



Review

Temporary ovarian suppression during chemotherapy to preserve ovarian function and fertility in breast cancer patients: A GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology



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Abstract The development of premature ovarian failure and subsequent infertility are possible consequences of chemotherapy use in pre-menopausal women with early-stage breast cancer. Among the available strategies for fertility preservation, pharmacological protection

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of the ovaries using luteinising hormone-releasing hormone analogues (LHRHa) during chemotherapy has the potential to restore ovarian function and fertility after anticancer treatments; however, the possible efficacy and clinical application of this strategy has been highly debated in the last years.

Following the availability of new data on this controversial topic, the Panel of the Italian Association of Medical Oncology (AIOM) Clinical Practice Guideline on fertility preservation in cancer patients decided to apply the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology around the relevant and current question on the clinical utility of temporary ovarian suppression with LHRHa during chemotherapy as a strategy to preserve ovarian function and fertility in breast cancer patients. To answer this question, preservation of ovarian function and fertility were judged as critical outcomes for the decision-making. Three possible outcomes of harm were identified: LHRHa-associated toxicities, potential antagonism between concurrent LHRHa and chemotherapy, and lack of the prognostic impact of chemotherapy-induced premature ovarian failure. According to the GRADE evaluation conducted, the result was a strong positive recommendation in favour of using this option to preserve ovarian function and fertility in breast cancer patients. The present manuscript aims to update and summarise the evidence for the use of this strategy in light of the new data published up to January 2016, according to the GRADE process.

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1. Introduction

Premature ovarian failure (POF) represents a possible side effect of chemotherapy administration in premenopausal women diagnosed with early-stage breast cancer [1]. POF is associated with several health-related negative consequences including infertility [2]. Fertility concerns are prevalent issues affecting young patients and might impact their choice and adherence to treatment and subsequent disease outcomes [3].

As recommended by major international guidelines, clinicians should discuss as early as possible with their young patients at risk of treatment-related POF the potential impact of anticancer therapies on ovarian function and fertility, and help with fertility preservation decisions [4–6]. Among the available strategies for fertility preservation, embryo/oocyte cryopreservation are considered standard procedures; however, these techniques cannot protect the ovaries from the gonadotoxic potential of anticancer therapies [4–6]. The use of temporary ovarian suppression with luteinising hormone-releasing hormone analogues (LHRHa) during chemotherapy is a widely available option with the potential to restore ovarian function after treatment; however, the possible efficacy and clinical application of this strategy has been highly debated in the last years [7].

Since 2012, the Italian Association of Medical Oncology (AIOM) has been publishing a practice guideline on fertility preservation for cancer patients (www.aiom.it). The guideline was developed to help all the physicians involved in the oncofertility counselling of young cancer patients who are interested in ovarian function/fertility preservation at the time of diagnosis (i.e. medical oncologist, surgical oncologists, radiation oncologists, obstetricians, gynaecologists, fertility

specialists and reproductive endocrinologists). It is yearly updated and controversial issues are investigated with the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) process [8]. The present manuscript aims to update and summarise the evidence for the use of temporary ovarian suppression with LHRHa during chemotherapy in preventing treatment-related POF and fertility in breast cancer patients in light of the new data published up to January 2016, according to the GRADE methodology.

2. Materials and methods

2.1. The AIOM Clinical Practice Guideline Panel and the question evaluated according to the GRADE methodology

The Panel of the AIOM Clinical Practice Guideline on fertility preservation in cancer patients includes academic and community practitioners in the field of medical oncology, obstetrics–gynaecology, reproductive medicine and methodologists.

Every year, the updated evidence-based guideline is sent to external reviewers before the final publication on the AIOM website (www.aiom.it). The external reviewers for the AIOM Clinical Practice Guideline on fertility preservation in cancer patients are two physicians, chosen by the AIOM deputy members, from each of the following scientific organisations: AIOM, Italian Society of Andrology, Italian Society of Gynecology and Obstetrics and Italian Society of Gynecology Oncology.

In the updated 2016 version of the AIOM guideline, the Panel decided to face a relevant and current question with the GRADE methodology: ‘Should temporary ovarian suppression with LHRHa during chemotherapy be

recommended to all pre-menopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation?"

To answer this question, preservation of ovarian function and fertility were judged as critical outcomes for the decision-making. Preservation of ovarian function was defined as proportion of patients with resumed menstrual periods at the longer time-point available after the end of chemotherapy, irrespectively of the definition of POF used in the studies; preservation of fertility was defined as proportion of patients achieving pregnancy after treatments.

The Panel identified three possible outcomes of harm: LHRHa-associated toxicities, potential antagonism between concurrent LHRHa and chemotherapy and lack of the prognostic impact of chemotherapy-induced POF. However, the Panel did not find the risk of these potential harms to be significant (as discussed in the following section).

2.2. Search strategy and selection of the evidence

A systematic search of the literature published on the topic with no date restriction up to January 31st, 2016 was conducted using PubMed, Embase and the Cochrane Library. The search strategy was built by inputting the keywords related to chemotherapy, breast cancer, luteinising hormone-releasing hormone and ovarian function in adult. To confirm retrieval of all possible pertinent trials, a cross-referencing from relevant studies and review articles on the topic was conducted. Titles and abstracts of the identified studies were independently evaluated by two reviewers (M.L. and L.D.M.); the Panel reviewed the search results to apply the eligibility criteria to both sets of search outcomes.

The included studies had to be randomised controlled trials designed to evaluate the efficacy of temporary ovarian suppression with LHRHa during chemotherapy in preventing treatment-related POF and/or preserve fertility in early-stage pre-menopausal breast cancer patients who were candidates to (neo)adjuvant chemotherapy. The following studies were excluded: retrospective studies, prospective non-randomised studies, studies published in abstract form at conferences but never published and ongoing studies which were not presented yet at conferences nor published nor available online at the time of the literature search. No language restriction was applied. When studies reported more than two treatment arms, we considered only those for the comparison of interest. For each eligible study, information on study design, characteristics of patients enrolled and treatments received as well as study results were collected.

2.3. Quality evaluation of the evidence

GRADE requires an evaluation of the quality of evidence for each considered outcome based on five specific

domains: study limitations, inconsistency of results, indirectness of the evidence, imprecision and publication bias [8]. Evidence from randomised controlled studies starts from high quality; however, the presence of any of the above limitations can downgrade the overall quality of the evidence. According to the design of the study and the presence of these factors, the quality of the evidence for each outcome can be judged as high, moderate, low or very low [8]. The development of specific recommendations is based on the overall rating of confidence (i.e. quality of the evidence) in estimates of effect for each important or critical outcome [8].

A balance between desirable and undesirable consequences of the alternative management options, the quality of the supporting evidence, estimates of values and preferences, and resource use were the information used by the Panel to make the recommendation (positive or negative, weak or strong).

Two reviewers (M.C. and I.M.) assessed trials according to the predefined quality criteria and any disagreement was solved in a consensus meeting within the Panel.

The appraisal of guidelines, research and evaluation (AGREE) II checklist was applied to guide the reporting of the present recommendation [9].

3. Results

The search strategy returned 727 records: 713 were excluded because not relevant for the purpose of the present analysis, leaving 14 potentially eligible records (Fig. 1) [10–23]. Once searched for the full-texts, two studies were excluded because they were presented only as abstract [20,22]. When more than one publication was available for a single study, results were extracted from the most updated. One study [19] represented an update of a previously published trial [13], leaving 11 different studies (12 records) to be included [10–19,21,23].

In the included studies, breast cancer patients who were candidates to (neo)adjuvant chemotherapy were randomly allocated to receive cytotoxic therapy with or without concurrent LHRHa. These studies showed differences in several characteristics: sample size, length of follow-up, definition/timing of the primary end-point (i.e. POF), age of patients at study entry, type of LHRHa administered, chemotherapy regimens and cycles of treatment, and use of endocrine therapy (Table 1).

3.1. Outcome of benefit: preservation of ovarian function

All but one study [18] reported number of patients with regular menses after the end of chemotherapy. The following time-point of evaluation for resumption of menstrual activity were available: 6 months [12,17], 8 months [10], 12 months [15,16,21,23], 24 months [14], 36 months [11] and 5 years [19].

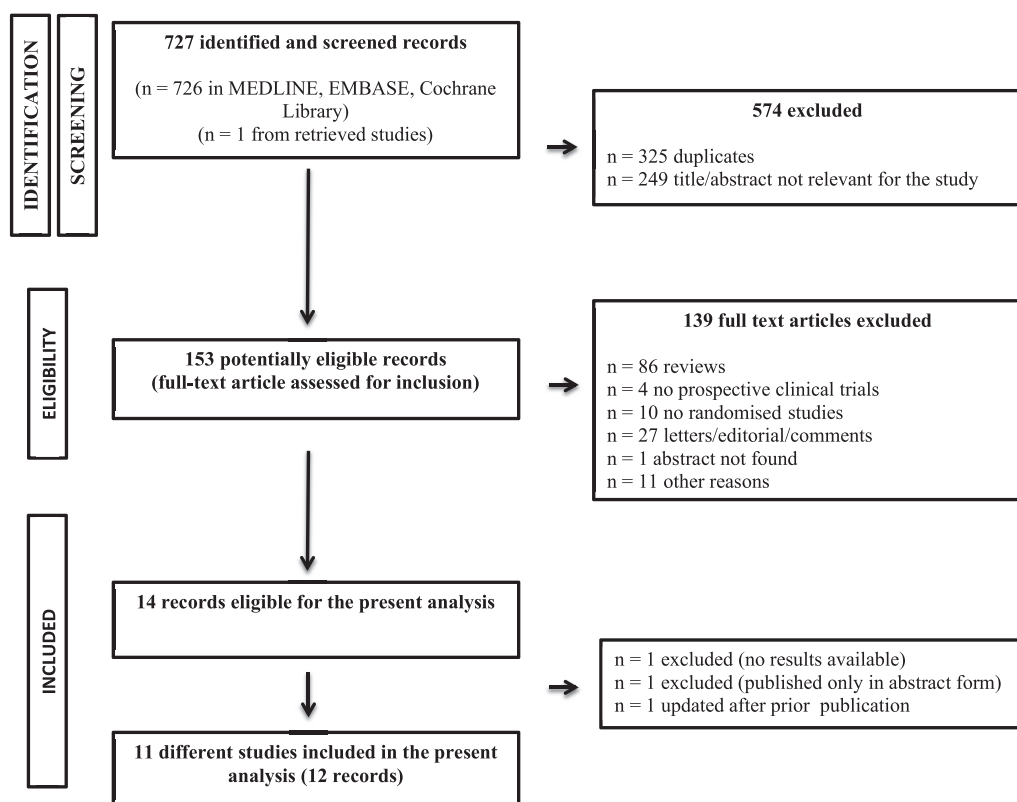


Fig. 1. The PRISMA flow chart summarising the process for the identification of the eligible studies.

Table 1

Characteristics of the randomised studies included in the analysis.

Author	Year	Definition of POF	Timing of POF evaluation (months)	Median age (years)	Type of LHRHa used	Type of chemotherapy	Cycles of chemotherapy (number)
Li M <i>et al.</i> [23]	2008	No resumption of menses	12	NR	Goserelin	AC or AC → T	4
Badawy <i>et al.</i> [10]	2009	No resumption of menses and ovulation	8	29–30	Goserelin	FAC	6
Sverrisdottir <i>et al.</i> [11]	2009	No resumption of menses	36	45–46	Goserelin	CMF	6
Gerber <i>et al.</i> [12]	2011	No resumption of two consecutive menstrual periods	6	35–38	Goserelin	FEC → T or EC → T or FEC or FAC or TAC or FEC → GEM or EC → TX	6–8
Sun <i>et al.</i> [21]	2011	No resumption of menses	12	32–33	Goserelin	NR	NR
Munster <i>et al.</i> [14]	2012	No resumption of menses	12	38–39	Triptorelin	AC or AC → P or FEC or FAC	4–8
Elgindy <i>et al.</i> [15]	2013	No resumption of menses	12	32–33	Triptorelin	FAC	6
Song <i>et al.</i> [16]	2013	Postmenopausal levels of FSH and E2 in the absence of menstrual activity	12	40–42	Leuprolide	AC or AC → T	4–6
Karimi-Zarchi <i>et al.</i> [17]	2014	No resumption of menses	6	37	Diphereline	TAC	NR
Del Mastro <i>et al.</i> [13]	2011	No resumption of menses and postmenopausal levels of FSH and E2	12	39	Triptorelin	CMF or E → CMF or EP → CMF or ET → CMF or AC or EC or FEC or AC → T or EC → T or EC → P or FEC → P or FEC → T or ET	4–8
Lambertini <i>et al.</i> [19]	2015						
Moore <i>et al.</i> [18]	2015	Amenorrhoea for the prior 6 months and postmenopausal levels of FSH	24	37–38	Goserelin	AC or CAF or TAC or CEF or AC → T or CMF	NR

Abbreviations: POF, premature ovarian failure; LHRHa, luteinising hormone-releasing hormone analogues; FSH, follicle stimulating hormone; E2, oestradiol; A, doxorubicin; C, cyclophosphamide; →, followed; T, docetaxel; F, 5-fluorouracil; M, methotrexate; E, epirubicin; GEM, gemcitabine; X, capecitabine; P, paclitaxel; NR, not reported.

Except three studies [12,14,15], for the other trials temporary ovarian suppression with LHRHa during chemotherapy showed to have a protective effect, with a variable degree of benefit among the different studies ranging from a risk ratio (RR) of 1.09 [19] to a RR of 3.34 [11] (Supplemental Table A.1).

The quality assessment of the studies reporting patients with regular menses after the end of chemotherapy is summarised in Supplemental Table A.1. The studies showing a protective effect included a larger number of patients and had an overall higher quality of evidence than those reporting no protective effect.

3.2. Outcome of benefit: preservation of fertility

Five studies reported number of patients achieving pregnancy after breast cancer treatment [12,14,15,18,19]. A total of 32 patients achieved pregnancy with the use of temporary ovarian suppression with LHRHa during chemotherapy as compared to 18 treated with chemotherapy alone. Two studies reported a positive effect for the use of this strategy [18,19], while three reported no effect [12,14,15] (Supplemental Table A.2).

The quality assessment of the studies reporting patients achieving pregnancy after the end of chemotherapy is summarised in Supplemental Table A.2. The two studies reporting a positive effect appeared to be the most reliable, being the two largest studies and those with the longest follow-up.

3.3. Overall quality of the evidence

GRADE suggests considering as overall quality the lowest level of critical outcomes quality [8].

The overall quality of evidence was rated as moderate (Table 2). The studies were heterogeneous for several characteristics, and most of them had inadequate sample size with consequent problems of inaccuracy of the estimate. For some studies, the possible risks of bias could not be assessed for lack of information; moreover, one of the larger studies available [18] had intrinsic methodological issues.

3.4. Benefits and harms, and final recommendation

The overall benefit of temporary ovarian suppression with LHRHa during chemotherapy in terms of preservation of ovarian function was considered equal to approximately a 50% reduced risk of developing treatment-induced POF, with the majority of the studies reporting a protective effect of this strategy. The real impact of temporary ovarian suppression with LHRHa during chemotherapy on the possibility of subsequent pregnancies was more controversial; however, recent data from the two largest randomised studies suggested a potential role of this option also as a fertility preservation strategy.

Regarding the possible outcomes of harm with the use of this technique, the Panel did not find the risk of these potential harms to be significant (as discussed in the following section).

Taking into account all these issues, the Panel voted the benefit/risk balance of the strategy as positive; four out of 5 members voted the strength of the recommendation as strong, and one as weak.

Hence, the following recommendation was released by the Panel: ‘Temporary ovarian suppression with LHRHa during chemotherapy should be recommended to all pre-menopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation’ (Table 2).

However, the Panel acknowledged that some important issues need to be further investigated: mechanisms of action, long-term efficacy and safety outcomes from the majority of the studies, final results of the ovarian protection trial in premenopausal breast cancer patients (OPTION) study [20], and fertility outcomes of patients who undergo cryopreservation strategies followed by temporary ovarian suppression with LHRHa during chemotherapy as compared to those of patients who undergo the two strategies alone.

All the external reviewers for the AIOM Clinical Practice Guideline on fertility preservation in cancer patients approved the current recommendation.

4. Discussion

In this manuscript, we summarised the GRADE evaluation conducted by the Panel of the AIOM Clinical Practice Guideline on fertility preservation in cancer patients around the question on the clinical utility of temporary ovarian suppression with LHRHa during chemotherapy as a strategy to preserve ovarian function and fertility in women with breast cancer. The result was a strong positive recommendation in favour of the use of this strategy in all patients undergoing chemotherapy who are interested in preserving ovarian function and/or fertility.

In 2013, the American Society of Clinical Oncology and European Society for Medical Oncology Guidelines on fertility preservation in cancer patients did not recommend the use of temporary ovarian suppression with LHRHa as a reliable strategy to preserve ovarian function and fertility (Table 3) [4,5]. Nevertheless, over the last years, new important data in this field consisting in two large randomised studies have become available for consideration [24]. In the prevention of early menopause study—Southwest oncology group (POEMS-SWOG) S0230 study (including 218 patients with endocrine-insensitive breast cancer), temporary ovarian suppression with LHRHa was associated with a significant reduction in the risk of treatment-related POF (8% versus 22%; odds ratio [OR]

Table 2

Summary of GRADE evaluation by the Italian Association of Medical Oncology.

Question: Should temporary ovarian suppression with LHRHa during chemotherapy be recommended to all pre-menopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation?

Recommendation: Temporary ovarian suppression with LHRHa during chemotherapy should be recommended to all pre-menopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation.

Strength of the recommendation: positive—strong

Motivation/comments on the benefit/risk balance:

The overall benefit of temporary ovarian suppression with LHRHa during chemotherapy in terms of preservation of ovarian function was considered equal to approximately 50% reduced risk of developing treatment-induced POF. Specifically, among the ten studies included in the analysis of this outcome, seven reported positive results on the possible protective role of this strategy (i.e. studies with larger number of patients and overall higher quality of evidence) while three showed no effect.

The real impact of temporary ovarian suppression with LHRHa during chemotherapy on the possibility of achieving subsequent pregnancies is more controversial; however, recent data suggest a potential role of this option also as a fertility preservation strategy. Five studies described patients achieving post-treatment pregnancies: two reported a greater number of pregnancies with the use of LHRHa and three reported no difference. However, the two studies reporting positive results appeared to be the most reliable: these are the two largest studies available, and with the longest follow-up.

No specific outcome of harm was considered by the Panel of critical importance. The possible harms of the treatment (i.e. LHRHa during chemotherapy) are known (e.g. hot flashes, sweating, headache, vaginal dryness and thromboembolic events) and can be considered clinically small in relation to the expected benefit, taking also into account the short duration of treatment and the concurrent administration of chemotherapy. Anyhow, the risks associated with the treatment were not reported in the majority of the studies.

Voting of the strength of the recommendation				Voting of the benefit/risk balance		
Positive—strong	Positive—weak	Negative—strong	Negative—weak	Favourable	Uncertain	Unfavourable
4	1			5	0	0

Implications for future research:

Some important issues need to be further investigated:

- the mechanisms of action by which temporary ovarian suppression with LHRHa reduces the gonadotoxicity of chemotherapy have not been completely elucidated yet;
- there is paucity of data available on long-term efficacy and safety outcomes of patients enrolled in the majority of the randomised studies that evaluated the efficacy of temporary ovarian suppression with LHRHa during chemotherapy as a strategy to preserve ovarian function and/or fertility; in particular, no studies have reported so far the age at menopause also in patients who have had a recovery of menstrual function after chemotherapy;
- the results of a large randomised trial (i.e. the OPTION study) has not become available yet: these results are important to clarify the role of temporary ovarian suppression with LHRHa during chemotherapy as a strategy to preserve ovarian function and/or fertility;
- no data are available on the fertility outcomes of patients undergoing temporary ovarian suppression with LHRHa during chemotherapy in combination with embryo/oocyte cryopreservation, as compared to those of patients who undergo the two strategies alone.

Quality of evidence

The overall quality of evidence was rated as moderate for the following reasons: most of the studies evaluated had inadequate sample size with consequent problems of inaccuracy of the estimate. The POEMS-SWOG S0230, one of the largest studies investigating the efficacy of temporary ovarian suppression with LHRHa, has intrinsic methodological issues due to an early interruption of patients' enrolment. In addition, there is lack of information to assess the possible risks of bias for some of the studies (especially to evaluate allocation concealment).

The studies were heterogeneous for several aspects: sample size, length of follow-up, definition/timing of the primary end-point (i.e. POF), age of patients at study entry, type of LHRHa administered, chemotherapy regimens and cycles of treatment, and use of endocrine therapy

Overall quality of evidence: moderate

Abbreviations: GRADE, Grades of Recommendation, Assessment, Development and Evaluation; LHRHa, luteinising hormone-releasing hormone analogues; POF, premature ovarian failure.

0.30; 95% confidence intervals [CI], 0.09–0.97) and an increased number of patients with pregnancies (22 versus 12; OR 2.45; 95% CI, 1.09–5.51) [18]. After the publication of these results, the 2015 St. Gallen International Expert Consensus Panel and the National Comprehensive Cancer Network (NCCN) Guidelines were updated to acknowledge the role of this strategy in preventing chemotherapy-induced POF of hormone receptor-negative breast cancer patients (Table 3) [25,26]. Even more recently, the prevention of menopause induced by chemotherapy: a study in early breast cancer patients—gruppo Italiano mammella 6

(PROMISE-GIM6) study (including 281 breast cancer patients, 80% with hormone receptor-positive disease) reported long-term follow-up data [19]. The study showed a significant protective effect with the use of this strategy in preserving ovarian function at 1 year after the end of chemotherapy (incidence of treatment-related POF: 9% versus 26%; OR 0.28; 95% CI, 0.14–0.59) [13] but also at long-term follow-up (5-year cumulative incidence estimate of menstrual resumption: 72.6% versus 64.0%; age-adjusted hazard ratio [HR] 1.48; 95% CI, 1.12–1.95) [19]. Although not significant, more patients treated with LHRHa during chemotherapy

Table 3

Current guidelines on the use of temporary ovarian suppression with LHRHa during chemotherapy in preventing treatment-related premature ovarian failure and fertility in breast cancer patients.

Guidelines	Year	Recommendations
ASCO [4]	2013	Insufficient evidence regarding the effectiveness of LHRHa and other means of ovarian suppression in fertility preservation. LHRHa should not be relied upon as a fertility preservation method.
ESMO [5]	2013	The use of LHRHa concomitantly with chemotherapy should not be regarded as a reliable means of preserving fertility. Data on long-term ovarian function and pregnancy rates are warranted.
St. Gallen [25]	2015	LHRHa therapy during chemotherapy proved effective to protect against premature ovarian failure and preserve fertility in young women undergoing chemotherapy. Hence, the Panel strongly supports the use of LHRHa during chemotherapy for hormone receptor-negative disease to preserve ovarian function and fertility.
NCCN [26]	2016	Ovarian suppression with LHRHa administered during adjuvant chemotherapy in pre-menopausal women with hormone receptor-negative disease may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhoea.
BCY2 [6]	2016	The most recent data suggested a protective ovarian effect of LHRHa in both patients with hormone receptor-positive and -negative disease with no signal for harm from a breast cancer recurrence standpoint. The BCY2 Panel therefore agreed this strategy can be discussed with patients interested in potentially preserving fertility and/or ovarian function.
AIOM	2016	Temporary ovarian suppression with LHRHa during chemotherapy should be recommended to all pre-menopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation.

Abbreviations: LHRHa, luteinising hormone-releasing hormone analogues; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; BCY2, International Consensus Conference for Breast Cancer in Young Women; AIOM, Italian Association of Medical Oncology.

achieved a pregnancy (8 versus 3; HR 2.40; 95% CI, 0.62–9.22) [19]. A recent meta-analysis including 12 randomised studies, confirmed the efficacy of this strategy in breast cancer patients [27]. The use of LHRHa during chemotherapy was associated with a significant reduction in the risk of treatment-induced POF (OR 0.36; 95% CI, 0.23–0.57) and a significant higher number of patients with subsequent pregnancies (33 versus 19 women; OR 1.83; 95% CI, 1.02–3.28) [27]. Following the publication of these results, the Panel of the International Consensus Conference for Breast Cancer in Young Women (BCY2) has recently released updated recommendations suggesting that this strategy can be discussed with patients interested in potentially preserving fertility and/or ovarian function (Table 3) [6].

The Panel of the AIOM Clinical Practice Guideline applied the GRADE methodology to update the 2016 recommendations on the role of temporary ovarian suppression with LHRHa during chemotherapy in breast cancer patients. The Panel considered preservation of ovarian function in terms of menstrual resumption after chemotherapy as outcome of critical importance. The overall benefit of this strategy was considered equal to approximately 50% reduced risk of developing long-term treatment-induced amenorrhoea, as shown by pooling together the results of all the randomised studies reporting this outcome (OR 0.55; 95% CI, 0.41–0.73) [27]. The second outcome of benefit considered of critical importance was preservation of fertility. Although, the real impact of temporary ovarian suppression with LHRHa during chemotherapy on the possibility of subsequent pregnancies was more controversial, recent data coming from the POEMS-SWOG S0230 and the PROMISE-GIM6 studies suggested a potential role of this option also as a fertility

preservation strategy. Although the absolute numbers remain low, by pooling the results of the five studies reporting this outcome, an 83% higher chance of subsequent pregnancies (OR 1.83; 95% CI, 1.02–3.28) in patients who received LHRHa concurrently with chemotherapy was observed [27].

Three possible outcomes of harm were identified: LHRHa-associated toxicities, potential antagonism between concurrent LHRHa and chemotherapy, and lack of the prognostic impact of chemotherapy-induced POF. However, the Panel did not find the risk of these potential harms to be significant. No significant increase in the occurrence of grade 3 or 4 LHRHa-associated toxicities (e.g. hot flashes, sweating, headache, vaginal dryness, and thromboembolic events) has been reported in the studies with concurrent administration of LHRHa and chemotherapy [13,18]. The safety concern on the potential antagonism between LHRHa and chemotherapy has been recently dispelled by the excellent survival data shown in patients enrolled in the Tamoxifen and exemestane trial (TEXT) who received chemotherapy with concurrent ovarian suppression [28]. In the POEMS-SWOG S0230 study, women in the LHRHa group showed a significant improvement in disease-free survival (DFS; HR 0.49; 95% CI, 0.24–0.97) [18]. No difference in DFS was observed in the PROMISE-GIM6 study among treatment arms at more than 7 years of median follow-up (HR 1.17; 95% CI, 0.72–1.92) [19]. Moreover, no apparent negative consequence on prognosis was shown between patients receiving chemotherapy concurrently with LHRHa and those receiving chemotherapy alone when pooling together the data of the three randomised trials on this topic with available DFS data (HR 1.00; 95% CI, 0.49–2.04) [27]. Finally, although still controversial,

chemotherapy-induced amenorrhoea seems to be associated with improved survival outcomes, especially in women with endocrine-sensitive breast cancer [29]. However, as recently shown in the Suppression of Ovarian Function Suppression of Ovarian Function Trial (SOFT), the safety concern on the lack of the occurrence of chemotherapy-induced amenorrhoea in this patient population can be overcome by re-administering LHRHa at the time of ovarian function recovery as part of adjuvant endocrine treatment [30].

Despite supporting the use of temporary ovarian suppression with LHRHa during chemotherapy, the Panel acknowledged that several issues have not yet been fully elucidated and require further investigations: mechanisms of its protective effect, paucity of data available on long-term efficacy and safety outcomes in the majority of the randomised studies and unavailability of the results of the large randomised OPTION trial [20]. Moreover, although not mutually exclusive, no data are available on the fertility outcomes of patients receiving LHRHa during chemotherapy after prior use of cryopreservation strategies as compared to those of women who undergo the two strategies alone.

Finally, the Panel acknowledged that all young cancer survivors should have access to and potential coverage for ovarian function and fertility services. The cost of 6 months of treatment with LHRHa during (neo) adjuvant breast cancer chemotherapy corresponds to approximately 1000 Euros for each patient. Over the past months, specific efforts were made by the AIOM society to have the recognition of the coverage for this procedure by the Italian Ministry of Health. The reimbursement of the 6-month treatment with LHRHa during chemotherapy to preserve ovarian function and fertility has been recently granted by the Italian Ministry of Health for all breast cancer patients irrespective of the hormone receptor status of their disease.

In conclusion, the Panel of the 2016 AIOM Clinical Practice Guideline on fertility preservation in cancer patients has acknowledged the role of temporary ovarian suppression with LHRHa during chemotherapy as a reliable strategy to potentially increase the likelihood of resuming menses and becoming pregnant after the end of chemotherapy. According to the GRADE evaluation conducted, this strategy should be recommended to all pre-menopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation. Final results of the MOMMY study, an ongoing individual patient data meta-analysis in breast cancer patients (PROSPERO registration number: CRD42014015638) [7], are awaited to corroborate this recommendation.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejca.2016.10.034>.

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