Maternity After Breast Cancer

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Outline

- Background
- Pregnancy effects on survival outcomes
- Fertility preservation options
- Pregnancy after breast cancer
- Other pathways to parenthood

Chemotherapy-Induced Amenorrhea and Premature Menopause

- Chemotherapy-induced amenorrhea may be temporary or result in premature menopause
- Recovery depends on several factors:
  - Accelerated rate of decline in follicle reserve with increasing age
  - Less recovery with low baseline Anti-Müllerian hormone (AMH)
  - Duration, dose, and treatment regimen:
    - Greater recovery with AC than CMF
    - Lower rates of amenorrhea without alkylating agents
    - Impact of additional chemotherapy on recovery unknown
  - Fertility declines naturally during the 5-10 years required to complete adjuvant endocrine therapy
- Must identify women at risk for treatment-related infertility who desire future fertility as soon as possible after diagnosis

Partridge Eu J Ca 2007 Sukumvanich Cancer 2010, Petrek JCO 2006 Ganz JCO 2011, Ruddy Breast Ca Res Treat 2014, Henry The Oncologist 2014, Dillon Fertility and Sterility 2013, Letourneau Cancer 2012 Abuseif Cancer 2010, Ruddy BCRT 2015, Jacobson Fertility Sterility 2016, Lambertini BMC Medicine 2016, Letourneau cancer 2012, Beodschi Future Oncol 2016

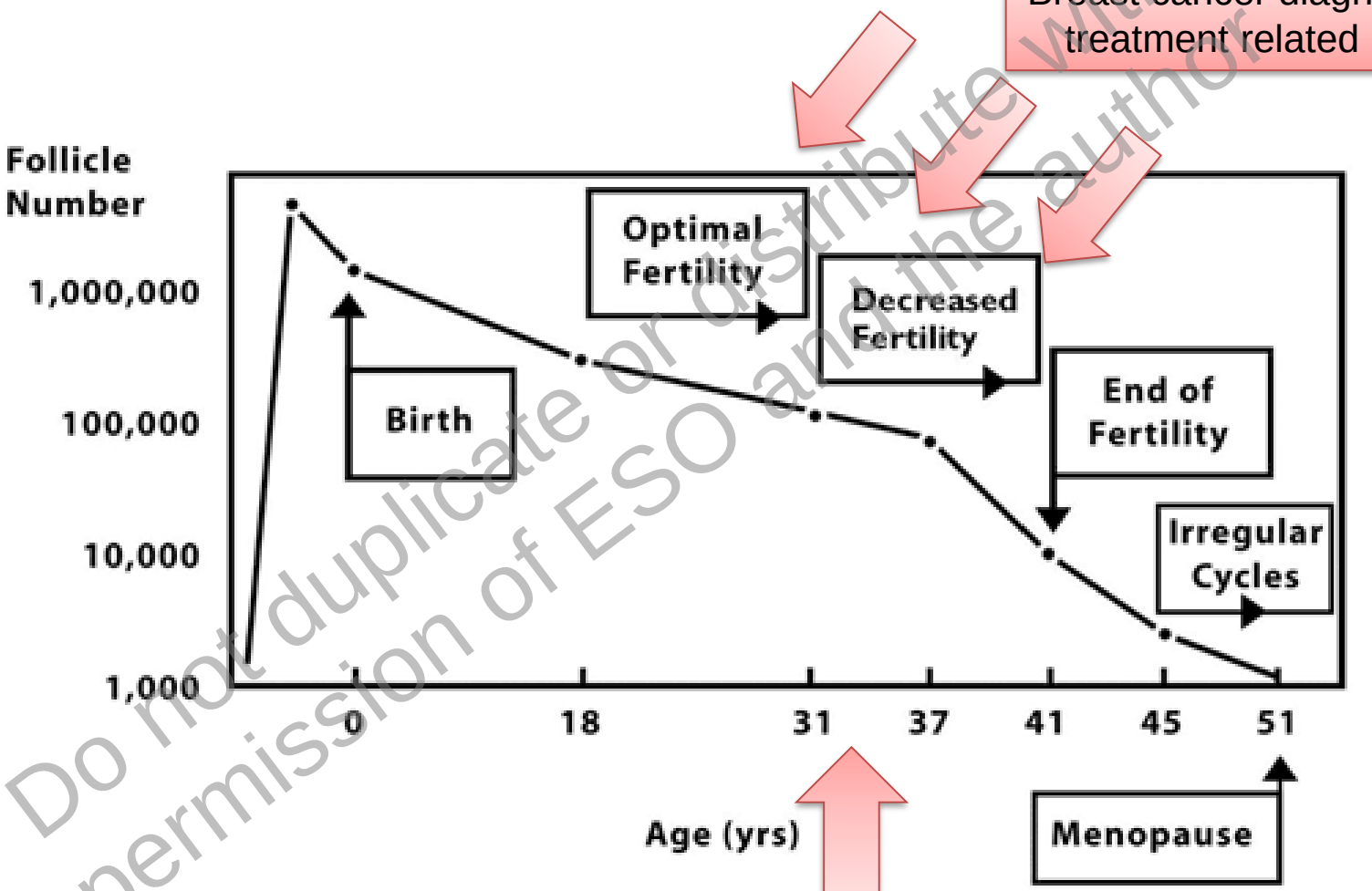
Rates of Pregnancy After Cancer: The Norwegian Cohort Study

Despite data suggesting pregnancy after cancer is safe, pregnancy rates particularly low among female survivors of cervical cancer, breast cancer and acute leukemia

	HR (95% CI) Comparing Rate of Pregnancy in Cancer Survivors to General Population by Cancer Type and Gender	
	Female	**Male**
Cervical Cancer (1988-2004)	0.35 (0.29-0.42)	
Breast Cancer (2001-2004)	**0.22 (0.13-0.38)**	
Testicular Cancer (1989-2004)		0.76 (0.70-0.83)
Stage I Ovarian Cancer (1988-2004)	0.67 (0.49-0.90)	
Hodgkin Lymphoma (1988-2004)	0.57 (0.46-0.71)	0.87 (0.73-1.04)
Acute Leukemia (1983-2004)	0.37 (0.23-0.62)	0.55 (0.38-0.80)

Stensheim Int J Cancer 2011

Oocytes Decline Over Time

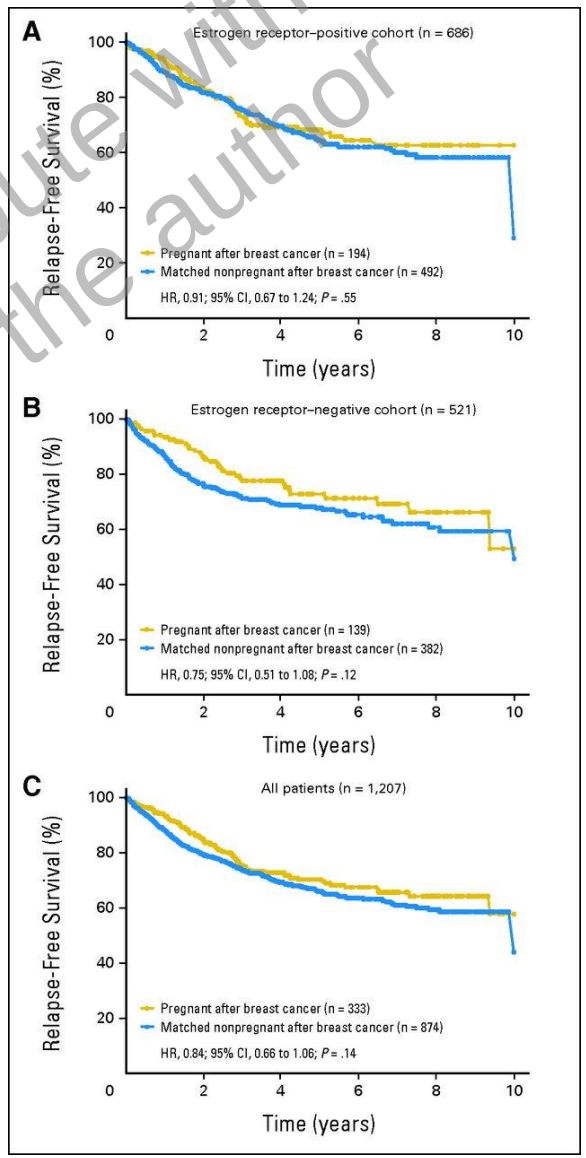


In the US, 45% of women with a college education will be >30 years old when they have their first child

Does Pregnancy after Breast Cancer Impact Prognosis?

- Multicenter retrospective cohort study
- Matched patients who became pregnant after breast cancer to patients who did not become pregnant (1:3)
- Median 2.4 years between diagnosis and conception
- Non-pregnant controls had DFS at least as long as the time between diagnosis and pregnancy for the cases
- Pregnancy is <u>not</u> associated with reduced DFS (regardless of ER status)

	HR	95% CI	P value
ER positive	0.91	0.67-1.24	0.55
ER negative	0.75	0.51-1.08	0.12
All	0.84	0.66-1.06	0.14



Azim JCO 2013

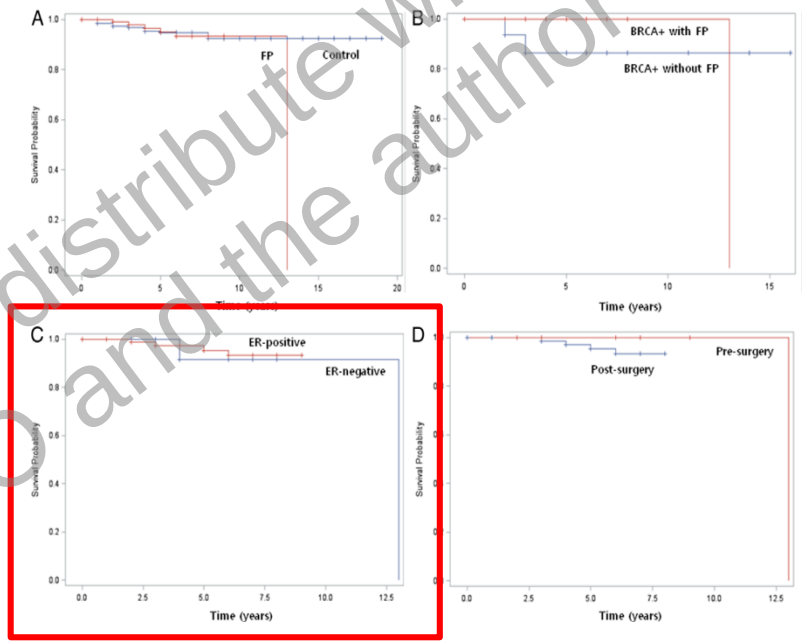
Impact of Pregnancy After Breast Cancer on DFS and OS: Meta-analysis

- 19 studies met inclusion criteria pregnancy following breast cancer diagnosis
  - cases = 1,829
  - controls = 21,907
- Reduced risk of death among women who become pregnant after breast cancer (pooled HR 0.63, 95% CI 0.51-0.79)
- Trend towards reduced risk of recurrence among women who become pregnant after breast cancer (pooled HR 0.84, 95% CI 0.69-1.02)
- Healthy mother effect

Hartman BCRT 2016

Fertility Preservation is not Associated with Increased Breast Cancer Recurrence Risk

- Prospective, non-randomized study of 337 women referred to reproductive endocrinology for possible fertility preservation (FP)
- 120 opted to undergo FP prior to breast cancer therapy and the remainder served as controls
- Median f/u 5 years in FP group, 6.9 years in control group
- Primary endpoint: Recurrence
- Results: Ovarian stimulation is safe
- No difference in RFS or OS between those who did and did not pursue FP with FSH/letrozole prior to systemic therapy, regardless of ER status



Relapse Free Survival analysis by Kaplan-Meier.

A, FP and control groups (log rank, P=.61).

B, BRCA mutation-positive patients pursuing and not pursuing COSTLES (log rank, P=.57).

C, Women with ER-positive and ER-negative breast cancer (log rank, P=.75).

D, Pre- and postsurgery groups (log rank, P=.44).

Kim J Clin Endocrinol Metab. 2016;101(4):1364-1371.

Fertility Preservation Options

Embryo cryopreservation

Oocyte cryopreservation

Ovarian tissue cryopreservation

Ovarian suppression with GnRH analogs

Donor egg

Short window of Opportunity:
2-4 weeks after surgery, prior to chemotherapy

Embryo Cryopreservation

- Well established
- Controlled ovarian hyperstimulation, oocyte retrieval, fertilization and then cryopreservation
- Embryos thawed and transferred to patient or gestational carrier
- Pregnancy rates ≥40% per transfer
- Requires 2-3 weeks

Role of Letrozole During Ovarian Stimulation

- Ovarian stimulation results in supraphysiologic levels of estrogen, 10-20 times normal menstrual cycles
- Theoretical concern about stimulating receptors on estrogen-responsive cells
- Letrozole, an aromatase inhibitor, can be added to IVF cycles to keep estrogen levels low
- Studies have shown no increased risk of breast cancer recurrence in women treated with letrozole during ovarian stimulation compared with those who did not undergo treatment

Cahill et al, Hum Reprod, 2000, Gupta and Keuperwasser, J Steroid Biochem Mol Biol, 2006, Azim et al, J Clinic Oncol, 2008

Oocyte Cryopreservation

- Option for women w/o male partner who do not want to use donor sperm, or for women who do not wish to freeze embryos
- Oocyte is largest cell in human body, largest water content
- Ice crystals damaging, more challenging than embryo cryopreservation
- Cryopreservation hardens the outer coat (zona pellucida)
- Intracytoplasmic sperm injection (ICSI) required for fertilization
- Methods: Slow-freezing, Vitrification
- Limited data available regarding live birth rate per embryo transfer using frozen eggs in cancer survivors, but appears comparable to non-cancer population
- In one study in 936 babies, no increase in rate of congenital anomalies

ASRM Fertility Preservation Guidelines Fertility and Sterility 2013, Cil Fertility and Sterility 2013, Martinez Repro Biomed Online 2014, Noyes et al, 2009

Ovarian Tissue Cryopreservaton

- Enables long-term storage of significant numbers of primordial follicles
- Experimental with approximately 100 centers worldwide offering this service under an Institution Review Board approved protocol
- Approximately 60 live births to date
- Ovarian tissue harvested at laparoscopy or laparotomy
- Tissue can be transplanted in the future
- Has not been commonly used in patients with breast cancer

Donor Oocytes

- For women whose egg supply is depleted
- For germline mutation carriers
- Involves use of an anonymous or known donor whose eggs are harvested and then fertilized with partner or donor sperm
- Can also use frozen banked eggs
- Embryo/s then transferred into recipient
- Success rates exceeding 60% per transfer

GnRH Analogs During Chemotherapy

- May consider as an option for ovarian protection
  - To prevent premature menopause
  - May help preserve fertility
- Rationale: Reduced ovarian activity at time of chemotherapy associated with reduced risk of gonadal failure (based on data in pre-pubertal children exposed to chemotherapy suggesting less ovarian failure)
- Mechanism of action uncertain
  - May prevent follicular recruitment and accelerated follicular atresia during chemotherapy
  - May reduce ovarian blood flow by inducing low estrogen state
  - Does not have direct effect as primordial follicles do not have gonadotropin receptors

Loren ASCO Fertility Preservation Guidelines 2013, Lambertini Ann Onc 2015, Moore NEJM 2015, Demeestere JCO 2016, Oktay JCO 2016, Lambertini JCO 2017, Lambertini JAMA 2015, Bloomenfeld Oncologist 2007, Oktay JCO 2016

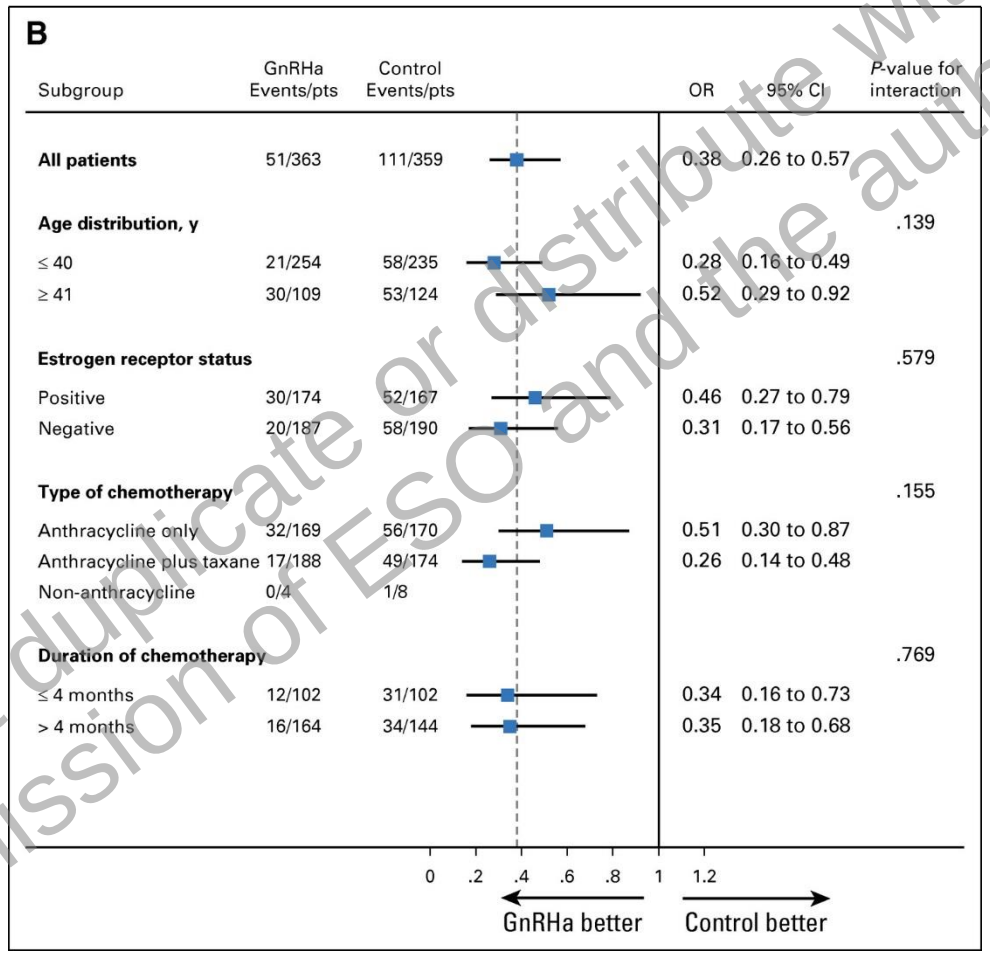
GnRH Agonists for Ovarian Protection During Chemotherapy in Premenopausal Patients with Breast Cancer: POEMS Trial

- A large randomized study of GnRH agonist for ovarian protection in breast cancer patients, N=218
- Pre-menopausal women with hormone receptor-negative early stage breast cancer receiving cyclophosphamide-based chemotherapy
- Data for primary endpoint (ovarian failure) available for 135 patients (measured by amenorrhea and post-menopausal hormone levels)
- Significance of DFS findings unclear, but demonstrate safety of goserelin

	Goserelin	No Goserelin	
Ovarian failure (amenorrhea + FSH in post menopausal range at 2 years)	8%	22%	OR 0.3
Pregnancy within 5 years	21%	11%	OR 2.23
4-year DFS	92%	82%	HR 0.43

Moore NEJM 2015

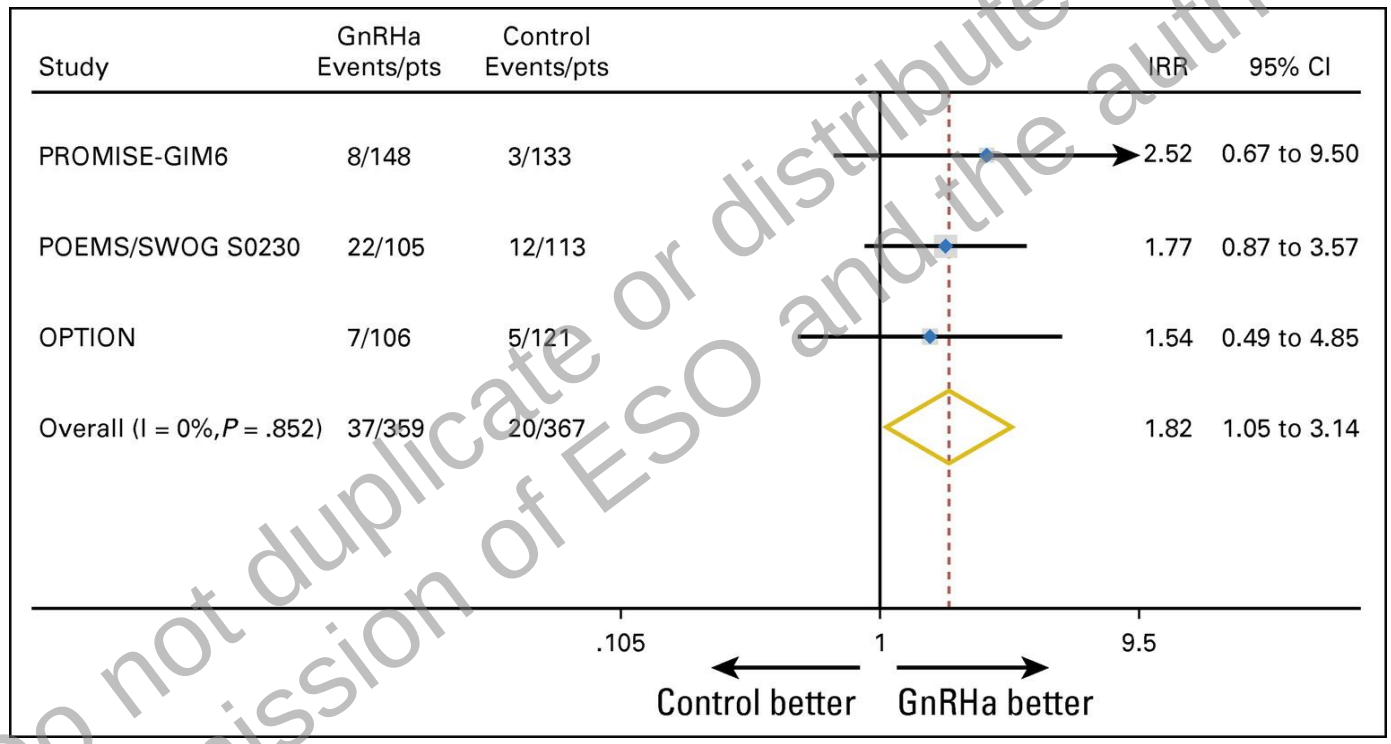
Premature Ovarian Insufficiency by Patient



*PROMISE-GIM6, POEMS/SWOG S0230, Angelo Celtic Group OPTION, GBG-37 ZORO, and a Moffitt trial

Lambertini, JCO 2018

Post-treatment Pregnancies by Trial



Lambertini, JCO 2018

GnRH Analogs for Ovarian Protection

- Overall, inconsistent results across studies
- Inconsistent/inadequate definitions of ovarian failure (e.g. resumption of menses ≠ ovarian recovery, not all used hormone levels), short follow-up, lack of blinding, lack of correction of data for pregnancy intent and pregnancy attempt
- Meta-analyses demonstrate higher rates of menses recovery or reduced risk of ovarian failure with GnRHa
- May be considered in appropriate patients instead of or in addition to oocyte/embryo cryopreservation, does not replace established methods of FP

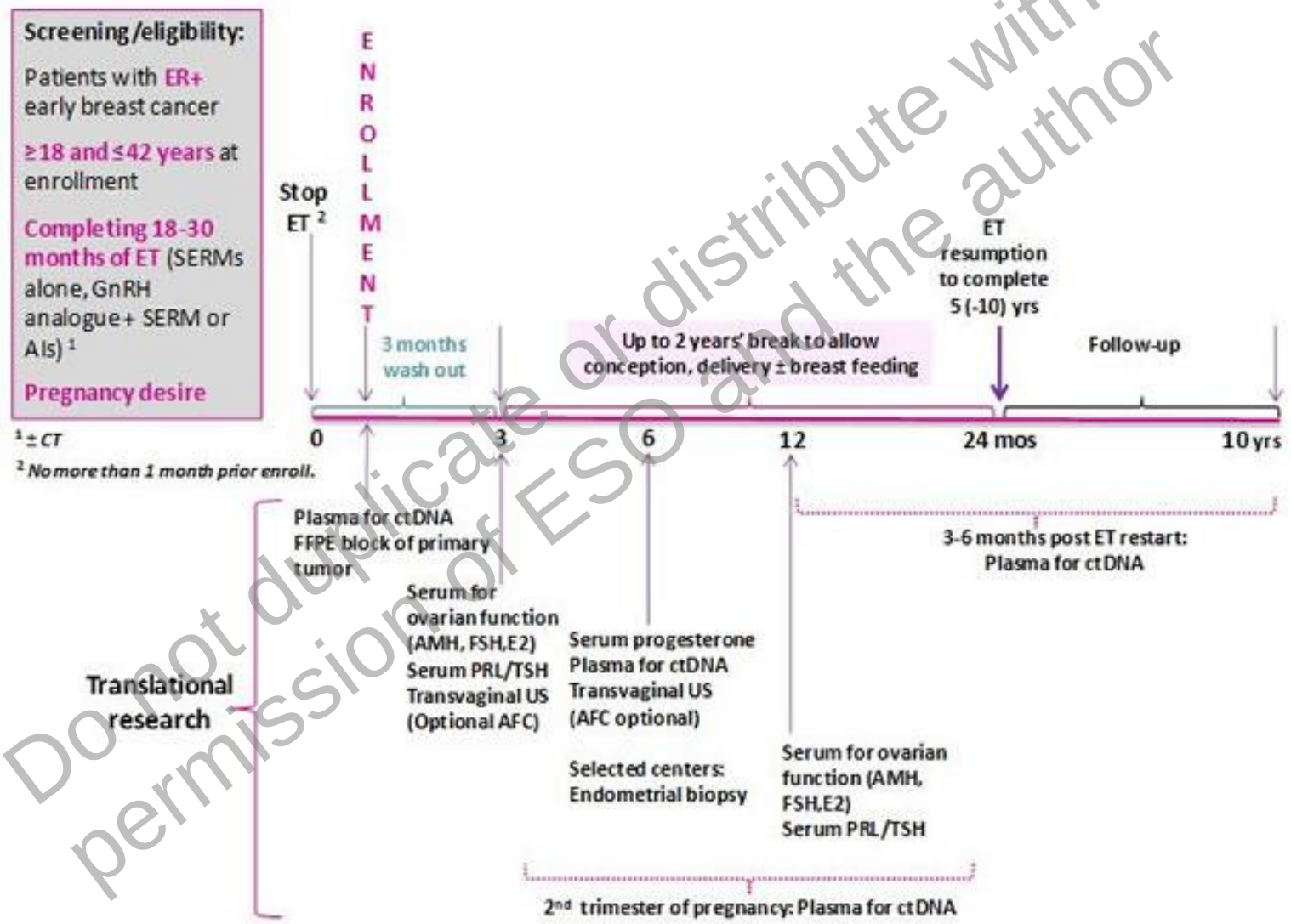
Munhoz JAMA Oncol 2016, Lanertini Ann Onc 2015, Silva Human Repro 2016, Lambertini SABCS 2017, Oktay JCO 2016, Demesteer JCO 2016, Oktay JCO 2018

Pregnancy After Breast Cancer: Timing

- Optimal timing uncertain
  - Wait a few years?
    - Wait until risk of recurrence is lower?
    - Wait until completion of all adjuvant therapy?
  - Concern regarding loss of fertility due to natural ovarian aging during 5-10 years of adjuvant therapy
  - Safety of interruption of adjuvant endocrine therapy for pregnancy being assessed in the **POSITIVE** trial (Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive Breast Cancer, IBCSG 48-14)

Peccatori Annals of Onc 2013
Partridge Breast 2014

IBCSG 48-14 POSITIVE



Use of a Gestational Carrier (Gestational Surrogate)

- When a woman carries a pregnancy for another woman, and the carrier is not the biological mother
- May be used for patients who have frozen embryos or eggs, may use donor egg
- Candidates include those who:
  - Have high risk of recurrent breast cancer
  - Had a hysterectomy
  - Do not want to wait until completion of endocrine therapy
  - Lifelong endocrine therapy
- Barriers include legal issues, cost

Adoption

- Several options
  - Private
  - Domestic
  - International
  - Foster-adoption
- Barriers
  - Variation by state, country
  - Process may be long
  - Cost
  - Difficulties due to history of cancer
  - Age

Utilization of Fertility Services

- ≤10% young women with breast cancer pursue fertility preservation
- Barriers to uptake
  - Time
  - Access
  - Cost/lack of insurance coverage
  - Lack of provider-led discussion
  - Lack of referral to fertility specialists by providers
  - Patient concerns about delaying breast cancer therapy
  - Difficult time emotionally at time of diagnosis
  - Disparities: age, having other children, non-white

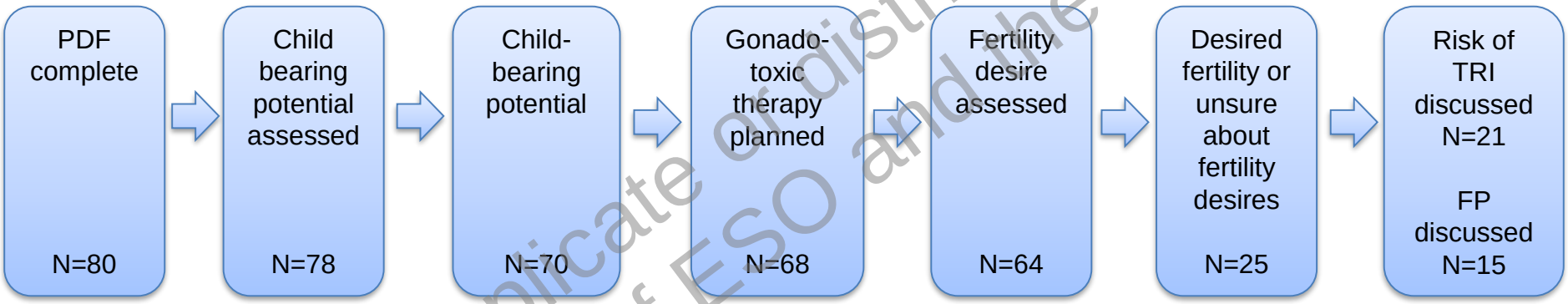
Kim Fert Steril 2012, Neuss JCO 2013, Quinn JCO 2009, Ruddy JCO 2014, Duffy JCO 2005, Forman Fertil Steril 2010, Clayman JNCCN 2013, Quinn Patient Educ Counsel 2009, McCray Ann Surg Onc 2016, Rotker Urol 2017, Kelvin JCO 2016 Lewin Supportive Care Cancer 2017, Partridge JCO 2004, Tschudin Human Repro Update 2009, Schover Cancer 1999, Armuand JCO 2012, Letourneau Cancer 2012, Thewes JCO 2005, Gorman J Ca Surv 2012, Ussher Repro Health 2018, Howard-Anderson JNCI 2012, Partridge Clin Breast Cancer 2008, King Oncologist 2012, Goodman Human Repro 2012, Campo-Engelstein JCO 2010

Institutions Should Improve Uptake of Fertility Preservation:
Johns Hopkins Quality Improvement (QI) Protocol

- Institutional QI protocol to improve the care of newly diagnosed young female breast cancer patients (age 18-44) by establishing a standard practice for:
  - Assessment of fertility goals, risk of treatment-related infertility (TRI), timely communication about the risk of TRI and fertility preservation (FP) options, timely referral to fertility specialists
- Structured provider documentation form (PDF) completed by breast surgeons and breast medical oncologists (or their designees) during or after clinic visits to track adherence to the steps in the QI protocol
- PDF and notes from first visits to medical oncology, surgery and radiation oncology were reviewed to describe adherence to the QI protocol during the first year after implementation
- Chart review to obtain information regarding fertility preservation

Johns Hopkins Quality Improvement (QI) Protocol: Fertility Preservation for Breast Cancer

- February 3, 2016- February 2, 2017, N=112.
- Provider Documentation Form (PDF) Results:



- Uptake of fertility care:
  - 27 referred to fertility specialist
  - 16 saw fertility specialist
  - 12 pursued fertility preservation

Conclusions

- Fertility preservation is integral for a comprehensive cancer plan
- A complex and expensive process
- Health care providers should initiate discussions and referrals to young women with breast cancer as early as possible
- There are several strategies that can help preserve fertility or provide other pathways to parenthood
  - Embryo and oocyte cryopreservation: standard practice
  - Ovarian tissue cryopreservation: may become standard
  - GnRH analog use: mixed data, may be offered to select patients undergoing chemotherapy, should not replace standard approach
  - Surrogacy and adoption
- Resources are available for financial assistance
- Early referral is essential!

Thank you…

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UNDER ARMOUR. POWER IN PINK

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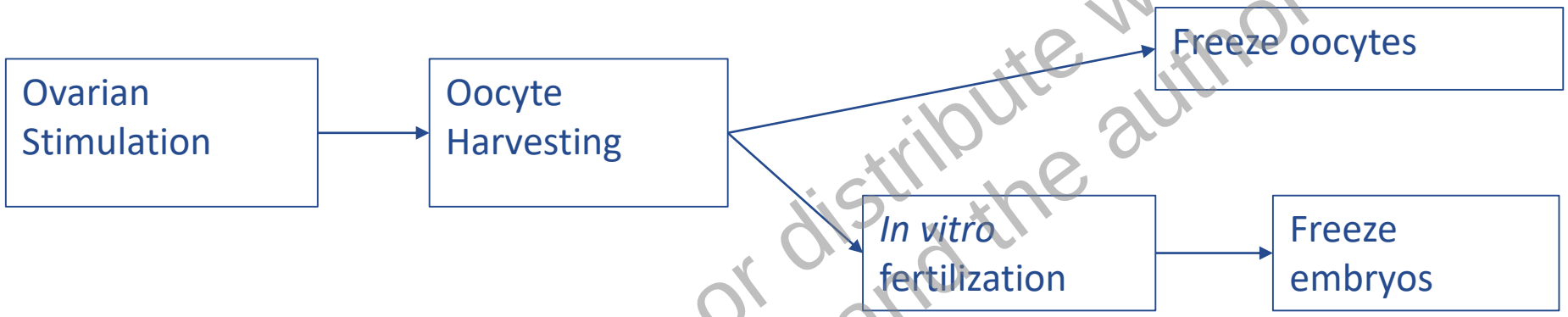
Process for Cryopreservation of Oocytes or Embryos



*Timing of ovarian stimulation and oocyte harvesting in relation to cancer treatment is determined collaboratively between patient, surgeon, medical oncologist and fertility specialist. Must do PRIOR to systemic therapy. May use random start to reduce delay. Stimulation takes 2-3 weeks. May sometimes do 2 cycles with early referral.

*Pregnancy using frozen eggs or embryos may be achieved later (after completion of cancer treatment). May transfer to self or to gestational carrier

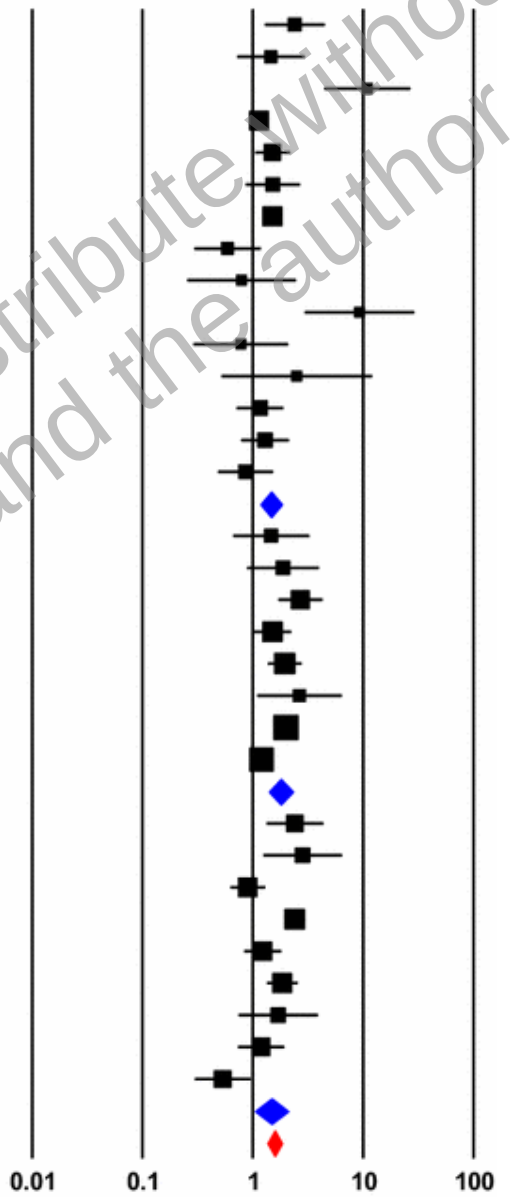
Loren ASCO Fertility Preservation Guidelines 2013
Oktay JCO 2008; Lee JCO 2010; Sonmezer Fert Steril 2011

Complex Process

- Legal aspects
  - Identify a lawyer or agency that pairs gestational carriers with families
  - Laws varies in different states, countries
- Identification of potential gestational carriers
  - Most agencies work with gestational carriers who already have children
  - Interview potential gestational carriers
  - Separate psychological evaluations for family and carrier
  - Legal contracts required
- Costly: $80,000-$100,000 (not covered by insurance).
- Social aspects: Family, Friends, Religious, Household

Meta-analysis: Association between breast cancer and diagnosed during pregnancy or <5ys postpartum on OS

Group by Definition	Study name	Hazard ratio	Lower limit	Upper limit	p-Value
PABC	Anderson	2.40	1.28	4.50	0.01
PABC	Bonnier	1.46	0.72	2.96	0.29
PABC	Mathelin	10.92	4.43	26.88	0.00
PABC	Rodriguez	1.14	1.00	1.29	0.04
PABC	Largillier	1.51	1.05	2.18	0.03
PABC	Moreira	1.52	0.86	2.69	0.15
PABC	Johansson 1	1.51	1.36	1.68	0.00
PABC	Murphy	0.59	0.29	1.19	0.14
PABC	Valentini	0.79	0.25	2.47	0.69
PABC	Dimitrakakis	9.28	2.94	29.28	0.00
PABC	Callihan	0.78	0.29	2.10	0.62
PABC	Bell	2.50	0.52	12.09	0.25
PABC	Johansson 2	1.16	0.71	1.90	0.55
PABC	Johansson 2 a	1.29	0.78	2.14	0.32
PABC	Genin	0.86	0.48	1.54	0.61
PABC		1.46	1.17	1.82	0.00
Postpartum	Tretli a	1.47	0.66	3.27	0.35
Postpartum	Guinee a	1.88	0.88	4.00	0.10
Postpartum	Daling	2.70	1.70	4.30	0.00
Postpartum	Whiteman	1.51	1.02	2.23	0.04
Postpartum	Stensheim a	1.95	1.36	2.79	0.00
Postpartum	Callihan a	2.65	1.09	6.43	0.03
Postpartum	Bladström a	2.00	1.90	2.10	0.00
Postpartum	Bladström b	1.20	1.03	1.40	0.02
Postpartum		1.79	1.39	2.29	0.00
Pregnancy	Tretli	2.41	1.32	4.39	0.00
Pregnancy	Guinee	2.83	1.24	6.45	0.01
Pregnancy	Ezzat	0.90	0.62	1.30	0.57
Pregnancy	Bladström	2.40	1.99	2.89	0.00
Pregnancy	Stensheim	1.23	0.83	1.82	0.30
Pregnancy	Johansson 1a	1.85	1.34	2.56	0.00
Pregnancy	Azim	1.70	0.74	3.90	0.21
Pregnancy	Amant	1.19	0.73	1.93	0.48
Pregnancy	Litton	0.53	0.30	0.96	0.04
Pregnancy		1.47	1.04	2.08	0.03
Overall		1.57	1.35	1.82	0.00



Hartman
BCRT
2016