Pregnancy after Breast Cancer

Dr Mahtab Vasigh
Isfahan University of Medical Sciences
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- *Breast cancer (BC) is the most common female cancer, and>12,000 new diagnoses occur in young adult women (aged < 40 years) annually, accounting for about 15% of all cases.*
- *Young women with early-stage BC have had good long-term survival rates*
- *With the trend of women delaying pregnancy and childbirth until later in life, fertility preservation after a diagnosis of breast cancer and future pregnancy is a growing concern.*
- *they face a number of unique concerns associated with having cancer at a younger age, including the risk of infertility and disruptions in family building*

- Younger age in developing countries:
  - cases < 40 y
    - 10% of BCs in developed areas
    - 25% of BC cases in developing areas

Introduction:

- Physicians are often approached by women of childbearing age with recent diagnoses of breast cancer who ask about the:
  - advisability of pregnancy
  - the potential harmful effects of cancer treatments which could impair their fertility (such as ovarian ablation, chemotherapy, and hormone therapies)
  - the effect of late pregnancy on the recurrence of the earlier breast cancer.
  - how long they should wait to conceive following cessation of their treatment.
- It has been proposed that the time elapsed from completion of breast cancer treatment to birth is relevant and that the longer the length between breast cancer diagnosis and pregnancy, the better the long-term prognosis

Safety of Py following BC -1

- BC is under the influence of female sex hormones

BC does not hold back the enthusiasm for childbearing among women and their husbands

What do patients want?

more than half of young patients query about **their fertility**

Because of severe

Patients always feared by:

- their therapeutic team
- and by survivors of BC

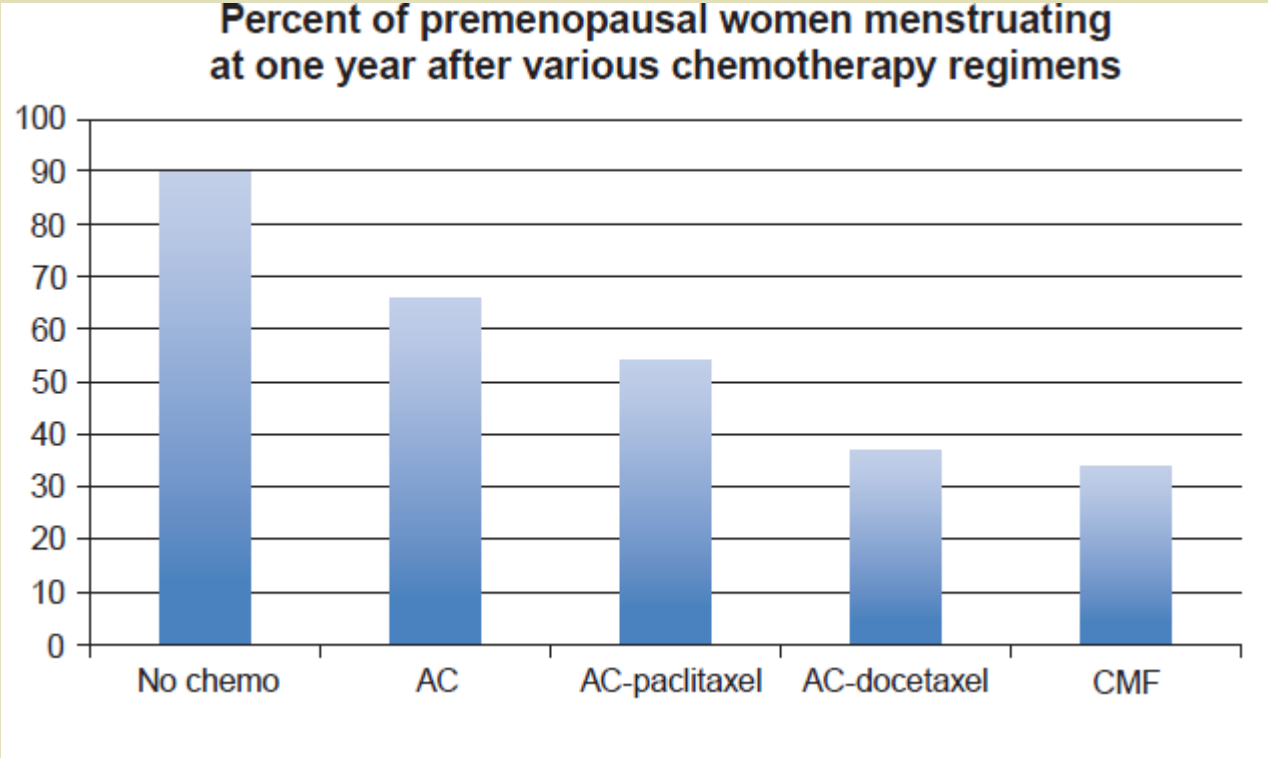
35% of *successfully treated patients advised to abort by their physicians*

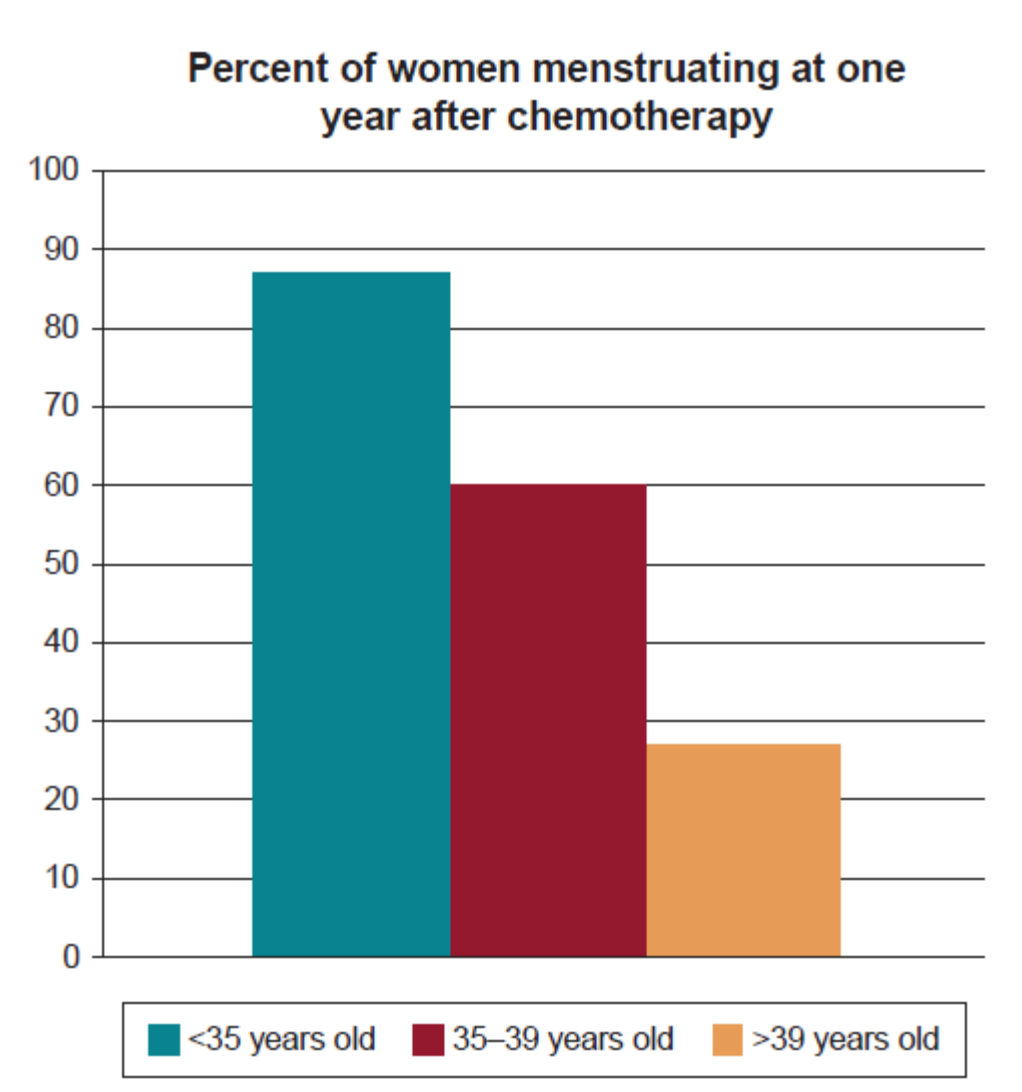
1. Assisted reproduction and its effect on long-term outcome.
2. Safety of pregnancy following breast cancer and the impact of pregnancy on breast cancer survival
3. Timing of pregnancy after breast cancer in hormone receptor positive breast cancer survivors.
4. Practical Issues Pertaining to Pregnancy and Lactation after Breast Cancer.
5. The risk of preterm birth and growth restriction in pregnancy after cancer

1-Assisted reproduction and its effect on long-term outcome.

The chance of being sterile was almost as devastating as my cancer diagnosis itself

- Many young wom
  undergo neoadjuvant
  agents that can damage the
  accelerated ovarian aging, a reduced ovarian reserve, and a risk of premature ovarian failure.
- Available data confirm that risk of CRA is related to increasing age and increasing cumulative dose of cytotoxic chemotherapy, in particular, alkylating agents.
- The risk of **premature ovarian failure and subsequent infertility could still be high even for those women who resume menses after chemotherapy.**


Percent of premenopausal women menstruating at one year after various chemotherapy regimens
100
90
80
70
60
50
40
30
20
10
0
No chemo
AC
AC-paclitaxel
AC-docetaxel
CMF


Percent of women menstruating at one year after chemotherapy
100
90
80
70
60
50
40
30
20
10
0
<35 years old
35–39 years old
>39 years old

Endocrine therapy:

- Adjuvant ET decreases the risk of recurrence and the incidence of contralateral disease and increases survival
- premenopausal women diagnosed with breast cancer are more likely to present with hormone receptor-negative disease compared with older women
- Two thirds of young premenopausal women will still have estrogen receptor positive tumors and should be offered tamoxifen.

- However, because of the potential teratogenic effects, women must avoid pregnancy during treatment
- Given the benefits seen in the TEXT (tamoxifen and exemestane trial) and SOFT (suppression of ovarian function trial), many YWBC, especially those < 35 years old, are now advised to take an OS plus an AI, rather than tamoxifen.
- Regardless of the type of ET used, adhering to treatment recommendations requires delaying childbearing for a significant period.

Approach to a Patient Concerned about Fertility

- ASCO:

1. The first step in counseling is to assess each pati
2. The second step i and/or infertility

- Fertility Preser

Oocyte cryopreservation by experienced centers is now nearly as effective as embryo cryopreservation in young women and is particularly appealing to patients who do not have a male partner and do not wish to use donor sperm.

Options	Considerations
Embryo cryopreservation	- Requires sperm so stimulation, increasing hormone levels
Oocyte cryopreservation	- Requires ovarian sti ation; efficacy dependent on experience of center
Ovarian tissue cryopreservation	- Invasive, potential for reintroduction of cancer; experimental
Ovarian suppression	- Menopausal symptoms and bone thinning; efficacy unknown

Provide ongoing counseling regarding fertility, menopausal, and family planning concerns in follow-up

Ovarian tissue

- in theory could allow
follicles (containing
without ovarian st
high hormone lev
remove the ovaria
- However, this metho
limitations, and there ha
reports of live births to date.
- This technique is also associate theoretical concerns about the reintroduction of cancer cells via the reimplanted ovarian tissue though a recent small *study showed no metastatic cells in 51 biopsies of cryopreserved ovaries from patients with breast cancer*

Cryopreservation of embryos following *in vitro* fertilization (IVF) is a standard procedure with a relatively high success rate in infertile women, with an approximately 20% to 40% live birth rate per transfer of 2 to 3 thawed embryos depending on maternal age

Ovarian Stimulation for Egg Retrieval

- ovarian stimulation for cryopreservation of oocytes or embryos ⇒ might increase the risk of cancer recurrence, particularly in the setting of hormone receptor-positive disease.
- Estradiol levels during traditional stimulated IVF cycles can be greater than 2,000 pg/mL, while levels average less than 300 pg/mL in the normal menstrual cycle

- ***Tamoxifen*** and ***letrozole*** have been used for ovarian stimulation in women with recently diagnosed early breast cancer
- When letrozole is used during ovarian stimulation, *estradiol levels are not substantially higher than in natural menstrual cycles*.
- The 2- to 6- week period required for this procedure prior to beginning systemic breast cancer treatment may not be prudent in some disease settings (e.g., inflammatory breast cancer) though this is reasonable for many patients, usually in the interval between surgery and the start of chemotherapy.

Assessment of Ovarian Function and Fertility After Breast Cancer

- Women with decreased ovarian reserve often have shorter menstrual cycles due to accelerated follicle development.
- FSH levels on the third day of menses >10 mIU/mL, resulting in E2 levels >75 pg/mL, cause early ovulation, which is associated with reduced fertility.
- Inhibin levels and anti-mullerian hormone (AMH) levels may also clarify fertility status.
- AMH is produced by early-stage ovarian follicles and, therefore, demonstrates ovarian reserve as reflected by the pool of remaining primordial follicles

- A multi-centre retrospective study in which women who were diagnosed with breast cancer between 2000 and 2009, and had a pregnancy following breast cancer diagnosis were eligible.
- Patients were divided into two groups *according to whether ART following primary systemic therapy was performed* to achieve pregnancy.
- ART procedures included:
  - ovulation induction (clomiphene citrate, gonadotropins) associated with intercourse or intra-uterine insemination (IUI)
  - controlled ovarian stimulation (COS) with gonadotropins for in vitro fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI)
  - egg donation

- Among those pregnant women, only 25 (12.6%) reported pregnancies following ART.
- Interestingly, we observed that women who underwent ART had somehow more favourable prognostic parameters, suggesting that physicians were probably more selective in offering ART to patients with relatively good prognosis.

- A retrospective chart review from 2006 to 2014 was performed to ***evaluate women aged 40 years and younger who were diagnosed with breast cancer and treated with chemotherapy and/or antihormonal therapy.***
- Pregnancy after treatment was more common among those pursuing IVF consultation or prescribed a GnRH agonist.
- In treating young breast cancer patients, **it is important to assess fertility desire, discuss treatment risks relating to fertility, and discuss preservation options.**

number	Fertility documentation	GnRH agonist and IVF consultation	IVF consultation	GnRH agonist	Pregnancy rate at amean of 3 years post treatment
303	80(26%)	5 (6%)	50 (63%)	16 (20%)	7%

- Ann Surg Oncol (2016) 23:3175–3181

2- Safety of pregnancy following breast cancer

- 19 studies met our inclusion criteria (cases = 1829; controls = 21,907) for pregnancy following breast cancer diagnosis.
- There was ***a decreased risk of recurrence or disease progression amongst women who became pregnant*** following a diagnosis of breast cancer compared to those who did not become pregnant.

number	HR (CI 95%) for OS	Pval
Case (n) 1829	0.65	0.02
Controls (n) 21907		

- Breast Cancer Res Treat (2016) 160:347–360

Table 2 Study characteristics (pregnancy after diagnosis) ($n = 19$)

First author	Year	Country	Study type	Cases	Controls	Age	Follow-up (years)	Outcomes measured	HME bias?
Cooper [48]	1970	America	CCS	28	56	<40	5	OS*	No
Ribeiro [49]	1977	United Kingdom	CCS	40	120	<45	10	OS+	No
Mignot [50]	1986	France	CCS	68	136	<45	10	OS+	No
Ariel [51]	1989	America	CCS	46	900	<45	10	OS*	No
Sankila [26]	1994	Finland	CCS	91	471	<40	15	OS	No
Von Schoultz [1]	1995	Sweden	Population based	50	2069	<50	7	DFS	Yes
Lethaby [52]	1996	New Zealand	Population based	14	334	<45	10	OS*	Yes
Valentgas [53]	1999	America	CCS	53	265	<45	15	OS	No
Gelber [57]	2001	International	CCS	94	188	<42	10	OS	No
Mueller [58]	2003	America	CCS	329	2002	<45	17	OS	No
Blakely [74]	2004	America	Hospital based	47	323	<35	22	OS*, DFS	Yes
Ives [59]	2007	Australia	Population based	123	2416	<45	21	OS	Yes
Kroman [60]	2008	Denmark	Population based	199	10,037	<45	30	OS	No
Largillier [56]	2009	France	Hospital based	118	762	<35	10	OS, DFS	Yes
Rippy [54]	2009	United Kingdom	Cohort	18	244	<45	5	OS*	Yes
Kranick [55]	2010	America	CCS	107	344	<45	12	OS, DFS	No
Cordoba [34]	2012	Spain	Population based	18	97	<36	5	OS*	Yes
Azim [27]	2013	Belgium	CCS	333	874	<48	5	OS, DFS	No
Valentini [40]	2013	Canada	Population based	53	269	<45	15	OS	No

Studies in bold are unique to this meta-analysis and were not included in previous meta-analyses

* Studies for which OR was calculated from crude data

- Of the 17 studies included in the analysis on OS, there were **9 studies that found a positive or null association between pregnancy following breast cancer and mortality.**
- Kranick et al. found no significant prognostic difference between women who had a pregnancy subsequent to diagnosis and those who did not. A small non-significant adverse effect was found for women who conceived within 12 months of diagnosis.

- In contrast, several studies have **demonstrated improved survival outcomes** for women conceiving after treatment for breast cancer.
- These findings, however, may be a result of the “healthy mother” effect.

Controlling for the “healthy mother effect”

- The “healthy mother effect” is a selection bias where only women who have had favourable outcomes following diagnosis are likely to conceive.
- Studies control for this bias by matching for **nodal status, ER status, disease-free interval and treatment.**

number	HR (CI 95%) for OS	Pval
Case 1387	0.65	0.06
Control 1749		

- Breast Cancer Res Treat (2016) 160:347–360

- There was not a significant decreased risk of recurrence and disease progression for women who became pregnant following diagnosis of breast cancer [pHR 0.93; 95 % CI 0.68–1.28, p = 0.21].
- data were only pooled across two studies.
- **The protective effect of pregnancy appears less pronounced in studies that have accounted for the "healthy mother effect" bias as would be expected**.

- Breast Cancer Res Treat (2016) 160:347–360

- Among the 7553 women in the study (mean age at diagnosis, 39.1 years; median, 40 years; range, 20-44 years) the 5-year actuarial survival rate was 87.5%(95%CI, 86.5%-88.4%)
- Pregnancy did not adversely affect survival in women with breast cancer.
- For breast cancer survivors who wish to conceive, the risk of death is lowest if pregnancy occurs 6 months or more after diagnosis.

	5 yr survival rate	HR
Women with no pregnancy	87.5%	
Women with pregnancy before breast cancer	85.3%	1.03
Pregnancy-associated breast cancer	82.1%	1.18
Women who had pregnancy 6 months or more after breast cancer diagnosis		0.22

JAMA Oncol. doi:10.1001/jamaoncol.2017.0248

A matched case control study by Azim et al.

- Large cohort of 333 patients
- Women who became pregnant after diagnosis experienced better OS (HR 0.72; 95 % CI 0.54–0.97) than the controls who did not
- women who became pregnant within 2 years of diagnosis had increased DFS compared to matched controls
- those who became pregnant more than 2 years after diagnosis had comparable outcomes

- Gorman et al. investigated the issue of healthy mother effect:
- by comparing physical and mental health
- in 27 young patients who became mother after their affection by breast cancer with 54 age- and stage-matched controls.
- Mental health scores were slightly superior in the case group but physical health scores were not different between the 2 groups.
- **They concluded that mental health may be part of the healthy mother effect**.

Safety of Py following BC- 5

- In **1997**, Kroman *et al*:
  - data of 5725 BC cases < 45 y from the Danish BC cooperative Group:
  - 173 cases of subsequent full-term Py
    - non-significant lower risk of death compared with those without full-term Py

- Study updated **after 10 y**
  - 10236 cases of BC < 45 y
    - 371 became pregnant
      - significant reduction in mortality in these

Author(s)	Publication year	Number of cases studied/ studies reviewed	F/U	Limitations/ Remarks	Results
Cooper et al [49]	1970	32 stage I pregnant out of 7,381 cases			no adverse effect of Py on 5-yr survival
Petrek [26]	1994	review of 11 studies		Small sample size in all studies	Very good survival
Kroman et al [50]	1997	173 cases			non-significant lower risk of death
Upponi et al [51]	2003	review of all previous works		serious limitations in all studies1	1)no adverse effect in any study, 2) better survival in some
Blakely et al [52]	2004	383 cases less than 35 yrs old	13 yrs		equal or better survival
Ives et al [27]	2007	175 pregnant out of 2539 cases			equal or better survival
Rippy et al [12]	2009	18 pregnant out of 164 cases less than 45 yrs			equal or better survival
Kroman et al [53]	2008	371 pregnant out of 10236 cases under 45 yrs		Update of previous study [14]	significant reduction in mortality
Kranick et al [54]	2010	107 cases	12 yrs		equal or better survival
Valachis et al [55]	2010	Review of all previous articles (20 eligible studies)		all studies had limitations1	1)lower survival in 1 2)no significant difference in 9 3) significant increased survival in 18[2]
De Bree et al [8]	2010	Review article			1)no inferior survival reported 2)statistically significant better survival in 4 of 7 population-based studies 3) no increased recurrence
Azim et al [56]	2011	1417 pregnant out of 20,000 cases in the review of 14 case–control, population-based and hospital-based studies			41% reduced risk of mortality below 35 yrs without axillary involvement

Several reviews investigated the issue of spontaneous abortion in weight for gestational age and five minute APGAR of the newborn

- From an international multi-center cohort study of 12,084 women with a BRCA1 or BRCA2 mutation, we identified ***128 case subjects who were diagnosed with breast cancer while pregnant or who became pregnant after a diagnosis of breast cancer***.
- These women were age-matched to 269 mutation carriers with breast cancer who did not become pregnant (controls).

number	15 Yr survival rate	HR CI 95%	P val
Case (n) 128	91.5%	0.76	0.56
Control (n) 269	88.6%		

Breast Cancer Res Treat (2013) 142:177–185

- **It is demonstrate that pregnancy is safe following a breast cancer diagnosis, and indeed associated with an improved prognosis.**
- This result is reassuring for women who have received treatment for breast cancer and are concerned that a pregnancy may worsen their chance of survival.

- The International Breast Cancer Study Group POSITIVE trial (pregnancy outcome and safety of interrupting therapy for women with endocrine responsive breast cancer) is **investigating the safety of ET interruption and conception in young women with HR+ BC.**

several hypotheses have been proposed as the mechanism of the apparent protective effect of pregnancy after breast cancer:

1. **Alloimmunisation against the cancer:**
   This hypothesis speculates that because breast cancer cells and foetal cells share common antigens, a mother's immune system is activated during pregnancy and eliminates not only circulating foetal cells but also quiescent tumour cells, resulting in improved prognosis.

2. **Substantial increase in oestrogen levels:**
   increase in oestrogen levels in pregnancy after deprivation may induce apoptosis in oestrogen-responsive breast cancer cells.

3- **More complete differentiation and increased DNA repair:** It makes them more resistant to cancerous transformation, stimulation of genes which program cell differentiation and death, and inducing a long-term protective effect over the breast by imprinting a genomic signature of pregnancy in mammary epithelium

3-Timing of pregnancy after breast cancer in hormone receptor positive breast cancer survivors

- A difference in breast cancer recurrence in women who became pregnant within 5 years after their diagnosis of early-stage breast cancer has not been demonstrated.

- Many women had interrupted their adjuvant endocrine therapy to become pregnant and breast feed after pregnancy and later returned to complete the standard 5 years of therapy.

Clinical Breast Cancer, Vol. -, No. -, --- ª 2017 Elsevier Inc.

- After completing anticancer therapy, it is generally advised to wait at least 3–6 months before attempting to get pregnant, to avoid genotoxic effects of cancer treatment
- A common recommendation is for breast cancer survivors to wait at least 2 years after treatment before attempting a pregnancy in an effort to get them beyond the period of highest risk of recurrence.

- However, the available data have not revealed that an earlier pregnancy impairs disease outcomes.
- Given that many women with breast cancer are at risk of recurrence long beyond the first few years after diagnosis, and given that fertility wanes with age, some women elect not to wait a substantial period of time to become pregnant after diagnosis.

- However, in a subgroup analysis of 5 studies, involving 187 and 353 patients, who became pregnant within 6–24 months or beyond 2 years, respectively, **early pregnancy did not affect overall outcome**

- Petrek revealed no difference in half of old studies and much better prognosis for an interval of 2 years.

- The improved survival shown by Ives et al in their study of patients in the Western Australian population in 1982-2003 was only significant for a time interval of more than 2 years, although they showed also a protective effect for a 6-24 months wait time.

- In their study in 2010, Verkooijen et al. showed that a time interval of 2 years lead to a more than threefold increased risk of death compared to 4 years.
- All other studies from then on were mostly in favor of the safety of early pregnancy in early breast cancer harboring low-risk features.
- However, because most tumor recurrences occur in the first 2 years following diagnosis, it is commonly regarded as safe to wait at least 2 years.

4- Practical Issues Pertaining to Pregnancy and Lactation after Breast Cancer

- **In a multicenter, retrospective review of 53 women who became pregnant after BCT:**
- one-third had some lactation from the affected breast. Many of these women reported low milk output or the baby preferring the untreated breast
- only 25% of women were able to successfully breast-feed from the treated breast.
- While it is evident that lactation works as primary prevention against breast cancer, there have been no efforts to evaluate the benefits of lactation in breast cancer survivors, in part because so few survivors have successfully breast-fed.

4- The risk of preterm birth and growth restriction in pregnancy after cancer

- In infants born to breast cancer survivors, a slightly higher risk of preterm birth is seen compared with women without cancer, and a moderately higher risk of low birth weight.
- estimated RR for preterm birth in breast cancer survivors was 1.3 (95% CI: 1.1, 1.6).
- A Danish study of births to breast cancer survivors diagnosed between 1943 and 2002 had a similar result
- Higher risks of very preterm birth in survivors of invasive breast cancer (RR1.7, 95% CI: 1.0, 2.8).

Conclusion:

- Many challenging issues surround pregnancy after breast cancer but we should continue to improve the dissemination of information, including all available treatment options.
- A comprehensive cancer care model should include educating women not only about their diagnosis and treatment but also about what impact it will have on their reproductive health and fertility.
- .

conclusion:

- In concordance with ASCO and NCCN guidelines, we propose that, for all premenopausal women diagnosed with breast cancer, a documented FD and appropriate referral become the new quality metric for dedicated breast cancer centers governed by the National Accreditation Program for Breast Centers.
- An FD should include assessing a women's desire for future fertility, the impact a specific treatment regimen may have on future fertility and, if desired, an exploration of options for fertility preservation

- ***Family-building*** is a key issue for many young women who successfully complete primary treatment of BC.
- Many YWBC want to have children in the future and are uncertain about their options or where to find reliable information and guidance.

THANK YOU