

Management of ovarian reserve in breast cancer patients seeking pregnancies (MORE BREAKS): A Delphi consensus

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ABSTRACT

Breast cancer is one of the most common tumors among women with 10 % of cases diagnosed in reproductive age. Estrogen positive forms are characterized by an excellent long-term prognosis with the 5-year survival rate of approximately 90 %. Recently, the temporary interruption of adjuvant endocrine therapy to attempt pregnancy in women good prognosis have been introduced. At present, there are no indications or protocols on the optimal management of conception during discontinuation of endocrine therapy for these patients. A Delphi consensus was carried out to obtain expert opinion from a global perspective to identify the optimal pathways to pursue childbearing with particular focus in strategies aimed at reducing time to live birth. The Delphi consensus was carried out involving one Scientific Coordinator and 6 additional experts. Each member of the Scientific Board suggested additional experts, resulting in a panel of 31 experts. The Scientific Board proposed 20 statements covering the following area of interest: 1) Resumption of menstrual cycle after the suspension of endocrine therapy; 2) Management of the washout period; 3) Fertility assessment; 4) Decision-making of reproductive planning; 5) Ovarian reserve evaluation; 6) Expectant management vs immediate fertility treatment; 6) Controlled ovarian stimulation protocols; 7) *In vitro* fertilization protocols. Eighteen statements reached the consensus. This Delphi consensus provides strategies to reduce the time to live birth in breast cancer patients' candidates for discontinuation of endocrine therapy.

1. Introduction

Breast cancer (BC) is one of the most common cancers among

women, with 10 % of cases diagnosed before the age of 40 (Runowicz et al., 2016). An estimated 12,000 new cases per year occur in the US alone, with even higher incidence in developing countries (Ellington

Abbreviations: ACOG, American Congress of Obstetricians and Gynecologists; AFC, antral follicle count; AIFA, Italian Drug Agency; AMH, anti-müllerian hormone; ART, assisted reproductive technology; ASRM, American Society for Reproductive Medicine; BC, breast cancer; BMI, body mass index; CLBR, cumulative live birth rate; E₂, serum estradiol levels; ET, embryo transfer; FSH, follicle-stimulating hormone; GnRH, gonadotropin releasing hormone; HR +, hormone receptor positive; IUI, intrauterine insemination; IUD, intrauterine device; IVF, in vitro fertilization; OPR, ongoing pregnancy rate; OS, ovarian stimulation; PGT-A, preimplantation genetic testing for aneuploidy; POI, premature ovarian insufficiency; POSEIDON, Patient-Oriented Strategies Encompassing Individualized Oocyte Number; TTLB, time to live birth; UEI, unexplained infertility.

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et al., 2022). Worldwide, there were approximately 2.1 million newly diagnosed female BC cases in 2018, accounting for nearly one in four cases of cancer among women and 630,000 BC-related deaths (Howlander et al., 2014). Nevertheless, in women with BC, the 5-year survival rate is nearly 90 % (Ellington et al., 2022); therefore, adequate health care plan should be proposed to post-treatment survivors (Ganz, 2009).

Currently, adjuvant endocrine therapy in hormone-sensitive premenopausal BC is based on the results of the SOFT and TEXT studies (Pagani et al., 2014; Francis et al., 2018). This treatment consists in the administration of tamoxifen or exemestane plus ovarian suppression by GnRH agonist for 5–10 years and has led to a drastic reduction in premenopausal BC recurrence and an increase in overall survival after 5–15 years of follow-up (Francis et al., 2018; Conforti et al., 2019a). These long-lasting therapies can often represent an insurmountable obstacle in achieving pregnancy. All cancer patients of reproductive age should receive oncofertility counseling as early as possible during treatment planning, regardless of the type and stage of the disease (ESHRE Guideline Group on Female Fertility Preservation et al., 2020). It is necessary to discuss current or future reproductive wishes of patients, their health and prognosis, and the potential impact of the disease and anticancer treatment on fertility. It is also necessary to discuss the need for and possibility of contraception along with possible pregnancy outcomes during anticancer treatment (Lambertini et al., 2020). Counseling should be personalized based on factors related to the patient/couple and the disease and its treatment.

On this basis, the safety of temporary suspension of endocrine treatment in young women with hormone sensitive BC is being evaluated. The POSITIVE (Pregnancy Outcome and Safety of

Interrupting Therapy for Women with Endocrine Responsive Breast Cancer) trial enrolled women with stage I-III hormone receptor positive (HR +) early BC between the ages of 18 and 42 who had received 18–30 months of adjuvant endocrine therapy and wished to interrupt endocrine therapy for family planning. As part of the study, patients must resume adjuvant therapy within 24 months of discontinuation; therefore, conception within 12–15 months of suspension would be desirable. The study foresees a washout of 3 months after the suspension of endocrine treatment, active attempts at pregnancy for 12 months, pregnancy, possible breastfeeding, and resumption of therapy at 24 months following suspension (Partridge et al., 2021). Among these women, temporary interruption of endocrine therapy to attempt pregnancy did not confer a greater short-term risk of breast cancer events, including distant recurrence, than that in the external control cohort (Partridge et al., 2023).

Managing such a specific time window requires attention from reproductive medicine experts to define the best strategies to reduce the time to live birth (TTLB). At present, there are no indications or protocols on the optimal management of conception during discontinuation of endocrine therapy for these patients. A Delphi consensus was therefore carried out to obtain expert opinion from a global perspective to identify the optimal pathways that allow women undergoing endocrine therapy for hormone-sensitive BC to pursue the desire for motherhood with particular focus in strategies aimed at reducing TTLB.

2. Materials and methods

2.1. Delphi technique

The Delphi process is a method that aids in structuring a group communication process and allows participants to deal with an intricate problem as a group (Hasson et al., 2000; Conforti et al., 2021; Zhong et al., 2015; Feferkorn et al., 2023). For the purpose of this study, a multidisciplinary group of experts in oncofertility was identified and involved in the present Delphi consensus. It focuses on strategies for reducing TTLB in women who suspend endocrine therapy for hormone-sensitive BC.

2.2. Consensus participants

The Delphi consensus initially involved a Scientific Board, comprising the Scientific Coordinator (CA) and 6 additional experts (Table 1). Each member of the Scientific Board suggested additional experts, resulting in a panel of 31 experts (Extended Panel) (Table 1).

2.3. The consensus process

The present Delphi consensus involved three steps (Fig. 1). The Scientific Coordinator and the Scientific Board generated the initial statements and supporting references based on an evaluation of the most up-to-date scientific literature. In Step 1, these statements were discussed during a web conference, wherein the proposed statements and references could be added, removed, or amended. The aim of Step 2 was to identify a consensus from the Extended Panel on the statements developed by the Scientific Board during Step 1. An online survey of the statements was then circulated to the Extended Panel. Each participant anonymously rated their level of agreement with each statement using a five-item Likert scale: 1 = absolutely disagree; 2 = disagree; 3 = agree; 4 = more than agree; 5 = absolutely agree. Participants were also asked to provide the main reasons (free text) for their chosen level of agreement or disagreement. Consensus was considered to have been achieved if the proportion of participants either disagreeing (responding 1 or 2) or agreeing with a statement (responding 3, 4 or 5) exceeded 66 %. If the proportion of participants agreeing or disagreeing with a statement did not reach the 66 % threshold, the statement was revised based on the feedback received. If the threshold was not reached after revision, the statement was reported with reasons for non-approval. In Step 3, an online survey of the statements was circulated to the Extended Panel via two web conferences. Statements that did not achieve consensus in Round 2 were discussed, revised and/or merged by the scientific board. The newly reworded statements, based on the comments of the Extended Panel, were approved or disagreed through an online survey during Round 3. The final selection of statements was decided by consensus and approved by the Scientific Coordinator and Scientific Board. Before discussing the results of the online survey, the previous stages of the Delphi consensus were briefly described, and the names of the Scientific Board members and Extended Panel were disclosed. These web conferences were not compulsory to attend and were intended to communicate the outcomes of Step 2 to participants to report on the level of consensus for each statement.

3. Results

The Scientific Board initially proposed 20 statements which were voted on by the Extended Panel of experts (Fig. 2). Thirty-seven experts were invited to join the Extended Panel, of which 31 completed the survey (84 %). These statements were related to predicting factors of menstrual cycle resumption after endocrine therapy suspension (n = 1), washout period management (n = 3), fertility assessment (n = 3), decision-making of reproductive planning (n = 3), ovarian reserve evaluation (n = 3), expectant management (n = 3), ovarian stimulation (OS) protocols (n = 1), *in vitro* fertilization (IVF) protocols (n = 4). Consensus was achieved after the first round of voting for all statements except n. 4 (use of condoms for active contraception) and 7 (timing of examination of tubal patency), with one statement (prognostic factors for menstruation resumption) achieving even 100 % consensus (Fig. 2). A high level of agreement (>80 % of votes were 'agree', more than agree' or 'absolutely agree') was achieved on ~80 % of statements. Statements 4 and 7 had a total agreement level of 61 % and 55 %, respectively. Statements are discussed in detail below.

Table 1
Scientific board and extended panel.

Scientific Board (n = 7)
Carlo Alviggi
Nicola Colacurci
Fedro Peccatori
Filippo Maria Ubaldi
Alessandro Conforti
Luigi Carbone
Roberta Vallone
Extended Panel (n = 31)
Adolfo Allegra
Silvia Ajossa
Alessandra Andrisani
Paola Anserini
Rosanna Apa
Andrea Borini
Laura Buffo
Carlo Bulletti
Ettore Cittadini
Mauro Costa
Giuseppe D'Amato
Francesco Fusi
Luca Gianaroli
Antonio La Marca
Paolo Levi-Setti
Claudia Livi
Luca Mencaglia
Mario Mignini Renzini
Roberto Palermo
Enrico Papaleo
Eleonora Porcu
Rocco Rago
Alberto Revelli
Giuseppe Ricci
Valeria Savasi
Paolo Scollo
Ida Strina
Elisabetta Trabucco
Roberta Venturella
Enrico Vizza
Fulvio Zullo

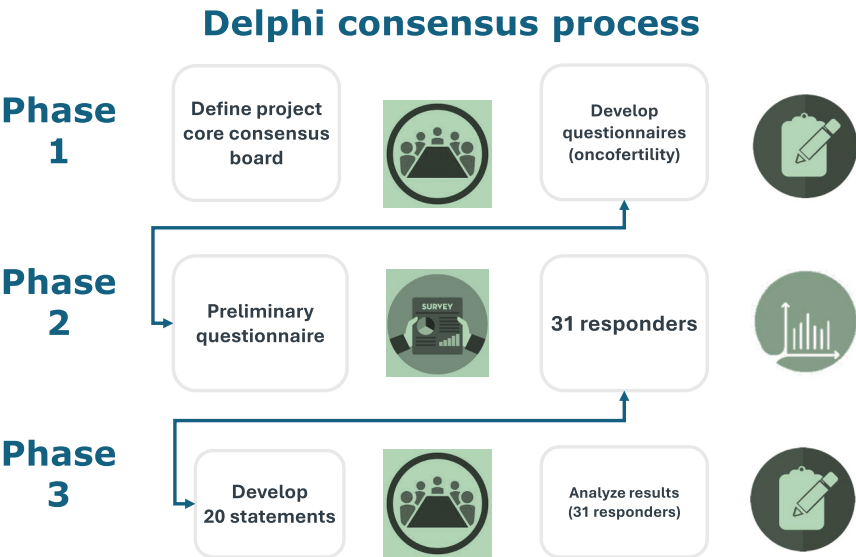


Fig. 1. Steps of the delphi consensus process.

3.1. Statement on the resumption of menstrual cycle after the suspension of endocrine therapy

Statement 1: Ovarian reserve before oncological therapy, chemotherapy before adjuvant endocrinotherapy, and age are the most relevant factors for

the resumption of the menstrual cycle within 3–6 months from endocrine therapy suspension.

This statement received 100 % agreement from the Extended Panel. Age, type and dose of gonadotoxic treatment, as well as pre-treatment AMH levels, predict the risk of post-treatment premature ovarian

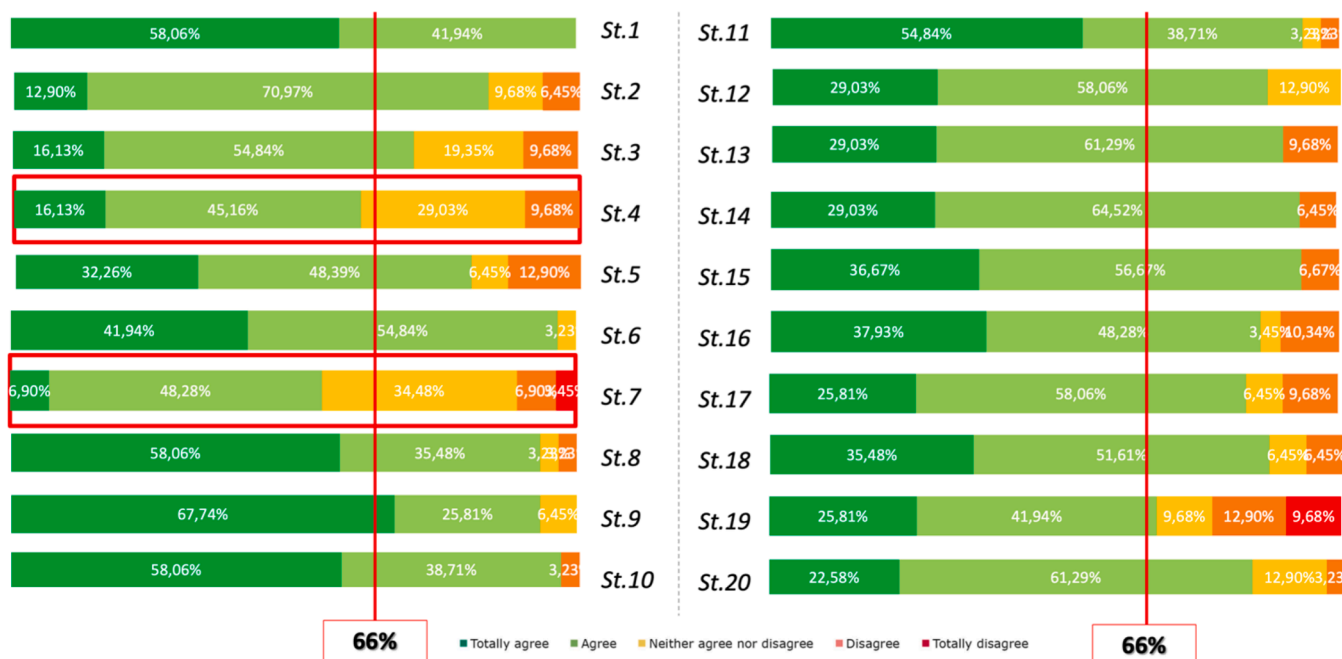


Fig. 2. Grading of the statements.

insufficiency (POI) in premenopausal women with a diagnosis of BC (ESHRE Guideline Group on Female Fertility Preservation et al., 2020; Peigné and Decanter, 2014). Several authors have shown that women with chemotherapy-related amenorrhea were older and had lower pre-chemotherapy serum AMH levels than those who still had menstrual periods (Anderson et al., 2013; Su et al., 2014; Barnabei et al., 2015). It has also been reported that women with higher serum AMH levels showed higher AMH levels after the first course of chemotherapy (Anderson et al., 2013; Su et al., 2014; Barnabei et al., 2015; Rosendahl et al., 2010). Dezellus et al. (2017) found a significantly higher cumulative decrease in patients with 'low' basal AMH levels than in patients with normal-high AMH levels (Dezellus et al., 2017). Dillon et al. (2013) observed that ovarian reserve decreased sharply during treatment and began to recover post-treatment (Dillon et al., 2013). Acute impairment of ovarian reserve appears to occur following chemotherapy-related destruction of ovarian follicles. Recovery reflects the restoration of follicle growth after therapy. However, primordial follicles destroyed during therapy are irreversibly lost, thus leading to impaired ovarian reserve in survivors. Patient age at the time of chemotherapy inversely correlates with the likelihood of post-chemotherapy amenorrhea (Taylan and Oktay, 2017).

3.2. Statements on management of the washout period

Statement 2: A 3-month washout period (which corresponds to 5 half-lives of tamoxifen) is recommended before attempting to conceive.

This statement received 84 % agreement from the Extended Panel. Tamoxifen represents a problem for breast cancer survivors and offspring. Indeed, the teratogenic and fetal toxic effects (low birth weight, miscarriages, birth defects, and stillbirths) of tamoxifen in animal studies are well known (Pugh and Sumano, 1982; Halakivi-Clarke et al., 2000). Tamoxifen also showed estrogen-like activity in the fetus, resulting in a risk of breast cancer and vaginal adenosis, usually described in association with diethylstilbestrol. However, the effects of tamoxifen appear to be species-specific and it is therefore not possible to relate these effects with certainty to humans (Lim et al., 2006; Cunha et al., 1987). Tamoxifen is also known to cause chromosomal aberrations by forming DNA adducts; perinatal exposure can thus induce precocious puberty, uterine abnormalities, uterine neoplasms, and

uterine atrophy (Kedia-Mokashi et al., 2010; Clark and Chua, 1989; Poulet et al., 1997). Exposure to tamoxifen during pregnancy in humans resulted in 16 live births with congenital malformations and a total of 122 live births without malformations (Braems et al., 2011). The AstraZeneca Safety Database reported 11 children with congenital malformations out of 44 live births; in addition, there were 18 fetal losses and 3 stillbirths (Barthelmes and Gateley, 2004). Tamoxifen is classified as a pregnancy category D medication by the Food Drug Administration. Guidelines contraindicate tamoxifen exposure during pregnancy and recommend the use of barrier contraception during 3 months after stopping tamoxifen due to the extended half-life of its metabolite N-desmethyl tamoxifen (Patterson et al., 1980; MacCallum et al., 2000). On this basis, all patients should be informed about a washout period of 3 months (which corresponds to 5 half-lives of tamoxifen) before conceiving. In case of inadvertent pregnancy, potential risks to the fetus/newborn should be discussed with the patient along with possible strategies to be implemented.

Statement 3: Active contraception for 3 months is recommended as a precaution to avoid the teratogenic risk of tamoxifen to allow pre-conceptional treatment with folic acid and adequate endometrial recovery.

This statement received 71 % agreement from the Extended Panel. Pregnancy has been reported in cancer survivors despite amenorrhea and levels of Follicle Stimulating hormone (FSH) suggestive of menopause (Ethics Committee of the American Society for Reproductive Medicine, 2005). Although international guidelines contraindicate the use of tamoxifen in pregnancy, it is not possible to draw definitive conclusions about the teratogenic risk following the use of this drug and each case of accidental exposure must be addressed individually (Buonomo et al., 2019). On these bases, POSITIVE study, adopted a prudential strategy of a three-month wash-out period before the search for pregnancy (Partridge et al., 2023). During these waiting period, the women should start folic acid supplementation that is recommended at least one month before conception (De-Regil et al., 2015). In women with elevated body mass index (BMI), 5 mg dosage of folic acid should be proposed (Denison et al., 2019).

Statement 4: During the 3-month washout period, active contraception is recommended with the use of condoms.

This statement received 61 % agreement from the Extended Panel. Statement 4 did not reach the minimum approval threshold and was

excluded. There was no univocal judgment on the use of the condom as a contraceptive method by the Extended panel: 55 % favored the use of condoms, 3 % favored the use of the contraceptive pill, while the remainder (42 %) did not express an opinion on the type of contraception to be used. Despite contraception is recommended during the 3 months wash out period, the POSITIVE trial did not specify the type of contraceptive strategy to be used (Partridge et al., 2023). Therefore, information should be provided on the relative effectiveness of available contraceptives (Schwarz et al., 2009). The rationale behind the use of condom proposed by the panel is to offer a low-cost and efficient contraceptive strategy avoiding sex hormone exposure. The panel choice was also consistent with World Health Organization guideline that contraindicates any hormonal contraception during BC treatment (World Health Organization, 2015). Indeed, several lines of evidence suggest that even the only progestin exposure could be detrimental for breast cancer (Briskin, 2013; Alviggi et al., 2017; Trabert et al., 2020). Alternatively, other contraceptive approaches for women with a history of BC could be suggested, such as intrauterine devices (IUDs). While copper IUD could be proposed as hormone-free method, the levonorgestrel-containing IUD could be opted for counteracting tamoxifen-induced endometrial changes without increasing the risk of BC recurrence (Mody et al., 2019; Dinger et al., 2011). However, the short-time frame, costs and the possible side effects during IUD insertions should be contemplated by the clinician.

3.3. Statements on fertility assessment

Statement 5: During the washout period, assessment of the couple's fertility is required.

Statement 6: The assessment of ovarian reserve, with the resumption of the menstrual cycle, is the most relevant exam to assess a woman's fertility. A spermiogram must be performed.

These statements received 81 % and 97 %. The most important fertility society recommends infertility assessment after 1 year of regular sexual intercourse (Infertility Workup for the Women's Health Specialist, 2019; ASRM, 2020). If the patient is over 35 years of age, evaluation after 6 months is recommended (American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee, 2014). More interventional approach in patients over 40 years and in those in whom clinical history suggests a possible impairment of reproductive function (American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee, 2014). Considering the narrow time window (24 months to carry a pregnancy to term) available to these patients, initial assessment of the couple's fertility during the three months of tamoxifen suspension would be desirable. Some members of the Extended Panel raised concerns about ovarian reserve assessment in the first 3 months of tamoxifen withdrawal for fear of possible ovarian reserve underestimation. Preliminary data shows that tamoxifen exposure does not influence AMH assessment after approximately 4 months of follow-up (Chung et al., 2013). Thus, an evaluation of ovarian reserve either at the resumption of a spontaneous cycle (that takes approximately 3 months) or at the end of 3-month period could be proposed.

The prompt evaluation of semen is strongly encouraged by the panel to better tailor ART approach for the couple optimizing the TTLB. At the same time, the three-month waiting period will allow for eventual andrological counselling and therapies.

Statement 7: Based on clinical judgment, the examination of tubal patency upon suspension of tamoxifen may be required.

This statement received 55 % agreement from the Extended Panel. Statement 7 did not reach the minimum approval threshold and was excluded. Although it was considered reasonable to perform an early assessment of tubal patency in these patients, most experts believe that the decision should be secondary to ovarian reserve, the woman's age, and semen analysis.

3.4. Statements on decision-making of reproductive planning

Statement 8: The narrow conception window (12–15 months) after the suspension of tamoxifen requires careful evaluation of strategies to achieve successful conception.

Statement 9: The most relevant factors for the decision-making of reproductive planning are age, ovarian reserve and tumor prognosis.

These statements received both 94 % agreement from the Extended Panel. In the POSITIVE study, almost three quarters of the women had at least one pregnancy, the majority of which (70.5 %) occurred within two years of enrolment (Partridge et al., 2023). More than 40 % of the women used assisted reproductive technology during the trial: this is probably due to the practice of using oocytes or embryos that were stored prior to gonadotoxic treatment to achieve pregnancy and quickly resume endocrine therapy (Waks and Partridge, 2016). Moreover, the percentage of women who became pregnant (53.6 % at 12 months) appears to be higher than the percentages reported among women of a similar age (regardless of breast cancer diagnosis) (American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee, 2014).

The patient's age plays a crucial role as a low rate of aneuploidies has been found between the ages of 26 and 30, with a predictable and steady increase until the age of 43, when the rate is about 85 % (Franasiak et al., 2014). Ata et al. (2012) reported that for every year of increase in female age, the euploidy rate decreased by 2.4 percentage points (Ata et al., 2012). The POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) group showed how the cumulative live births rate is influenced not only by quality (age of the woman) but also by quantity (number of oocytes) (Esteves et al., 2019, 2021a). Although ovarian reserve appears to have a limited impact on euploidy rates, it remains a key prognostic factor for having at least one euploid embryo available for transfer due to its impact on oocyte production (Reig et al., 2023; Esteves et al., 2022). The number of oocytes retrieved should be maximized to increase cumulative live birth rate (CLBR). The percentage of women with at least one euploid embryo increases as more oocytes are collected. Both antral follicle count (AFC) and anti-müllerian hormone (AMH) provide acceptable and equivalent accuracy in predicting oocyte production. Clinicians should adopt the biomarker that best reflects their clinical context. AMH and AFC are not able to predict clinical pregnancy in candidates patients for IVF under 40 years (Sahmay et al., 2012). Korsholm et al. (2018) associated high AMH values with higher pregnancy rates (Korsholm et al., 2018). However, the time to pregnancy reflected a large variability between similar AMH concentrations. Schumacher et al. (2018) reported that AMH appears to be a predictor of the risk of miscarriage: women with severely diminished ovarian reserve are at increased risk of miscarriage (Lyttle Schumacher et al., 2018). AMH and AFC, along with chronological age, can be used in decision-making of reproductive planning (Alviggi et al., 2009).

Finally, tumor prognosis is a crucial factor for reproductive planning. The Positive trial include ER positive women with different breast cancer staging (I, II, III cancer staging), thereby presenting different prognosis (Aldrees et al., 2021). In women with the worse prognosis (i.e. Stage III), reproductive planning should be offered, having as goal the achievement of pregnancy before the incidental relapse of the breast cancer tumor. In other word, these women required medical assisted approaches that could optimize the time to pregnancy (immediate ART treatment, PGT analysis of the embryos). Conversely, in women with best prognosis (i.e. Stage I) expectant management could be offered postponing more advanced and expensive ART procedures. In conclusion, decision-making of reproductive planning is a complex and multidisciplinary approach that should be tailored per each taking into account not only the reproductive potential expressed by ovarian reserve markers and chronological age, but also tumor prognosis expressed mainly by the anatomical staging of breast cancer tumor. In this holistic view, the financial aspect should be taken into account,

always choosing the most advantageous option for patients.

3.5. Statements on ovarian reserve evaluation

Statement 10: Ovarian reserve evaluation is one of the most important aspects to assess fertility and define possible treatments in women following therapy with tamoxifen.

Statement 11: The antral follicle count and dosage of Anti-Müllerian hormone are the main factors to evaluate reproductive potential, and in cancer patients both should be assessed for early identification of indications for assisted reproductive technology.

Statement 12: Serum FSH and estradiol levels in the early follicular phase can complete ovarian reserve evaluation.

These statements received 97 %, 94 % and 87 % agreement from the Extended Panel, respectively. Ovarian reserve is affected by age, genetics, and environmental factors (Lyttle Schumacher et al., 2018; Tal and Seifer, 2013, 2017). AMH, AFC, and FSH levels (in the first three days of the cycle) are the tools through which it is possible to estimate ovarian reserve. Several authors have hypothesized that AMH could be used to predict the last menstrual period and menopausal age (Broer et al., 2011; Freeman et al., 2012a, 2012b; Depmann et al., 2016; Dölleman et al., 2015; Aydogan and Mirkin, 2015). However, in the general population the estimate of last period remains difficult, and it is not possible to accurately know the age at menopause (Nelson et al., 2023; de Kat et al., 2021). Testing for AMH in young cancer patients both before and after treatment has become a useful tool to assess iatrogenic damage to the ovarian follicular reserve inflicted by gonadotoxic chemotherapy or pelvic irradiation and can aid in counseling (Anderson and Wallace, 2013). In particular women with BC pre-treatment AMH levels < 0.54 ng/ml are associated with significantly higher risk of post-treatment amenorrhea (Anderson et al., 2013).

AFC is the sum of follicles in both ovaries seen on ultrasound in the early follicular phase (day 2–4) of the menstrual cycle. Antral follicles are defined as those measuring 2–10 mm in the largest mean diameter in the two-dimensional plane (Broekmans et al., 2010). Compared to AMH, which is closely related to primordial and pre-antral follicles, AFC allows the measurement of antral follicles and therefore allows a more precise estimate of the ovarian response to OS. However, AFC tends to overestimate the number of FSH-sensitive follicles and oocytes recovered as it inevitably measures even atretic follicles of the same size (Anderson and Wallace, 2013; Broekmans et al., 2010; Fleming et al., 2015). Furthermore, AFC is limited by the variability between sonographers, technologies, and menstrual cycles (Broer et al., 2009). Low AFC values (3–4 follicles in both ovaries) are associated with ovarian response eventually during in vitro fertilization, but has poor predictability for pregnancy (Broekmans et al., 2006).

Early follicular phase FSH is an indirect assessment of ovarian reserve and is based on the inhibition of pituitary FSH secretion by ovarian factors (Toner et al., 1991; Scott et al., 1989; Muasher et al., 1988). However, FSH test has several important limitations: i) intercycle and intracycle variability; ii) it must be combined with estradiol (Scott et al., 1990; Kwee et al., 2004). Especially in women with reduced ovarian reserve, it is essential to relate estradiol to FSH. In fact, FSH levels can be falsely low in the presence of high estradiol values, even in the first days of the cycle. Despite its limitations, FSH is commonly used as an ovarian reserve test and elevated values have been associated with both poor ovarian response and failure to achieve pregnancy (Tal and Seifer, 2017). FSH values > 10 IU/l (10–20 IU/L) have a high specificity (45–100 %) in predicting poor response to OS, but low sensitivity (11–86 %) (Broekmans et al., 2006). In addition, with regards to the prediction of conception, the FSH test is still specific (50–100 %), but not very sensitive (3–65 %). Moreover, a single high baseline FSH value is not predictive of poor ovarian response to controlled OS (Roberts et al., 2005). For these reasons, the Extended Panel considered FSH assessment to be useful as a diagnostic supplement to AMH and AFC.

3.6. Statements on expectant management versus immediate treatment

Statement 13: In the absence of ascertained factors of infertility (male and female), the expectant management period of 2–4 months is subject to age and ovarian reserve.

Statement 14: In women over the age of 35, in the absence of proven male and female infertility factors, expectant management (2–4 months) is subordinated to the ovarian reserve.

These statements received 90 % and 94 % agreement from the Extended Panel, respectively. There is no data on how to manage the discontinuation of endocrine therapy, and particularly an expectant management period. POSITIVE trial reported that more than 40 % of patients used IVF to achieve pregnancy. However, these data were probably due to the practice of using cryopreserved oocytes or embryos banked prior to gonadotoxic treatment. Although the patient group in this survey does not fit into the canons of unexplained infertility (UI), some concepts can be adapted. Limited data are available on the comparison between expectant management and an interventional approach in patients with UI (Gunn and Bates, 2016). Expectant management in these patients is subordinated to patient's age and ovarian reserve and should never be considered in women > 40 years. It is possible to hypothesize that in patients with a narrow reproductive window it is equally important to evaluate the feasibility of expectant management. In 10–30 % of infertile couples, no etiology was identified (Gunn and Bates, 2016). In these patients, any treatment is empirical and there is no uniform protocol for clinical practice. Alternatives include expectant management, superovulation, and IVF. Most women seeking pregnancy after BC have postponed their pregnancy for various reasons and the greatest threat to their fertility is age. Pregnancy is often postponed due to lack of a stable partner or career or financial problems (Dolmans and Manavella, 2019). The age at which women attempt their first pregnancy has steadily increased in recent years. Buckett et al. (2019) have proposed some recommendations: i) in couples with good prognosis (based on age and duration of infertility) expectant management can be offered (Level 1 A); ii) IVF can be offered as an effective first line treatment in UI (Level 1B); IVF should be offered to couples with UI after 3 cycles of OS/intrauterine insemination (IUI) have failed (Level 1 A) (Buckett and Sierra, 2019). Hull et al. (1985) showed that with expectant management the cumulative 2-year pregnancy rate in young women was 72 % and decreased to 45 % in women over 35 years of age (Hull et al., 1985). While in young women expectant management seems to be acceptable, women with advanced age and reduced ovarian reserve deserve faster IVF treatment considering their reduced reproductive prognosis comparing with general IVF population (American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee, 2014; Esteves et al., 2019, 2022; Yang et al., 2020; Esteves et al., 2021b). In conclusion, the choice between expectant management and immediate recourse to IVF should be tailored on the basis of ovarian reserve and women age.

Statement 15: IUI insemination is not a recommended option for cancer patients during hormone therapy suspension.

This statement received 93 % agreement from the Extended Panel. Ainsworth et al. (2020) found that women aged ≥ 38 years have a predicted probability of viable birth below 0.05 when using oral medications or clomiphene plus gonadotropins for OS, regardless of inseminate motility (Ainsworth et al., 2020). Even with gonadotropins only and optimal inseminate motility, the viable birth rate does not exceed 10 % per cycle. The use of ovulation/superovulation and IUI is only recommended for women ≤ 37 years, while IVF is used directly for women of advanced reproductive age (Goldman et al., 2014). In addition, it must be considered that the higher pregnancy rates associated with gonadotropin use fall within the context of the known risk of multiple gestation (Gleicher et al., 2000). Goldman et al. (2014) compared pregnancy rates in women aged 38–42 years who were treated with 2 courses of ovarian hyperstimulation/IUI or who had immediate recourse to IVF, respectively. In older women with UI, pregnancy rates were higher in the IVF

group (Goldman et al., 2014). In the only RCT examining IUI alone versus expectant management, no significant difference was found in the CLBR after 6 months (Bhattacharya et al., 2008). Given the low success rates and non-applicability in older women, IUI should not be considered. Buckett et al. (2019) reported that natural cycle IUI does not offer any benefit over expected management and should not be offered in UI (Level 1 A) (Buckett and Sierra, 2019).

3.7. Statements on controlled ovarian stimulation protocols

Statement 16: *The addition of letrozole with a daily dose of 2.5 or 5 mg in patients with a history of hormone sensitive BC can be considered during OS, with administration of gonadotropins and GnRH antagonist protocol.*

This statement received 86 % agreement from the Extended Panel. To limit high hormone concentrations, letrozole has been adopted to reduce estrogen levels in women affected by hormone-sensitive cancers (Oktay et al., 2015). Letrozole (5 mg/day) is started on day 2 or 3 of the cycle and daily injections of recombinant FSH are added 2 days later. The starting dose of recombinant FSH ranges from 150 to 300 IU based on ovarian reserve, age, and BMI of patients, with possible dose modifications during the cycle. When the size of the dominant follicle has reached an average diameter of 13 mm, a gonadotropin releasing hormone (GnRH) antagonist (0.25 mg/day) is administered; this dose is continued until the trigger day. Oocyte maturation is triggered with human chorionic gonadotropin or 1 mg of leuprolide acetate. Letrozole is discontinued on the triggering day. This stimulation regimen produces results comparable to standard protocols associated with significantly lower E2 levels (Turan et al., 2018). In the early years after the introduction of aromatase inhibitors, concerns were raised about their potential impact on the resulting pregnancy. Indeed, in an animal study, letrozole was shown to be teratogenic when fetuses were exposed during organogenesis (Tiboni, 2004). However, clinical trials did not associate letrozole with birth abnormalities when used as an ovulation inducer. Tulandi et al. (2006) evaluated 911 infants born after induction of ovulation with letrozole or clomiphene for 5 days on days 3–7 of the cycle in a sterile population (Tulandi et al., 2006). The study found no differences in overall rates of fetal malformations or chromosomal abnormalities among infants of mothers who conceived after treatment with letrozole or clomiphene citrate (Tulandi et al., 2006). Although Goldrat et al. (2022) have shown that in women with hormone-sensitive breast cancer the risk of recurrence is comparable in patients stimulated with or without letrozole (Goldrat et al., 2022) In Italy the use of letrozole limited to breast cancer women candidates for oocytes cryopreservation (Alviggi et al., 2017).

3.8. Statements on in vitro fertilization

Statement 17: *In case of indication to in vitro fertilization it is advisable to calculate, based on the patient's age, the number of oocytes that gives the maximum probability of having at least one euploid blastocyst (see Poseidon) and proceed, where indicated, to strategies of oocyte accumulation.*

This statement received 84 % agreement from the Extended Panel. The POSEIDON group has introduced the ART calculator, which is able to calculate the minimum number of mature oocytes needed to obtain at least one euploid embryo for transfer (81–82). This can be used as an intermediate marker of successful outcomes in IVF/intracytoplasmic sperm injection cycles. The ART calculator has the main purpose of being a counseling tool for infertile couples who undertake an IVF pathway and who would like to gather information on their chances of success. However, this tool can be used in conjunction with clinical knowledge for treatment planning as well as to raise patient awareness on fertility preservation and the impact of female age on fertility. It is therefore possible to individualize treatment according to the characteristics of the patient, adapting the type of GnRH analogue, type of gonadotropin, and starting dose and regimen (Drakopoulos et al., 2018; Conforti et al., 2019a, 2019b; Alviggi et al., 2018; Cimadomo et al.,

2018; Vaiarelli et al., 2018). Double stimulation in the same ovarian cycle (Duo-Stim) approach is one of the most promising regimen, especially for the treatment of poor-prognosis patients (advanced maternal age and/or reduced ovarian response) and patients requiring fertility preservation for medical reasons (Vaiarelli et al., 2020). It combines two consecutive stimulations in the follicular and luteal phases of the same ovarian cycle, aimed to maximize the number of oocytes retrieved and embryos produced in the short timeframe. In the Extended Panel, some experts believe that this approach is applicable only in a setting of preimplantation genetic testing for aneuploidy (PGT-A) in order to avoid unnecessary repeated stimulations in patients with a hormone-sensitive tumor. According to other experts, this strategy should only be applied for pre-chemotherapy oocyte cryopreservation.

Statement 18: *In patients covered by this survey, in order to balance the effectiveness of the technique and cancer risk, it is appropriate to implant only single embryo at a time at the blastocyst stage.*

This statement received 87 % agreement from the Extended Panel. Elective single embryo transfer in women < 38 years of age resulted in a decrease in multiple gestation rates with no significant impact on clinical live birth rates (Mancuso et al., 2016). The American Society for Reproductive Medicine (ASRM) recommends: i) transfer of a euploid embryo should be limited to one, regardless of the patient's age; ii) patients < 35 years should be strongly encouraged receive a single embryo transfer, regardless of the embryo stage; iii) for patients between 35 and 37 years old, a single embryo transfer should be strongly considered (Practice Committee of the American Society for Reproductive Medicine and the Practice Committee for the Society for Assisted Reproductive Technologies, 2021). As for patients 38–42 years, which is the most frequent among patients looking for pregnancy after BC, the ASRM recommends that no more than 3 untested cleavage-stage embryos or 2 blastocysts should be transferred. However, it is important to underline that the transfer of more than one embryo in patients with a coexisting medical condition, for which a multiple pregnancy may increase the risk of significant morbidity, is not recommended. Considering the increased risk of preterm delivery and low birth weight in pregnancies after BC (Sun et al., 2018a), a single embryo transfer is desirable (Practice Committee of the American Society for Reproductive Medicine and the Practice Committee for the Society for Assisted Reproductive Technologies, 2021). Patients should be informed about these risks (Hartman and Eslick, 2016; Sun et al., 2018b; Lee et al., 2019; Schuurman et al., 2019; Lambertini et al., 2019). In donor-oocyte cycles, the age of the donor should be used to determine the appropriate number of embryos to transfer (Practice Committee of the American Society for Reproductive Medicine and the Practice Committee for the Society for Assisted Reproductive Technologies, 2021). Furthermore, single blastocyst stage transfer is associated with higher ongoing pregnancy rate and delivery rate comparing to single cleavage stage transfer (Li et al., 2021). Zacà et al. (2018) reported a higher CLBR in frozen transfer at the blastocyst stage compared to the conventional strategy of ET at the cleavage stage (Zacà et al., 2018).

Statement 19: *The execution of PGT-A can be considered based on the characteristics of the couple (e.g.: advanced maternal age, polyabortivity, severe male infertility).*

This statement received 68 % agreement from the Extended Panel. The value of PGT-A as a universal screening test for all IVF patients is yet to be determined (Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology, 2018). PGT-A does not appear to improve the “chances of having a baby” but does reduce the time to pregnancy and increase the ongoing pregnancy rate for embryo transfer in the subgroup of women aged 35–40 years who have had two or more embryos that could be biopsied. Furthermore, in women < 42 years transfer of a single euploid blastocyst resulted in similar pregnancy rates to transfer of 2 untested blastocysts dramatically reducing the risk of twins (Forman et al., 2013). The Canadian Fertility and Andrology Society Guidelines recommend: i) in infertility patients undergoing IVF with at least two blastocysts,

physicians may consider using PGT-A to improve the ongoing pregnancy or delivery rate per embryo transfer; ii) in patients aged 35–40 years undergoing IVF with at least two blastocysts, clinicians may consider the use of PGT-A to improve the ongoing pregnancy rate (OPR) per embryo transfer (Chan et al., 2021). ASRM stated that there was insufficient evidence to recommend the routine use of preimplantation genetic testing-aneuploidy in all infertile women (Practice Committee of the American Society for Reproductive Medicine and the Practice Committee for the Society for Assisted Reproductive Technology, 2021). However, in patients with a limited time window to get pregnant, it seems reasonable to use PGT-A, even if it cannot increase the efficacy.

Statement 20: Egg donation can be considered for women with low ovarian reserve or age > 40 years.

This statement received 84 % agreement from the Extended Panel. The ASRM recommends egg donation in women of advanced reproductive age or who have diminished ovarian reserve (Practice Committee of the American Society for Reproductive Medicine and the Practice Committee for the Society for Assisted Reproductive Technology, 2021). Despite having reached the approval threshold, the comments made by the Extended Panel mainly concerned the age limit. According to some experts, age should be considered only in relation to ovarian reserve, while for others the threshold should be moved beyond 41–42 years. Bercovich et al. (2022) reported that women over 43.5 years of age with fewer than four oocytes collected in the first IVF cycle should be offered egg donation as their live birth rate in subsequent cycles is negligible (Bercovich et al., 2022). The Board of the Society of Obstetricians and Gynaecologists of Canada stated that the only effective treatment for ovarian aging is oocyte donation: a woman with decreased ovarian reserve should be offered oocyte donation as an option because pregnancy rates associated with this treatment are significantly higher than those associated with controlled ovarian hyperstimulation or IVF with a woman's own eggs (II-2B) (Liu and Case, 2017). Hourvitz et al. (2009) showed that for women ≥ 42 , live birth rates drop to below 5 %. Serour et al. (2010) reported for women aged 40–42 a live birth rate of 7.4 % and only 1.1 % for women ≥ 43 (Hourvitz et al., 2009; Serour et al., 2010).

Extended panel underlined that in the case of endometrial preparation for embryo transfer, where possible, the spontaneous cycle should be preferred over hormone replacement therapy.

4. Discussion

This Delphi consensus, with 18 endorsed statements, provides a real-world clinical perspective on how to approach the key steps of fertility assessment and management of TTLB in women with hormone-sensitive breast cancer. The fertility experts participating in the consensus were from a diverse range of global regions of Italy, including different fertility center from Northern, middle and Southern of Italy, reflecting the quality of healthcare and different approaches to infertility treatment. The consensus allowed to include a wider list of topics than what would have been typically considered in a systematic review or in a guideline, which are usually based on strict methodology, limiting the scope of the investigation.

As far as we know, this is the first consensus specifically focused on fertility evaluation and management of time to pregnancy and ART in breast cancer women. The Delphi methodology represents a strength of this work, which benefited also from the knowledge of an Italian panel of highly respected experts in the field. However, there are a few limitations; firstly, the consensus does not represent an exhaustive list of statements, and the statements only represent the collective opinion of the experts included. Not all statements reached 100 % agreement, with some statements reaching consensus even though some participants disagreed with them. Moreover, the statements have been conceived considering the evidence from literature, which is quite heterogeneous and limited by the small sample size of the studies performed so far. Although these statements represent the point of view of the experts, an

individualized management with regards to treatment options should always be planned in relation to patients' needs and clinical features. Our consensus highlights the importance of proper fertility assessment and counselling, especially in relation to women's age and the inherent reduction of fertility with ageing.

Our survey emphasizes that the management of patients with such a short reproductive window must be carried out by highly specialized healthcare professionals. Moreover, the interplay between oncologist and gynecologist is crucial to optimize management. This work should also prompt IVF centres to facilitate access to these patients by reducing waiting times.

The POSITIVE study provided data on the safety of discontinuing endocrine therapy to attempt pregnancy in women with previous hormone receptor-positive early breast cancer. MORE BREAKS study seeks to provide guidance to clinicians on how to optimize time to pregnancy in breast cancer patients in such a limited period.

5. Conclusions

This Delphi consensus provides 18 statements by expert opinions on specific approaches to manage a specific time window and define the best strategies to reduce the TTLB in breast cancer patients during the discontinuation of endocrine therapy.

An appropriate management of fertility in such a narrow time is crucial to optimize childbearing desire in BC women avoiding useless examination and time-consuming procedures. Of course, the referral to center of excellence in IVF and the possibility to offer a multidisciplinary approach is crucial for the proper management of these women. Finally, we hope that this Consensus will encourage further investigation into optimizing reproductive outcomes in breast cancer patients and facilitate their access to ART.

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