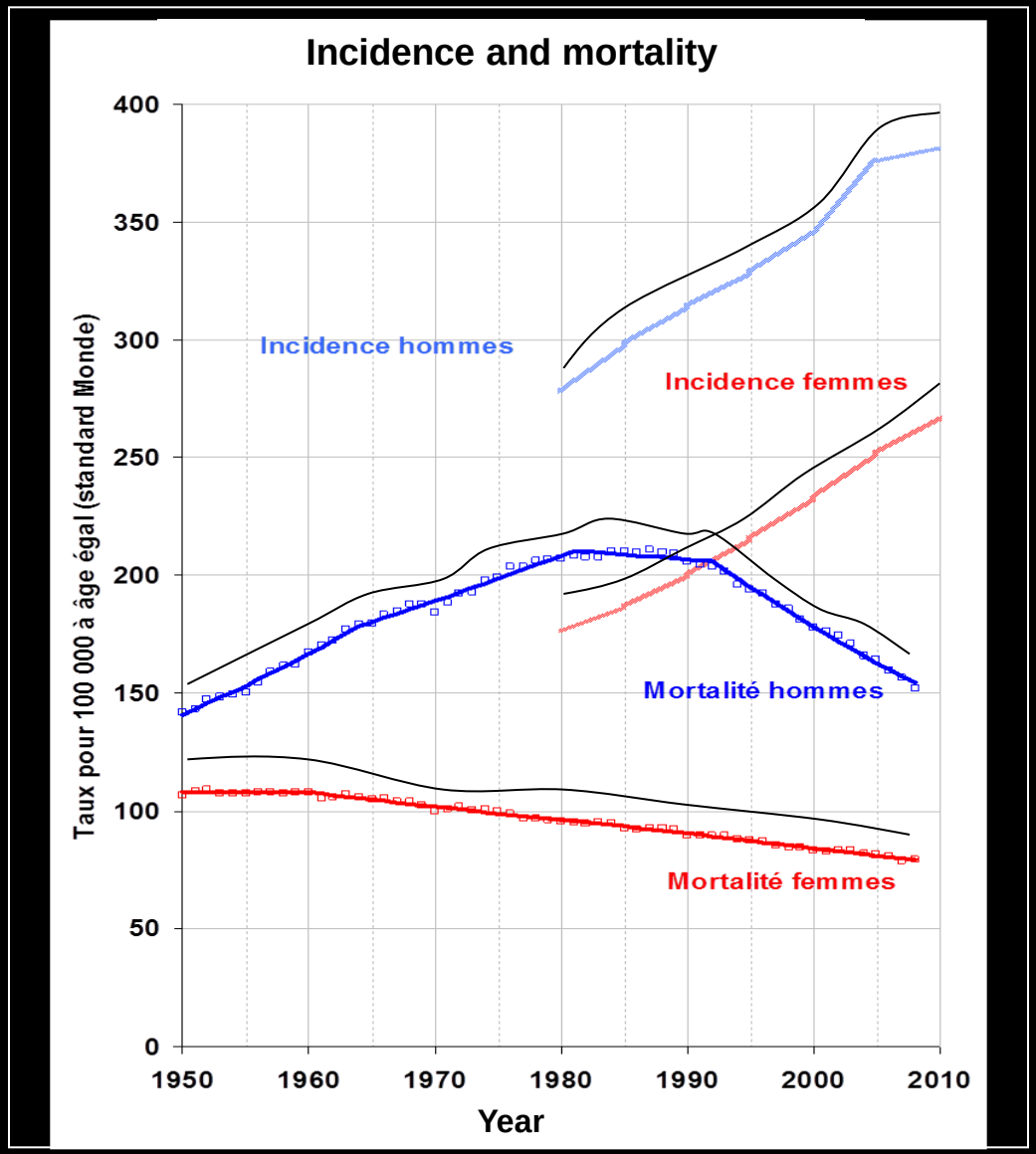
Comment stimuler les patientes en AMP après un cancer ?

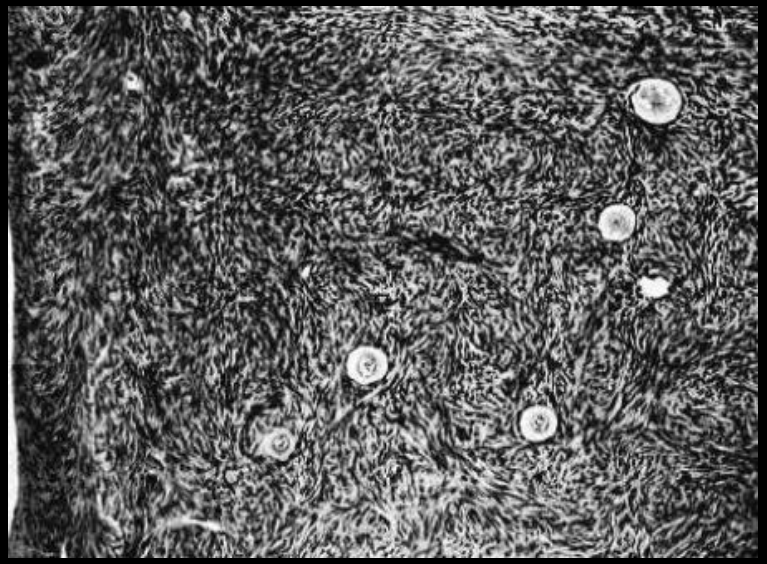
Michaël Grynberg, M.D., Ph.D.

Unité de Médecine de la Reproduction
Hôpital Antoine Béclère, Université Paris-Sud
INSERM U782
Clamart-France

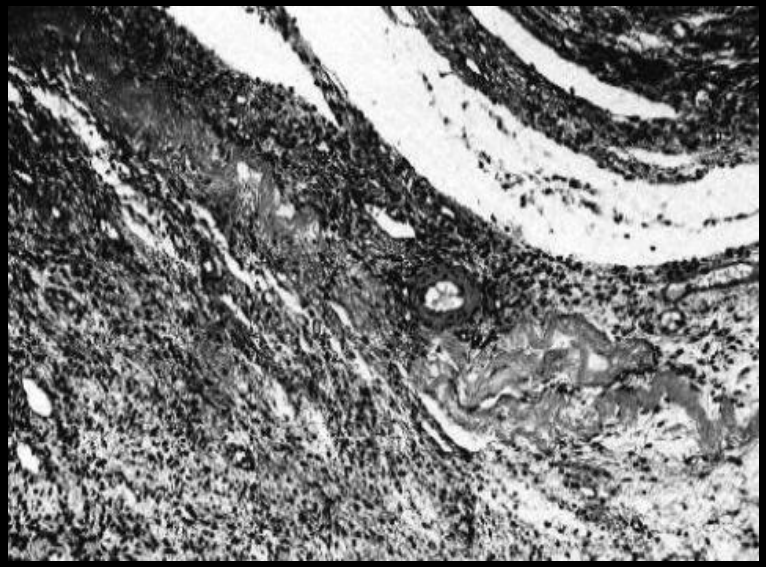
Epidemiology



Ovarian toxcity



Before chemotherapy



After chemotherapy

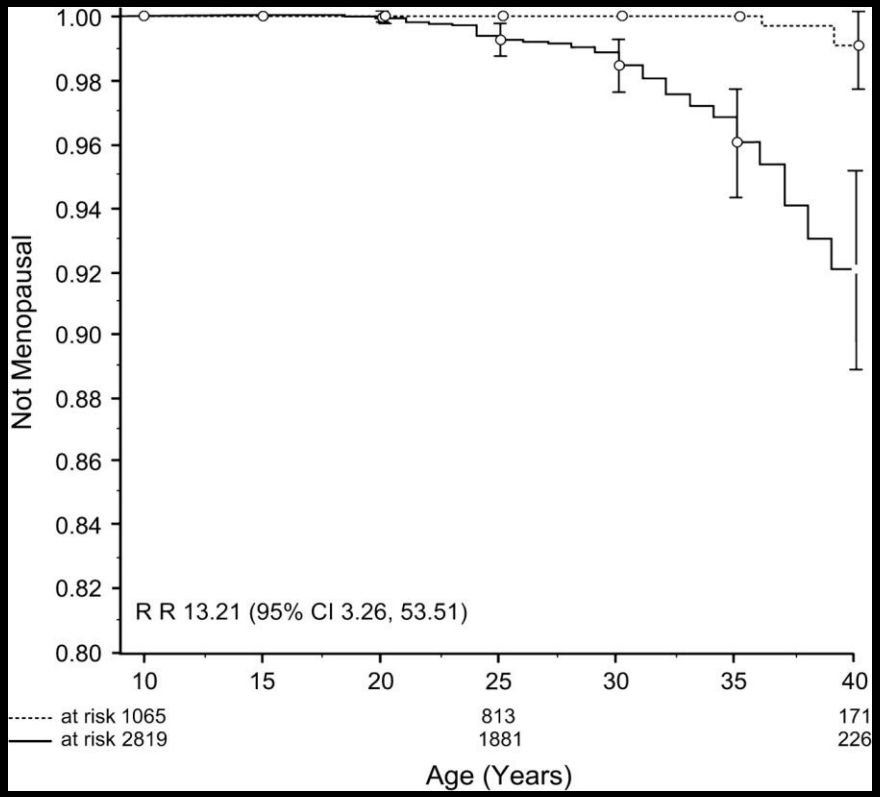
Ovarian toxcity

- Side effect of chemo / radiotherapy
- Mechanisms unclear
- Ovarian tissue fibrosis
- Apoptosis of primordial and primary follicles
- Vascular damage
- Follicular activation: burn-out

Blumenfeld et al., Best Pract Res Clin Obstet Gynaecol. 2012

Premature menopause

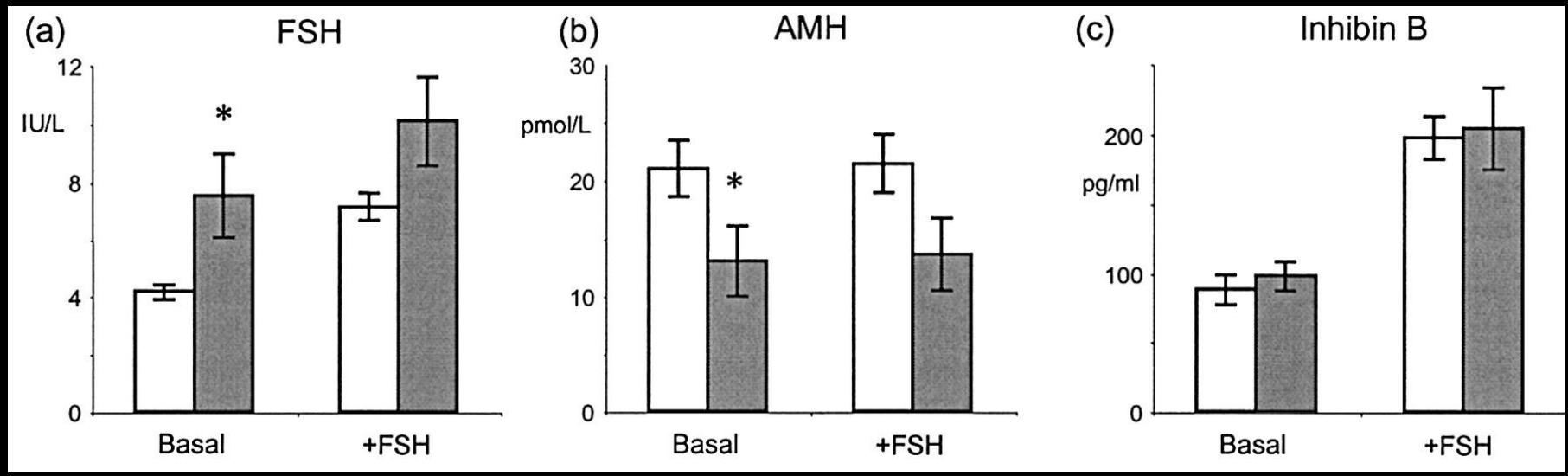
2819 survivors of childhood cancer and 1065 female siblings



Cumulative incidence of premature menopause higher for cancer survivors than for siblings

Sklar J. Nat. Cancer., 2006

Premature ovarian failure



Alteration of the follicular ovarian status in childhood cancer survivors having retained regular menstrual cycle

Bath et al., Hum. Reprod., 2003

Ovarian function after CT

Comparison of reproductive hormones in unexposed reproductive-age participants, cancer survivors (low-dose and high-dose), and late-reproductive-age women, restricted to regularly menstruating participants not using hormones [illegible] the past year.

Hormone	Unexposed (n = 63)	Low-dose exposure (n = 27)	High-dose exposure (n = 22)	Late-reproductive (n = 69)
FSH (mIU/mL)	6.93 (6.09–7.89)	7.93 (6.63–9.47)	10.60[a] (8.68–12.95)	8.15[b] (7.19–9.23)
E_2 (pg/mL)	31.81 (27.27–37.10)	24.54[b] (19.85–30.3[illegible])	22.95[b] (18.10–29.11)	37.45 (32.27–43.47)
Inhibin B (pg/mL)	39.75 (29.88–52.89)	37.90 (25.54–56.2[illegible])	30.37 (19.33–47.73)	30.70 (23.40–40.29)
AMH (ng/mL)	3.07 (2.17–4.36)	1.99 (1.23–3.24)	0.52[a] (0.30–0.90)	0.19[a] (0.13–0.26)

Note: Geometric mean (95% CI) hormone levels are shown. Models adjusted for mean BMI and race. High-dose exposure defined as AAD ≥ 3 or exposure to pelvic radiation including TBI. Low-dose exposure defined as any cancer treatment that does not meet criteria for "high dose exposure."

[a] $P < .001$ vs. reference unexposed group.

[b] $P < .05$ vs. reference unexposed group.

Gracia. Ovarian reserve after cancer. *Fertil Steril* 2012.

Impaired ovarian reserve in a dose-dependent manner among cancer survivors compared with unexposed females of similar age.

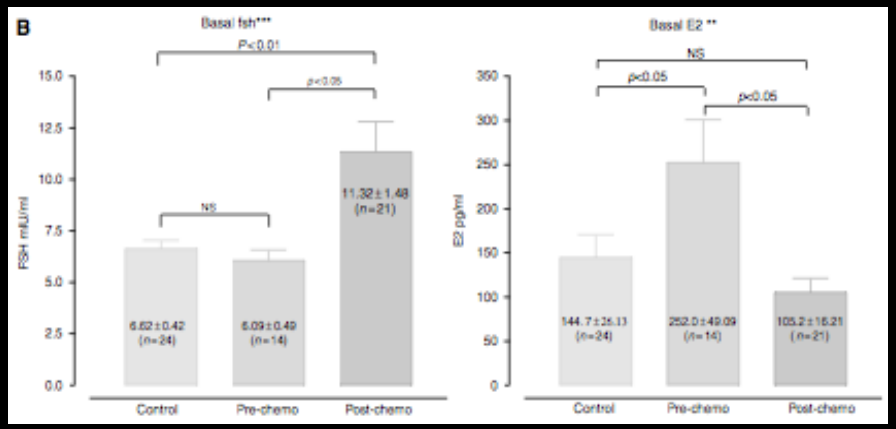
Reproductive hormone levels in menstruating survivors exposed to high-dose therapy are similar to those in late-reproductive-age women.

Gracia et al., Fertil. Steril., 2012

Ovarian function after CT

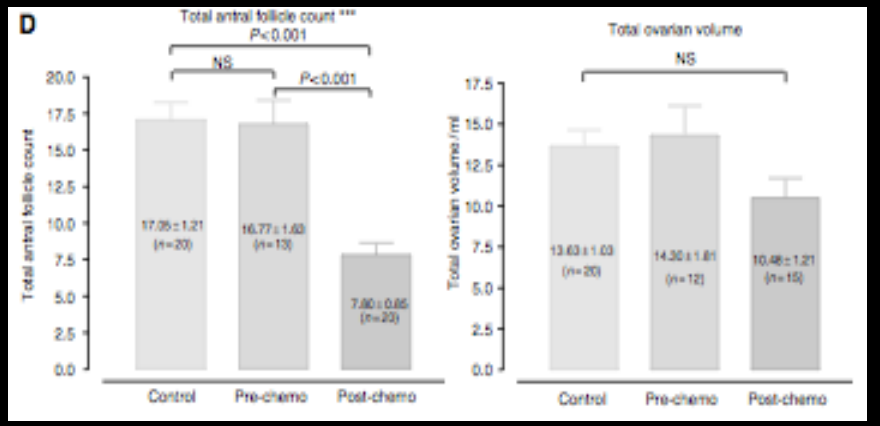
Breast cancer

FSH



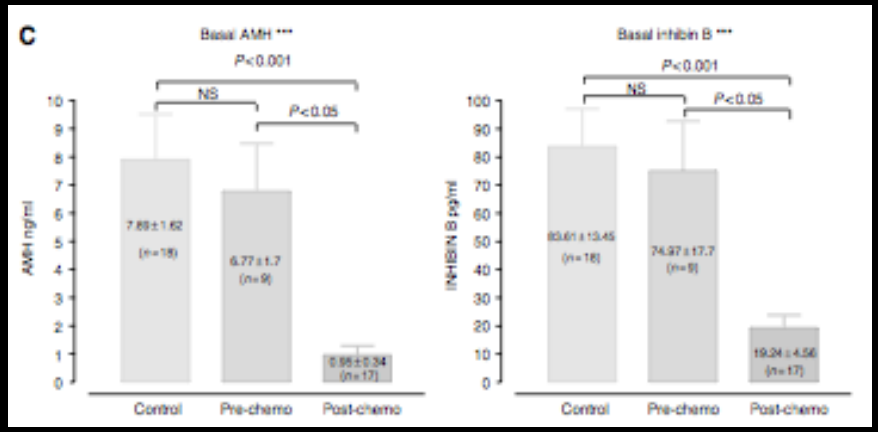
E_2

AFC



Ov. vol

AMH



Inhibin B

Lutchman Singh et al., British. J. Cancer., 2007

Antral follicle count

	Controls (n = 21)	Spontaneous cycle (n = 70)[b,h]	OC cycle (n = 13)	HRT cycle (n = 17)[c]	*P*-value[d]
Ovarian volume per ovary (cm^3)[e]	6.8 (4.4–14.1)	4.8 (1.1–9.5)	2.9 (1.9–5.6)	0.8 (0.0–2.0)	<0.001[f]
Small follicles per ovary (n)[e] (2–5 mm)	8.0 (5.5–12.5)	5.0 (0.0–15.0)	6.0 (3.0–10.0)	0.0 (0.0–1.5)	<0.001[f]
Total follicles per ovary (n)[e] (2–10 mm)	11.0 (6.5–15.5)	7.5 (0.0–18.5)	7.0 (3.5–10.0)	0.0 (0.0–1.5)	<0.001[f]

Smaller ovarian volume per ovary and a lower number of antral follicles per ovary in childhood cancer survivors when compared to controls

Larsen et al., JCE&M., 2003

Risk calculator

fertileHOPE
fertility resources for cancer patients

women / risk of amenorrhea
from chemotherapy and radiation treatments for cancer

The following table represents a compilation of both clinical experience and the published research on the impact of common cancer treatments on menstruation. Generally, studies have not focused on other measures of reproductive capacity, such as hormone levels or follicle counts which may more accurately reflect reproductive capacity.

Degree of Risk	Treatment Protocol	Common Usage
High Risk >80% of women develop amenorrhea post-treatment	Whole abdominal or pelvic radiation doses ≥ 6 Gy in adult women	Multiple cancers
	Whole abdominal or pelvic radiation doses ≥ 15 Gy in pre-pubertal girls ≥ 10 Gy in post-pubertal girls	Wilms' tumor, neuroblastoma, sarcoma, Hodgkin lymphoma
	TBI radiation doses	Bone marrow transplant/stem cell transplant (BMT/SCT)
	CMF, CEF, CAF x 6 cycles in women 40 +	Breast cancer
	Cyclophosphamide 5 g/m² in women 40+	Multiple cancers
	Cyclophosphamide 7.5 g/m² in girls < 20	Non-Hodgkin lymphoma (NHL), neuroblastoma, acute lymphoblastic leukemia (ALL), sarcoma
	Alkylating chemotherapy (e.g., cyclophosphamide, busulfan, melaphan) conditioning for transplant	BMT/SCT
	Any alkylating agent (e.g., cyclophosphamide, ifosfamide, busulfan, BCNU, CCNU) + TBI or pelvic radiation	BMT/SCT, ovarian cancer, sarcoma, neuroblastoma, Hodgkin lymphoma
	Protocols containing procarbazine: MOPP, MVPP, COPP, ChlVPP, CNVPP/EVA, BEACOPP, MOPP/ABVD, COPP/ABVD	Hodgkin lymphoma
	Cranial/brain radiation ≥40 Gy	Brain tumor
Inter-mediate Risk ~30-70% of women develop amenorrhea post-treatment	CMF or CEF or CAF x 6 cycles in women 30-39	Breast cancer
	AC in women 40+	Breast cancer
	Whole abdominal or pelvic radiation 10-<15 Gy in prepubertal girls	Wilms' tumor
	Whole abdominal or pelvic radiation 5-<10 Gy in postpubertal girls	Wilms' tumor, neuroblastoma
	Spinal radiation ≥25 Gy	Spinal tumor, brain tumor, neuroblastoma, relapsed ALL or NHL
Low Risk <20% of women develop amenorrhea post-treatment	AC in women 30-39	Breast cancer
	CMF, CEF, or CAF x 6 cycles in women under 30	Breast cancer
	Non-alkylating chemotherapy: ABVD, CHOP, COP	Hodgkin lymphoma, NHL
	AC (anthracycline, cytarabine)	Acute myeloid leukemia (AML)
	Multi-agent therapies	ALL
Very Low/ No Risk Negligible effect on menses	MF (methotrexate, 5-FU)	Breast cancer
	Vincristine (used in multi-agent therapies)	Leukemia, Hodgkin lymphoma, NHL, neuroblastoma, rhabdomyosarcoma, Wilms' tumor, Kaposi's sarcoma
	Radioactive iodine	Thyroid cancer
Unknown Risk	Paclitaxel, docetaxel (Taxanes used in AC protocols)	Breast cancer
	Oxaliplatin	Ovarian cancer
	Irinotecan	Colon cancer
	Bevacizumab (Avastin)	Colon, non-small cell lung
	Cetuximab (Erbitux)	Colon, head & neck
	Trastuzumab (Herceptin)	Breast cancer
	Erlotinib (Tarceva)	Non-small cell lung, pancreatic
	Imatinib (Gleevec)	Chronic myeloid leukemia (CML), gastrointestinal stromal tumor (GIST)

Ovarian function after cancer treatments

Age

Ovarian follicular status

Sensitivity/ chemo

Type of cancer

Chemo regimens

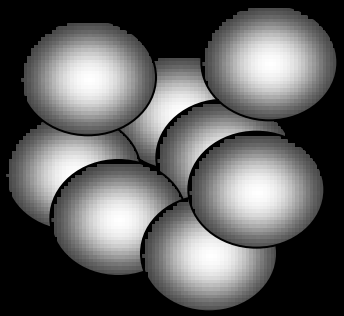
Doses of chemo

Predicting ovarian function after radio- / chemotherapy remains a challenge

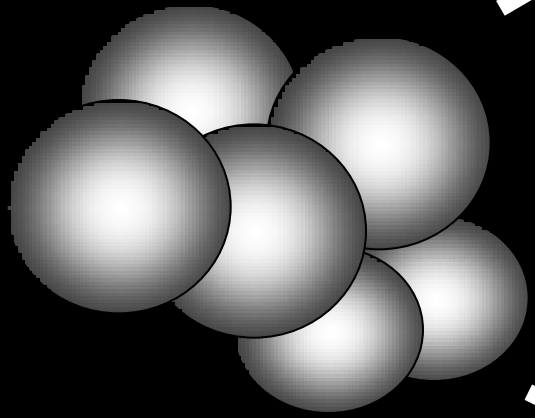
Controlled ovarian hyperstimulation

Serum E2 levels ⬆ ⬆

Exogenous FSH administration

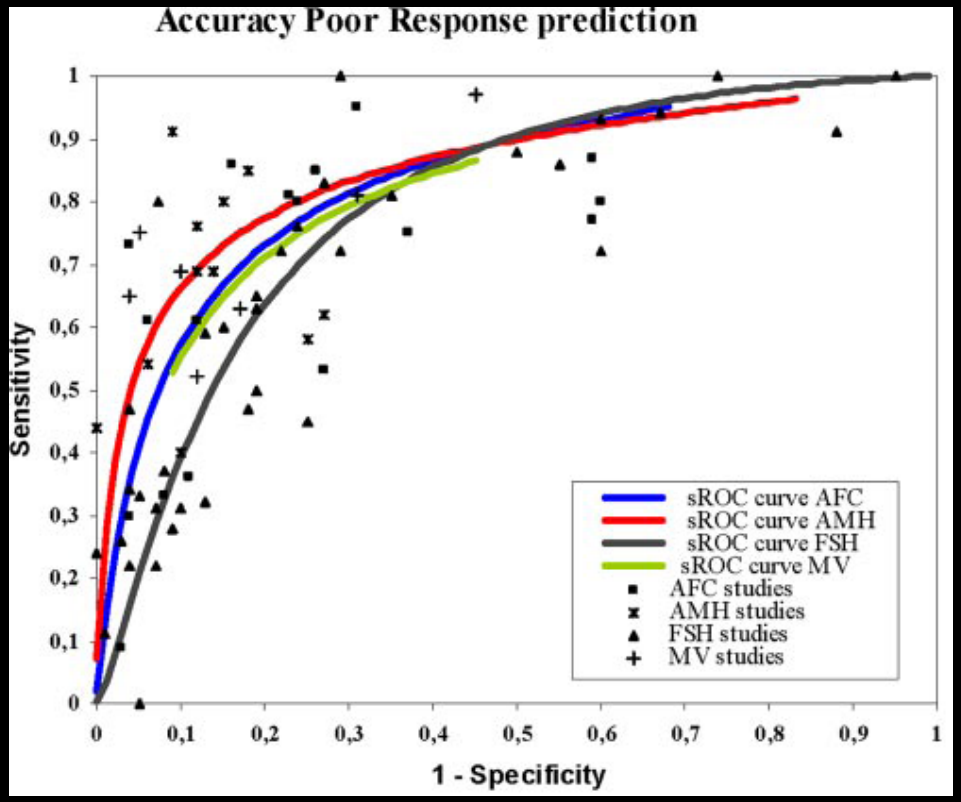


Antral follicles



Preovulatory follicles

Ovarian response to COH



AMH & AFC: best markers of poor ovarian response

Broekmans et al., Endocrine Reviews, 2009

Ovarian stimulation after cancer treatment

- 113 cycles in 69 couples candidates for GIFT
- 50 couples in which the women was a cancer survivor
- Comparison with cancer patients undergoing IVF-ET before CT/RT
- Trend to have a lower No of oocytes recovered in cancer survivors (18.7 ± 3.2 vs. 14.5 ± 1.2, *P= NS*)
- Trend to have a lower No of embryos in cancer survivors (11.3 ± 1.9 vs. 7.5 ± 0.7, *P= NS*)

Ginsburg et al., Fertil Steril 2001

Ovarian stimulation after cancer treatment

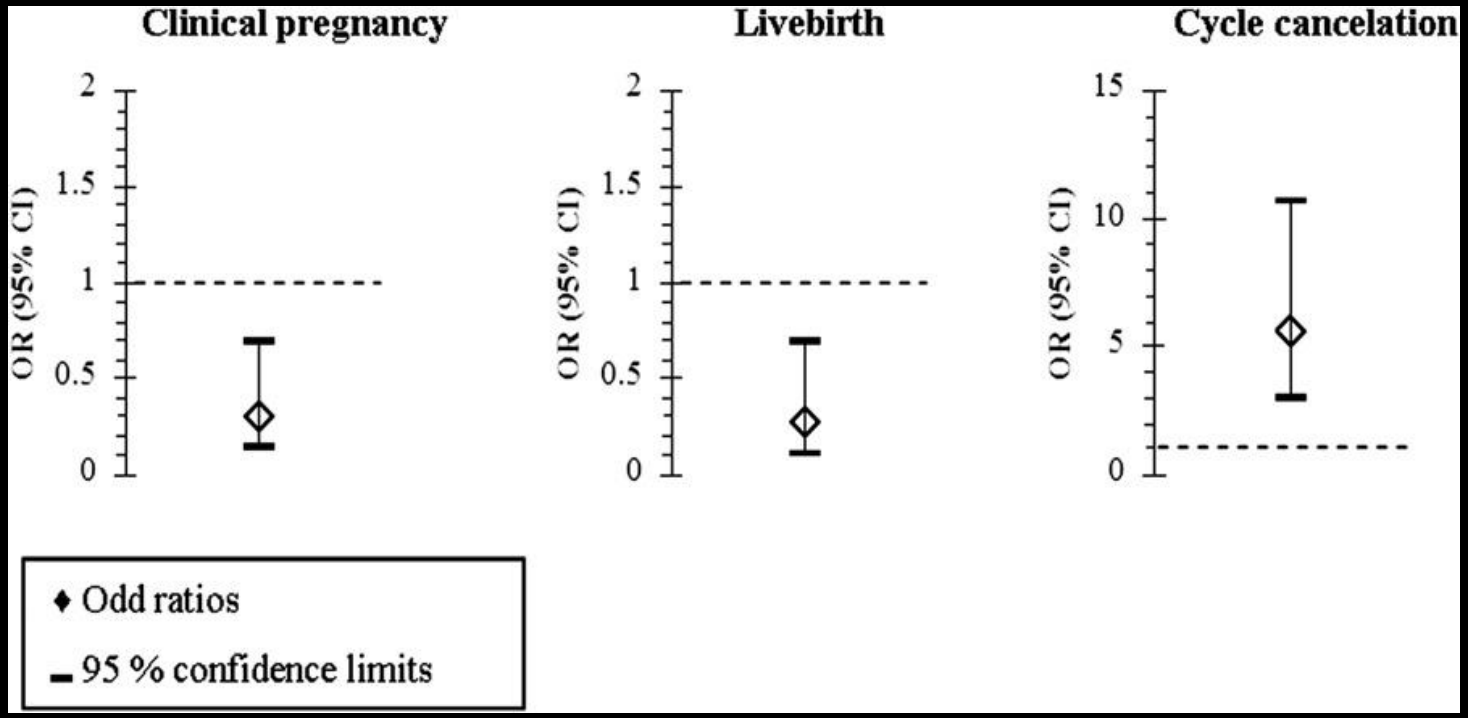
ART outcomes in cancer survivors vs. with all other infertility patients

	Survivors (n = 53)	All infertility (n = 7,030)	Male-factor infertility (n = 1,153)
Female age at cycle start (y)	34.2 (19.3–43.9)	35.8 (19.3–43.9)	35.0 (19.7–43.9)
Day 3 FSH (mIU/mL)	7.3 (2.6–43.0)	7.3 (0.1–52.0)	7.0 (1.0–10.0)
Poor-responder protocol	13 (24.5%)	1,048 (14.9%)	73 (6.3%)
Total dose of gonadotropins (IU)	5,025.0 (1,500.0–13,500.0)	3,300.0 (225.0–12,000.0)	2,700.0 (712.5–10,200.0)
Peak E_2 (pg/mL)	1,186.5 (14.0–3,980.0)	1,748.0 (<assay–12,385.0)	1,978.0 (<assay–8,856.0)
Days of stimulation to hCG	11.0 (6.0–23.0)	11.0 (5.0–21.0)	10.0 (6.0–20.0)
No. of oocytes retrieved	8 (0–36)	13 (0–68)	14 (0–68)
No. of embryos obtained	4 (0–18)	7 (0–51)	8 (0–51)
No. of embryos transferred	2.0 (0.0–8.0)	2.0 (0.0–10.0)	2.0 (0.0–10.0)

Barton et al., Fertil Steril 2012

Ovarian stimulation after cancer treatment

ART outcomes in cancer survivors vs. with all other infertility patients



Barton et al., Fertil Steril 2012

Ovarian stimulation after cancer treatment

ART outcomes in cancer survivors vs. with all other infertility patients

Cancer type		NA	NA
Leukemia	4 (7.5%)		
Hodgkin lymphoma	13 (24.5%)		
Non-Hodgkin lymphoma	5 (9.4%)		
Sarcoma	2 (3.8%)		
Neuroblastoma	1 (1.9%)		
Kidney (Wilm)	3 (5.7%)		
Breast	17 (32.1%)		
Gynecologic	8 (15.1%)		
Treatment type		NA	NA
No alkylating agents nor pelvic/abdominal RT	24 (45.3%)		
Alkylating agents, no pelvic/abdominal RT	18 (34.0%)		
Pelvic/abdominal RT, no chemotherapy	5 (9.4%)		
Any chemotherapy with pelvic/abdominal RT	6 (11.3%)		

But heterogenous population (type of cancer and different treatments)

Barton et al., Fertil Steril 2012

Hypothalamic / Pituitary radiotherapy

< 24 Gy: Low risk of amenorrhea (< 20%)

> 24 Gy: High risk of amenorrhea (> 80%)

Restoration of ovulation through exogenous gonadotropin admininstration

Cervical cancer

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Reproductive outcomes of patients undergoing radical trachelectomy for early-stage cervical cancer

C.H. Kim [a], N.R. Abu-Rustum [a], D.S. Chi [a], G.J. Gardner [a], M.M. Leitao Jr. [a], J. Carter [b], R.R. Barakat [a], Y. Sonoda [a,*]

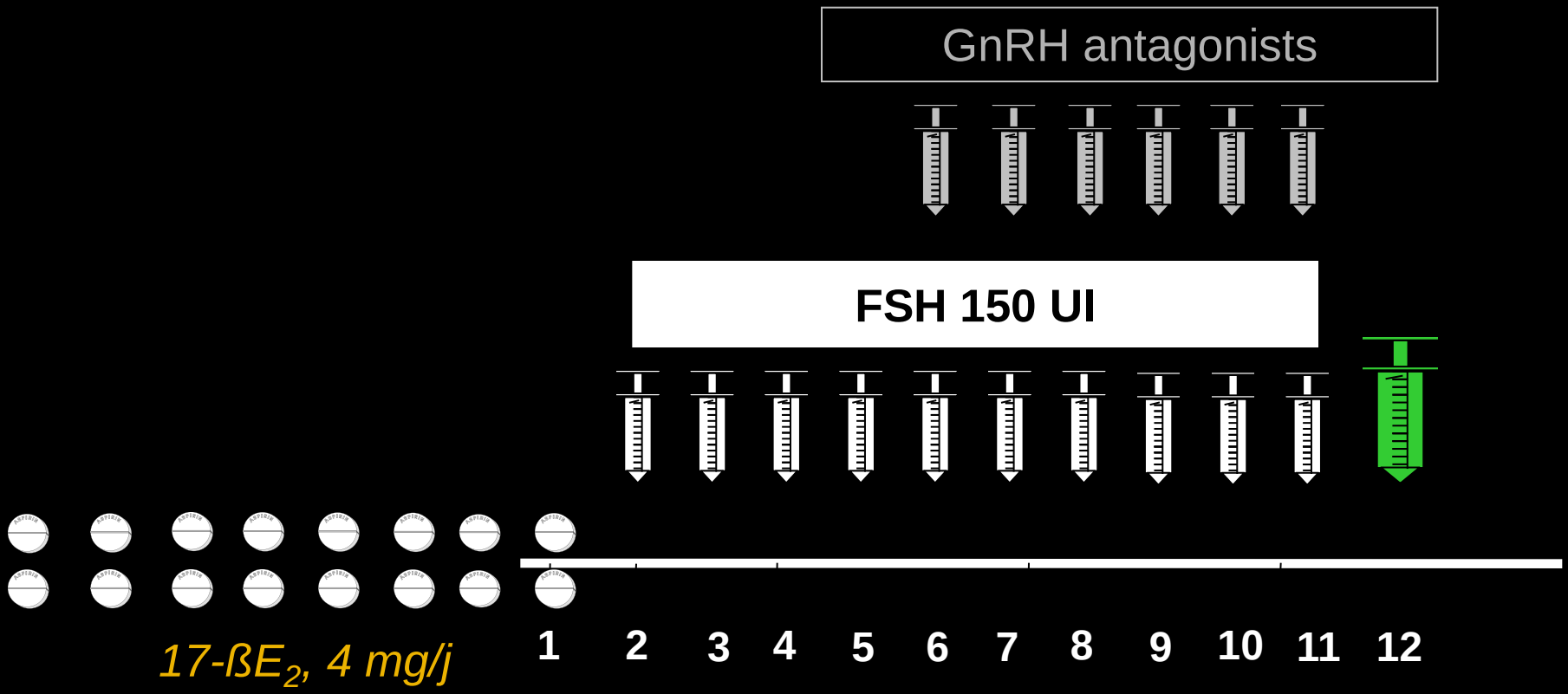
Methods of conception in women attempting pregnancy.

Total women attempting conception	35
# successful	23 (66%)
Attempting conception spontaneously	17
# successful	12 (71%)
Attempting conception with ART	18
# successful	11 (61%)

In clinical practice

- Oncologist authorization for pregnancy
- Fertility evaluation after 6 months of infertility
- Evaluation of uterine function if previous pelvic radiotherapy
- IVF-ET / ICSI +++

GnRH antagonist protocol



AMH & pregnancies

Table II Pregnancy outcomes in 128 IVF patients with extremely low AMH levels (0.1–0.4 ng/ml).

	All patients (n = 128/254)[a]	95% CI	≤Age 42 years (n = 70/145)[a]	95% CI	>Age 42 years (n = 58/109)[a]	95% CI	P
Clinical pregnancies per cycle	20 (7.9%)	[4.9%–11.9%]	16 (11.0%)	[6.4%–17.3%]	4 (3.7%)	[1.0%–9.1%]	0.031
Clinical pregnancies per patient	20 (15.6%)	[9.8%–23.1%]	16 (22.9%)	[13.7%–34.5%]	4 (6.9%)	[1.9%–16.7%]	0.013
Deliveries after 1st IVF cycle	8 (6.3%)	[2.7%–11.9%]	7 (10.0%)	[4.1%–19.5%]	1 (1.7%)	[0.04%–9.2%]	0.055
Deliveries per patient	12 (9.4%)	[4.9%–15.8%]	10 (14.3%)	[7.1%–24.7%]	2 (3.4%)	[0.4%–11.9%]	0.036

[a]Patients/ART cycles.

Pregnancies are possibly obtained in women having extremely low AMH levels

Weghofer *et al., JCE&M, 2011*

Live births after Transplantation of frozen ovarian tissue

Worldwide frozen ovarian cortical tissue transplantations live births.

Case no.	Diagnosis	Age at cryopreservation (y)	Chemotherapy before cryopreservation	Conception	Babies	Authors
1	Hodgkin's lymphoma	25	No	Natural	1	Donnez et al.
2	Neuroturnor	19	No	Natural	1	Donnez et al.
3	Non-Hodgkin's lymphoma	28	Yes	IVF-ET	1	Meirow et al.
4	Hodgkin's lymphoma	24	Yes	Natural	2	Demeestere et al.
5	Ewing sarcoma	27	No	IVF-ET and natural	2	Andersen et al.
6	Hodgkin's lymphoma	25	Yes	IVF-ET	1	Andersen et al.
7	Premature ovarian failure	25	No	Natural	1	Silber et al.
8	Hodgkin's lymphoma	20	No	Natural	2	Silber et al.
9	Polyangiitis	27	Yes	IVF-ET	1	Piver et al.
10	Breast cancer	36	No	IVF-ET	2	Pellicer et al.
11	Sickle cells	27	No	Natural	1	Piver et al.
12	Thalassemia	19	No	IVF-ET	2	Revel et al.
13	Hodgkin's lymphoma	27	Yes	Ovulation induction	1	Dittrich et al.

Note: Total, 13 patients and 18 babies.

Grynberg. Ovarian and follicle transplantation. Fertil Steril 2012.

13 patients, 18 babies

Grynberg et al., Fertil Steril 2012

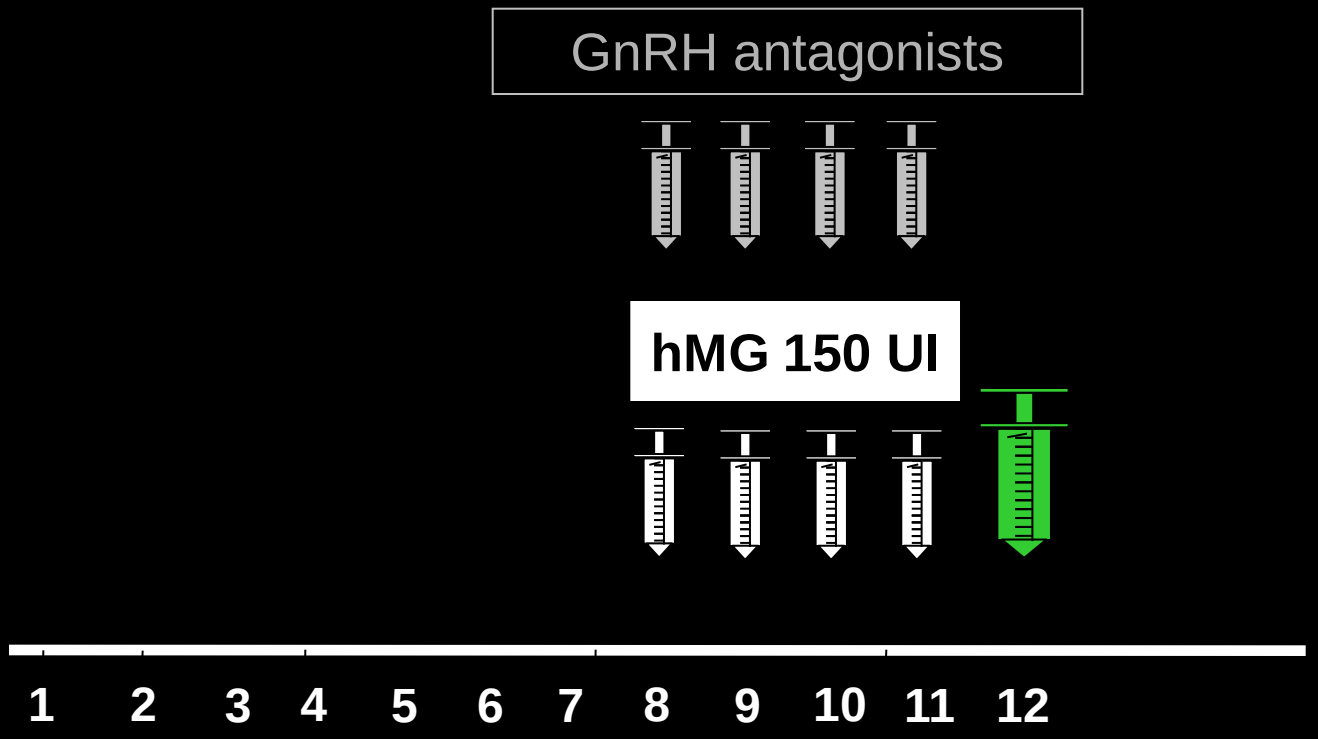
Ovarian stimulation after Transplantation of frozen ovarian tissue

Patient	Diagnosis	Chemo before OTC	Stimulation protocol	Foll size (mm) day −2	E2 (pg/ml) day −2	LH (mIU/ml) day −2	Oocyte number	Oocyte maturation/ aspect	Fertilization	Day 3 embryos stage/score
P1	Drepanocytosis	No	1: hMG + antag + hCG	19	269	15	0	No	/	
			2: hMG + antag+hCG	17	174	4.4	1	M I	/	
			3: rec FSH + antag + hCG	20+15	103	5.6	0	No	/	
			4: rec FSH + antag + hCG	17	58	42.5	1	One oocyte: lysis (empty zona pellucida)	/	
			5: spontaneous	17 (day of OPU)	89	86.5	1	One oocyte: lysis (abnormal)	/	
			6: spontaneous	17 (day of OPU)	53	64.7	1	MI: granular PVS	/	
			7: spontaneous	19 (day of OPU)	62	62.8	1	M II, brown, vacuolar, granular	Abnormal	
P 2	Hodgkin's lymphoma	Yes	1: spontaneous	17	276	13.2	0	No	/	
			2: spontaneous + hCG	21+16	502	15	1	Empty zona pellucida and extruded cytoplasm	/	
			3: spontaneous + hCG	22+19+16	395	29.3	0	No	/	
			4: hMG + antag + hCG	18	69	14.7	1	2-cell embryo-like structure	/	
			5: spontaneous + hCG	24	576	30	1	M II, ovoid	No	
			6: hMG + antag + hCG	16	169	4.8	1	M II	No	
P 3	Non-Hodgkin's lymphoma	Yes	1: hMG + antag + hCG	17+10	167		1	M II	Yes	7-cell, grade 2
			2: hMG + antag + hCG	18	164	13.7	0	No	/	
			3: hMG + antag + hCG	18	314	8	1	M II	Yes	10-cell, grade 2
			4: hMG + antag + hCG	16	108	7.6	1	M II	Yes	morula, grade 2
P 4	Wegener's granulomatosis	No	1: spontaneous + hCG	16+14	122	10.2	0	No	/	
			2: hMG + hCG	16	98	19.2	1	M II, brown, vacuolar, granular	No	
			3: hMG + antag + hCG	15	77	11.2	1	MII, 2 vacuoles	Yes	12-cell, grade 2
			4: hMG + antag + hCG	17+15	241	6.0	2	2 MII	1 normal + 1 abnormal	12-cell, grade 2
			21 cycles	>= 15 mm (15–27)	58–576		6 empty foll/ 21 cycles	6 'abnormal' oocytes/16 oocytes	3 no fertiliz°/10 MII oocytes	5 embryos
								10 MII oocytes/16 oocytes	2 abnl fertiliz°/10 MII oocytes	
									5 nl fertiliz°/10 MII oocytes	

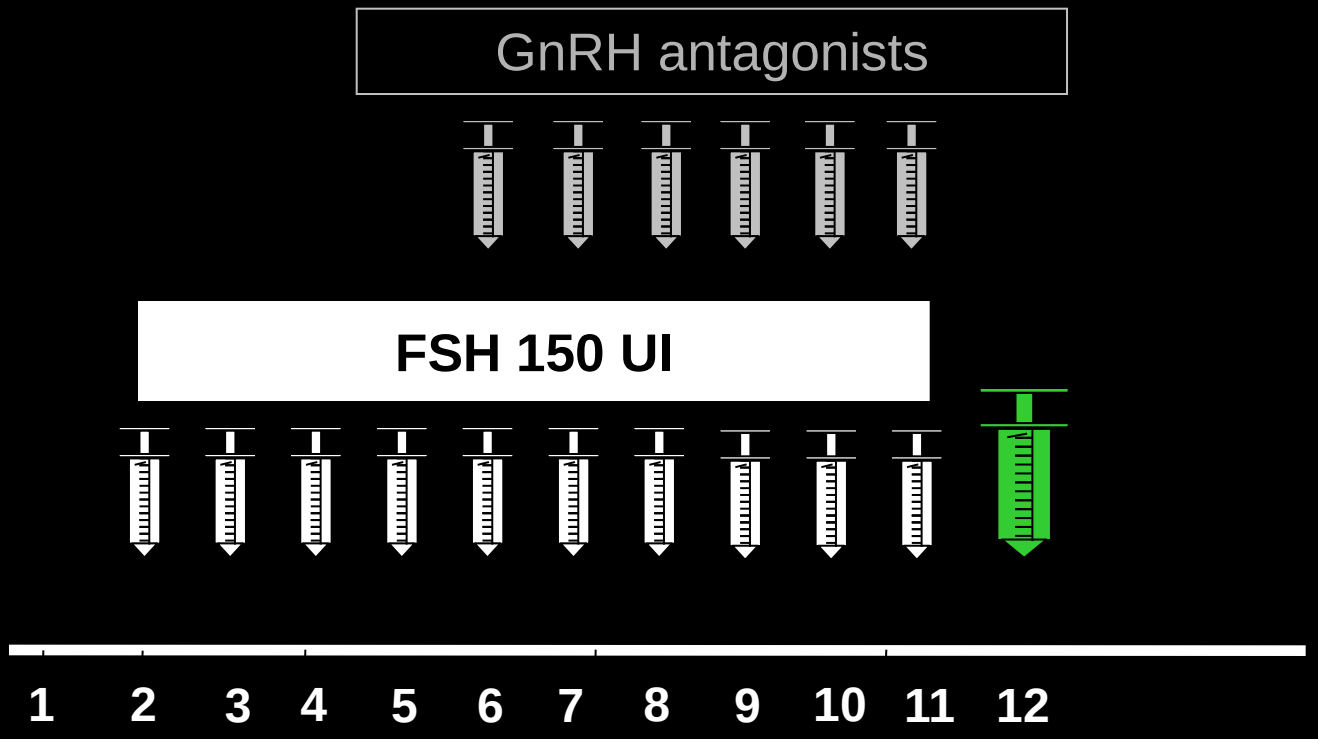
Dolmans et al., Hum Reprod 2009

Breast cancer survivors

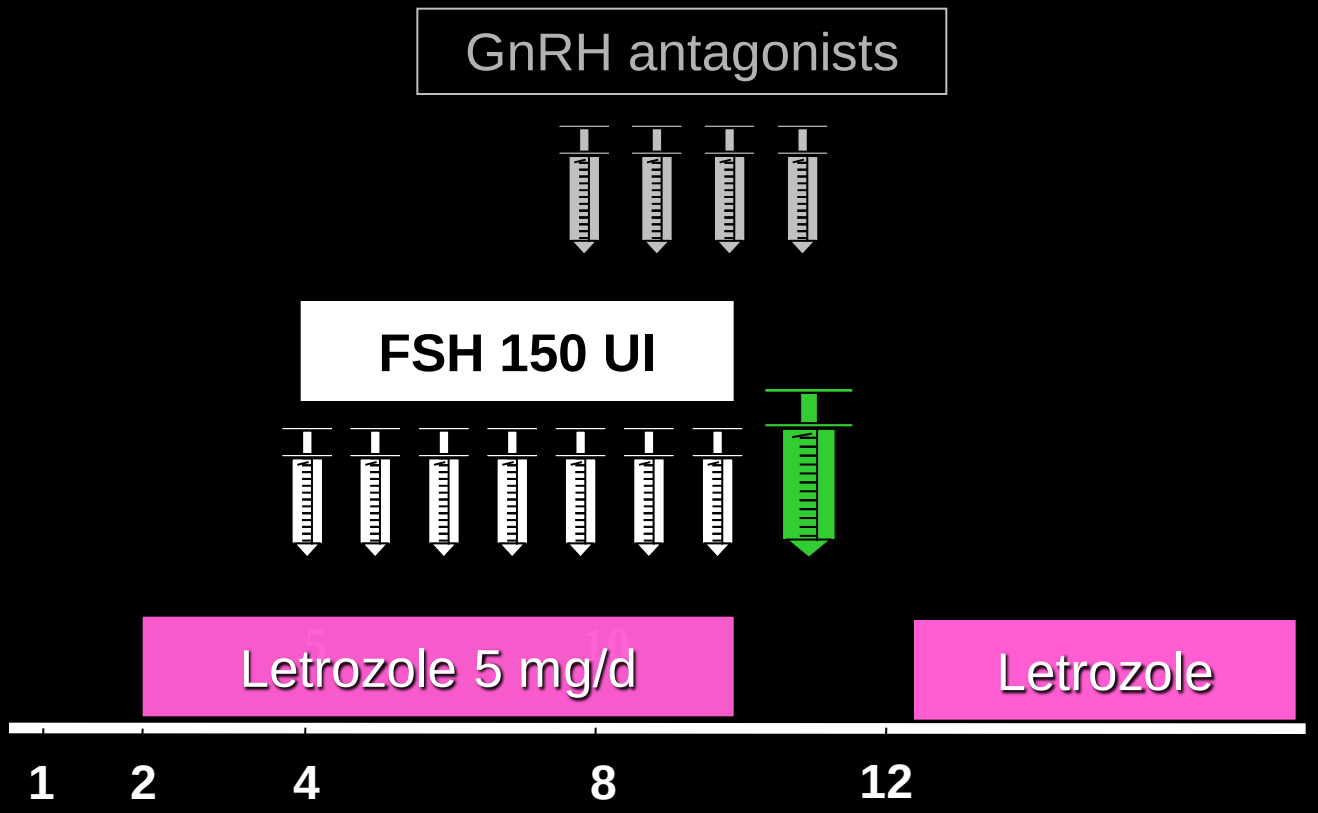
Modified natural cycle



GnRH antagonist protocol



Ovarian stimulation + aromatase inhibitors



Oktay et al., JCE&M 2006

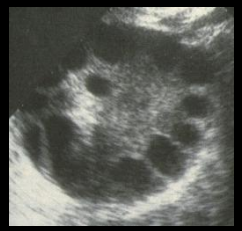
IVM Protocol

10.000 IU hCG

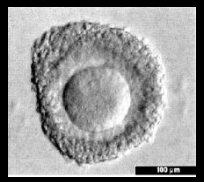
Cycle d1

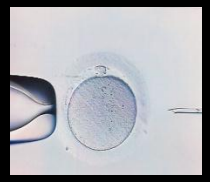
17-β estradiol

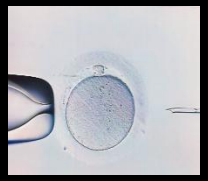
d0 d1 d2 d3

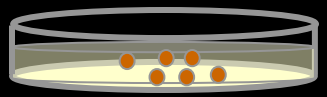


Oocyte retrieval ICSI ICSI ET



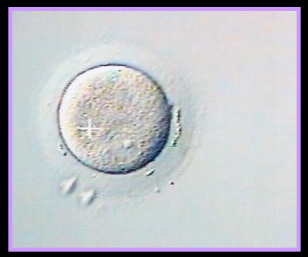




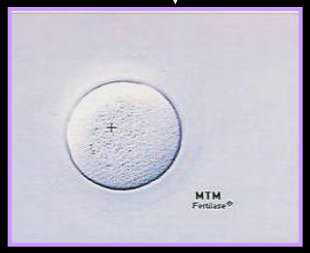


IVM

Nuclear maturation



Prophase I: VG



Métaphase I: GVBD

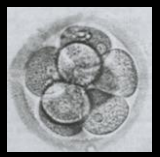
Métaphase II: 1st PG extrusion

Cytoplasmic maturation

Stock RNAm and proteins

Support the first steps of embryo development



Genome

In clinical practice

- Oncologist authorization for pregnancy (2 – 5 years after chemo)
- Fertility evaluation after 6 months of infertility
- IVF-ET / ICSI +++

OBAMA study

134 patients, 26-43 years of age, having undergone chemotherapy for breast cancer

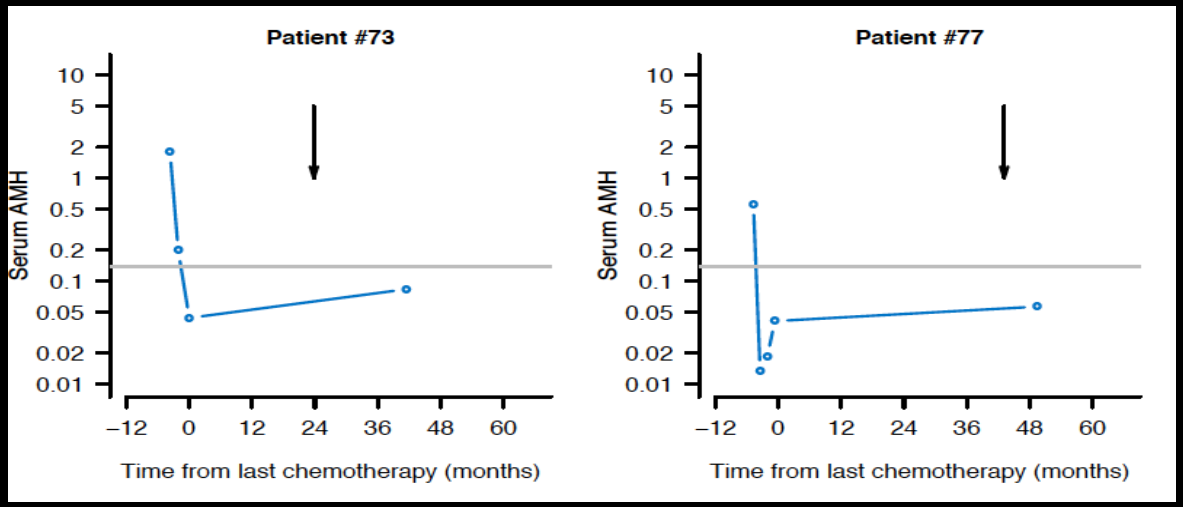
Median follow-up: 39 months

- 38 recurrences
  - 12 patients deceased
- 18 pregnancies and live births in 13 patients
  - All natural
  - ~ 30% in patients with undetectable serum AMH

At least 3 ongoing pregnancies

Hamy et al., unpublished data

OBAMA study



41 ans au diagnostic, G1P1, cycles réguliers

AMH basale = 1.8ng/mL

CCI 25 mm, RE+ RP+ her2-, N-/15

6 cycles de FEC 75, RT, Tamoxifène

Aménorrhée chimio induite pendant 5 mois;

Délai 23 mois après dernière chimiothérapie, grossesse spontanée à l'âge de 43 ans, ANAT

38 ans au diagnostic, G2P2, cycles réguliers

AMH basale = 0.55 ng/mL

Tumeur 55 mm, RE-RP-, her2-

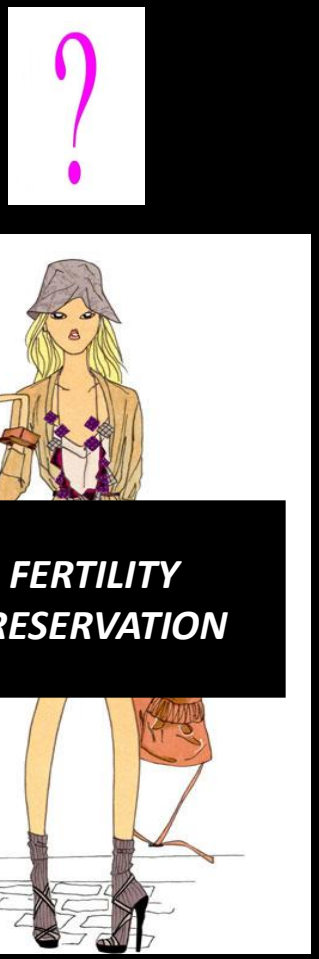
Chimiothérapie néoadjuvante ECT (anthra cyclo puis taxanes) 8 cures, chir, RT

Aménorrhée chimio induite : 14 mois

Grossesse spontanée à 41 ans, (42 mois après chimiothérapie) suivie ANAT

Malgré AMH restées indétectables après la chimiothérapie….

Fertility preservation



Oocyte cryopreservation

Ovarian tissue cryopreservation

Embryo cryopreservation

Medical treatment

Conclusions

1. Radiotherapy and chemotherapy may significantly alter the ovarian function and lead to loss of the fertility potential
2. Infertility in cancer survivors represents a major concern and patients seeking pregnancy should be offer an evaluation of the follicular ovarian status
3. Since women having undergone gonadotoxic treatments should be considered as poor-responders, IVF-ET should be rapidly proposed
4. Efficiency of ART in cancer survivors remains ill-established since there is a remarkable lack of published data
5. ART in patients having healed from breast cancer represents a major concern. IVF-ET after modified natural cycle or IVM are currently the only available options to treat their infertility
6. A plea for fertility preservation