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REVIEW – CLINICAL ONCOLOGY

Breast cancer: an update on treatment-related infertility

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Abstract
Breast cancer (BC) is the most common malignancy in women with a significant increasing incidence during the reproductive life. However, based on the newest anti-cancer molecular targeting drugs, successful treatments lead to the disease healing particularly in young patients, thus refreshing their motherhood programs. However, as effect of the BC treatment, a premature depletion of the ovarian follicle reserve occurs in more than one-third of patients resulting in permanent infertility. To prevent the cancer treatment-related infertility (CTRI), several options are today utilized. Besides the ovary suppression by gonadotropin-releasing hormone agonist (GnRHa), other procedures include either oocytes or embryos cryopreservation as well as ovarian cortex cryopreservation that are currently adopted before anti-cancer therapies. These modern techniques appear variably successful in terms of pregnancy rate though their safety concerning the hormonal stimulation to promote the folliculogenesis is still debated in relation to the potential oncogenic risk in patients bearing hormone-sensitive tumors as BC, while the ovarian cortex re-implantation often results in a low number of regenerated follicles including oocytes of unknown quality. Recent studies on ovarian stem cells (OSCs) suggest their use for future application in CTRI. In fact, OSCs from ovarian cortex have been shown to differentiate in vitro into oocyte-like cells (OLCs) and express molecular markers of mature oocytes. Once the OSC technology will be optimized and translated to clinical use, oocytes derived from these cells will be molecularly assessed before fertilization to assure their best embryo quality resulting in a safe procedure to treat CTRI in patients as young women with BC.

Keywords Anti-cancer treatments · Ovarian failure · Fertility preservation · Ovarian stem cells

Abbreviations

BC	Breast cancer
CTRI	Cancer treatment-related infertility
GnRHa	Gonadotropin-releasing hormone agonist
OSCs	Ovarian stem cells
OLCs	Oocyte-like cells
MFG	Multiple follicular growth
Her-2	Human epidermal growth factor receptor 2
CMF	Cyclophosphamide–methotrexate–fluorouracil
AC	Adriamycin and cyclophosphamide
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
AMH	Anti-Müllerian hormone
ASCO	American Society of Clinical Oncology
ESMO	European Society for Medical Oncology
IVF	In vitro fertilization
ART	Assisted reproduction technique
COH	Controlled ovary hyperstimulation
E2	Estradiol
AIs	Aromatase inhibitors

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Introduction

Breast cancer (BC) is the most common female malignancy worldwide (Cardoso et al. 2019). Since the late 1970s, the incidence of this tumor has significantly increased even in patients aged 20–39 years, becoming the leading cause of cancer-related death in both pre- and post-menopausal ladies (Cardoso et al. 2019; Bardia and Hurvitz 2018). In 2018, about 2.1 million new diagnoses were registered worldwide, with an estimated age-adjusted annual incidence in Europe of 144.9/100,000 (Cardoso et al. 2019). Despite this, recent diagnostic and therapeutic advances prompted a personalized disease management which significantly improved patient life expectancy, leading to a 8.7% reduction of the mortality rate in Europe for 2019, as compared to 2014 (Malvezzi et al. 2019; Senkus et al. 2015).

In most cases, BC etiology remains unknown, although several risk factors have been identified so far, including long-term exposure to both endogenous and exogenous estrogens, therapeutic irradiation of the chest wall, western dietary habits and positive family history for BC (Cardoso et al. 2018, 2019). In particular, women bearing deleterious germline BRCA1 and BRCA2 gene mutations experience a 72% and a 69% lifetime risk to develop breast malignancies, respectively (Kotsopoulos 2018), with a median age at the time of diagnosis of 42 compared to 53 years in women with sporadic BC (Van der Kolk et al. 2010). However, knowledge of the major pathogenetic factors involved in BC onset at pre-menopausal age is limited by the small number of young patients in most clinical trials (Romieu et al. 2018).

Although at variable stages of the disease at the time of BC diagnosis, a consistent percentage of patients are successfully treated in particular with the newest drugs acting through molecular targeting of cancer cells and with conventional chemotherapy, and an average 5 years of survival occurs in 88.1% of BC patients at all ages, whereas 87.1% of patients under 45 years undergo the same relative survival (Toi et al. 2010). Therefore, in relation to the optimized treatments, the survival is greatly extended today, and particularly in patients with healed disease the achievement of motherhood programs definitely improves the quality of life (Trivers et al. 2014; Ben-Aharon and Shalgi 2012).

In the majority of clinical centers for infertility treatment, the oocyte retrieval and cryopreservation as well as embryo freezing, performed before starting neo-adjuvant systemic chemotherapy, surgery or radiation treatments, are currently used for fertility preservation approach. These procedures requiring a preventive estro-progestinic stimulation to induce multiple follicular growth (MFG) are not always safe for patients with hormonal-dependent cancers, for the intrinsic risk of cancer cell proliferation and tumor progression (Kasum et al. 2014). On the other hand, alternative possibilities for BC women include autologous ovarian cortex transplantation, eggs or embryo donation, or the potential application of stemness technologies using ovarian stem cells (OCSs) which have been described to differentiate in vitro into OLCs.

Hence, we revisit here the spectrum of therapeutic strategies that are nowadays available for fertility preservation in young BC patients with the purpose to focus a topic which is frequently overlooked by both clinicians and patients before cancer treatments.

Breast cancer treatments and infertility risk

Invasive BC is a highly heterogeneous disease whose prognosis primarily depends upon both histopathological and molecular features (Deniz et al. 2019). In particular, the most common prognostic factors include the expression of hormone receptors (i.e. estrogen, progesterone and androgen receptors; ER, PgR and AR, respectively), human epidermal growth factor receptor 2 (Her-2) status, primary tumor size and grading, as well as the presence of vascular invasion and lymph node metastases (Deniz et al. 2019; Kraby et al. 2018). In women aged 40 years or less, approximately 2/3 of breast tumors express hormone receptors, despite having a worse prognosis than those diagnosed in peri/post-menopausal patients (Bardia and Hurvitz 2018). Triple negative and Her-2 positive malignancies have also been reported in a not negligible proportion of young patients in some case series (Goksu et al. 2014; Ihemelandu et al. 2007). Interestingly, age at the time of first and last pregnancies as well as time between menarche and first pregnancy have been shown to correlate with molecular features of breast malignancies (Romieu et al. 2018).

Treatment of early BC relies on both loco-regional and systemic approaches, with the latter ranging from standard chemotherapy to hormone therapies and targeted agents, whose adoption is based on biological tumor features (Cardoso et al. 2018, 2019). Thus, in relation to treatment optimization and life expectancy improvement, the achievement of parenthood programs represents often a critical issue in young cancer survivors. Indeed, following systemic anticancer treatments, female fertility is frequently affected, in terms of either transient or permanent iatrogenic amenorrhea, as well as early menopause onset (Trivers et al. 2014; Ben-Aharon and Shalgi 2012).

Therapeutic agents administered to BC patients are known for their risk of inducing exhaustion of the ovarian reserve. In particular, as an alkylating agent, cyclophosphamide is one of the most gonadotoxic drugs, whose effects are

mediated by its metabolite phosphoramide mustard. Granulosa cells represent the primary targets of this agent in the ovary, and undergo cell membrane and protein alkylation as well as DNA damage, whereas oocytes are affected afterwards, through the gap junctions in their connection with the granulosa cells (Pfeilschifter and Diel 2000). Doxorubicin has also been found capable to promote dose-dependent ovarian failure by inducing double-strand-DNA breaks in primordial follicles as well as in oocytes and granulosa cells, as proved in mice models (Soleimani et al. 2011).

Concerning the molecular targeting agents, despite the known cardiotoxicity of Her-2 binding by trastuzumab and pertuzumab, the effect on oocyte viability and in general on fertility is still debated (Lambertini et al. 2019; Silva et al. 2019), while no data have been described with respect to CDK 4/6 and PI3K inhibitors so far. On the contrary, a putative protective effect of everolimus as mTOR inhibitor has been described in mice on the chemotherapy-induced ovarian toxicity (Tanaka et al. 2018).

The incidence of iatrogenic ovarian failure depends on several factors, including patient age and type of administered anti-cancer treatment. Indeed, the risk ranges from 22 to 61% in women younger than 40 years and from 61 to 97% in those older than 40 years. However, there is a proportion of young ladies who may also experience amenorrhea, suggesting the involvement of further, individual factors in the loss of fertility (Lambertini et al. 2013). The rate of chemotherapy-induced amenorrhea also varies among different case series (Fornier et al. 2005; Ganz et al. 2011).

It must be emphasized that the onset of amenorrhea does not necessarily implies infertility development and, on the other hand, the resume of menses is not always a sign of fertility recovery (de Pedro et al. 2015). During treatment with the cyclophosphamide–methotrexate–fluorouracil (CMF) regimen, more than half patients experience amenorrhea and this percentage raise up to 80% after 3 years; on the other hand, the amenorrhea observed in patients receiving adriamycin and cyclophosphamide (AC) regimen tends to recover within 9 months from treatment suspension (Ter Welle-Butalid et al. 2019). Despite this, only 3% of BC survivors, aged less than 45 years at the time of diagnosis, have at least one full-term pregnancy after cancer remission (Del Mastro et al. 2006).

Besides fertility impairment, iatrogenic ovarian failure may have a dramatic impact on the quality of life in patients particularly after the cancer healing. The lower hormone bioavailability related to the exhausted ovarian reserve is primarily causal for the premature menopause which occurs with typical vasomotor symptoms as well as sleep and genitourinary disorders (Rosenberg and Partridge 2013; Alder et al. 2008), while the early hypoestrogenism drives cardiovascular diseases (Naftolin et al. 2019) and osteoporosis worsening the cancer treatment induced bone loss (Handforth et al. 2018; D'Oronzo et al. 2015) that exposes these patients to increased fracture risk and limited mobility (Table 1).

However, although novel therapeutic options for fertility preservation have recently allowed successful pregnancies in young BC survivors (Garrido-Marín et al. 2019), the attention towards this topic is frequently disregarded by physicians.

Current fertility preservation strategies

Major advancements in cancer diagnosis and treatments have definitely extended survival rates until complete healing and particularly in young female BC patients, the maternity desire is considered as a highly human incentive after the cancer suffering.

Several approaches are currently adopted for the fertility preservation and restitution of the reproductive

Table 1 Major anti-cancer drugs employed in BC treatment and mechanisms of potential ovarian failure

Anti-cancer drug class	Mechanisms involved in gonadotoxicity	Risk of ovarian failure	References
Alkylating agents	Granulosa cell damage through cell membrane and protein alkylation as well as DNA breaks Subsequent oocyte damage through gap junctions between oocytes and granulosa cells	High	Pfeilschifter and Diel (2000)
Taxanes	Damage of growing follicles without apparent effect on primordial follicles	Intermediate	Sonigo et al. (2019)
Antimetabolites	Cytotoxicity towards mitotic non-luteinized granulosa cells	Low	Yuksel et al. (2015)
Antracyclines	Double-strand-DNA breaks in primordial follicles, oocytes and granulosa cells	Low	Soleimani et al. (2011)
Her-2 targeting agents	Unknown	Unknown	Lambertini et al. (2019)
mTOR inhibitors	Potential preventive effect through prevention of follicle activation and inhibition of apoptosis in growing follicles	Unknown	Tanaka et al. (2018)
CDK 4/6 inhibitors	Unknown	Unknown	–

function in these patients after heavy gonadotoxic regimens, radiotherapy and invasive surgical procedures (Meirow et al. 2010; Meistrich 2009). To this, the international guidelines for fertility preservation in oncology, recommend an early personalized counseling for all patients in reproductive age to screen if they are good candidates for a fertility preservation program in relation to the evaluation of their ovarian reserve.

To measure the ovarian reserve, besides the ultrasonography enumeration of antral follicles during the follicular phase, a commonly used procedure includes the evaluation of follicle-stimulating hormone (FSH) circulating levels on the third day of the menstrual cycle to avoid the estradiol negative feedback control, while the anti-Müllerian hormone (AMH) serum amounts reflect the potential of differentiation to mature oocytes in follicles, and may thus suggest the most suitable procedure for fertility preservation in relation to the patient's age, cancer type and expected oncological treatment (William et al. 2008).

On the other hand, besides the simplistic gonad shielding during radiotherapy or the ovarian suppression by GnRHa (Blumenfeld 2007), both American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) recommend the cryopreservation of oocytes and/or embryos as standard strategies in postpuberal female patients. These techniques, however, although innovative require the hormonal stimulation to induce a multiple follicular growth and are thus not completely free of additional cancer risk particularly in patients with hormone-dependent tumors including primarily the BC as well as uterus and ovary cancers (Loren et al. 2013; Peccatori et al. 2013). Also, the ovarian cortex cryopreservation is another procedure for both prepuberal girls upcoming anti-cancer treatments and adult patients with anti-cancer therapeutical urgency which cannot delay treatments for the timing necessary to induce folliculogenesis (Loren et al. 2013; Peccatori et al. 2013).

Besides these procedures, a potential application of recent discoveries in the ovarian stemness field, concerns the recruitment of OSCs from ovarian cortex. Recent studies have showed that once isolated and grown in vitro, these cells undergo their final differentiation into OLCs (Silvestris et al. 2019), thus opening new avenues to innovative and modern programs for the fertility preservation also in oncologic patients.

Therefore, women with BC and functional reproductive status, before anti-cancer treatments should be referred to a multidisciplinary team including the reproduction specialist, in addition to other professional competences provided by oncologists, surgeons and others, to evaluate the most suitable technique to preserve their fertility, whose most common procedures are next summarized in Table 2 and briefly revisited.

Ovarian suppression with GnRHa (gonadotropin-releasing hormone agonists)

The inhibition of oocyte maturation, by GnRHa as goserelin, triptorelin, buserelin and leuprolide, is a simple and efficient modality of fertility preservation in cancer patients using only drug assumption without requirement of invasive in vitro fertilization (IVF) technologies or unsuitable delay of chemotherapy.

These molecules are decapeptides showing a molecular structure similar to native GnRH and high affinity to the GnRH receptors (-R), that once bound and internalizated, induce continuous gonadotropin release resulting in a flare-up effect. After a few days of administration, a desensitization mechanism is generated with a decrease of the total number of functional GnRH-R, ultimately resulting in reduction of both FSH and luteinizing hormone (LH)-circulating levels (Rivkees and Crawford 1988).

It has been also reported that the gonadotoxic effect induced by chemotherapy leads to increased bioavailability of FSH in association with a decreased levels of estrogen and inhibin. Therefore, since GnRHa induce a reduction of both FSH levels and the primordial follicles' recruitment, its administration in cancer patients at least 1 week before chemotherapy, provides a hormonal gonadic dormancy during the treatments resulting in a reduction of toxicity for ovarian cell components including oogonial cells (Rivkees and Crawford 1988).

Despite the GnRHa adoption for fertility preservation programs in oncological patients before anti-cancer treatments is controversial for its efficacy, this procedure is still considered the most suitable approach for BC patients necessary of urgent treatments with common chemotherapic agents (Cakmak et al. 2015).

Oocyte cryopreservation

The oocyte cryopreservation is a useful method based on the oocytes exposition to highly negative temperatures freezing the cells biological activity to preserve cell populations for future fertility treatment (Oktay et al. 2018). This procedure is also commonly adopted by patients affected of primary infertility who attend general programs of the assisted reproduction technique (ART).

After revealing a functional consistency of the ovarian reserve in BC patients, a controlled ovary hyperstimulation (COH) by gonadotropin injections to support the MFG is maintained for 10 days, while the follicle maturation is monitored by both periodic ultrasound examination and hormonal biomarkers blood measuring as increased estradiol (E2) levels. Thus, as the ovulation is induced and oocytes are retrieved by ultrasound-guided pick-up, these cells are primarily evaluated in their quality by embryologists and then

Table 2 Schematic description of major procedures for fertility preservation techniques

Methods	Age	Advantages	Disadvantages	References
Ovarian suppression with GnRHa	Postpuberal women	Simple technique No need to delay oncological treatment No need for COH	Conflicting data of effectiveness Menopausal symptoms	Rivkees and Crawford (1988) Cakmak et al. (2015)
Oocyte cryopreservation	Postpuberal women	Well-established technique	Need for COH and cycle dependence Need to delay oncological treatment Oncogenic risk for hormonal-cancers Good OR	Baka et al. (1995) Shaw et al. (2000) Parmegiani et al. (2009) Smith et al. (2010) Taylan and Oktay (2017) Oktay et al. (2018)
Embryo cryopreservation	Postpuberal women	Well-established technique	Need for COH and cycle dependence Need to delay oncological treatment Oncogenic risk for hormonal-cancers Good OR Limited to few countries	Rall and Fahy (1985) De Jong et al. (2002) Konc et al. (2014)
Ovarian cortex cryopreservation	Prepuberal women Postpuberal women	No need to delay oncological treatment No need for COH or cycle dependence No oncogenic risk for hormonal- cancers	Experimental technique Pelvic surgery Oncogenic risk after replantation Good OR Limited to expert infertility centers	Gosden et al. (1994) Von Wolff et al. (2009) Silber et al. (2010) Donnez et al. (2013) Pacheco and Oktay (2017)
Ovarian Stem Cells (OSCs)	Prepuberal women Postpuberal women	No need to delay oncological treatment No need for COH or cycle dependence No need of pelvic surgery OR independence No oncogenic risk for hormonal-cancers	Theoretical application Only animal models available Needs to be investigated in humans	Johnson et al. (2004) Telfer and Albertini (2012) Silvestris et al. (2018) Akahori et al. (2019)

COH controlled ovarian hyperstimulation, *OR* ovarian reserve

stored in liquid nitrogen following a slow-freezing procedure which is critical to obtain future viable cells. To this, it has been reported that rapid freezing of eggs drives intracellular damage for the formation of cytoplasmic ice, while the oocyte thawing process also needs to be slowly completed to obtain good quality and functional oocytes for fertilization practice (Shaw et al. 2000; Baka et al. 1995).

Recent advances in cryopreservation methods, dealing with cryoprotectant early and seeding temperatures as well as timing of oocyte recovery, led to the vitrification technique which significantly improved the mature oocyte survival rate after thawing resulting in both fertilization and implantation rates similar for freshly picked-up oocytes (Parmegiani et al. 2009; Smith et al. 2010).

An alternative to mature oocyte cryopreservation includes the freezing and storage of immature oocytes or in vitro matured oocytes (Taylan and Oktay 2017). However, this technique is under evaluation by clinical researchers and since is virtually COH-independent or requiring only a short time of hormone stimulation up to 3–5 days, should be perhaps suggested to BC patients showing anti-cancer treatment urgency.

Embryo cryopreservation

Despite ethical and legal concerns and restrictions of the embryo cryopreservation in several countries, this practice is largely adopted as most conventional procedure for BC patients although it may delay anti-cancer treatments up to 6 weeks before obtaining a suitable endometrial nesting. In fact, as for the oocyte recruitment, this method implies a protocol of COH to induce the MFG for the mature oocyte recovery, and a subsequently in vitro fertilization which follows the cryopreservation (Konc et al. 2014). Similar to oocytes, the embryo vitrification is largely used for cryostorage of embryos with the purpose to prevent the formation of ice crystals in cytoplasms and other intracellular sites (Rall and Fahy 1985). However, despite concurrent improvements

of this procedure and utilization of novel cryoprotective additives to freeze embryos, the average potential of a thawed embryo to become a living child lies in the order of 4%. Therefore, while appearing a relative fruitful procedure, the embryo cryopreservation and transfer in oncologic patients bearing the BC still includes the oncogenic risk for estrogen hormonal hyperstimulation which is also associated to the high serum progesterone levels induced for the best endometrial nesting on the day of transfer (De Jong et al. 2002).

Ovarian cortex cryopreservation

A 'safe' procedure implying a minor risk of hormone stimulation in BC patients is the ovarian tissue cryopreservation after laparoscopic or laparotomic surgical biopsies followed by its orthotopic or heterotopic re-implantation after the cancer healing. Besides avoiding the COH, major advantage of this procedure includes its feasibility independently from the menstrual cycle, both in prepubertal and adult cancer patients with adequate ovarian reserve and anti-cancer treatment urgency. This method has been applied in the past years using the slow-freezing approach for the cortex specimen storage (Gosden et al. 1994) contrarily to the recently introduced vitrification (Silber et al. 2010).

Besides its hormone safety in primarily infertile women or in cancer female patients, the autologous re-implantation of ovarian cortex biopsies is described as functional procedure producing a pregnancy rate up to 37% with endocrine renovation in approximately 65% of women receiving this treatment (Pacheco and Oktay 2017). Thus, the restoration of a hormone steady state by re-implantation of the autologous ovarian cortex may represent a gain of this procedure particularly in young BC patients survived to the disease who apparently reach normal FSH serum levels within 5 months from ovarian cortex re-implantation resulting in reactivation of folliculogenesis and feasibility in attempting natural conception (Donnez et al. 2013).

Despite the reported advantages of the ovarian cortex cryopreservation related to its recruitment independent from both hormone stimulation and menstrual cycle phases, this technique implies indeed a few drawbacks. In fact, the recovered oocyte pool, from the thawed fragment, is often inadequate for both number of oocytes and viability. Furthermore, if after thawing is obtained an adequate oocyte pool, it is still hard to identify the best eggs to be fertilized as both morphology and genomic properties since the fragment with the whole population needs to be quickly re-implanted. Finally, the risk to re-introduce malignant cells originally resident in frozen ovarian cortex, as leukemia cells, should not be underestimated in this fertility preservation practice (Von Wolff et al. 2009).

Ovarian stem cells (OSCs)

A potentially safe procedure for fertility preservation in women, also bearing hormone-dependent cancers, is based on the future use of OSCs obtained from the cortex which can be differentiated in vitro to mature oocytes.

At present, there is only consistent scientific evidence that it is possible to separate these cells from small biopsies of the women ovarian cortex and induce their differentiation to oocyte-like cells capable to express molecular markers of mature oocytes. To this, it has been demonstrated in female murine models treated with highly gonadotoxic drugs, that once re-implanted in sterilized ovaries, the OSCs are capable to generate fertilizable eggs (Telfer and Albertini 2012). Intensive studies in human research also showed that it is possible to isolate OSCs from both young and post-menopausal women thus supporting a contrary interpretation of the central dogma of reproductive sciences suggesting that a fixed number of oocytes are committed in the woman at the birth (Johnson et al. 2004). To this regard, in agreement with work from others, we recently showed that even OSCs from post-menopausal ovarian cortex, undergo differentiation in vitro to OLCs (Fig. 1) expressing the final markers of oocyte maturation, namely both SYCP3 and GDF9, which in the physiology of egg maturation interact with granulosa cells to generate the cumulus peri-ovocyte cells (Silvestris et al. 2018; Akahori et al. 2019).

This stemness technology represents a great opportunity for future studies in fertility preservation programs both in women affected by primary as well as in those with cancer-related infertility. Several groups of researchers investigating this aspect of OSCs in women have showed that once in vitro differentiated to the final stage of OLCs, these cells also

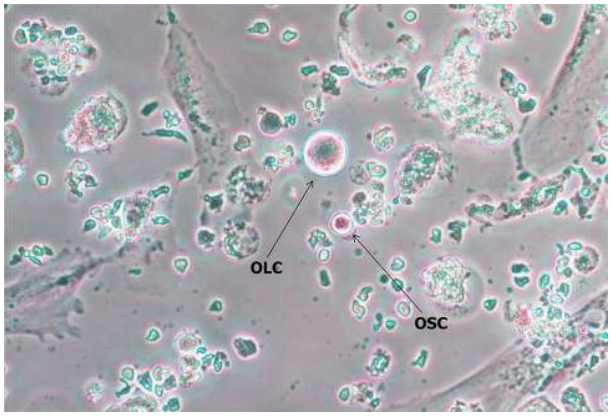

Fig. 1 In vitro differentiation of ovarian stem cells (OSCs) to oocyte-like cells (OLCs). After 21 days of culture, OLCs are distinguishable in culture in relation to the size up to 80 µm, as well as prominent nuclei, whereas undifferentiated OSCs maintain their original small size

express a DNA haploid content that reflects their promptness to be fertilized (Silvestris et al. 2018). The opportunity which emphasizes the translation of OSCs to the cancer-related infertility is provided by the possibility to develop in vitro a progeny of OLCs from a single OSC, thus favoring the selection of good quality eggs to be frozen and subsequently utilized in fertilization programs. In collaboration with embryologists and possibly with molecular biologists, it will be, therefore, possible in future to identify eggs of the best quality concerning both morphologic and genomic properties (Akahori et al. 2019). Although this is a future perspective in using OSCs to the treatment of the human infertility, the production of viable and molecularly intact eggs is a main utilization of the precision medicine applied to the infertility field.

A further advantage offered by the OSC development technology is also related to the absence of hormone stimulation to induce the MFG. OSCs could be, indeed, isolated independently on the menstrual cycle and easily recovered by ovarian cortex fragments by minor surgery approaches as laparoscopy or mini-laparotomy. In patients with BC, particularly in young women, this procedure will provide a definitive outcome based on the best selection of eggs to be fertilized after their cancer healing.

In conclusion, since the development of OSC studies has been also participated by ourselves, we do trust that the application of stemness studies to improve the fertility in BC patients will be fruitful in generating new opportunities in pregnancy programs of these women.

Controversial aspects of controlled ovarian stimulation for fertility preservation

Recently, intensive focusing on fertility preservation strategies has suggested the most suitable techniques for young BC patients with a maternity project (Azim et al. 2011).

Preliminary studies and meta-analyses have evaluated the safety of pregnancy after BC (Kroman et al. 2008), and a recent report by Azim and Coworkers confirmed its safety also in women with endocrine-sensitive disorders (Azim et al. 2011). This information primed the interest of both scientists and patients towards the potential applicability of ART to achieve pregnancy on cancer outcome (Azim et al. 2013).

In an additional study, Goldrat and colleagues it has been emphasized both feasibility and harmlessness of ART in women with BC history in whom the linkage between ART, BC clinical-pathological features, pregnancy and long-term cancer survival. In fact, the authors conduced a multi-center retrospective study enrolling a total of 198 patients with primary non-metastatic BC, who spontaneously become pregnant, or after ART procedure which included COH by gonadotropins for in IVF, or by intra-cytoplasmic sperm injection and egg donation. In both groups, they observed no significant differences in tumor progression and long-term cancer outcome, thus concluding that based on encouraging data of the extended follow-up in ART-treated patients, these techniques are suitable and feasible (Goldrat et al. 2015).

However, when a young BC patient at the end of anti-cancer treatments is interested in ART procedure, or when a young woman with a diagnosis of BC, wishes to preserve her fertility before starting anti-cancer treatments, conflicting thoughts may arise on the potential risk of BC progression after COH (Yager and Davidson 2006). In fact, since this procedure is based on the increased bioavailability of E2 levels which raise approximately up to 20 times the natural concentrations (Cahill et al. 2000) and both estrogen and relative metabolites would be potentially enrolled in BC dissemination (Yager and Davidson 2006), the traditional protocols using the ovarian stimulation are not to be considered entirely safe (Ayhan et al. 2004).

To avoid the potential risks of E2 level rising during COH, Oktay and coworkers for the first time (Oktay et al. 2005), and subsequently Azim and Colleagues, published their studies concerning the use of aromatase inhibitors (AIs) as letrozole in association to gonadotropins during the COH procedure to induce the MFG. They found that E2 levels remain at concentrations similar to those reached in unstimulated cycles, and that both oocytes and embryos retrieved were comparable to those obtained by standard ovarian stimulation protocols (Azim et al. 2008). Therefore, they reported that low E2 peaks with concomitant sufficient oocyte recruitment were not associated to increase of BC progression, thus supporting the postulated therapeutic safety of this aromatase inhibitor when used during a stimulation protocol.

However, despite the convincement of safety by AI using protocols in hormone-sensitive tumors as BC, several studies have shown a major susceptibility to this tumor in women receiving the ART procedure (Venn et al. 1999) as well as in those treated with gonadotropins for more than 6 months (Burkman et al. 2003), and a general increasing risk in women with positive family history (Gauthier et al. 2004). To this regard, Venn and Coworkers investigated in 10 Australian IVF-dedicated clinics, a cohort of 20,656 women treated by ART, with the aim to evaluate the incidence of invasive breast, ovary, and uterus tumors in relation to fertility drugs assumption. The Authors demonstrated on 143 breast, 13 ovarian and 12 uterus cancers occurred among these women, an higher incidence of both breast (14.4%) and uterine cancers (16.7%) after 12 months from the COH procedure though the different combinations of fertility drugs used need to be definitely assessed also in relation to other variants including parity, previous use of oral contraceptives, and both menarche and menopause times (Venn et al. 1999).

Later Jensen and colleagues tried to clarify the controversial results concerning the implication of fertility drugs on BC risk, investigating a larger cohort of 54,362 Danish women, and analyzed the histologic subtypes of developed tumors. Hence, the authors did not find a direct relation and thus suggested a long-term follow-up to better evaluate the BC risk after hormone stimulation (Jensen et al. 2007).

Therefore, considering that the underlying mechanisms for a potential interference of COH with BC biology are unclear and need extended studies to support or refuse this relation, the implementation with an AI to fertility drugs, would represent the most safety option.

In search of a safety procedure for fertility preservation

The reported controversial studies open a direct question on the most safety procedure to be suggested to BC patients as well as to all female patients suffering of hormone-sensitive tumors.

Both oocyte and embryo cryopreservations definitely provide successful pregnancies in BC patients but would probably enhance the oncogenic risk of tumor progression, whereas the ovarian suppression by GnRHa is generally considered safe for the BC evolution though debated as method to preserve the oocyte reserve and fertility (Akahori et al. 2019). The ovarian cortex recruitment, cryopreservation, and re-implantation after BC healing represent a definitely harmless procedure under the oncogenic point of view, but its effectiveness in improving the oogenesis appears needs to be assessed by extended studies. In fact, besides the low number of follicles available in re-implanted cortex biopsies, there is no way to evaluate the quality of oocytes as well as to select the most viable ones. On the other hand, there is no general agreement on the best thawing method to provide suitable viability in defrosted oocytes (Von Wolff et al. 2009).

Innovative COH protocols, particularly those adopting AIs for fertility programs in BC women with hormone-sensitive tumors, are indeed a practicable option which reduces the functionally oncogenic E2 concentrations while lowering the cancer-recurrence and extending the survival rate (Azim et al. 2013). However, despite these encouraging data, the tumor progression or relapse is reported to occur in a minority of patients, namely less than 1% of women treated by AI-based COH (Venn et al. 1999).

Although in progress of standardization and translation to treat the female infertility, it is our opinion that the recruitment and utilization of OSCs in oncologic female patients, including primarily those bearing hormone-dependent tumors as BC, can represent the most safe and innovative procedure for fertility preservation (Silvestris et al. 2018). This model is in line with the application of regenerative medicine to restore the ovarian reserve and undoubtedly offers several advantages with respect to the other procedures. First, the absence of hormone conditioning and the timing which is independent for the menstrual cycle thus allowing to isolate as soon as possible, the OSCs before any anti-cancer treatment. Furthermore, after their differentiating in vitro to OLCs, it is possible to obtain a progeny of oocytes to be selected by dedicated embriologists as the most viable ones to be cryopreserved. The possibility to select the best oocytes within a large subset of differentiated OCSs also offers the opportunity to investigate by molecular analysis those reputed suitable by embriologists to guarantee good quality eggs. This selection could be assessed after in vitro OCS differentiation to OLCs and their subsequent cryostorage would also assure the patients on the best quality of their stored oocytes to be fertilized after the cancer (Silvestris et al. 2018).

In conclusion, the OSC technology needs to be intensively investigated with the aim to offer to all BC patients undergoing anti-cancer treatments not only the safety to not receive hormonal stimulus capable to influence the tumor progression as provided by COH, AIs or other fertility drugs, but also the possibility to guarantee the best quality of oocytes for fertility utilization (Silvestris et al. 2018).

Conclusion

BC is the most common female malignancy worldwide, both in pre- and post-menopausal women. Thanks to recent diagnostic and therapeutic advances, patient life expectancy has significantly improved in the last decades, suggesting that the achievement of motherhood programs might represent an important issue to deal with, especially for the very young BC survivors. Indeed, systemic anti-cancer treatments often affect female fertility, either transiently or permanently, making personalized fertility preservation/restoring strategies essential.

To this regard, several approaches have been developed, including the cryopreservation of oocytes, embryos and ovarian cortex, whose adoption should be carefully evaluated by a dedicated reproductive medicine multidisciplinary team to select the most suitable procedure for each patient.

Moreover, the recruitment and utilization of OSCs will represent in future the safest procedure for fertility preservation, whose peculiarities rely on the lack of preliminary hormone stimulation and the possibility to differentiate and select OLCs in vitro, for which further investigation are warranted.

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Compliance with ethical standards

Conflict of interest None.

References

Akahori T, Woods DC, Tilly LJ (2019) Female fertility preservation through stem cell-based ovarian tissue reconstitution in vitro and ovarian regeneration in vivo. Clin Med Insights Reprod Health. 13:1–10

Alder J, Zanetti R, Wight E et al (2008) Sexual dysfunction after premenopausal stage I and II breast cancer: do androgens play a role? J Sex Med. 5(8):1898–1906. https://doi.org/10.1111/j.1743-6109.2008.00893.x

Ayhan A, Salman M, Celick H et al (2004) Association between fertility drugs and gynecologic cancers, breast cancer, and childhood cancers. Acta Obstet Gynecol Scand 83:1104–1111

Azim AA, Costantini-Ferrando M, Oktay K (2008) Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. J Clin Oncol 26:2630–2635

Azim HA Jr, Peccatori FA, de Azambuja E et al (2011a) Motherhood after breast cancer: searching for la dolce vita. Expert Rev Anticancer Ther 11:287–298

Azim HA Jr, Santoro L, Pavlidis N et al (2011b) Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer 47:74–83

Azim HA Jr, Kroman N, Paesmans M et al (2013) Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. J Clin Oncol 31:73–79

Baka SG, Toth TL, Veeck LL et al (1995) Evaluation of the spindle apparatus of in vitro matured human oocytes following cryopreservation. Hum Reprod 10:1816–1820

Bardia A, Hurvitz S (2018) Targeted therapy for premenopausal women with HR+, HER2- advanced breast cancer: focus on special considerations and latest advances. Clin Cancer Res. https://doi.org/10.1158/1078-0432.CCR-18-0162

Ben-Aharon I, Shalgi R (2012) What lies behind chemotherapy-induced ovarian toxicity? Reproduction 144(2):153–163

Blumenfeld Z (2007) How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embrya, oocytes or ovaries. Oncologist. 12:1044–1054

Burkman R, Tang M, Malone K et al (2003) Infertility drugs and the risk of breast cancer: findings from the national institute of child health and human development women's contraceptive and reproductive experiences study. Fertil Steril 79:844–851

Cahill DJ, Wardle PG, Harlow CR et al (2000) Expected contribution to serum oestradiol from individual ovarian follicles in unstimulated cycles. Hum Reprod 15:1909–1912

Cakmak H, Rosen MP. Cancer treatment and the ovary. Chapter 8: Current Clinical approaches to protecting the ovary: GnrH Analogues. 2015, pp 109-132

Cardoso F, Senkus E, Costa A et al (2018) 4th ESO-ESMO International consensus guidelines for advanced breast cancer (ABC 4). Ann Oncol 29:1634–1657

Cardoso F, Kyriakides S, Ohno S et al (2019) Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 30:1194–1220

De Jong D, Eijkemans MJ, Beckers NG et al (2002) The added value of embryo cryopreservation to cumulative ongoing pregnancy rates per IVF treatment: is cryopreservation worth the effort? J Assist Reprod Genet. 19(12):561–568

de Pedro M, Otero B, Martin B (2015) Fertility preservation and breast cancer: a review. Cancer 9:503

Del Mastro L, Catzeddu T, Venturini M (2006) Infertility and pregnancy after breast cancer: current knowledge and future perspectives. Cancer Treat Rev 32:417–422

Deniz M, DeGregorio A, DeGregorio N et al (2019) Differential prognostic relevance of patho-anatomical factors among different tumor-biological subsets of breast cancer: results from the adjuvant success a study. Breast 44:81–89

Donnez J, Dolmans MM, Pellicer A et al (2013) Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. Fertil Steril 99:1503–1513

D'Oronzo S, Stucci S, Tucci M, Silvestris F (2015) Cancer treatment-induced bone loss (CTIBL): pathogenesis and clinical implications. Cancer Treat Rev 41(9):798–808. https://doi.org/10.1016/j.ctrv.2015.09.003

Fornier MN, Modi S, Panageas KS et al (2005) Incidence of chemotherapy induced, long-term amenorrhea in patients with breast carcinoma age 40 years and younger after adjuvant anthracycline and taxane. Cancer 104:1575–1579

Ganz PA, Land SR, Geyer CE Jr et al (2011) Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. J Clin Oncol 29:1110–1116

Garrido-Marín M, Argacha PM, Fernández L et al (2019) Full-term pregnancy in breast cancer survivor with fertility preservation: a case report and review of literature. World J Clin Cases 7(1):58–68

Gauthier E, Paoletti X, Clavel-Chapelon F et al (2004) Breast cancer risk associated with being treated for infertility: results from the French E3N cohort study. Hum Reprod 19:2216–2221

Goksu SS, Tastekin D, Arslan D et al (2014) Clinicopathologic features and molecular subtypes of breast cancer in young women (age ≤ 35). Asian Pac J Cancer Prev 15(16):6665–6668

Goldrat O, Kroman N, Peccatori FA et al (2015) Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome. Eur J Cancer 51(12):1490–1496

Gosden RG, Baird DT, Wade JC et al (1994) Restoration of fertility to oophorectomized sheep by ovarian autografts stored at −196 degrees C. Hum Reprod 9:597–603

Handforth C, D'Oronzo S, Coleman R et al (2018) Cancer treatment and bone health. Calcif Tissue Int 102(2):251–264. https://doi.org/10.1007/s00223-017-0369-x

Ihemelandu CU, Leffall LD, Dewitty RL et al (2007) Molecular breast cancer subtypes in premenopausal and postmenopausal african-american women: age-specific prevalence and survival. J Surg Res. 143:109–118

Jensen A, Sharif H, Svare EI et al (2007) Risk of breast cancer after exposure to fertility drugs: results from a large Danish cohort study. Cancer Epidemiol Biomarkers Prev 16:1400–1407

Johnson J, Canning J, Kaneko T et al (2004) Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature 428:145–150

Kasum M, Beketic-Oreskovic L, Peddi PF et al (2014) Fertility after breast cancer treatment. Eur J Obstet Gynecol Reprod Biol 173:13–18

Konc J, Kanyó K, Kriston R et al (2014) Cryopreservation of embryos and oocytes in human assisted reproduction. Biomed Res Int 2014:307268

Kotsopoulos J (2018) BRCA Mutations and breast cancer prevention. Cancers 10:524. https://doi.org/10.3390/cancers10120524

Kraby MR, Valla M, Opdahl S et al (2018) The prognostic value of androgen receptors in breast cancer subtypes. Breast Cancer Res Treat 172:283–296

Kroman N, Jensen MB, Wohlfahrt J et al (2008) Pregnancy after treatment of breast cancer-a population-based study on behalf of Danish breast cancer cooperative group. Acta Oncol 47:545–549

Lambertini M, Anserini P, Levaggi A et al (2013) Fertility counseling of young breast cancer patients. J Thoracic Dis 5(1):S68–S80

Lambertini M, Campbell C, Bines J et al (2019) Adjuvant anti-her2 therapy, treatment-related amenorrhea, and survival in premenopausal her2-positive early breast cancer patients. J Natl Cancer Inst 111(1):094

Loren AW, Mangu PB, Beck LN et al (2013) Fertility preservation for patients with cancer: American society of clinical oncology clinical practice guideline update. J Clin Oncol 31(19):2500–2510

Malvezzi M, Carioli G, Bertuccio P et al (2019) European cancer mortality predictions for the year 2019 with focus on breast cancer. Ann Oncol 30:781–787

Meirow D, Biederman H, Anderson RA et al (2010) Toxicity of chemotherapy and radiation on female reproduction. Clin Obstet Gynecol 53(4):727–739

Meistrich ML (2009) Male gonadal toxicity. Pediatr Blood Cancer 53(2):261–266

Naftolin F, Friedenthal J, Nachtigall R etal (2019) Cardiovascular health and the menopausal woman: the role of estrogen and when to begin and end hormone treatment. F1000Res. https://doi.org/10.12688/f1000research.15548.1

Oktay K, Buyuk E, Libertella N et al (2005) Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. J Clin Oncol 23:4347–4353

Oktay K, Harvey BE, Partridge AH et al (2018) Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. https://doi.org/10.1200/JCO.2018.78.1914

Pacheco F, Oktay K (2017) Current success and efficiency of autologous ovarian transplantation: a meta-analysis. Reprod Sci. 24(8):1111–1120

Parmegiani L, Bertocci F, Garello C et al (2009) Efficiency of human oocyte slow freezing: results from five assisted reproduction centres. Reprod Biomed Online. 18:352–359

Peccatori FA, Azim HA Jr, Orecchia R et al (2013) Cancer, pregnancy and fertility: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 24(Suppl 6):vi160–vi170

Pfeilschifter J, Diel IJ (2000) Osteoporosis due to cancer treatment: pathogenesis and management. J Clin Oncol 18:1570–1593

Rall WF, Fahy GM (1985) Ice-free cryopreservation of mouse embryos at − 196°C by vitrification. Nature 313:573–575

Rivkees SA, Crawford JD (1988) e relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA 259:2123–2125

Romieu I, Biessy C, Carayol M et al (2018) Reproductive factors and molecular subtypes of breast cancer among premenopausal women in Latin America: the PRECAMA study. Sci Rep. 8:13109

Rosenberg SM, Partridge AH (2013) Premature menopause in young breast cancer: effects on quality of life and treatment interventions. J Thorac Dis. 5(Suppl 1):S55–S61. https://doi.org/10.3978/j.issn.2072-1439.2013.06.20

Senkus E, Kyriakides S, Ohno S et al (2015) Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 26(Supplement 5):v8–v30

Shaw JM, Oranratnachai A, Trounson AO (2000) Fundamental cryobiology of mammalian oocytes and ovarian tissue. Theriogenology 53:59–72

Silber S, Kagawa N, Kuwayama M et al (2010) Duration of fertility after fresh and frozen ovary transplantation. Fertil Steril 94:2191–2196. https://doi.org/10.1016/j.fertnstert.2009.12.073

Silva C, Ribeiro Rama AC, Reis Soares S et al (2019) Adverse reproductive health outcomes in a cohort of young women with breast cancer exposed to systemic treatments. J Ovarian Res. 12(1):102. https://doi.org/10.1186/s13048-019-0581-6

Silvestris E, Cafforio P, D'Oronzo S et al (2018) In vitro differentiation of human oocyte-like cells from oogonial stem cells: single-cell isolation and molecular characterization. Hum Reprod 33:464–473

Silvestris E, Cafforio P, Felici F et al (2019) Ddx4 + oogonial stem cells in postmenopausal women's ovaries: a controversial, undefined role. Cells 250:1–14

Smith GD, Serafini PC, Fioravanti J et al (2010) Prospective randomized comparison of human oocyte cryopreservation with slow-rate freezing or vitrification. Fertil Steril 94:2088–2095

Soleimani R, Heytens E, Darzynkiewicz Z et al (2011) Mechanisms of chemotherapy-induced human ovarian aging: double strand DNA breaks and microvascular compromise. Aging. 3(8):1–12

Sonigo C, Beau I, Binard N, Grynberg M (2019) The impact of Chemyotherapy on the ovaries: molecular aspect and the preventions of the ovarian damage. Int J Mol Sc 20(21):E5342. https://doi.org/10.3390/ijms20215342

Tanaka Y, Kimura F, Zheng L et al (2018) Protective effect of a mechanistic target of rapamycin inhibitor on an in vivo model ofcisplatin-induced ovarian gonadotoxicity. Exp Anim. 67(4):493–500. https://doi.org/10.1538/expanim.18-0042

Taylan E, Oktay K (2017) Current state and controversies in fertility preservation in women with breast cancer. World J Clin Oncol. 8(3):241–248

Telfer EE, Albertini DF (2012) The quest for human ovarian stem cells. Nat Med 18:353–354

Ter Welle-Butalid, Vriens IJH, Derhaag JG et al (2019) Counseling young women with early breast cancer on fertility preservation. J Assisted Reprod Genet 36(12):2593–2604

Toi M, Iwata H, Yamanaka T et al (2010) Clinical significance of the 21-gene signature (Oncotype DX) in hormone receptor-positive early stage primary breast cancer in the Japanese population. Cancer 116(13):3112–3118

Trivers KF, Fink AK, Partridge AH et al (2014) Estimates of young breast cancer survivors at risk for infertility in the US. Oncologist. 19(8):814–822

Van der Kolk DM, de Bock GH, Leegte BK et al (2010) Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in BRCA1 and BRCA2 families: high cancer incidence at older age. Breast Cancer Res Treat 124:643–651

Venn A, Watson L, Bruinsma F et al (1999) Risk of cancer after use of fertility drugs with in vitro fertilization. Lancet 354:1586–1590

Von Wolff M, Donnez J, Hovatta O et al (2009) Cryopreservation and autotransplantation of human ovarian tissue prior to cytotoxic therapy-a technique in its infancy but already successful in fertility preservation. Eur J Cancer 45(9):1547–1553

William ER, Wendy J et al (2008) Biomarkers of ovarian reserve. Biom Insig. 3:259–268

Yager J, Davidson N (2006) Estrogen carcinogenesis in breast cancer. N Engl J Med 354:270–282

Yuksel A, Bildik G, Senbabaoglu F, Akin N, Arvas M, Unal F, Kilic Y, Karanfil I, Eryılmaz B, Yilmaz P, Ozkanbaş C, Taskiran C, Aksoy S, Guzel Y, Balaban B, Ince U, Iwase A, Urman B, Oktem O (2015) The magnitude of gonadotoxicity of chemotherapy drugs on ovarian follicles and granulosa cells variesdepending upon the category of the drugs and the type of granulosa cells. Hum Reprod 30(12):2926–2935. https://doi.org/10.1093/humrep/dev256