J Breast Cancer. 2022 Dec;25(6):443-453
https://doi.org/10.4048/jbc.2022.25.e45
pISSN 1738-6756·eISSN 2092-9900

Journal of Breast Cancer JBC

Original Article

Pregnancy After Breast Cancer – Prognostic Safety and Pregnancy Outcomes According to Oestrogen Receptor Status: A Systematic Review

Katie Nolan, Michael R. Boland, Arnold D.K. Hill

Department of General/Breast & Endocrine Surgery, Beaumont Hospital and The Royal College of Surgeons in Ireland, Dublin, Ireland

Received: Jun 28, 2022
Revised: Sep 14, 2022
Accepted: Sep 29, 2022
Published online: Nov 9, 2022

Correspondence to
Katie Nolan
Department of General/Breast & Endocrine Surgery, Beaumont Hospital and The Royal College of Surgeons in Ireland, Beaumont Road, Dublin 9, Ireland.
Email: katiemnolan@rcsi.ie

ORCID iDs
Katie Nolan
https://orcid.org/0000-0003-4650-4776
Michael R. Boland
https://orcid.org/0000-0002-6724-5630
Arnold D.K. Hill
https://orcid.org/0000-0001-9617-7983

Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Writing - original draft: Nolan K; Writing - review & editing: Boland MR, Hill AD.

ABSTRACT

Purpose: Breast cancer is the primary cause of cancer-related death in women. Women diagnosed with estrogen receptor (ER)-positive breast cancer have prolonged treatment durations. Owing to the paucity of research and lack of consensus regarding conception planning and pregnancy for patients with ER-positive breast cancer, we aimed to assess pregnancy and survival outcomes in women with ER-positive breast cancer during and after treatment.
Methods: We conducted a systematic review of the available studies on pregnancy after ER-positive breast cancer. The assessed outcomes included overall survival (OS), disease-free survival (DFS), hormonal therapy duration, and pregnancy outcomes.
Results: Ultimately, 2,669 patients from five studies were included in this study. When all breast cancer receptor subtypes were included in the analysis, pregnancy after breast cancer was associated with a time-dependent protective effect on both DFS and OS. This protective effect was not evident when examining ER-positive patients with subsequent pregnancies, and no significant differences in DFS were observed. ER-positive patients who became pregnant received significantly lower rates of hormonal therapy. Hormonal treatment at the time of pregnancy was correlated with increased rates of termination owing to concerns about teratogenic effects.
Conclusions: Pregnancy after breast cancer did not significantly affect DFS in ER-positive patients over a follow-up period of 5–10 years from diagnosis, although did significantly affect hormonal treatment duration in the reviewed studies. Further analysis and in-depth studies are required to assess the effects of altered hormonal treatment times, as well as patient management related to pregnancy planning after breast cancer.

Keywords: Breast Neoplasms; Pregnancy Outcome; Receptors, Estrogen

INTRODUCTION

Breast cancer is the leading cause of cancer-related death in women and is the most commonly diagnosed malignancy during childbearing years [1-3]. Advances in local and systemic treatments combined with earlier targeted diagnoses through screening and triple assessment comprised of clinical examination, imaging, and cytology/histopathology have improved patient survival and reduced recurrence rates [4,5]. A significant proportion of

women today are postponing motherhood to pursue career and lifestyle goals [6,7]. The consequence of this delay is a higher proportion of patients who survive breast cancer and then begin to consider their fertility and start planning for their first child [8].

Currently, limited clinical guidelines exist for patients regarding conception and pregnancy planning after breast cancer diagnosis. The Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guidelines emphasize the importance of individualized planning, although advise that the majority of patients should wait to conceive for two years following breast cancer treatments [9]. Patients with estrogen receptor (ER)-positive breast cancer who are receiving tamoxifen treatment are advised to complete at least 5 years of treatment, while patients in their 30s are advised to complete at least 2–3 years of tamoxifen treatment prior to conceiving [9]. Previous studies have examined pregnancy outcomes following breast cancer and their effects on overall survival (OS) [10]. Previous studies were unable to identify a negative impact of pregnancy on breast cancer outcomes; indeed, data from these studies identified a protective effect of pregnancy on survival when compared with nulliparous women with breast cancer [11]. Furthermore, pregnancy after breast cancer was not associated with increased rates of stillbirths or miscarriages [11].

Breast cancer is a heterogeneous disease categorized into distinct subtypes differentiated by hormonal, genetic, and histopathological characteristics [12]. Young patients diagnosed with ER-positive breast cancer have a significant risk of long-term recurrence, and a previous pregnancy is considered detrimental to recurrence risk owing to increased endocrine stimulation [13,14]. To date, a paucity of evidence exists regarding the management and counseling of ER-positive breast cancer patients who wish to conceive or plan for pregnancy following treatment. This study aimed to systematically review the effect of ER status on pregnancy and survival outcomes in patients with a previous breast cancer diagnosis.

METHODS

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Institutional Review Board approval was not required for this study. All authors contributed to the development of the study protocols. Two researchers designed the literature search, retrieved the relevant manuscripts, appraised the selected studies, and analyzed the study data. A review by senior authors was conducted for any disagreement regarding the included studies. The study protocol was registered with the International Prospective Register of Systematic Reviews.

This systematic review was performed using the Population, Intervention, Comparison, Outcomes (PICO) framework as follows:

Population: Patients with breast cancer and subsequent pregnancy.
Intervention: Pregnancy, defined as pregnancy following breast cancer diagnosis and treatment (including surgery, chemotherapy, radiotherapy, and hormonal therapy).
Comparison: Patients with breast cancer who did not become pregnant.
Outcomes: The primary outcomes included OS, disease-free survival (DFS), and incidence of hormonal therapy. Secondary outcomes of interest included pregnancy complication and full-term birth rates and subsequent changes to hormonal therapy during pregnancy. Continuous outcomes of interest included age, tumor size, tumor grade, and breast cancer treatment.

https://doi.org/10.4048/jbc.2022.25.e45

Search strategy and study inclusion

An electronic search of relevant databases was performed, including PubMed, Embase, and Cochrane Collaboration databases. Additional manual searches were performed using Google Scholar and the relevant publication reference sections. The following terms were searched: "pregnancy," "breast cancer," "breast carcinoma," "survival," "outcome," and "prognosis." The last day of the search was March 2nd 2021.

The following types of studies were included: randomized control trials, cohort studies, or observational studies with retrospective or prospective study designs that reported ER receptor status (tumors found on immunohistochemistry with ERs present in > 1% of cells) and evaluated reproductive outcomes after breast cancer treatment. The included studies were required to report one of the following: odds ratio, hazard ratio (HR) estimates with 95% confidence intervals (CIs), standard error, or number of events necessary to calculate the outcomes of interest. All studies included women diagnosed with breast cancer at any age and were reported in English and published in peer-reviewed journals.

Studies were excluded for the following reasons: 1) No data on ER status or pregnancy outcomes; 2) Assessed patients with pregnancy-associated breast cancer or breast cancer diagnosed after pregnancy; 3) Involved patients diagnosed with primary cancer other than breast cancer; or 4) The study was published as a conference abstract, commentary, literature review, or meta-analysis.

Terminology regarding the reporting of pregnancy outcomes varied: when the terms "miscarriage" and "pregnancy termination" were not specifically used, spontaneous abortion was considered miscarriage, while induced abortion was considered pregnancy termination.

Data extraction and quality assessment

Two reviewers independently reviewed and extracted the articles according to the study design (KN and MRB). In cases of disagreement between reviewers, a consensus was obtained by consulting a third reviewer (ADKH). The selected articles were assessed for inclusion and subsequently verified by all authors.

The Newcastle-Ottawa Scale was used to assess the quality of all included studies. This scale determines the study quality through the assessment of patient selection, cohort comparability, and outcome analysis. The maximum achievable score is 9 for high-quality studies that meet all criteria.

RESULTS

Study selection

The initial search produced 4,267 studies, of which 1,654 were excluded due to duplication. The remaining titles and abstracts were screened according to the inclusion and exclusion criteria, and 30 were deemed eligible. We excluded review articles, studies investigating pregnancy-associated breast cancer, case reports, and studies that did not report ER receptor status. Following full-text evaluation, five studies were included in the systematic review (**Figure 1**) [14-18]. Of the included studies, four were retrospective cohort studies and one was a case-control study (**Table 1**). The included studies resulted in a total patient cohort of 2,669 individuals.

https://doi.org/10.4048/jbc.2022.25.e45

Table 1. Characteristics of included studies

Reference	Study type	Sample size	Country	ER positive	Length of follow-up	
					Median	Mean
Lambertini et al., 2018 [14]	Case Control-Multicentre	1,207	Europe (Italy, Spain, Denmark, Belgium)	686	7.2 years (4.8–8.7)	NR
Nye et al., 2017 [15]	Retrospective-Single Centre	61	North America	61	NR	7.8 years
Cordoba et al., 2012 [18]	Retrospective-Single centre	115	Spain	66	NR	6 years
Ives et al., 2006 [16]	Retrospective-Multicentre	123	Australia	42	10.6 years (6.6–15)	NR
Chuang et al., 2019 [17]	Retrospective-Multicentre	1,163	Taiwan	398	NR	4.04 years

ER = estrogen receptor; NR = not reported.

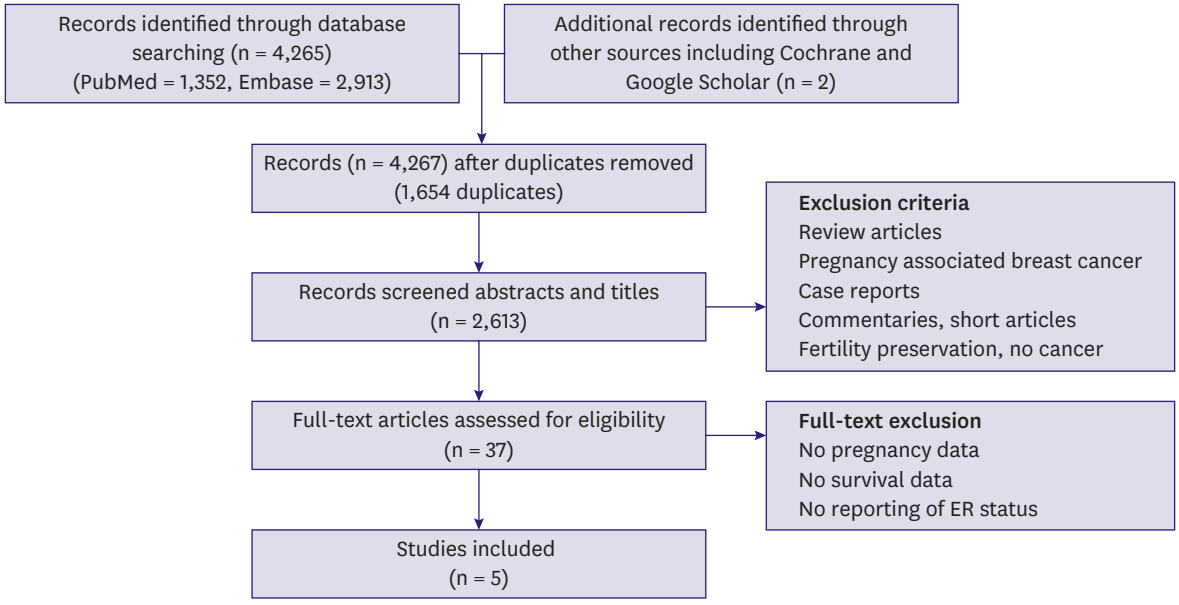

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram detailing the systematic search strategy.
ER = estrogen receptor.

Patient characteristics

Tumor size, tumor grade, nodal status, ER status, and breast cancer treatment were analyzed in all included studies (**Table 2**). The median age was reported in two studies [16,18] while the mean age was reported in three studies [14,15,17]. The age range among all studies was 31–36.1 years. The majority of tumors were less than 2 cm (56.3%) and grade 3 (poorly differentiated). The majority of patients were negative for lymph node involvement (62.4%), while 34.5% presented with nodal involvement. ER status was reported in all five included studies. Among the included studies, 47% of patients were diagnosed with ER-positive breast cancer. Furthermore, 41% of study participants underwent hormonal treatment for breast cancer. In addition, 73% of patients underwent chemotherapy as part of their treatment regimen. Mastectomy was performed in 47.8% of patients, whereas 48.8% underwent breast conserving surgery.

ER status and pregnancy and oncological outcomes

DFS

Two studies examined the effect of ER status on DFS [14,15]. Neither study reported any significant differences in DFS for ER-positive patients in the pregnant and nonpregnant groups ($p = 0.68$ and $p = 0.69$) at 7.2 and 9 years of follow-up, respectively [14,15]. Additionally, two studies reported DFS rates in pregnant and nonpregnant cohorts at follow-up, irrespective of ER status [14,18].

https://doi.org/10.4048/jbc.2022.25.e45

Table 2. Patient characteristics included in meta-analysis

Reference	Ives et al. [16]		Chuang et al. [17]		Lambertini et al. [14]		Nye et al. [15]		Cordoba et al. [18]		Total
	Pregnant	Non pregnant	Pregnant	Non pregnant	Pregnant	Non pregnant	Pregnant	Non pregnant	Pregnant	Non pregnant	
No. of subjects	123	2,416	249	914	333	874	32	29	18	97	2,669
Age	35		31	32.2	32	35	34.2	36.1	31.5	33	
Tumor size (cm)											
< 2	58 (47%)	NR	150 (60.2%)	505 (55.3%)	185 (55.5%)	500 (57%)	18 (58%)	18 (62%)	15 (83.3%)	55 (59.1%)	1,504 (56.3%)
> 2	51 (42%)	NR	97 (38.9%)	394 (43.1%)	135 (40.5%)	359 (41%)	13 (42%)	11 (38%)	2 (11.1%)	32 (34.4%)	1,043 (39%)
Tumor grade											
1	14 (11%)	NR	40 (16.1%)	146 (16%)	37 (11%)	103 (12%)	6 (21%)	5 (18%)	0	4 (4.6%)	355 (13.3%)
2	28 (23%)	NR	97 (39%)	340 (37.2%)	96 (29%)	253 (29%)	9 (31%)	12 (43%)	8 (44.4%)	39 (44.8%)	882 (33%)
3	46 (37%)	NR	75 (30.1%)	325 (35.6%)	114 (34%)	346 (39%)	14 (48%)	11 (39%)	9 (50%)	44 (50.6%)	984 (36.8%)
Positive nodes	37 (30%)	NR	54 (21.7%)	211 (23.1%)	144 (43%)	376 (43%)	14 (45%)	11 (38%)	10 (55.5%)	64 (68.8%)	921 (34.5%)
Negative nodes	79 (64%)	NR	173 (69.5%)	657 (71.9%)	188 (57%)	498 (57%)	17 (55%)	18 (62%)	8 (44.5%)	29 (31.2%)	1,667 (62.4%)
ER positive	42 (34%)	NR	87 (65.4%)	311 (68.5%)	194 (58%)	492 (56%)	32 (100%)	29 (100%)	7 (41.2%)	59 (64.8%)	1,253 (47%)
ER negative	29 (24%)	NR	46 (34.6%)	143 (31.5%)	139 (42%)	382 (44%)	0%	0%	NR	NR	739 (27.6%)
Hormonal treatment	7 (6%)	NR	111 (44.6%)	535 (58.5%)	86 (26%)	238 (27%)	19 (63%)	23 (82%)	7 (38.9%)	66 (72.5%)	1,092 (41%)
Radio-therapy	53 (43%)	NR	120 (48.2%)	394 (43.1%)	NR	NR	19 (61%)	23 (82%)	9 (52.9%)	54 (52.1%)	672 (25%)
Chemo-therapy	50 (41%)	NR	148 (59.4%)	670 (73.3%)	264 (79%)	714 (82%)	NR	NR	16 (89.9%)	88 (93.6%)	1,950 (73%)
Mastectomy	53 (43%)	NR	81 (32.5%)	379 (41.5%)	167 (50%)	503 (58%)	12 (38%)	13 (45%)	11 (61.1%)	58 (60.4%)	1,277 (47.8%)
Breast conserving surgery	70 (57%)	NR	148 (59.4%)	512 (56%)	166 (50%)	371 (42%)	20 (63%)	16 (55%)	n/a	n/a	1,303 (48.8%)

ER = estrogen receptor; NR = not reported; n/a = not applicable.

Lambertini et al. [14] found no statistically significant improvement in DFS among all breast cancer patients who became pregnant less than two years after a breast cancer diagnosis (HR, 1.22; 95% CI, 0.83–1.80; $p = 0.31$). Cordoba et al. [18] identified significantly improved 5-year DFS among all breast cancer patients who subsequently became pregnant compared with that in patients who did not (94% vs. 64%, $p = 0.009$). The other two studies did not report DFS at follow-up [16,17].

OS

Two studies examined the effect of ER status on OS [14,17]. Chuang et al. [17] identified significantly lower mortality among patients in the ER-positive breast cancer cohort who subsequently became pregnant compared with that in the ER-positive, nonpregnant cohort (HR, 0.23; 95% CI, 0.07–0.77, p=0.03) with a mean follow-up of 4 years [17]. However, Lambertini et al. [14] found no significant difference in OS for ER-positive patients in both the pregnant and nonpregnant groups (HR, 0.84; 95% CI, 0.60–1.18; $p = 0.32$) at 7.2 years after pregnancy.

Four studies reported comparisons of OS between pregnant and nonpregnant cohorts, irrespective of hormone receptor status [14,16,17,18]. Chuang et al. [17] identified a protective effect of pregnancy on OS (HR, 0.44; 95% CI, 0.23–0.84), which was particularly evident for women who waited 3 years or more after breast cancer diagnosis before becoming pregnant (HR, 0.19; 95% CI, 0.05–0.78). Similarly, Ives et al. [16] identified a significant protective effect on OS in women who subsequently became pregnant after breast cancer (HR, 0.59; 95% CI, 0.37–0.95; $p = 0.03$). This protective effect was time-dependent in women who waited at least 24 months to conceive, and showed significant protective effects on survival (HR, 0.48; 95% CI, 0.27–0.83; $p = 0.009$), which was not evident in women with pregnancies 24 months prior to diagnosis [16]. Lambertini et al. [14] reported significant improvements in OS in pregnant patients compared with that in nonpregnant patients (HR, 0.57; 95% CI, 0.36–0.90; $p = 0.01$); however, they did not report any significant impact of pregnancy timing on survival outcomes. Cordoba et al. [18] reported that 100% of the breast cancer patient group who became pregnant after treatment were alive after 5 years compared with 80% of patients in the nonpregnant group after 5 years. Nye et al. [15] did not report data on OS at follow-up.

https://doi.org/10.4048/jbc.2022.25.e45

Recurrence

Three studies reported breast cancer recurrence in the patient cohort during the follow-up period [15,16,18]. Nye et al. [15] reported eight (26%) breast cancer recurrences in the ER-positive, pregnant cohort during follow-up, three of which were > 5 years from diagnosis, and found no statistically significant differences in breast cancer recurrence between women who became pregnant within five years of diagnosis and nonpregnant patients. Ives et al. [16] identified a 39% recurrence rate (48/123 patients) with a median recurrence time of 42 months (20–75 months) using a Cox proportional hazard model for survival, which suggested a trend towards recurrence risk in patients who conceived within 6 to 12 months from diagnosis. Cordoba et al. [18] reported one patient in the pregnancy group with liver metastasis, although no further breast cancer recurrences at follow-up. Two studies did not report the incidence of recurrence during follow up [14,17].

Hormonal treatment

All five studies reported data on endocrine therapy use in ER-positive patients [14-18]. Only two studies commented on the hormonal therapy duration (**Table 3**) [14,15]. Nye et al. [15] identified a significantly shorter duration of tamoxifen treatment in the pregnant cohort (n = 32) compared with that in nonpregnant controls (n = 29; 20.9 vs. 42.3). Additionally, Nye et al. [15] reported that of the 19 pregnant patients taking tamoxifen who subsequently shortened their course of treatment during pregnancy planning, four had associated recurrences during the follow-up period. Lambertini et al. [14] identified a median treatment time of 60 months for pregnant (range, 6–69) and nonpregnant (range, 7–69) patient groups. Furthermore, Lambertini et al. [14] conducted a subgroup analysis involving 57 patients receiving endocrine therapy who became pregnant and compared hormonal therapy durations of < 5 and > 5 years, which did not provide evidence of a significant effect of hormonal therapy duration on DFS (HR, 0.98; 95% CI, 0.31–3.10). Cordoba et al. [18] demonstrated that hormonal treatment was utilized significantly more in patients who did not become pregnant (72.5% [66/97 nonpregnant patients] vs. 38.9% [7/18 pregnant patients], $p = 0.01$). This result was mirrored by Chuang et al. [17], who identified significantly more patients who received hormonal therapy in the nonpregnant group compared with that in the pregnant group (58.5% vs. 44.6%, $p = 0.01$). Only 6% of patients in the Ives et al. [16] study cohort received hormone therapy during follow-up, even though 34% of had ER-positive breast cancer. However, the authors did not comment on treatment durations.

Non-hormonal treatment

Four studies reported trends among nonhormonal treatment choices in breast cancer patients who became pregnant [14,15,17,18]. Chuang et al. [17] reported that women treated for breast cancer with subsequent pregnancies were more likely to undergo breast conserving surgery (59.4% vs. 56%) and less likely to receive chemotherapy (59.4% vs. 73.3%, $p < 0.01$) compared with nonpregnant patients. Similar results were reported by Nye et al. [15], with increased rates of breast-conserving surgery (BCS) in ER-positive patients with subsequent

Table 3. Hormonal treatment analysis of pregnant patients

Reference	No. of patients in pregnancy cohort receiving hormonal treatment	Treatment cessation prior to conceiving	Delayed or postponed treatment during pregnancy	Duration of treatment months	No. of patients on treatment during pregnancy	Total terminations
Nye et al. [15]	19 (63%)	7	12	Mean 20.9 (0–72)	0	Not reported
Chuang et al. [17]	111 (44.6%)	Not reported	Not reported	Not reported	Not reported	Not reported
Cordoba et al. [18]	7 (38.9%)	Not reported	Not reported	Not reported	Not reported	4
Lambertini et al. [14]	86 (26%)	Not reported	Not reported	Median 60 (6–69)	Not reported	Not reported
Ives et al. [16]	7 (6%)	Not reported	Not reported	Not reported	Not reported	Not reported

https://doi.org/10.4048/jbc.2022.25.e45

pregnancies (63% vs. 55%, $p = 0.61$). Lambertini et al. [14] also reported increased rates of BCS in their pregnant cohort (50% vs. 42%), irrespective of ER status. Cordoba et al. [18] identified reduced rates of chemotherapy in their pregnant cohort compared with that in nonpregnant patients (89.9% and 93.6% respectively), whereas mastectomy and radiation therapy rates were comparable.

Pregnancy outcomes

Complete pregnancy data were included in all five studies, with data on terminations described in four studies [14,16,17,18] and miscarriage rates provided in three studies [14,16,18] (**Table 4**). Live births were reported for 68.2% of patients (515/755 total pregnancies), while terminations (abortions/miscarriages) accounted for 22.6% of pregnancies (171/755 pregnancies). Lambertini et al. [14] reported a larger proportion of abortions (67.4%, n = 91) compared with that of miscarriages (16.3%, n = 22). Chuang et al. [17] identified 30 women (12%, n = 249) who underwent terminations at follow-up; however, the authors did not differentiate between abortions and miscarriages. Ives et al. [16] identified a statistically significant increase in terminations among patients who conceived within 2 years of diagnosis (47%, < 2 years vs. 21%, > 2 years; $p = 0.012$). This was accompanied by a statistically significant difference in termination rates when comparing conception rates between patients who conceived within and after 24 months (45%, < 24 months vs. 21%, > 24 months; $p = 0.021$) [16]. Cordoba et al. [18] identified seven pregnant patients who were receiving tamoxifen prior to conception, four of which underwent termination in the first trimester owing to concerns regarding the teratogenic risks of tamoxifen. Cordoba et al. [18] reported no miscarriages in their pregnant cohort.

Study quality

All included studies achieved a Newcastle-Ottawa score of 7–8 indicating high-quality studies with a low risk of bias in the study design. Most studies were biased by the length of the follow-up period.

DISCUSSION

Guidelines regarding pregnancy planning after breast cancer diagnosis are broad, and little information is available for patients. Furthermore, a significant paucity of evidence exists regarding the interaction between ER-positive breast cancer and subsequent pregnancy to support the development of patient guidelines and best practices. A diagnosis of breast cancer is always devastating, although for young women who are considering family planning, the lack of available patient information makes the process more traumatic. In our systematic review, we aimed to analyze the available literature regarding outcomes among

Table 4. Systematic review of pregnancy outcomes following breast cancer

Variable	Ives et al. [16]	Chuang et al. [17]	Lambertini et al. [14]	Nye et al. [15]	Cordoba et al. [18]	Total
Pregnant						
No.	123	249	333	32	18	755
Time to pregnancy						
Months	23	39.7	28.8	60	44.5	
Pregnancy outcomes						
Termination	42/123 (34%)	30/249 (12%)	91/333 (67.4%)	NR	8/18 (44.4%)	171 (22.6%)
Miscarriage	15/123 (12%)	NR	22/333 (16.3%)	NR	0/115	37 (5%)
Live birth	66/123 (53.6%)	219/249 (87.9%)	188/333 (56.5%)	32/32 (100%)	10/18 (55.5%)	515 (68.2%)

NR = not reported.

https://doi.org/10.4048/jbc.2022.25.e45

ER-positive breast cancer patients who are attempting to conceive with a specific focus on hormonal treatment to provide more clarity on this topic.

Our systematic review is the first to identify studies that examined pregnancy after breast cancer, with a focus on ER receptor status and survival. Our analysis of DFS and OS in the five included studies indicated that pregnancy had a protective effect on overall mortality irrespective of other variables. These results are similar to those previously published on pregnancy after breast cancer [19-21]. Since the completion of this review, Lambertini et al. [22] published a meta-analysis of 39 studies, the largest of its kind, examining pregnancy after breast cancer. Notably, they identified a 35% reduction in the likelihood of subsequent pregnancy after diagnosis. Patients with pregnancy after breast cancer diagnosis demonstrated better DFS (HR, 0.66; 95% CI, 0.49–0.89) and OS (HR, 0.56; 95% CI, 0.45–0.68) [22]. This meta-analysis referenced only two studies that assessed pregnancy after ER-positive breast cancer and did not analyze the outcomes associated with ER-positive breast cancer and subsequent treatment. Although our study included a smaller study population, it is the first review to specifically collate data on ER receptor-positive breast cancer and pregnancy outcomes.

All included studies acknowledge the "healthy mother effect" as a confounding bias. This theory centers on the idea that healthy women with favorable prognostic factors are more likely to conceive, and therefore, may bias the study population when assessing survival [23]. Cordoba et al. [18] compared prognostic factors between their cohorts and did not find a significant difference in distribution, which might introduce bias. Their data reported a higher frequency of early stage and lymph node-positive cancer with low lymphovascular invasion in the pregnancy group, which supports a role for bias by the healthy mother effect, although this was challenged by a higher incidence of triple-negative and poorly differentiated tumors observed in this group [18]. Chuang et al. [17] controlled for this by including control patients with longer disease-free time periods than the time interval between cancer diagnosis and pregnancy in a pregnant cohort. While this method is cited as a potential method to reduce bias in a cohort, and with all studies acknowledging the "healthy mother effect" as a risk for bias, there are currently no guidelines in the literature for controlling this variable [24]. Another type of selection bias, the "guaranteed time" or "immortal time" bias, is well-documented in perinatal studies examining pregnancy and birth complications [25]. This bias is introduced when conducting an analysis timed from enrollment and compared across groups defined by a specific event during follow-up [26]. Lambertini et al. [14] controlled for guaranteed time bias by ensuring that each nonpregnant patient in the cohort had a disease-free interval longer than that between breast cancer diagnosis and conception among pregnant patients. No other study in our systematic review controlled for guaranteed time bias, which can be considered a limitation of data interpretation in retrospective studies without a scope for prospective analysis.

The role of endocrine therapy following the diagnosis of ER-positive breast cancer and guidance on discontinuation of therapy during pregnancy are areas of ongoing debate. The Adjuvent Tamoxifen: Longer Against Shorter (ATLAS) trial highlighted improved mortality and reduced recurrence rates among ER-positive breast cancer patients following 10 years of endocrine therapy. While these data are encouraging, for patients wishing to conceive, other variables and timeframes should be considered. [27] A retrospective cohort study published in 2021 examined the effect of hormone receptor status on pregnancy after breast cancer found no significant differences in DFS and OS between pregnant and nonpregnant

https://doi.org/10.4048/jbc.2022.25.e45

ER-positive patients [20]. Given that pregnancy does not increase mortality following ER-positive breast cancer, the authors highlighted the clinical implications of endocrine therapy in these patients and reported improved DFS in patients who received > 30 months of endocrine therapy prior to conception compared with patients who received < 30 months (p = 0.01) [20]. The authors further highlighted the need for dedicated clinical trials to assess the duration and safety of endocrine treatment during pregnancy. While all five studies analyzed comments on hormonal therapy use in their cohorts, no study examined the effect of hormonal therapy discontinuation on DFS and OS. The authors are aware of an ongoing clinical trial to assess the safety of temporary interruptions in endocrine therapy during pregnancy, the results of which will help further guide patient management (IBCSG-BIG-NABCG POSITIVE study, [NCT02308085]) [28]. The pilot data of 517 participants provided insight into patient demographics and treatment differences by region. The median patient age was 37 years, and 74.9% were nulliparous at enrollment. Tamoxifen was the most frequently prescribed hormonal treatment (41.8%), and 59.8% of American patients received tamoxifen alone. Considering that many patients rely on tamoxifen treatment, obtaining a better understanding of the risks and planning of treatment interruption during pregnancy is imperative [29]. The majority of studies identified a significantly higher uptake of hormonal therapy among patients in nonpregnant cohorts [15,17,18]. Cordoba et al. [18] identified a proportion of patients in the pregnancy termination cohort who cited the risks of teratogenicity secondary to tamoxifen as a contributing factor. A recently published case series of three patients who inadvertently became pregnant while receiving tamoxifen did not identify any fetal malformations. However, a recent systematic review of the literature identified a major fetal malformation rate of 17.6%, which is higher than the major malformation prevalence of 3% among the general US population [30]. Based on this systematic review of the literature, the authors could not make definitive conclusions on the teratogenic risks of tamoxifen use in pregnancy and suggest adhering to the current guidance regarding the 3-month washout period prior to conceiving, as described in the RCOG guidelines [9,30]. A 2018 survey of 273 physicians' knowledge and attitudes regarding fertility and pregnancy after breast cancer identified that approximately 40% of respondents were unaware of the available guidelines, with a further 18.3% of respondents unsure of the fertility preservation pathways available to their patients [31]. These results highlight the need for further research on the safety of cancer therapies during pregnancy and the development of guidelines and educational initiatives for both doctors and patients.

We assessed pregnancy outcomes across all five studies and identified a rate of 68.2% for live births, 22.6% for terminations, and 5% for miscarriages. The reasons for termination included pregnancy within 6 months of diagnosis [16], patient concerns over the detrimental effect of pregnancy after breast cancer [14], and teratogenic risks of adjuvant therapy [16,18]. None of the selected studies examined the effects of pregnancy after breast cancer on birth weight, gestation, or delivery type. A meta-analysis currently in publication that examined a range of pregnancy outcomes after breast cancer demonstrated that in comparison with that in the general population, breast cancer survivors had a 50% increased risk of low birth weight, 45% increased risk of preterm labor, and 14% increased risk of caesarean section at delivery [32].

The current literature review highlights the paucity of data on pregnancy after breast cancer in ER-positive breast cancer. Meta-analysis of the available data was not possible because of heterogeneity in both the study design and data analysis among studies. All studies were limited by small sample sizes in the pregnant cohorts. Furthermore, the retrospective nature of the studies meant that not all variables were accounted for or accurately recorded. Further

https://doi.org/10.4048/jbc.2022.25.e45

studies with prospective study designs may improve the effects of confounding variables associated with smaller sample sizes and heterogeneous populations.

In conclusion, this systematic review highlights the safety of pregnancy after breast cancer, regardless of ER status, and reinforces the need for clear dialogue and patient guidance. Our analysis clearly demonstrates the need for further studies with more robust study designs and a focus on ER status and pregnancy outcomes. Given the ubiquitous use of tamoxifen in ER-positive breast cancer patients, the authors welcome new studies that assess the safety of tamoxifen treatment discontinuation for pregnancy planning and provide evidence for guidelines on pregnancy planning for patients with ER-positive breast cancer.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
PUBMED | CROSSREF
2. Salani R, Billingsley CC, Crafton SM. Cancer and pregnancy: an overview for obstetricians and gynecologists. Am J Obstet Gynecol 2014;211:7-14.
PUBMED | CROSSREF
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.
PUBMED | CROSSREF
4. Giordano SH, Buzdar AU, Smith TL, Kau SW, Yang Y, Hortobagyi GN. Is breast cancer survival improving? Cancer 2004;100:44-52.
PUBMED | CROSSREF
5. Punglia RS, Morrow M, Winer EP, Harris JR. Local therapy and survival in breast cancer. N Engl J Med 2007;356:2399-405.
PUBMED | CROSSREF
6. Martin LJ. Delaying, debating and declining motherhood. Cult Health Sex 2021;23:1034-49.
PUBMED | CROSSREF
7. Molina-García L, Hidalgo-Ruiz M, Cocera-Ruíz EM, Conde-Puertas E, Delgado-Rodríguez M, Martínez-Galiano JM. The delay of motherhood: reasons, determinants, time used to achieve pregnancy, and maternal anxiety level. PLoS One 2019;14:e0227063.
PUBMED | CROSSREF
8. Lopresti M, Rizack T, Dizon DS. Sexuality, fertility and pregnancy following breast cancer treatment. Gland Surg 2018;7:404-10.
PUBMED | CROSSREF
9. Royal College of Obstetricians and Gynaecologists. 2011. Pregnancy and Breast Cancer (Green-top Guideline No.12). https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_12.pdf. Accessed March 12th, 2021.
10. Gerstl B, Sullivan E, Ives A, Saunders C, Wand H, Anazodo A. Pregnancy outcomes after a breast cancer diagnosis: a systematic review and meta-analysis. Clin Breast Cancer 2018;18:e79-88.
PUBMED | CROSSREF
11. Iqbal J, Amir E, Rochon PA, Giannakeas V, Sun P, Narod SA. Association of the timing of pregnancy with survival in women with breast cancer. JAMA Oncol 2017;3:659-65.
PUBMED | CROSSREF
12. Testa U, Castelli G, Pelosi E. Breast cancer: a molecularly heterogenous disease needing subtype-specific treatments. Med Sci (Basel) 2020;8:E18.
PUBMED | CROSSREF
13. Fu J, Zhong C, Wu L, Li D, Xu T, Jiang T, et al. Young patients with hormone receptor-positive breast cancer have a higher long-term risk of breast cancer specific death. J Breast Cancer 2019;22:96-108.
PUBMED | CROSSREF
14. Lambertini M, Kroman N, Ameye L, Cordoba O, Pinto A, Benedetti G, et al. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. J Natl Cancer Inst 2018;110:426-9.
PUBMED | CROSSREF

15. Nye L, Rademaker A, Gradishar WJ. Breast cancer outcomes after diagnosis of hormone-positive breast cancer and subsequent pregnancy in the tamoxifen era. Clin Breast Cancer 2017;17:e185-9.
PUBMED | CROSSREF

16. Ives A, Saunders C, Bulsara M, Semmens J. Pregnancy after breast cancer: population based study. BMJ 2007;334:194.
PUBMED | CROSSREF

17. Chuang SC, Lin CH, Lu YS, Hsiung CA. Mortality of pregnancy following breast cancer diagnoses in Taiwanese women. Oncologist 2020;25:e252-8.
PUBMED | CROSSREF

18. Córdoba O, Bellet M, Vidal X, Cortés J, Llurba E, Rubio IT, et al. Pregnancy after treatment of breast cancer in young women does not adversely affect the prognosis. Breast 2012;21:272-5.
PUBMED | CROSSREF

19. Azim HA Jr, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer 2011;47:74-83.
PUBMED | CROSSREF

20. Li Y, Zhang Y, Wang S, Lu S, Song Y, Liu H. The effect of subsequent pregnancy on prognosis in young breast cancer patients (≤35 years old) according to hormone receptor status. Cancer Manag Res 2021;13:1505-15.
PUBMED | CROSSREF

21. Azim HA Jr, Kroman N, Paesmans M, Gelber S, Rotmensz N, Ameye L, et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. J Clin Oncol 2013;31:73-9.
PUBMED | CROSSREF

22. Lambertini M, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, et al. Pregnancy after breast cancer: a systematic review and meta-analysis. J Clin Oncol 2021;39:3293-305.
PUBMED | CROSSREF

23. Valachis A, Tsali L, Pesce LL, Polyzos NP, Dimitriadis C, Tsalis K, et al. Safety of pregnancy after primary breast carcinoma in young women: a meta-analysis to overcome bias of healthy mother effect studies. Obstet Gynecol Surv 2010;65:786-93.
PUBMED | CROSSREF

24. Savignoni A, Giard C, Tubert-Bitter P, Rycke YD. Matching methods to create paired survival data based on an exposure occurring over time: a simulation study with application to breast cancer. BMC Med Res Methodol 2014;14:83.
PUBMED | CROSSREF

25. Neophytou AM, Kioumourtzoglou MA, Goin DE, Darwin KC, Casey JA. Educational note: addressing special cases of bias that frequently occur in perinatal epidemiology. Int J Epidemiol 2021;50:337-45.
PUBMED | CROSSREF

26. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol 2013;31:2963-9.
PUBMED | CROSSREF

27. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381:805-16.
PUBMED | CROSSREF

28. Pagani O, Ruggeri M, Manunta S, Saunders C, Peccatori F, Cardoso F, et al. Pregnancy after breast cancer: are young patients willing to participate in clinical studies? Breast 2015;24:201-7.
PUBMED | CROSSREF

29. Partridge AH, Niman SM, Ruggeri M, Peccatori FA, Azim HA Jr, Colleoni M, et al. Who are the women who enrolled in the POSITIVE trial: a global study to support young hormone receptor positive breast cancer survivors desiring pregnancy. Breast 2021;59:327-38.
PUBMED | CROSSREF

30. Buonomo B, Brunello A, Noli S, Miglietta L, Del Mastro L, Lambertini M, et al. Tamoxifen exposure during pregnancy: a systematic review and three more cases. Breast Care (Basel) 2020;15:148-56.
PUBMED | CROSSREF

31. Lambertini M, Di Maio M, Pagani O, Curigliano G, Poggio F, Del Mastro L, et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients. Breast 2018;42:41-9.
PUBMED | CROSSREF

32. American Society of Clinical Oncology. 2020. SABCS 2020: Meta-analysis of pregnancy outcomes in breast cancer survivors. https://ascopost.com/news/december-2020/meta-analysis-of-pregnancy-outcomes-in-breast-cancer-survivors/. Accessed August 20th, 2022.