

Safety of fertility preservation techniques before and after anticancer treatments in young women with breast cancer: a systematic review and meta-analysis

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STUDY QUESTION: Is it safe to perform controlled ovarian stimulation (COS) for fertility preservation before starting anticancer therapies or ART after treatments in young breast cancer patients?

SUMMARY ANSWER: Performing COS before, or ART following anticancer treatment in young women with breast cancer does not seem to be associated with detrimental prognostic effect in terms of breast cancer recurrence, mortality or event-free survival (EFS).

WHAT IS KNOWN ALREADY: COS for oocyte/embryo cryopreservation before starting chemotherapy is standard of care for young women with breast cancer wishing to preserve fertility. However, some oncologists remain concerned on the safety of COS, particularly in patients with hormone-sensitive tumors, even when associated with aromatase inhibitors. Moreover, limited evidence exists on the safety of ART in breast cancer survivors for achieving pregnancy after the completion of anticancer treatments.

STUDY DESIGN, SIZE, DURATION: The present systematic review and meta-analysis was carried out by three blinded investigators using the keywords 'breast cancer' and 'fertility preservation'; keywords were combined with Boolean operators. Eligible studies were identified by a systematic literature search of Medline, Web of Science, Embase and Cochrane library with no language or date restriction up to 30 June 2021.

PARTICIPANTS/MATERIALS, SETTING, METHODS: To be included in this meta-analysis, eligible studies had to be case-control or cohort studies comparing survival outcomes of women who underwent COS or ART before or after breast cancer treatments compared to breast cancer patients not exposed to these strategies. Survival outcomes of interest were cancer recurrence rate, relapse rate, overall survival and number of deaths. Adjusted relative risk (RR) and hazard ratio (HR) with 95% CI were extracted. When the number of events for each group were available but the above measures were not reported, HRs were estimated using the Watkins and Bennett method. We excluded case reports or case series with <10 patients and studies without a control group of breast cancer patients who did not pursue COS or ART. Quality of data and risk of bias were assessed using the Newcastle-Ottawa Assessment Scale.

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MAIN RESULTS AND THE ROLE OF CHANCE: A total of 1835 records were retrieved. After excluding ineligible publications, 15 studies were finally included in the present meta-analysis (n=4643). Among them, 11 reported the outcomes of breast cancer patients who underwent COS for fertility preservation before starting chemotherapy, and 4 the safety of ART following anticancer treatment completion. Compared to women who did not receive fertility preservation at diagnosis (n=2386), those who underwent COS (n=1594) had reduced risk of recurrence (RR 0.58, 95% CI 0.46–0.73) and mortality (RR 0.54, 95% CI 0.38–0.76). No detrimental effect of COS on EFS was observed (HR 0.76, 95% CI 0.55–1.06). A similar trend of better outcomes in terms of EFS was observed in women with hormone-receptor-positive disease who underwent COS (HR 0.36, 95% CI 0.20–0.65). A reduced risk of recurrence was also observed in patients undergoing COS before neoadjuvant chemotherapy (RR 0.22, 95% CI 0.06–0.80). Compared to women not exposed to ART following completion of anticancer treatments (n=540), those exposed to ART (n=123) showed a tendency for better outcomes in terms of recurrence ratio (RR 0.34, 95% CI 0.17–0.70) and EFS (HR 0.43, 95% CI 0.17–1.11).

LIMITATIONS, REASONS FOR CAUTION: This meta-analysis is based on abstracted data and most of the studies included are retrospective cohort studies. Not all studies had matching criteria between the study population and the controls, and these criteria often differed between the studies. Moreover, rate of recurrence is reported as a punctual event and it is not possible to establish when recurrences occurred and whether follow-up, which was shorter than 5 years in some of the included studies, is adequate to capture late recurrences.

WIDER IMPLICATIONS OF THE FINDINGS: Our results demonstrate that performing COS at diagnosis or ART following treatment completion does not seem to be associated with detrimental prognostic effect in young women with breast cancer, including among patients with hormone receptor-positive disease and those receiving neoadjuvant chemotherapy.

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Introduction

Breast cancer is the most common malignancy and the leading cause of death in young women aged ≤ 40 years (Miller *et al.*, 2020). Considering both the prognostic value of young age at diagnosis and the biology of tumors arising in these patients (Azim and Partridge, 2014; Partridge *et al.*, 2016), premenopausal women with breast cancer are often candidate to receive multimodal treatments that include chemotherapy (Oktay *et al.*, 2018; Lambertini *et al.*, 2020). Long-term side effects of chemotherapy include premature ovarian insufficiency (POI) and subsequent impaired fertility (Lambertini *et al.*, 2020; The ESHRE Guideline Group on Female Fertility Preservation *et al.*, 2020). Many women have not completed their family planning at the time of breast cancer diagnosis. For this reason, gonadotoxicity of anticancer treatment, fertility preservation and family planning are crucial issues to be addressed during oncofertility counseling with all women of reproductive age with a newly diagnosed breast cancer (Lambertini *et al.*, 2020; The ESHRE Guideline Group on Female Fertility Preservation *et al.*, 2020).

Among the possible strategies to counteract the risk of chemotherapy-induced impaired fertility, controlled ovarian stimulation

(COS) for oocyte/embryo cryopreservation before starting chemotherapy is standard of care for young women interested in fertility preservation (Lambertini *et al.*, 2020; The ESHRE Guideline Group on Female Fertility Preservation *et al.*, 2020).

Despite the recent availability of a growing number of studies demonstrating no increased risk of recurrence for patients undergoing COS, some oncologists still remain concerned about the safety of COS, particularly in patients who are candidates for neoadjuvant therapy and in the case of hormone-sensitive tumors (Lambertini *et al.*, 2018). Nowadays, most breast cancer patients, especially those with hormone-receptor positive disease, undergoing oocyte or embryo cryopreservation are candidate to receive COS in combination with an aromatase inhibitor (AI) to reduce the levels of circulating estrogens or tamoxifen (Lambertini *et al.*, 2020; The ESHRE Guideline Group on Female Fertility Preservation *et al.*, 2020). Including an AI in the protocol for COS has proven to be effective in reducing circulating estrogen levels while it does not affect the efficacy of the protocol in terms of number of collected oocytes, their maturation and fertilization rates (Bonardi *et al.*, 2020).

Many women that did not have access to fertility preservation before starting treatment and that fail to conceive spontaneously may

need to access the fertility units during oncology follow-up after completing anticancer therapies. More limited evidence exists on the safety of ART in breast cancer survivors after anticancer treatment completion with only few studies including a small number of patients that have addressed this issue (Goldrat *et al.*, 2015; Rosenberg *et al.*, 2019; Condorelli *et al.*, 2021b), leaving an important unmet medical need in the oncofertility field (Lambertini *et al.*, 2020).

Due to the limited available evidence, many physicians are still uncomfortable to deal with fertility treatments in breast cancer patients and survivors. Many women are still not properly informed about these important issues, reducing their chances of future conception after the end of treatment (Lambertini *et al.*, 2019; Hershlag *et al.*, 2020).

To provide up to date evidence on this important topic and to help physicians during the oncofertility counseling, we performed a systematic review and meta-analysis aiming to assess the safety of fertility treatments before or after anticancer treatments in young women with early breast cancer.

Materials and methods

This was a quantitative synthesis of studies evaluating the safety of COS before starting (neo)adjuvant chemotherapy and of studies assessing ART performed after completion of treatment in early breast cancer patients. Survival outcomes of patients exposed to COS or ART were compared to those of patients who did not undergo these techniques.

Search methods and study selection

Eligible studies were identified by a systematic literature search of Medline, Web of Science, Embase and Cochrane library with no language or date restriction up to 30 June 2021. The search strategy was carried out using the keywords 'breast cancer' and 'fertility preservation'. Specific keywords were combined with Boolean operators. The systematic literature search was carried out independently by three authors (L.A., E.B. and M.M.L.) and any discrepancies were solved by discussion with a fourth author (M.L.). Cross-referencing from relevant studies was performed to confirm retrieval of all possible studies. Data on study design, study population characteristics, inclusion criteria, type of fertility preservation or ART and oncological outcomes were extracted. This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.*, 2009).

Selection criteria and data extraction

To be included in this meta-analysis, eligible studies had to satisfy the following inclusion criteria: (i) retrospective or prospective case-control or cohort studies comparing survival outcomes of women who underwent COS before starting gonadotoxic treatments for breast cancer and/or ART at the end of treatments to a control group of breast cancer patients without access to these strategies; (ii) studies with available information on one or more survival endpoints (including cancer recurrence rate, event-free survival (EFS), overall survival, number of deaths); (iii) availability or possibility to estimate hazard ratio (HR) or relative risk (RR) and 95% CI. Adjusted RR and HR with 95%

CI were extracted. When the number of events for each group were available but the above measures were not reported, HRs were estimated using the Watkins and Bennett method (Watkins and Bennett, 2018).

Exclusion criteria were: (i) absence of a control group of breast cancer patients who did not pursue COS or ART. (ii) Case reports and case series with <10 enrolled patients.

From all the included studies the name, year of publication, study design, number and median age of patients, follow-up time, type of fertility preservation techniques applied, survival status and type of events, and time between breast cancer diagnosis and start of oncological treatments were extracted. Quality assessment and risk of bias were performed using the Newcastle-Ottawa Assessment Scale (NOS) (Wells *et al.*, 2014). The NOS assigns a maximum of 9 points according to three risks of bias domain for case-control or cohort study: selection of study participants, comparability, and exposure or outcomes bias. Studies were classified as follow: low risk of bias (9 points), moderate risk of bias (from 8 to 7 points) and high risk of bias (6 points or below) according to the different score obtained.

Study objectives

The main objectives of this analysis were to evaluate breast cancer recurrence rate, EFS and mortality ratio (MR) in patients who underwent COS or ART as compared to patients not exposed to these techniques. Subgroup analyses were performed to evaluate the prognostic impact of COS in patients with hormone receptor-positive disease and in those receiving neoadjuvant chemotherapy.

A potential delay in time to start chemotherapy in patients performing COS before starting oncological treatments was also evaluated.

Statistical analysis

Pooled RRs and HRs with their 95% CI were calculated with the method of DerSimonian and Laird using the random effects model (DerSimonian and Laird, 1986). Higgins I^2 index was used to evaluate the quantitative measure of the degree of inconsistency in the results of the included studies (Higgins and Thompson, 2002). Egger's asymmetry test was used to assess the probability of publication bias (Egger *et al.*, 1997).

Pooled RRs and HRs were considered statistically significant with a P value of < 0.05 (two-sided). Sensitivity analyses were conducted to assess whether the pooled estimates were stable or depended on one single included study.

Differences in mean time from diagnosis to chemotherapy were analyzed using the random effects model. For studies reporting median values and ranges, mean values were estimated with the Hozo method (Hozo *et al.*, 2005).

Results

A total of 1835 records were retrieved. Among the 22 records assessed for eligibility, three were excluded because of overlapping population (Oktay *et al.*, 2005; Moravek *et al.*, 2018; Marklund *et al.*, 2020), two because of the absence of a control group (Turan *et al.*, 2013; Meirow *et al.*, 2014), one because it did not assess oncological

outcomes (Ben-Haroush *et al.*, 2011) and another because it included a small case series of patients (Takuwa *et al.*, 2018).

Finally, 15 studies were included in the present meta-analysis (Azim *et al.*, 2008; Goldrat *et al.*, 2015; Kim *et al.*, 2016; Chien *et al.*, 2017; Rodriguez-Wallberg *et al.*, 2018; Muñoz *et al.*, 2019; Rosenberg *et al.*, 2019; Letourneau *et al.*, 2020; Vriens *et al.*, 2020; Fredriksson *et al.*, 2021; Greer *et al.*, 2021; Marklund *et al.*, 2021; Moravek *et al.*, 2021; Condorelli *et al.*, 2021a,b), of which 11 reporting on the outcomes of patients who underwent COS for fertility preservation before starting chemotherapy (Azim *et al.*, 2008; Kim *et al.*, 2016; Chien *et al.*, 2017; Rodriguez-Wallberg *et al.*, 2018; Muñoz *et al.*, 2019; Letourneau *et al.*, 2020; Vriens *et al.*, 2020; Fredriksson *et al.*, 2021; Greer *et al.*, 2021; Marklund *et al.*, 2021; Moravek *et al.*, 2021) and 4 studies reporting the outcomes of survivors who underwent ART following anticancer treatment completion (Goldrat *et al.*, 2015; Rosenberg *et al.*, 2019; Condorelli *et al.*, 2021a,b). Among the latter group of studies, one (Condorelli *et al.*, 2021a) has been published after the literature search was performed on 30 June 2021, but it has been included because data were property of two of the authors (M.C. and M.L.) (Fig. 1).

Main characteristics of the included studies are reported in Table I. Among them, 2 were prospective nonrandomized controlled studies (Azim *et al.*, 2008; Kim *et al.*, 2016), 1 was a prospective cohort study

(Vriens *et al.*, 2020), 1 was ambispective (Muñoz *et al.*, 2019) and 10 were retrospective cohort studies (Goldrat *et al.*, 2015; Chien *et al.*, 2017; Rodriguez-Wallberg *et al.*, 2018; Rosenberg *et al.*, 2019; Letourneau *et al.*, 2020; Fredriksson *et al.*, 2021; Greer *et al.*, 2021; Marklund *et al.*, 2021; Moravek *et al.*, 2021; Condorelli *et al.*, 2021b).

COS was performed in association with concomitant AI or tamoxifen in all but one study (Moravek *et al.*, 2021), although in some studies only a portion of the included women were treated with concomitant AI or tamoxifen during COS (Rodriguez-Wallberg *et al.*, 2018; Letourneau *et al.*, 2020; Fredriksson *et al.*, 2021; Greer *et al.*, 2021) (Table I).

The timing of COS differed between the included studies, being before or after surgery in one (Kim *et al.*, 2016), before neoadjuvant chemotherapy in one (Chien *et al.*, 2017), before adjuvant therapy in three (Azim *et al.*, 2008; Vriens *et al.*, 2020; Fredriksson *et al.*, 2021) and both before neoadjuvant or adjuvant chemotherapy in the remaining six studies (Rodriguez-Wallberg *et al.*, 2018; Muñoz *et al.*, 2019; Letourneau *et al.*, 2020; Greer *et al.*, 2021; Marklund *et al.*, 2021; Moravek *et al.*, 2021) (Supplementary Fig. S1).

Follow-up time ranged from 23.4 months (Azim *et al.*, 2008) to 79 months (Chien *et al.*, 2017) in studies evaluating COS and between

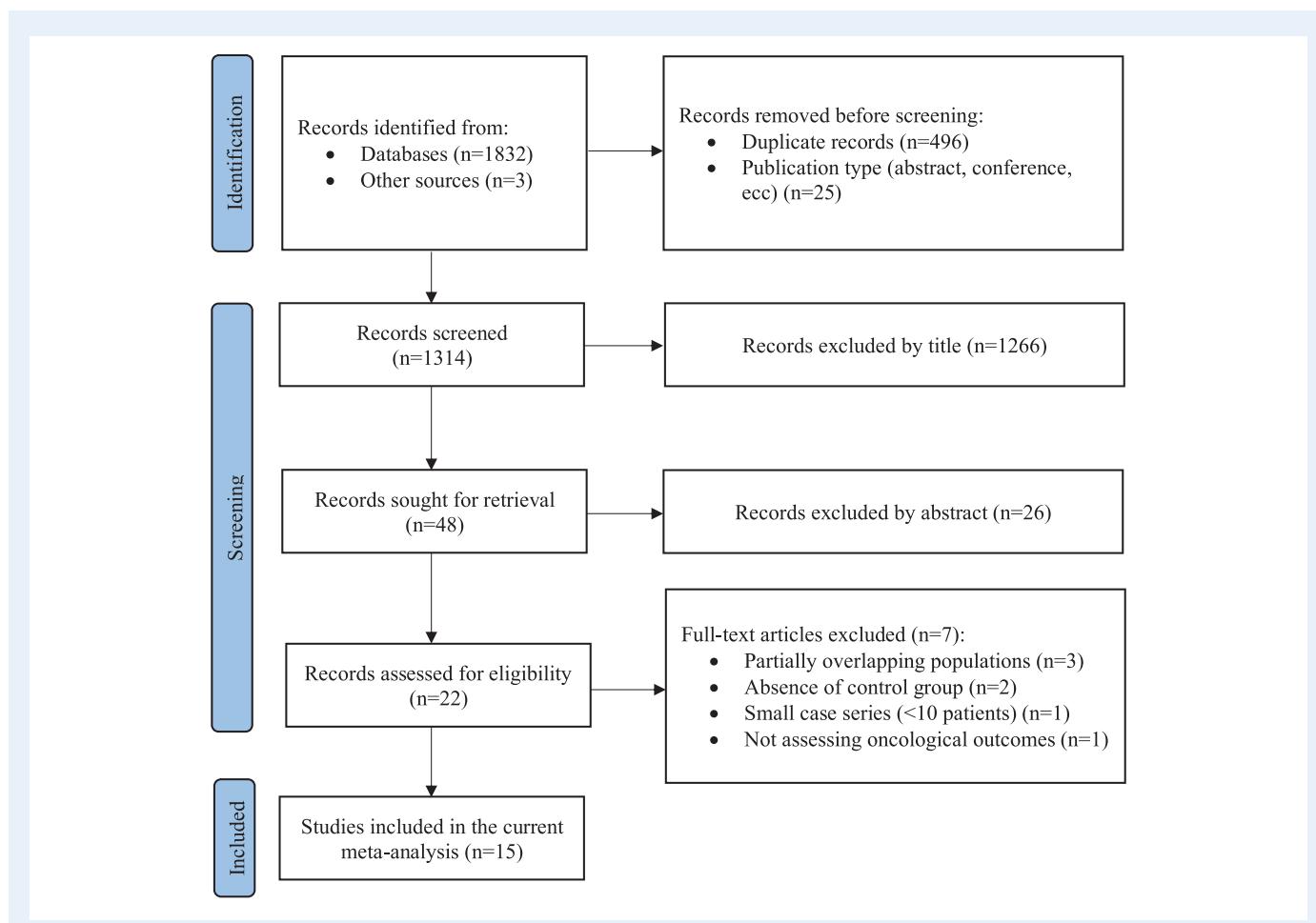


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram of study selection process.

Table I Main characteristics of the studies included in the present meta-analysis.

Reference	Country	Years	Study design	Patients exposed to COS or ART, n	Patients not exposed to COS or ART, n	Timing of ovarian stimulation, n, (%)	FP strategy and concomitant medications	Mean/median follow-up time in FP vs no FP cohort	Matching criteria for choosing controls/controlling factors	Baseline differences between study populations and controls	Outcomes	Risk of bias*
Azim et al. (2008) ¹	USA	2002–2007	Prospective non-randomized controlled study	79	136	Before adjuvant chemotherapy	COS + AI (100%)	FP: 23.4 months (7.5–63.6) No FP: 33.05 months (4.5–63.6)	N.R.	No statistically significant differences between populations (p=0.02) than controls	Delay to treatments, recurrence rate, RFS	Moderate
Kim et al. (2016) ¹	USA	2002–2014	Prospective non-randomized controlled study	120	217	14 (11.7) Before surgery 106 (88.3) After surgery	COS + AI (100%)	FP: 5 years (±2.1) No FP: 6.9 years (±3.6)	N.R.	FP patients had lower node involvement (p=0.02) than controls	Recurrence rate, RFS	Moderate
Chien et al. (2017) ²	USA	2010–2017	Retrospective study	34	48	Before neoadjuvant chemotherapy	N.R.	FP: 79 months No FP: 79 months	N.R.	No statistically significant differences between populations	Delay to treatments, recurrence rate, RFS	Moderate
Rodríguez-Wallberg et al. (2018) ²	Sweden	1999–2013	Retrospective cohort study	148	378	23 (15.5) Before neoadjuvant chemotherapy 123 (83.1) Before adjuvant chemotherapy 2 (1.3) N.R.	COS ± AI (46%)	FP: 5.8 years (0.3–17.9) No FP: 5.8 years (0.3–17.9)	Age at diagnosis; adjustments for confounders: tumor size, node involvement, estrogen receptor status and chemotherapy administered	No statistically significant differences between populations	Recurrence rate	Low
Muñoz et al. (2019) ²	Spain	2008–2016	Ambispective cohort study	148	111	20 (13.5) Before neoadjuvant chemotherapy 128 (86.5) Before adjuvant chemotherapy	COS + AI (100%)	FP: 5 years No FP: 5 years	Patients with same characteristics but who did not want to preserve their fertility	No statistically significant differences between populations	DFS	Moderate
Letourneau et al. (2020) ²	USA	2007–2017	Retrospective cohort study	207	122	85 (41.1) Before neoadjuvant chemotherapy 122 (58.9) Before adjuvant chemotherapy	COS + AI or TAM in positive breast cancer	FP: 42 months (2–114) No FP: 46 months (10–132)	Demographic, reproductive health, cancer treatments and tumor characteristics considered as potential confounders and included in the multivariable survival analysis in case of $P < 0.2$	No statistically significant differences between populations (p=0.04)	Recurrence rate, DFS	High
Vriens et al. (2020) ²	The Netherlands	2008–2015	Prospective cohort study	34	84	Before adjuvant chemotherapy	COS + AI (100%)	FP: 52 months (48–58) No FP: 51 months (42–63)	FP patients had lower tumor size at diagnosis (p=0.04)	Recurrence rate, DFS	Moderate	
Marklund et al. (2021) ²	Sweden	1994–2017	Retrospective cohort study	425	850	105 (24.7) Before neoadjuvant	N.R.	FP: 5.8 years (±4.2)	Age at diagnosis (5-year periods), time of neoadjuvant	FP patients were younger ($P < 0.001$), MR	Moderate	

(continued)

Table I Continued

Reference	Country	Years	Study design	Patients exposed to COS or ART, n	Patients not exposed to COS or ART, n	Timing of ovarian stimulation n, (%)	FP strategy and concomitant medications	Mean/median follow-up time in FP vs no FP cohort	Matching criteria for choosing controls/controlling factors	Baseline differences between study populations and controls	Outcomes	Risk of bias*
Moravek et al. (2021)	USA	2005–2018	Retrospective cohort study	150	165	39 (26.0) Before neoadjuvant chemotherapy 111 (74.0) Before adjuvant chemotherapy	COS without any AI or TAM	FP: 4 years (0.48–12.40) No FP: 6.19 years (0.72–11.12)	N.R.	No statistically significant differences between populations	Delay to treatments, recurrence rate, MR	High
Fredriksson et al. (2021)	Sweden	2005–2014	Retrospective cohort study	126	126	Before adjuvant chemotherapy	COS ± AI	FP: N.R. No FP: N.R.	Age at breast cancer diagnosis ± 5 years, tumor size and node involvement	No statistically significant differences between populations	Recurrence rate, RFS	Moderate
Greer et al. (2021)	USA	2007–2017	Retrospective cohort study	123	149	37 (30.1) before neoadjuvant chemotherapy 86 (69.9) before adjuvant chemotherapy	COS ± AI (60.2%), or TAM (3.3%)	FP: 50 months (32–71) No FP: 49 months (31–75)	N.R.	More FP patients were BRCA mutation carriers ($P = 0.021$)	Delay to treatments, DFS, OS	Moderate
Goldrat et al. (2015)	Belgium, Italy, Spain and Denmark	2000–2009	Retrospective cohort study	25	173	After adjuvant chemotherapy	ART	FP: 102 months (81–131) No FP: 107 months (85–123)	N.R.	Patients not exposed to ART were younger ($P = 0.009$) and higher grade 3 tumors ($P = 0.033$)	Recurrence rate	Moderate
Rosenberg et al. (2019)	Sweden	1982–2014	Retrospective cohort study	37	148	After adjuvant chemotherapy	ART	FP: 10.3 years (±4.2) No FP: 10.7 years (±4.4)	Breast cancer stage and year of diagnosis (± 5 years)	No statistically significant differences between populations	Recurrence rate	Low
Condorelli et al. (2019)	Belgium	2006–2016	Retrospective cohort study	39	73	After adjuvant chemotherapy	ART	FP: 9.4 years (4.5–22.2) No FP: 12.1 years (6.8–19.8)	BRCA status, breast cancer stage, anticancer treatments and age	ART patients were younger than controls ($P < 0.001$)	Recurrence rate, RFS	Low

(continued)

Table I Continued

Reference	Country	Years	Study design	Patients exposed to COS or ART, n	Patients not exposed to COS or ART, n	Timing of ovarian stimulation, n, (%)	FP strategy and concomitant medications	Mean/median follow-up time in FP vs no FP cohort	Matching criteria for choosing controls/controlling factors	Baseline differences between study populations and controls	Outcomes	Risk of bias*
Condorelli et al. (2021a)	Europe, USA and Israel	2000–2012	Retrospective cohort study	22	146	After adjuvant chemotherapy	ART	FP: 7.5 years (3.0–16.0) No FP: 8.8 years (2.5–18.4)	NR	ART patients were older ($P = 0.004$), had lower grade ($P = 0.008$) and higher hormone-receptor positive ($P = 0.016$) tumors	DFS, OS	High

AI, aromatase inhibitors; COS, controlled ovarian stimulation; DFS, disease-free survival; FP, fertility preservation; MR, mortality rate; NR, not reported; OS, overall survival; RFS, relapse-free survival; TAM, tamoxifen.

*Quality assessment and risk of bias performed using the Newcastle–Ottawa Assessment Scale.

1Partially overlapping population.

2Partially overlapping population.

7.5 and 10.3 years (Rosenberg et al., 2019) in studies evaluating ART treatments in breast cancer survivors.

A total of 4643 breast cancer patients were included in these studies, of whom 1594 underwent COS for fertility preservation before starting anticancer treatments and 2386 did not undergo fertility preservation strategies at time of breast cancer diagnosis, 123 breast cancer survivors were exposed to ART after the end of anticancer treatments and 540 breast cancer survivors were not exposed to ART.

Safety of COS in breast cancer patients before starting (neo)adjuvant treatments

Among the 11 studies included in the analysis, 10 reported recurrence rate (Azim et al., 2008; Kim et al., 2016; Chien et al., 2017; Rodriguez-Wallberg et al., 2018; Muñoz et al., 2019; Letourneau et al., 2020; Vriens et al., 2020; Fredriksson et al., 2021; Greer et al., 2021; Moravek et al., 2021), 7 EFS (4 as relapse-free survival (Azim et al., 2008; Kim et al., 2016; Chien et al., 2017; Fredriksson et al., 2021), 3 disease-free survival (Letourneau et al., 2020; Vriens et al., 2020; Greer et al., 2021)) and 4 mortality rate (Muñoz et al., 2019; Marklund et al., 2020; Greer et al., 2021; Moravek et al., 2021). Sensitivity analyses of all outcomes are available as Supplementary Tables SI, SII, SIII.

Overall, 100 recurrences (8.6%) occurred among the 1167 women who underwent COS at the time of breast cancer diagnosis whereas 246 (16.2%) occurred among the 1523 patients who did not undergo COS. Compared to women who did not receive fertility preservation at diagnosis, those who underwent COS had a reduced risk of recurrence (RR 0.58, 95% CI 0.46–0.73, $P < 0.001$) (Fig. 2A). No heterogeneity ($I^2 = 0.0\%$, $P = 0.497$) nor publication bias ($P = 0.109$) were observed (Supplementary Table SI).

No detrimental effect of COS was observed in terms of EFS (HR 0.76, 95% CI 0.55–1.06, $P = 0.112$; $I^2 = 0.0\%$, $P = 0.971$) (Fig. 2B) (Supplementary Table SII).

Patients exposed to COS had a reduced risk of dying, with 40 deaths (5.5%) observed among the 724 patients that pursued COS and 132 (10.9%) among the 1206 patients not exposed to COS (RR 0.54, 95% CI 0.38–0.76, $P < 0.001$; $I^2 = 0.0\%$, $P = 0.803$) (Fig. 2C) (Supplementary Table SIII).

Two studies (Rodriguez-Wallberg et al., 2018; Letourneau et al., 2020) reported a subgroup analysis of EFS in patients with hormone-receptor positive breast cancer. Similarly to the results of the main analysis, a tendency for a better outcome in terms of EFS was observed in patients with hormone-receptor positive breast cancer who underwent COS as compared to those not exposed to fertility preservation procedures (HR 0.36, 95% CI 0.20–0.65) (Fig. 3).

Among the included studies, three evaluated differences in time to therapy initiation between patients undergoing or not COS (Azim et al., 2008; Chien et al., 2017; Moravek et al., 2021). Different definitions of time to therapy were used: Azim et al. (2008) computed the time between surgery and start of adjuvant chemotherapy, Chien et al. (2017) the time between the date of invasive breast cancer diagnosis by biopsy to the first dose of neoadjuvant chemotherapy, and Moravek et al. (2021) the time between the first contact with reproductive team to cancer treatment start. Overall, patients that underwent COS had a 6-day longer time to chemotherapy compared to

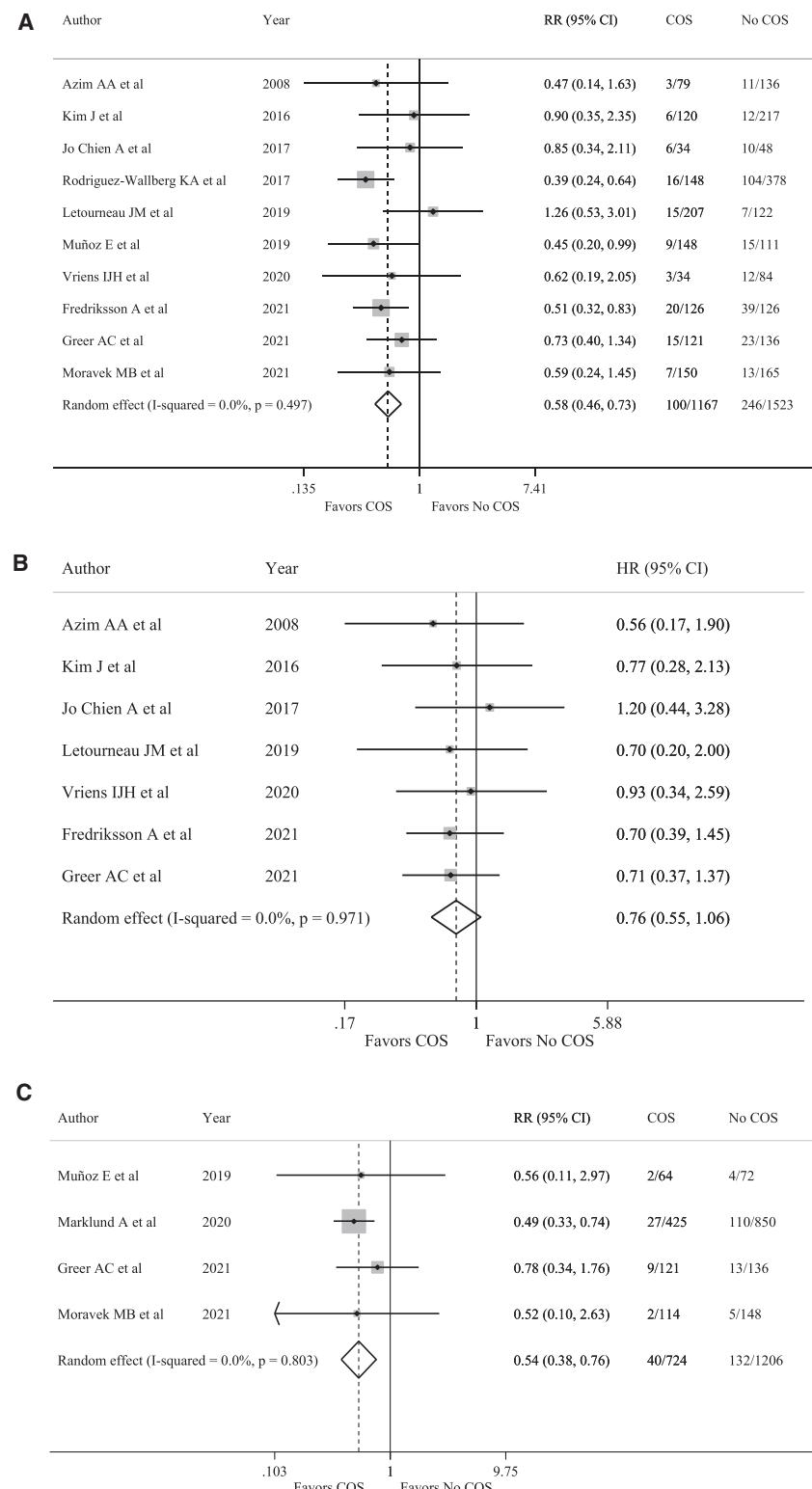


Figure 2. Forest plots describing breast cancer recurrence, event-free survival and mortality in patients undergoing controlled ovarian stimulation before starting oncological treatments. Solid vertical line: Significance line (line of no effect). Gray squares: represents the weighted mean (point estimate) of each study. Horizontal bars: 95% CI line. Diamond: represents the mean of effect sizes obtained by the meta-analysis. Its width corresponds to its 95% CI. **(A)** Recurrence rate in patients undergoing COS. **(B)** Event-free survival in patients undergoing COS. **(C)** Mortality rate in patients undergoing COS. COS, controlled ovarian stimulation; HR, hazard ratio; RR, relative risk. I^2 index (Higgins and Thompson, 2002).

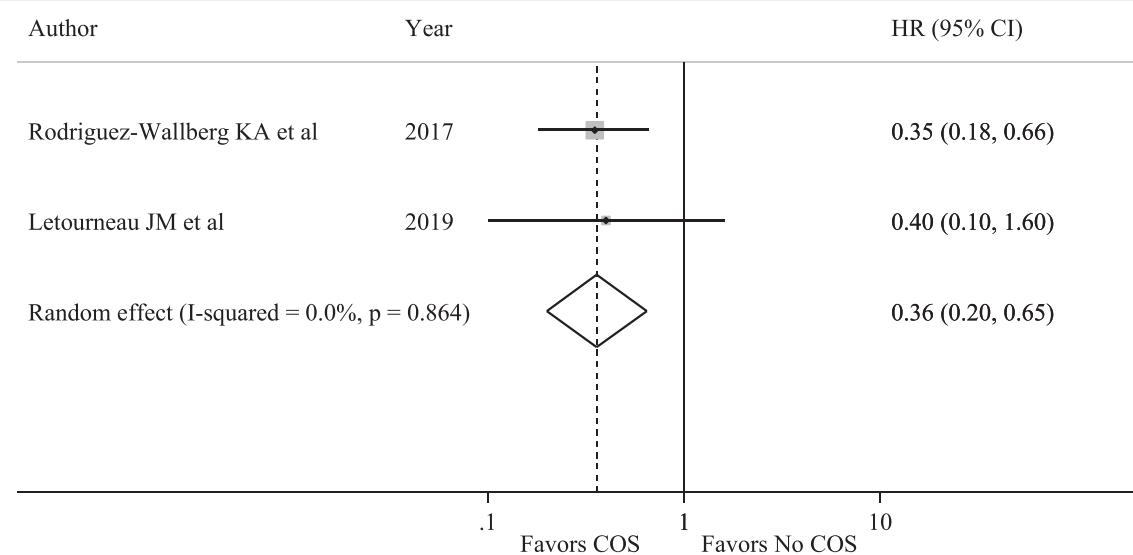


Figure 3. Forest plot describing analysis of event-free survival in hormone-receptor positive disease in patients undergoing controlled ovarian stimulation. COS, controlled ovarian stimulation; HR, hazard ratio. I^2 -squared is Higgins I^2 index (Higgins and Thompson, 2002).

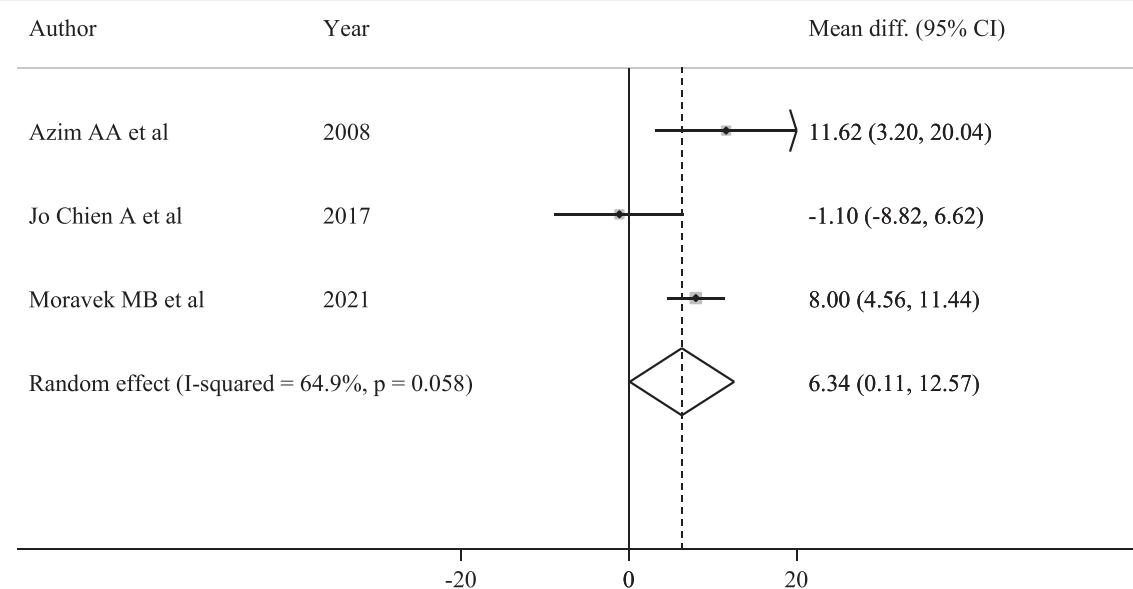


Figure 4. Forest plot describing analysis of delay-time to start of treatments in patients undergoing controlled ovarian stimulation. I^2 -squared is Higgins I^2 index (Higgins and Thompson, 2002).

patients not exposed to COS (mean difference 6.34, 95% CI 0.11–12.57, $P=0.046$) (Fig. 4).

Two studies (Rodriguez-Wallberg et al., 2018; Moravek et al., 2021) reported data on breast cancer recurrences in patients who received COS before neoadjuvant chemotherapy as compared to controls and in those who received COS before adjuvant chemotherapy as compared to controls. A reduced risk of recurrence was observed among patients receiving COS before starting neoadjuvant chemotherapy (RR

0.22, 95% CI 0.06–0.80, $P=0.021$) (Fig. 5A) and in those receiving COS before initiation of adjuvant therapy (RR 0.51, 95% CI 0.31–0.82, $P=0.005$) (Fig. 5B).

Safety of ART in breast cancer survivors

Among the four included studies, recurrence rates were reported in all studies (Goldrat et al., 2015; Rosenberg et al., 2019; Condorelli

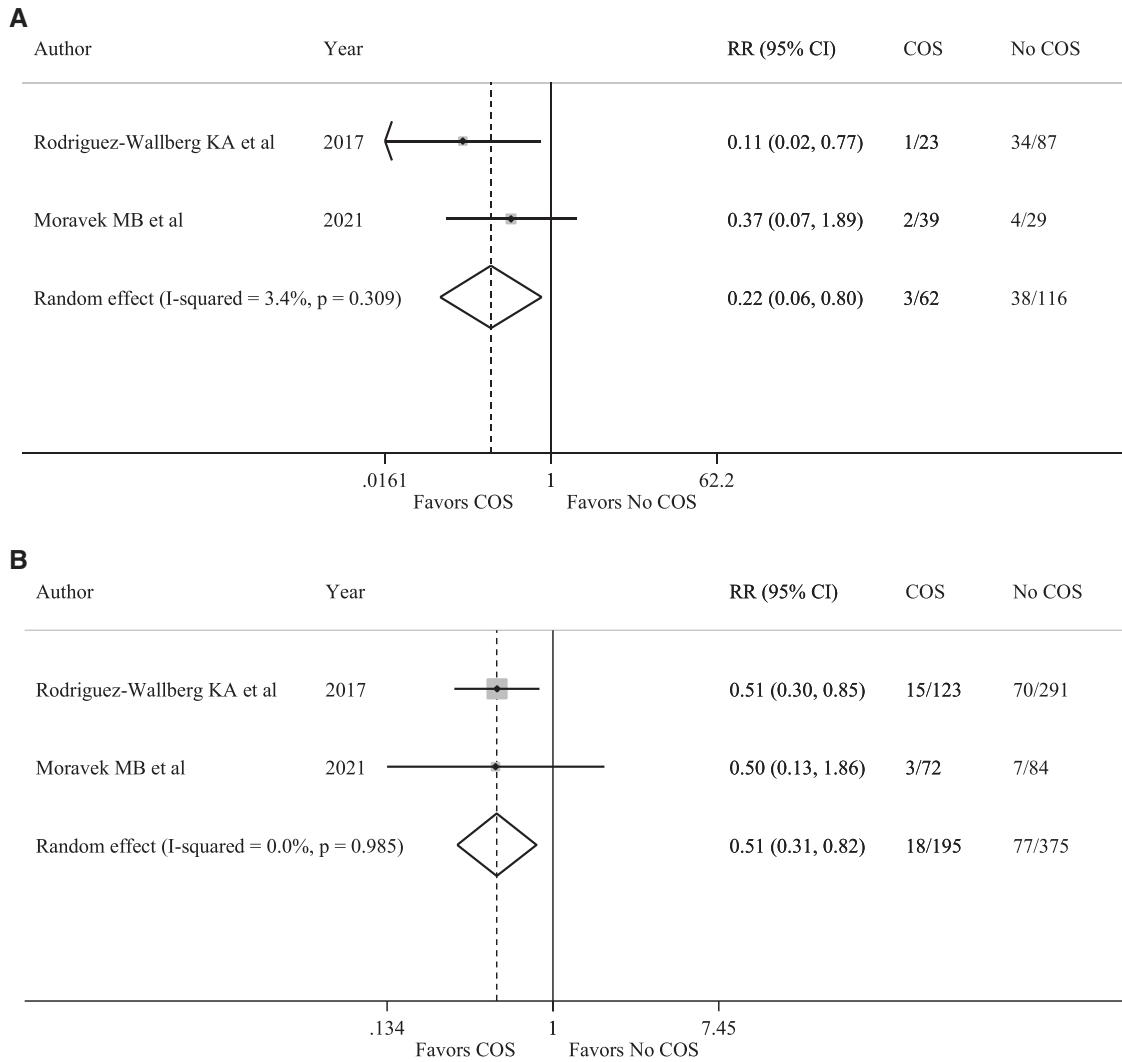


Figure 5. Forest plots describing analysis of recurrence rate among patients undergoing controlled ovarian stimulation before chemotherapy. (A) Recurrence rate among patients undergoing COS before neoadjuvant chemotherapy compared to patients who did not receive fertility preservation techniques. **(B)** Recurrence rate among patients undergoing COS before adjuvant chemotherapy compared to patients who did not receive fertility preservation techniques. RR, relative risk; COS, controlled ovarian stimulation. I^2 -squared is Higgins I^2 index (Higgins and Thompson, 2002).

et al., 2021a,b), and EFS in two (Condorelli et al., 2021a,b). Fewer recurrences were observed in patients receiving ART with 7 (5.7%) among the 123 patients who underwent ART and 119 (22.0%) among the 540 patients in the control group (RR 0.34, CI 95% 0.17–0.70, $P = 0.003$; $I^2 = 0.0\%$, $P = 0.493$) (Fig. 6A) (Supplementary Table SIV).

Moreover, no detrimental effect in terms of EFS was observed (HR 0.43, 95% CI 0.17–1.11, $P = 0.081$; $I^2 = 0.0\%$, $P = 0.866$) (Fig. 6B).

Discussion

To our knowledge, this is the first systematic review and meta-analysis assessing the safety of hormonal stimulation in young women with breast cancer before starting anticancer treatments and in survivors

who underwent ART after anticancer treatment completion. Among women who were exposed to COS before starting chemotherapy, we observed fewer recurrences and deaths as compared to patients not exposed to fertility preservation strategies, with no difference in EFS. A 6-day delay in the time to chemotherapy start was found in patients who had access to COS for fertility preservation. Similarly, we observed no apparent detrimental prognostic effect of ART in breast cancer survivors with a tendency for lower recurrences in patients exposed to ART as compared to those not exposed to ART, with no difference in EFS.

Nowadays, it is imperative to ensure that all young patients are given the chance to potentially complete their family planning after cancer diagnosis and treatment (Perachino et al., 2020). Therefore, oncofertility counseling should be offered to all young women at

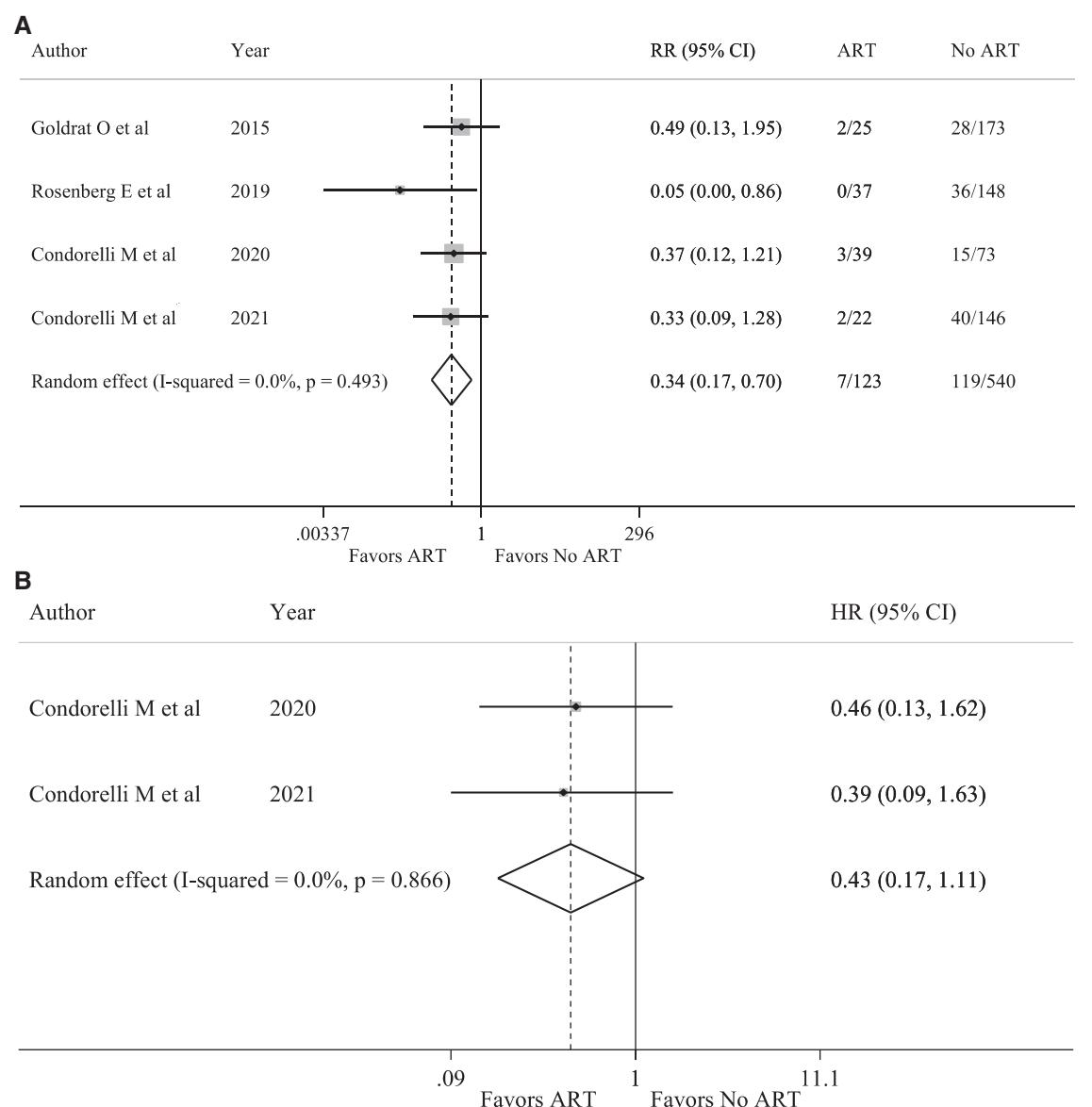


Figure 6. Forest plots describing breast cancer recurrence rate and event-free survival in breast cancer survivors undergoing assisted reproductive technologies. (A) Recurrence rate in survivors that performed assisted reproductive technologies. **(B)** Event-free survival in survivors that performed ARTs. HR, hazard ratio; RR, relative risk. I^2 -squared is Higgins I^2 index (Higgins and Thompson, 2002).

the time of breast cancer diagnosis to discuss the risk of chemotherapy-induced POI and subsequent impaired fertility and the available strategies for counteracting these side effects, including ovarian function and fertility preservation (Lambertini et al., 2020; The ESHRE Guideline Group on Female Fertility Preservation et al., 2020).

However, being breast cancer a hormonally driven tumor, both young patients and their oncologists are still concerned about the safety of fertility treatments that include ovarian stimulation. This is mainly due to the limited safety evidence available regarding these techniques as well as the limitations of the studies addressing this important issue (e.g. short-term follow-up, different inclusion criteria,

timing of hormonal manipulations and type of COS performed). Our results provide more robust evidence on the safety of COS in breast cancer patients.

We included studies that were mainly retrospective, enrolled patients from different countries around the world (particularly from Europe and America) and used different fertility preservation techniques (i.e. random vs. conventional start, COS associated or not with concomitant AI or tamoxifen). Despite the limitations of the included studies, overall, we observed clearly no detrimental prognostic effect of COS with a similar trend of no alarming signals in all the studies.

As reported in a recent meta-analysis (Bonardi et al., 2020), concomitant use of letrozole reduces circulating estrogen levels

and it does not impair the efficacy of COS. Therefore, the inclusion of letrozole in the protocol for COS could be considered as alternative to standard stimulations in breast cancer patients. Notably, only one study included in the present meta-analysis did not use AI or tamoxifen as part of the protocol for COS (Moravek *et al.*, 2021).

Many oncologists are still concerned about whether patients with hormone-receptor positive tumors should undergo COS. Although only two studies reported survival outcomes according to hormone receptor status of the tumor, our results indicate no detrimental effect of COS in this setting.

A recent analysis of the Pregnancy and Fertility (PREFER) study (Blondeaux *et al.*, 2021) has shown that 11.7% of young breast cancer patients refuse to preserve their fertility mainly because of the concerns about a possible delay in cancer treatment. In our meta-analysis, we observed a 6-day longer time to chemotherapy start. In the breast cancer setting, differently from aggressive hematologic diseases, such short additional time should not be considered a contraindication to the procedure for the majority of patients. In fact, adjuvant chemotherapy is equally effective up to 12 weeks after definitive surgery, although this time should be kept within a maximum of 60 days for patients with more aggressive malignancies at higher risk of relapse (i.e. those with triple-negative or human epidermal growth factor receptor 2 positive disease) (Lohrisch *et al.*, 2006; de Melo Gagliato *et al.*, 2014). Similar considerations apply for neoadjuvant chemotherapy but taking into account that shortening the interval to treatment initiation would be particularly relevant in this setting (de Melo Gagliato *et al.*, 2020).

Among the included studies, the time from diagnosis to anticancer treatments initiation ranged from a median of 35 days (Moravek *et al.*, 2021) to 45 days (Azim *et al.*, 2008). Despite being statistically significant, the short delay of 6 days that we observed in our analysis does not appear to be clinically relevant and would not lead to exceeding the 60-day cutoff.

These results are also indirectly confirmed by a further analysis showing no increased risk of breast cancer recurrence in patients receiving COS before undergoing neoadjuvant or adjuvant chemotherapy as compared to controls. Though evidence remains limited, these data are encouraging in showing that performing COS before starting neoadjuvant chemotherapy does not seem to worsen the prognosis of breast cancer patients. Even if this strategy is not allowed in the neoadjuvant setting in some countries, our data support the current recommendation that COS for fertility preservation is not contraindicated (Lambertini *et al.*, 2020).

In this work, the safety of ART in breast cancer survivors following anticancer treatment completion was also assessed. This is a very controversial area where limited data are available. Indeed, only four studies fulfilled the inclusion criteria and thus could be included in this analysis (Goldrat *et al.*, 2015; Rosenberg *et al.*, 2019; Condorelli *et al.*, 2021a,b). Despite the small number of women included in these studies ($n=663$), reduced recurrences in women undergoing ART and no differences in EFS were found suggesting again no apparent detrimental prognostic effect. Among the four included studies, only one demonstrated a statistically significant reduction in recurrences in breast cancer patients exposed to ART (Rosenberg *et al.*, 2019), while the other three did not reach statistical significance (Goldrat *et al.*, 2015; Condorelli *et al.*, 2021a,b). It should be noted that these studies were

retrospective and included a low number of patients, particularly those deemed at low risk of recurrence, such as patients with luminal-like disease, generally with small tumor size and low nodal involvement. This may be due to the fact that ART in breast cancer survivors is not considered standard of care and many physicians are uncomfortable to suggest it after the end of anticancer therapies.

Although these data demonstrate that performing COS at diagnosis or ART following treatment completion do not seem to worsen the prognosis of young breast cancer patients, it should be noted that there are several limitations in our work. First of all, our meta-analysis is based on abstracted data and the majority of the studies included were retrospective cohort studies, with different matching criteria between the study population and controls. Among all the studies included in our analysis, less than half of them reported a trend towards less aggressive baseline breast cancer characteristics (i.e. smaller tumor size, less nodal involvement and grading, higher frequency of hormone receptor-positive disease) in patients undergoing fertility preservation techniques as compared to controls (Goldrat *et al.*, 2015; Kim *et al.*, 2016; Vriens *et al.*, 2020; Greer *et al.*, 2021; Marklund *et al.*, 2021; Condorelli *et al.*, 2021a,b).

Moreover, most of the studies reported just the rate of cancer recurrence without reporting 'time-to-event' endpoints and follow-up is relatively short for many of the included studies. Even if breast cancer recurrences are higher during the first 5 years from diagnosis, some patients like those with hormone receptor-positive disease are also at high risk of late recurrence (Pan *et al.*, 2017). Median follow-up was shorter than 5 years in six of the included studies, thus results are to be considered immature to capture long-term differences in this setting and longer follow-up is needed. The risk of bias in the selection of patients with favorable prognostic characteristics and the relatively short follow-up of some of the studies included in this meta-analysis are the two main factors that were considered in the risk of bias assessment. The results of risk of bias assessment and potential confounding factors in the included studies must be considered in the overall interpretation of our results. Although our results seem to indicate a better prognosis of patients undergoing fertility preservation strategies, considering these limitations, we conclude that COS and ART are unlikely to increase the risk of breast cancer recurrence more than having a protective effect. However, despite these limitations, our meta-analysis provides important updated evidence that accessing COS at diagnosis or ART following breast cancer treatment completion does not appear to be associated with any detrimental prognostic effect in young women, including patients with hormone receptor-positive disease or those receiving neoadjuvant chemotherapy, while it is associated with a short and non-clinically relevant 6-day delay in starting anticancer treatments. These results are important to reassure patients and oncologists on the safety of these procedures in order to increase patients' chances of future conception. However, future well-designed prospective studies with long-term follow-up are needed to further strengthen these findings.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article are available on Medline, Web of Science, Embase and Cochrane library.

Authors' roles

L.A., E.B. and M.L. conceived and designed the work. L.A., E.B., M.M.L., A.B., C.M., M.G.R., D.F., S.S., M.C., C.M., O.G., L.D.M., I.D. and M.L. acquired the data and revised the manuscript for important intellectual content. M.B., M.C. and E.B. performed the statistical analysis. All authors interpreted the data. L.A., E.B. and M.L. drafted the work and all other authors revised it critically and gave final approval for publication.

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Conflict of interest

M.L. acted as consultant for Roche, Pfizer, Novartis, Lilly, AstraZeneca, MSD, Exact Sciences, Gilead, Seagen and received speaker honoraria from Roche, Pfizer, Novartis, Lilly, Ipsen, Takeda, Libbs, Knight, Sandoz outside the submitted work. F.S. acted as consultant for Novartis, MSD, Sun Pharma, Philogen and Pierre Fabre, and received speaker honoraria from Roche, Novartis, BMS, MSD, Merck, Sun Pharma, Sanofi, and Pierre Fabre outside the submitted work. I.D. has acted as a consultant for Roche, has received research grants from Roche and Ferring, has received reagents for academic clinical trial from Roche diagnostics, speaker's fees from Novartis, and support for congresses from Theramex and Ferring outside the submitted work. L.D.M. reported honoraria from Roche, Novartis, Eli Lilly, MSD, Pfizer, Ipsen, Novartis and had an advisory role for Roche, Eli Lilly, Novartis, MSD, Genomic Health, Pierre Fabre, Daiichi Sankyo, Seagen, AstraZeneca, Eisai outside the submitted work. The other authors declare no conflict of interest. The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review or approval of the manuscript and decision to submit the manuscript for publication.

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