancy/live born rates following stimulation and embryo banking in these patients. While this imperative data is pending, COH should be recommended as long as it does not compromise patient's safety. Seemingly, this is likely to be the case in the majority of newly diagnosed breast cancer patients. The importance of an early referral to fertility preservation experts cannot be overstated. In the face of a recent cancer diagnosis, every young patient who contemplates future pregnancy should clearly be informed with possible reproductive risks and relevant fertility preservation measures. In the following years, information on success rates of these measures will gradually become more available. With the accumulation of such data, efficacies and limitations of all available fertility preservation strategies should be re-examined and defined, along with proper adjustments in clinical recommendations and guidelines.

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## References


1. Johnson RH, Chien FL, Bleyer A. Incidence of breast cancer with distant involvement among women in the United States, 1976 to 2009. JAMA. 2013;309(8):800–5.
2. Merlo DF et al. Breast cancer incidence trends in European women aged 20–39 years at diagnosis. Breast Cancer Res Treat. 2012;134(1):363–70.
3. Azim Jr HA et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. J Clin Oncol. 2013;31(1):73–9.
4. Anders CK et al. Breast carcinomas arising at a young age: unique biology or a surrogate for aggressive intrinsic subtypes? J Clin Oncol. 2011;29(1):e18–20.
5. Anders CK et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. J Clin Oncol. 2008;26(20):3324–30.
6. Cardoso F et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer. 2012;48(18):3355–77.
7. Meirow D et al. Toxicity of chemotherapy and radiation on female reproduction. Clin Obstet Gynecol. 2010;53(4):727–39.
8. Demeestere I et al. Multiple approaches for individualized fertility protective therapy in cancer patients. Obstet Gynecol Int. 2012;2012:961232.
9. Lee SJ et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24(18):2917–31.
10. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update. 2001;7(6):535–43.
11. Okanami Y et al. Incidence of chemotherapy-induced amenorrhea in premenopausal patients with breast cancer following adjuvant anthracycline and taxane. Breast Cancer. 2011;18(3):182–8.
12. Letourneau JM et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer. 2012;118(6):1710–7.
13. Schover LR et al. Having children after cancer. A pilot survey of survivors' attitudes and experiences. Cancer. 1999;86(4):697–709.
14. Loren AW et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(19):2500–10.
15. Partridge AH et al. First international consensus guidelines for breast cancer in young women (BCY1). Breast. 2014;23(3):209–20.
16. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160–70.
17. Moore HC et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 2015;372(10):923–32.
18. Courbiere B et al. Emergency IVF for embryo freezing to preserve female fertility: a French multicentre cohort study. Hum Reprod. 2013;28(9):2381–8.
19. Johnson LN et al. Response to ovarian stimulation in patients facing gonadotoxic therapy. Reprod Biomed Online. 2013;26(4):337–44.
20. Michaan N et al. Ovarian stimulation and emergency in vitro fertilization for fertility preservation in cancer patients. Eur J Obstet Gynecol Reprod Biol. 2010;149(2):175–7.
21. Robertson AD, Missmer SA, Ginsburg ES. Embryo yield after in vitro fertilization in women undergoing embryo banking for fertility preservation before chemotherapy. Fertil Steril. 2011;95(2):588–91.
22. Cardozo ER et al. Ovarian stimulation and in-vitro fertilization outcomes of cancer patients undergoing fertility preservation compared to age matched controls: a 17-year experience. J Assist Reprod Genet. 2015;32(4):587–96.
23. Ovarian tissue cryopreservation: a committee opinion. Fertil Steril. 2014;101(5):1237–43.
24. Cobo A et al. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? Fertil Steril. 2013;99(6):1485–95.
25. Cobo A et al. Obstetric and perinatal outcome of babies born from vitrified oocytes. Fertil Steril. 2014;102(4):1006–15.e4.
26. Potdar N, Gelbaya TA, Nardo LG. Oocyte vitrification in the 21st century and post-warming fertility outcomes: a systematic review and meta-analysis. Reprod Biomed Online. 2014;29(2):159–76.
27. Garcia-Velasco JA et al. Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indications. Fertil Steril. 2013;99(7):1994–9.
28. Kim SS, Klemp J, Fabian C. Breast cancer and fertility preservation. Fertil Steril. 2011;95(5):1535–43.
29. Martinez M et al. Obstetric outcome after oocyte vitrification and warming for fertility preservation in women with cancer. Reprod Biomed Online. 2014;29(6):722–8.
30. Porcu E et al. Healthy twins delivered after oocyte cryopreservation and bilateral ovariectomy for ovarian cancer. Reprod Biomed Online. 2008;17(2):265–7.
31. Sanchez-Serrano M et al. Twins born after transplantation of ovarian cortical tissue and oocyte vitrification. Fertil Steril. 2010;93(1):268.e11–3.
32. Yang D et al. Live birth after the transfer of human embryos developed from cryopreserved oocytes harvested before cancer treatment. Fertil Steril. 2007;87(6):1469.e1–4.

33. Chung K et al. Emergency IVF versus ovarian tissue cryopreservation: decision making in fertility preservation for female cancer patients. Fertil Steril. 2013;99(6):1534–42.
34. Meirow D, Schiff E. Appraisal of chemotherapy effects on reproductive outcome according to animal studies and clinical data. J Natl Cancer Inst Monogr. 2005;34:21–5.
35. Agarwal A, Said TM. Implications of systemic malignancies on human fertility. Reprod Biomed Online. 2004;9(6):673–9.
36. Knopman JM et al. Women with cancer undergoing ART for fertility preservation: a cohort study of their response to exogenous gonadotropins. Fertil Steril. 2009;91(4 Suppl):1476–8.
37. Quintero RB et al. Ovarian stimulation for fertility preservation in patients with cancer. Fertil Steril. 2010;93(3):865–8.
38. Klock SC, Zhang JX, Kazer RR. Fertility preservation for female cancer patients: early clinical experience. Fertil Steril. 2010;94(1): 149–55.
39. Domingo J et al. Ovarian response to controlled ovarian hyperstimulation in cancer patients is diminished even before oncological treatment. Fertil Steril. 2012;97(4):930–4.
40. Engmann L et al. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril. 2008;89(1):84–91.
41. Pal T et al. Fertility in women with BRCA mutations: a case–control study. Fertil Steril. 2010;93(6):1805–8.
42. Smith KR et al. Effects of BRCA1 and BRCA2 mutations on female fertility. Proc Biol Sci. 2012;279(1732):1389–95.
43. Finch A et al. Frequency of premature menopause in women who carry a BRCA1 or BRCA2 mutation. Fertil Steril. 2013;99(6): 1724–8.
44. Collins IM et al. Do BRCA1 and BRCA2 mutation carriers have earlier natural menopause than their noncarrier relatives? Results from the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer. J Clin Oncol. 2013;31(31): 3920–5.
45. Valentini A et al. Chemotherapy-induced amenorrhea in patients with breast cancer with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2013;31(31):3914–9.
46. Michaelson-Cohen R et al. BRCA mutation carriers do not have compromised ovarian reserve. Int J Gynecol Cancer. 2014;24(2): 233–7.
47. van Tilborg TC, Broekmans FJM, Schrijver LH, Mooij TM, Pijpe A, Oosterwijk JC, Verhoef S, Gómez Garcia EB, van Zelst-Stams WAG, Adank MA, van Asperen CJ, van Doorn HC, van Os TAM, Rookus MA, Ausems MGEM. BRCA1/2 mutation carriers do not have earlier natural menopause compared to proven non-carriers: report from the Dutch hereditary breast and ovarian cancer study group (HEBON). Munich, Germany; 2014.
48. Verpoest W, Elsen E, Mackens S, De Rycke M, Bonduelle M, Van de Velde H, Blockeel C, De Vos M, Polyzos N, Tournaye H. Ovarian response in BRCA1 carriers: a case–control study, in European Soc of Hum Reprod (ESHRE). Munich, Germany; 2014.
49. Rzepka-Gorska I et al. Premature menopause in patients with BRCA1 gene mutation. Breast Cancer Res Treat. 2006;100(1): 59–63.
50. Oktay K et al. Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks. J Clin Oncol. 2010;28(2): 240–4.
51. Lin WT et al. Comparison of age at natural menopause in BRCA1/2 mutation carriers with a non-clinic-based sample of women in northern California. Cancer. 2013;119(9):1652–9.
52. Titus S et al. Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans. Sci Transl Med. 2013;5(172):172ra21.
53. Wang ET et al. BRCA1 germline mutations may be associated with reduced ovarian reserve. Fertil Steril. 2014;102(6): 1723–8.
54. Oktay K et al. Fertility preservation in breast cancer patients: IVF and embryo cryopreservation after ovarian stimulation with tamoxifen. Hum Reprod. 2003;18(1):90–5.
55. Oktay K et al. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. J Clin Oncol. 2005;23(19):4347–53.
56. Oktay K, Turkcuoglu I, Rodriguez-Wallberg KA. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. Reprod Biomed Online. 2010;20(6):783–8.
57. Oktay K et al. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. J Clin Endocrinol Metab. 2006;91(10): 3885–90.
58. Kim JH et al. Efficacy of random-start controlled ovarian stimulation in cancer patients. J Korean Med Sci. 2015;30(3):290–5.
59. Revelli A et al. Is letrozole needed for controlled ovarian stimulation in patients with estrogen receptor-positive breast cancer? Gynecol Endocrinol. 2013;29(11):993–6.
60. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. J Clin Oncol. 2008;26(16):2630–5.
61. Meirow D, et al. Tamoxifen co-administration during controlled ovarian hyperstimulation for in vitro fertilization in breast cancer patients increases the safety of fertility—preservation treatment strategies. Fertil Steril. 2014.
62. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687–717.
63. Davies C et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011;378(9793): 771–84.
64. Goldhirsch A et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013;24(9):2206–23.
65. Senkus E et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi7–23.
66. Cold S et al. Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG). Br J Cancer. 2005;93(6):627–32.
67. Lohrisch C et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol. 2006;24(30):4888–94.
68. Turan V et al. Safety and feasibility of performing two consecutive ovarian stimulation cycles with the use of letrozole-gonadotropin protocol for fertility preservation in breast cancer patients. Fertil Steril. 2013;100(6):1681–5.e1.
69. Baerwald AR, Adams GP, Pierson RA. A new model for ovarian follicular development during the human menstrual cycle. Fertil Steril. 2003;80(1):116–22.
70. Baerwald AR, Adams GP, Pierson RA. Ovarian antral folliculogenesis during the human menstrual cycle: a review. Hum Reprod Update. 2012;18(1):73–91.

71. Bentov Y et al. An ongoing pregnancy from two waves of follicles developing during a long follicular phase of the same cycle. Fertil Steril. 2010;94(1):350.e8–11.
72. Anderson RA, Kinniburgh D, Baird DT. Preliminary experience of the use of a gonadotrophin-releasing hormone antagonist in ovulation induction/in-vitro fertilization prior to cancer treatment. Hum Reprod. 1999;14(10):2665–8.
73. Bedoschi GM et al. Ovarian stimulation during the luteal phase for fertility preservation of cancer patients: case reports and review of the literature. J Assist Reprod Genet. 2010;27(8):491–4.
74. von Wolff M et al. Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. Fertil Steril. 2009;92(4):1360–5.
75. Cakmak H et al. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. Fertil Steril. 2013;100(6):1673–80.
76. Nayak SR, Wakim AN. Random-start gonadotropin-releasing hormone (GnRH) antagonist-treated cycles with GnRH agonist trigger for fertility preservation. Fertil Steril. 2011;96(1):e51–4.
77. Checa MA et al. Random-start GnRH antagonist for emergency fertility preservation: a self-controlled trial. Int J Womens Health. 2015;7:219–25.
78. Kuang Y et al. Luteal-phase ovarian stimulation is feasible for producing competent oocytes in women undergoing in vitro fertilization/intracytoplasmic sperm injection treatment, with optimal pregnancy outcomes in frozen-thawed embryo transfer cycles. Fertil Steril. 2014;101(1):105–11.