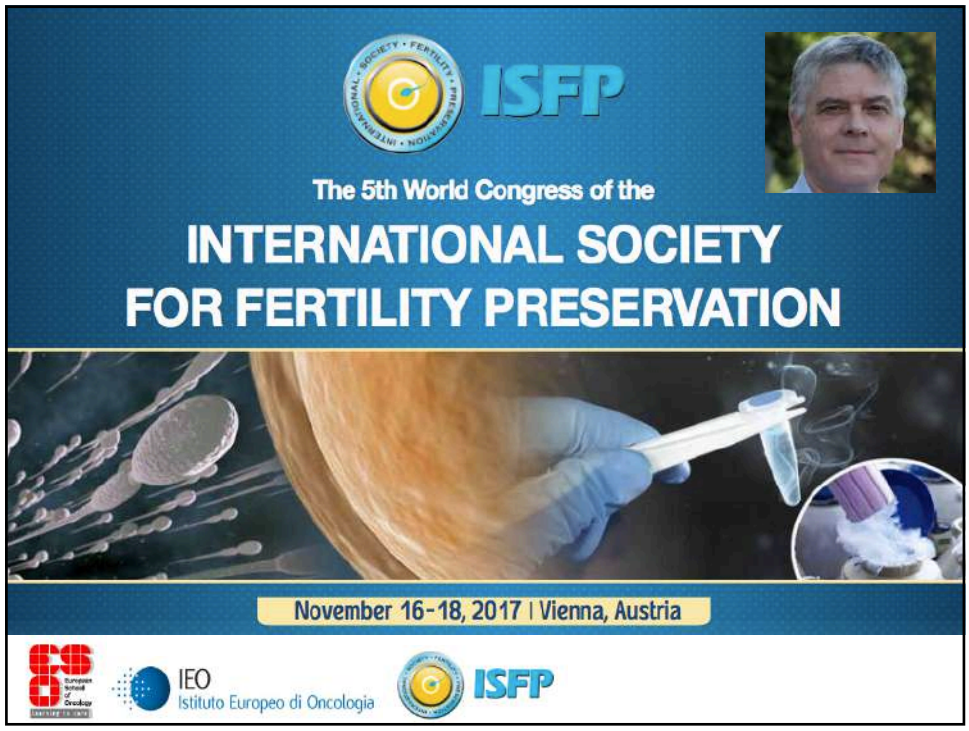

Pregnancy in breast cancer patients: Timing, safety, and treatment approaches (during and post-cancer)

Fedro A Peccatori, MD PhD
European Institute of Oncology
European School of Oncology
MILAN, ITA

Disclosures

No relevant relationships to disclose

Lecture outline

- Safety and timing of spontaneous pregnancy in BC survivors
- Safety and feasibility of ART pregnancy in BC survivors
- Pregnancy outcome in BC survivors
- Breast cancer during pregnancy: a need for action

SAFETY AND TIMING OF SPONTANEOUS PREGNANCY IN BC SURVIVORS

GYNECOLOGICAL ENDOCRINOLOGY

http://informahealthcare.com/gye
ISSN: 0951-3590 (print), 1473-0766 (electronic)

Gynecol Endocrinol, 2015; 31(6): 458–464
 DOI: 10.3109/09513590.2014.1003293

informa healthcare

BREAST CANCER AND FERTILITY

Attitudes on fertility issues in breast cancer patients: an Italian survey

Nicoletta Biglia[1]*, Rosalba Torrisi[2]*, Marta D'Alonzo[1]*, Giovanni Codacci Pisanelli[3], Selene Rota[2], and Fedro Alessandro Peccatori[3]

[1]*Department of Gynaecology and Obstetrics, University of Turin, Turin, Italy,* [2]*Department of Hematology and Oncology, Humanitas Cancer Center, Milan, Italy, and* [3]*Fertility and Procreation Unit, Division of Gynecologic Oncology, European Institute of Oncology (IEO), Milan, Italy*

Attitudes on fertility issues in breast cancer patients: an Italian survey

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10. May a pregnancy in women previously affected by BCa increase the risk of recurrence?

Only 51% of oncologists believed that pregnancy does not affect the prognosis of BCa patients, while 49% of them supports that an increase in estrogen levels during pregnancy could stimulate the growth of hidden tumor cells (Statement 10).

Pregnancy after breast cancer

Safety of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies

Hatem A. Azim Jr. [a,b], *Luigi Santoro* [c], *Nicholas Pavlidis* [d], *Shari Gelber* [e], *Niels Kroman* [f], *Hamdy Azim* [g], *Fedro A. Peccatori* [h,*]

Eur J Cancer. 2011 Jan;47(1):74-83.

Safety: meta-analysis

14 studies

7 case control studies
4 population based studies
3 hospital based studies

1244 cases e 18145 controls
Median time to pregnancy: 33 months
Follow-up 5-30 years

Data pooling using random effect

Sensitivity analysis and subgroup analysis

Safety of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies

Hatem A. Azim Jr. [a,b], Luigi Santoro [c], Nicholas Pavlidis [d], Shari Gelber [e], Niels Kroman [f], Hamdy Azim [g], Fedro A. Peccatori [h,]*

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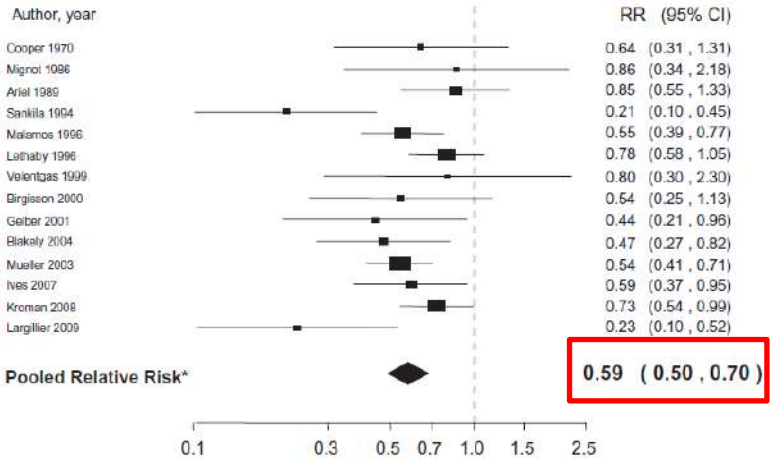
Safety: meta-analysis

All studies, 41% reduction of death



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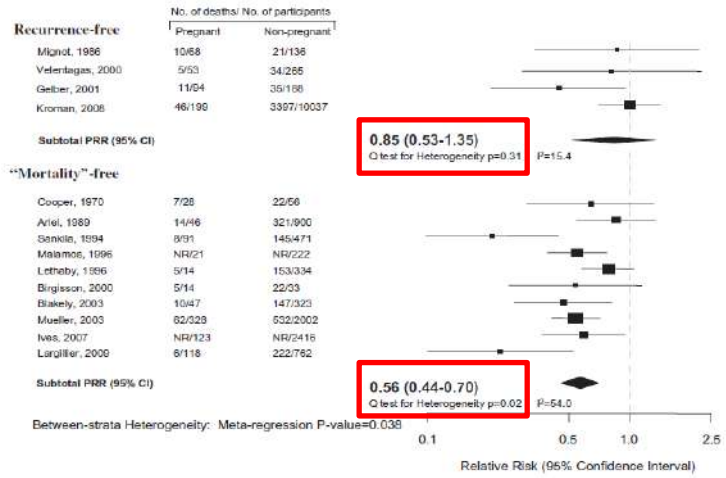
Safety: meta-analysis

15% reduction of death with more stringent criteria



Safety of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies

Hatem A. Azim Jr. [a,b], Luigi Santoro [c], Nicholas Pavlidis [d], Shari Gelber [e], Niels Kroman [f], Hamdy Azim [g], Fedro A. Peccatori [h,]*

Time to pregnancy

187 patients who became pregnant within 6-24 months
353 patients who became pregnant after 2 years

	No. of studies	PRR (95% CI)	p-value[a]	I^2 parameter, %	χ^2 for heterogeneity p-value
Time since BC diagnosis to pregnancy (months)					
6–24	5	0.34 (0.13–0.90)			71.5
>24	5	0.55 (0.36–0.84)		0.584	39.2

Shorter time to pregnancy not associated with a worse prognosis

Safety of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies

Hatem A. Azim Jr. [a,b], Luigi Santoro [c], Nicholas Pavlidis [d], Shari Gelber [e], Niels Kroman [f], Hamdy Azim [g], Fedro A. Peccatori [h,]*

Pregnancy after breast cancer

Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study

Hatem A. Azim Jr, Niels Kroman, Marianne Paesmans, Shari Gelber, Nicole Rotmensz, Lieveke Ameye, Leticia De Mattos-Arruda, Barbara Pistilli, Alvaro Pinto, Maj-Britt Jensen, Octavi Cordoba, Evandro de Azambuja, Aron Goldhirsch, Martine J. Piccart, and Fedro A. Peccatori

J Clin Oncol. 2013 Jan 1;31(1):73-9

Pregnancy after breast cancer

BRIEF COMMUNICATION

Long-term Safety of Pregnancy Following Breast Cancer According to Estrogen Receptor Status

Matteo Lambertini, Niels Kroman, Lieveke Ameye, Octavi Cordoba, Alvaro Pinto, Giovanni Benedetti, Maj-Britt Jensen, Shari Gelber, Maria Del Grande, Michail Ignatiadis, Evandro de Azambuja, Marianne Paesmans, Fedro A. Peccatori, Hatem A. Azim Jr.

JNCI J Natl Cancer Inst (2018) 110(4): djx206

Multicenter study in ER+/ER- patients

Retrospective, multicenter cohort study (7 Institutions)

Primary endpoint: DFS ER+ pts.
(Two sided test a= 5% , b=20%, 226 events 645 pts for HR 0.65)

Secondary endpoints: DFS in ER- pts., OS

Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study

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Multicenter study in ER+/ER- patients

333 cases with pregnancy after breast cancer
874 non pregnant controls
matched for ER, stage, adjuvant treatment, age, year at diagnosis

Mean age: 32y (21-44)
Node positive: 43%
ER+: 58%
Chemo: 79%

323 pregnancies
188 live birth
135 abortions or miscarriages
Median time to pregnancy: 27 months

Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study

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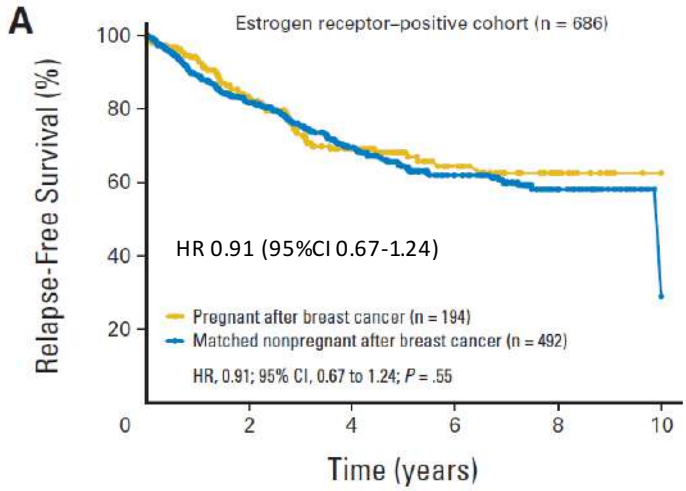
RFS in ER+ patients



Median time from diagnosis to pregnancy 2.4 years

Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study

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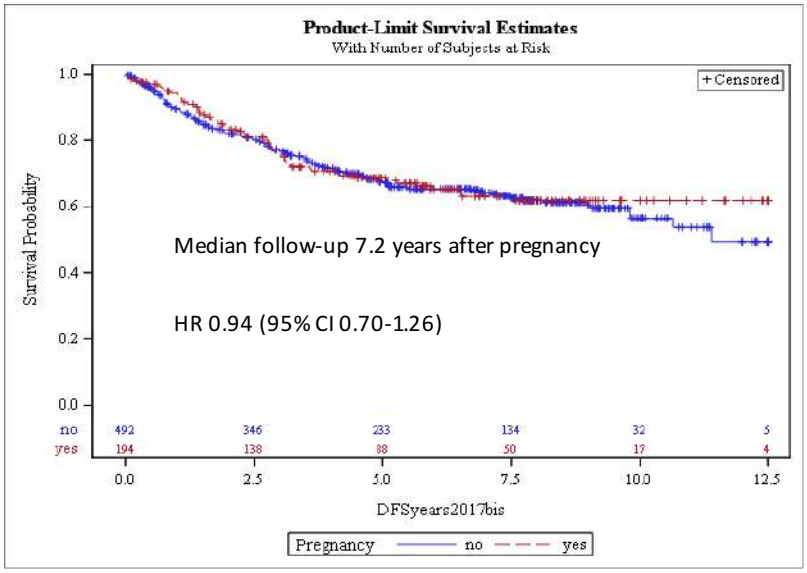
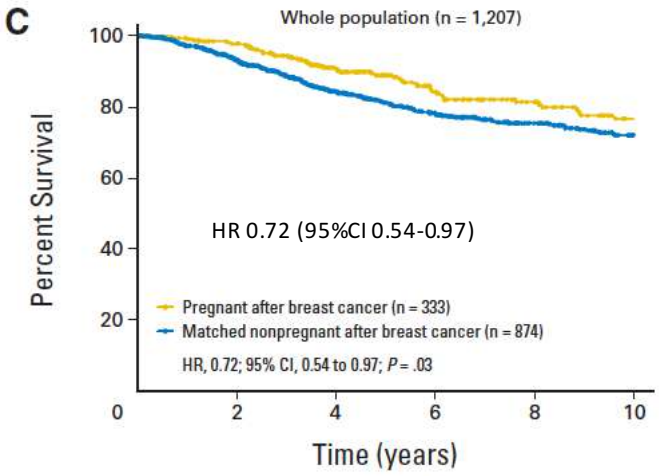
RFS in ER+ patients



JNCI J Natl Cancer Inst (2018) 110(4): djx206

OS in ER+/ER- patients



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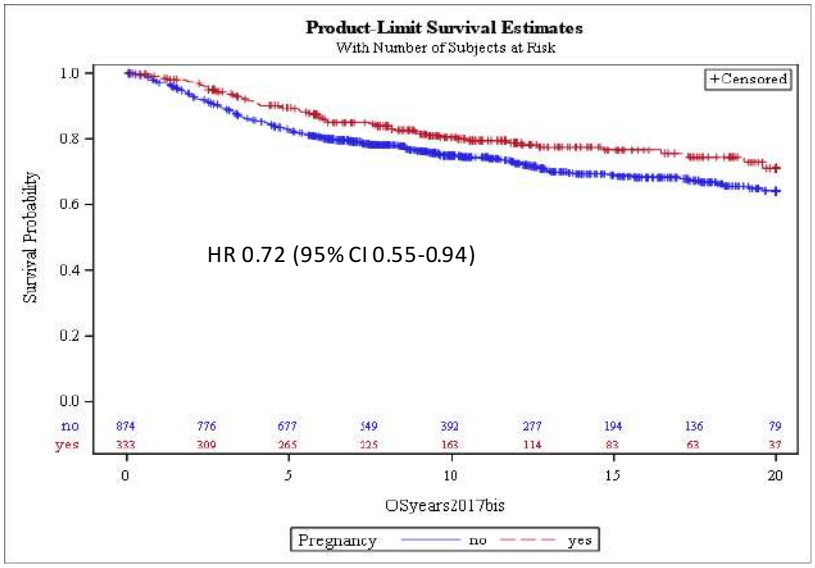
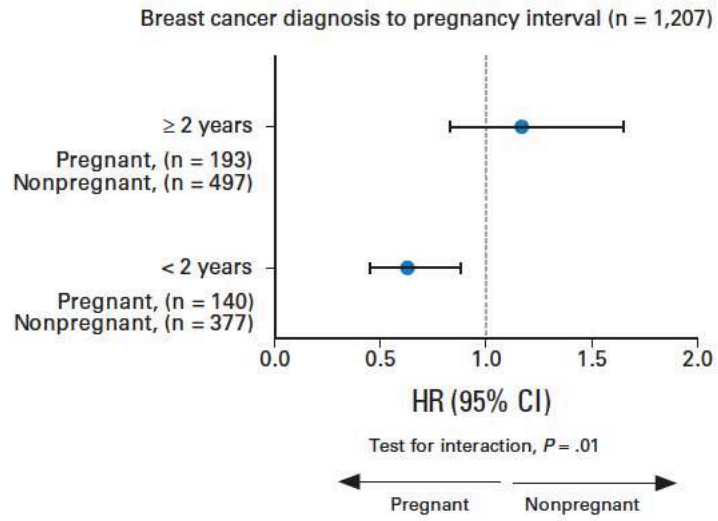
OS in ER+/ER- patients



JNCI J Natl Cancer Inst (2018) 110(4): djx206

Pregnancy outcome according to time to pregnancy



Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study

SAFETY AND TIMING OF SPONTANEOUS PREGNANCY IN BC SURVIVORS

- ✓ Pregnancy in breast cancer survivors is safe: no increased risk of relapse or mortality in ER negative or ER positive tumors
- ✓ Timing of pregnancy after breast cancer is still debated: no increased risk when pregnancy occurred after 6 months from diagnosis, but most data are for pregnancy after 2 years.

SAFETY AND FEASIBILITY OF ART PREGNANCY IN BC SURVIVORS

Pregnancy with ART in BC survivors

Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome

Oranite Goldrat [a,b], Niels Kroman [c], Fedro A. Peccatori [d], Octavi Cordoba [e], Barbara Pistilli [f], Oejvind Lidegaard [g], Isabelle Demeestere [b], Hatem A. Azim Jr. [h,*]

Eur J Cancer. 2015;51:1490-1496

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Safety of pregnancy with ART in BC survivors

Institution/Group	Spontaneous preg, n	ART, n	
Number	173	25	
Mean age at diagnosis (range)	31.4 (29-34)	33.7 (31-37	P=0.009
Tumor size > T2	10 (5.8%)	0	
Nodal status • Negative • Positive	 100 (58%) 73 (42%)	 19 (76%) 6 (24%)	 P=0.12
Histological grade • 1 • 2 • 3 • unknown	 16 (9%) 43 (25%) 103 (60%) 11 (6%)	 5 (20%) 10 (40%) 9 (36%) 1 (4%)	
ER status • Negative • Positive	 91 (53%) 82 (47%)	 17 (68%) 8 (32%)	 P=0.19
Adjuvant chemotherapy received	118 (68%)	15 (60%)	
Median duration of hormonal therapy in months (range)	48 (30-60)	33 (24-44)	

EJC

Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome
Oranite Goldrat [a,b], Niels Kroman [c], Fedro A. Peccatori [d], Octavi Cordoba [e], Barbara Pistilli [f], Oeivind Lidegaard [g], Isabelle Demeestere [h], Hatem A. Azim Jr. [h,*]

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Safety of pregnancy with ART in BC survivors

Table 2
Pregnancy outcomes.

	Spontaneous pregnancy group, $N = 247$ (%)	ART pregnancy group, $N = 34$ (%)
Mean age at conception (years)	35.3	38.5
Interquartile range	33–38	34–43
Median time from diagnosis to conception (mo)	42	48
Interquartile range	24–63	36–84
Outcomes		
Miscarriage	31 (12.6)	8 (23.5)
Induced abortion	24 (9.7)	0
Term pregnancy	190 (76.9)	26 (76.5)
Other*	2 (0.8)	0
Live birth	$N = 190$	$N = 26$
Single	184 (99.8)	24 (92.3)
Twins	6 (3.2)	2 (7.7)

Assisted reproductive technology (ART):
13 egg donation; 13 IVF; 11 ovulation induction (clomid)

EJC

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Safety of pregnancy with ART in BC survivors

Table 3
Long-term survival outcome.

	Spontaneous pregnancy group, $N = 173$ (%)	ART pregnancy group, $N = 25$ (%)
Interval diagnosis-last clinical FU (mo)	107	102
Interquartile range	81–131	85–123
Interval conception-last clinical FU (mo)	63	50
Interquartile range	37–89	27–72
Cancer related events (%)	28 (16)	2 (8)
Local recurrence	8 (4.6)	0
Distant recurrence	10 (5.7)	2 (8)
Contralateral breast cancer	7 (4)	0
2nd primary cancer (non-breast)	3 (1.7)	0
Death (n)	11 (6.3)	1 (4)

ART, assisted reproductive technology; FU, follow-up; mo, months.

EJC

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How effective is ART after cancer treatment ?

ORIGINAL ARTICLE *Reproductive epidemiology*

Assisted reproductive technology use and outcomes among women with a history of cancer†

Barbara Luke[1,*], Morton B. Brown[2], Stacey A. Missmer[3,4,5], Logan G. Spector[6], Richard E. Leach[1], Melanie Williams[7], Lori Koch[8], Yolanda R. Smith[9], Judy E. Stern[10], G. David Ball[11], and Maria J. Schymura[12]

[1]Department of Obstetrics, Gynecology, and Reproductive Biology, College of Human Medicine, Michigan State University, East Lansing, MI, USA [2]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA [3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA [4]Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [5]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [6]Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA [7]Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, USA [8]Illinois State Cancer Registry, Illinois Department of Public Health, Springfield, IL, USA [9]Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA [10]Department of Obstetrics and Gynecology, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA [11]Seattle Reproductive Medicine, Seattle, WA, USA [12]Bureau of Cancer Epidemiology, New York State Cancer Registry, New York State Department of Health, Albany, NY, USA

*Correspondence address. Tel: +1-517-353-1678; Fax: +1-517-353-1663; E-mail: lukeb@msu.edu

Human Reproduction, Vol.31, No.1 pp. 183–189, 2016
Advanced Access publication on November 17, 2015 doi:10.1093/humrep/dev288

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How effective is ART after cancer treatment ?

- ✓ 441 women diagnosed with cancer, 53.426 controls
- ✓ 133 breast cancer patients
- ✓ Median age at ART treatment 34.8 and 35.1 y/o, respectively
- ✓ Results stratified by autologous oocyte or donor oocytes


Assisted reproductive technology use and outcomes among women with a history of cancer†

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How effective is ART after cancer treatment ?

Cancer status and diagnosis	Women using only autologous oocytes		Women who ever used donor oocytes	
	n, women	%	*n*	%
	Probability of conception			
No cancer	48 138	55.0	4847	74.2
All cancers	393	28.8	48	70.8
		$P < 0.0001$		$P = 0.62$
	Probability of a live birth given conception			
No cancer	26 492	86.7	3598	86.9
All cancers	113	85.8	34	85.3
		$P = 0.78$		$P = 0.80$
	Probability of a live birth			
No cancer	48 138	47.7	4847	64.5
All cancers	393	24.7	48	60.4
		$P < 0.0001$		$P = 0.55$

Assisted reproductive technology use and outcomes among women with a history of cancer[1]

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Fertility and Sterility® Vol. 112, No. 6, December 2019 0015-0282/$36.00 https://doi.org/10.1016/j.fertnstert.2019.08.079

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SAFETY AND FEASIBILITY OF ART PREGNANCY IN BC SURVIVORS

- ✓ Pregnancy with assisted reproductive technology (ART) in breast cancer (BC) survivors is still rare
- ✓ No apparent increase in BC relapse or mortality after ART pregnancy
- ✓ IVF/ICSI with autologous oocytes after BC treatment is quite ineffective
- ✓ Egg donation can be considered in BC survivors with outcome that are not different from non-cancer patients

ISFP

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PREGNANCY OUTCOMES IN BC SURVIVORS

Pregnancy outcomes

Pregnancy Outcomes After a Breast Cancer Diagnosis: A Systematic Review and Meta-analysis

Brigitte Gerstl,[1] Elizabeth Sullivan,[2] Angela Ives,[3] Christobel Saunders,[4] Handan Wand,[5] Antoinette Anazodo[6]

Clinical Breast Cancer, 2017 article in press

Pregnancy outcomes

- ✓ 16 studies identified (7 population based, 9 cohort/control)
- ✓ 2,523 pregnancies after BC and 22,964 controls
- ✓ Mean time to pregnancy 29 months (11-63), mean time to first birth 40 months (10-228)

Clinical Breast Cancer, 2017 article in press

Pregnancy outcomes

COHORT and CASE/CONTROL studies

- ✓ Of 1,287 women who received systemic treatment after surgery (median age 33y), 14% became pregnant
- ✓ 12% experienced a miscarriage, 21% terminated pregnancy
- ✓ 72% had a live birth

Clinical Breast Cancer, 2017 article in press

Pregnancy outcomes

MATCHED POPULATION BASED studies

- ✓ Of 711 women, only 3% subsequently conceived
- ✓ Women with ER positive tumors were 4 times less likely to become pregnant compared to ER negative tumors

Clinical Breast Cancer, 2017 article in press

Pregnancy outcomes

RESEARCH ARTICLE Open Access

Prevalence of preterm, low birthweight, and small for gestational age delivery after breast cancer diagnosis: a population-based study

Kristin Zeneé Black[1*], Hazel B. Nichols[2], Eugenia Eng[1] and Diane Louise Rowley[3]

Black et al. Breast Cancer Research (2017) 19:11
DOI 10.1186/s13058-017-0803-z

IEO Istituto Europeo di Oncologia

Pregnancy outcomes

- ✓ North Carolina Cancer and birth registries (1990-2009)
- ✓ 512 births from mothers with previous breast cancer
- ✓ Average age at diagnosis 31.8 y, mean time to delivery 3.3 y
- ✓ Data were adjusted for multiple variables, including ethnicity and compared to general population (1,911,757 women)
- ✓ Prevalence ratios (PR) were estimated for:
  - Preterm birth (PTB)
  - Low birth weight (LBW)
  - Small for gestational age (SGA)

Prevalence of preterm, low birthweight, and small for gestational age delivery after breast cancer diagnosis: a population-based study

Breast Cancer Research (2017) 19:11

IEO Istituto Europeo di Oncologia

Pregnancy outcomes

RESULTS

- ✓ Increased prevalence rate of PTB, LBW and SGA for women with breast cancer history

PTB: 21.1% vs 10.8% PR 1.67 (95% CI 1.42-1.97)

LBW: 14.8% vs 8,8% PR 1.50 (95% CI 1.23-1.84)

SGA: 13.3% vs 11.2% PR 1.30 (95% CI 1.05-1.61)

- ✓ Risk was higher if BC patients received chemotherapy (2x) or births occurred within 2 years (2.5x)
- ✓ Data coherent with Australian, Swedish and Norwegian studies

Prevalence of preterm, low birthweight, and small for gestational age delivery after breast cancer diagnosis: a population-based study

Kristin Zenné Ruck[1*], Hazel B. Nichols[2], Eugenia Trig[1] and Diane Louise Rowley[1]

Breast Cancer Research (2017) 19:11

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PREGNANCY OUTCOME IN BC SURVIVORS

- ✓ Pregnancy in breast cancer survivors is still a rare event (3-15%).
  - Prospective studies of women seeking pregnancy needed
- ✓ Possibly increased risk of miscarriage and terminations.
  - Prospective studies and healthcare education needed
- ✓ Possibly increased prevalence of PTB, LBW and SGA.
  - Careful monitoring and prospective studies needed

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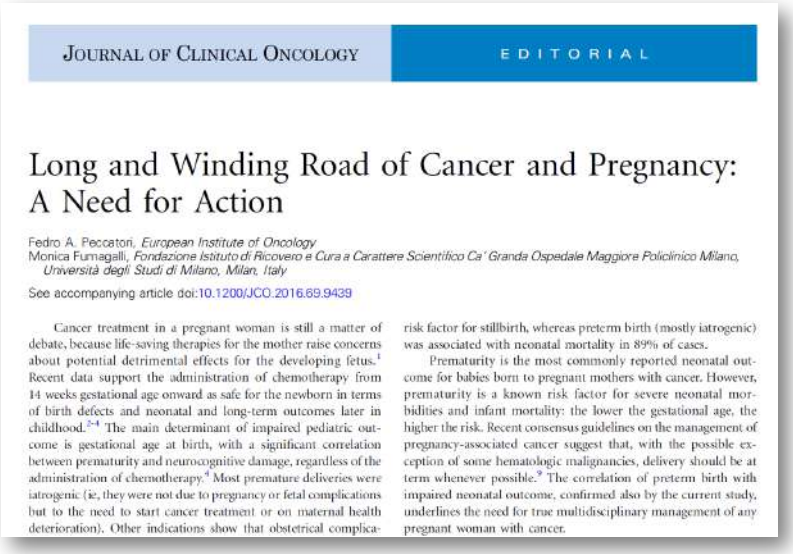
BREAST CANCER DURING PREGNANCY: A NEED FOR ACTION

Breast Cancer during Pregnancy



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Long and Winding Road of Cancer and Pregnancy: A Need for Action

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See accompanying article doi:10.1200/JCO.2016.69.9439

Cancer treatment in a pregnant woman is still a matter of debate, because life-saving therapies for the mother raise concerns about potential detrimental effects for the developing fetus.[1] Recent data support the administration of chemotherapy from 14 weeks gestational age onward as safe for the newborn in terms of birth defects and neonatal and long-term outcomes later in childhood.[2-4] The main determinant of impaired pediatric outcome is gestational age at birth, with a significant correlation between prematurity and neurocognitive damage, regardless of the administration of chemotherapy.[4] Most premature deliveries were iatrogenic (ie, they were not due to pregnancy or fetal complications but to the need to start cancer treatment or on maternal health deterioration). Other indications show that obstetrical complications risk factor for stillbirth, whereas preterm birth (mostly iatrogenic) was associated with neonatal mortality in 89% of cases.

Prematurity is the most commonly reported neonatal outcome for babies born to pregnant mothers with cancer. However, prematurity is a known risk factor for severe neonatal morbidities and infant mortality: the lower the gestational age, the higher the risk. Recent consensus guidelines on the management of pregnancy-associated cancer suggest that, with the possible exception of some hematologic malignancies, delivery should be at term whenever possible.[9] The correlation of preterm birth with impaired neonatal outcome, confirmed also by the current study, underlines the need for true multidisciplinary management of any pregnant woman with cancer.

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