
'An ounce of prevention is worth a pound of cure': the case for and against GnRH-agonist for fertility preservation
Z. Blumenfeld[1]*, G. Katz[2] & A. Evron[1]
Annals of Oncology 25: 1719–1728, 2014
Blumenfeld, Zur, Dann. Oncologist. 2015;20:1283.
GnRHa cotreatment preserves fertility & increases pregnancy rate in survivors
ISFP
The 5th World congress of the
INTERNATIONAL SOCIETY FOR FERTILITY PRESERVATION
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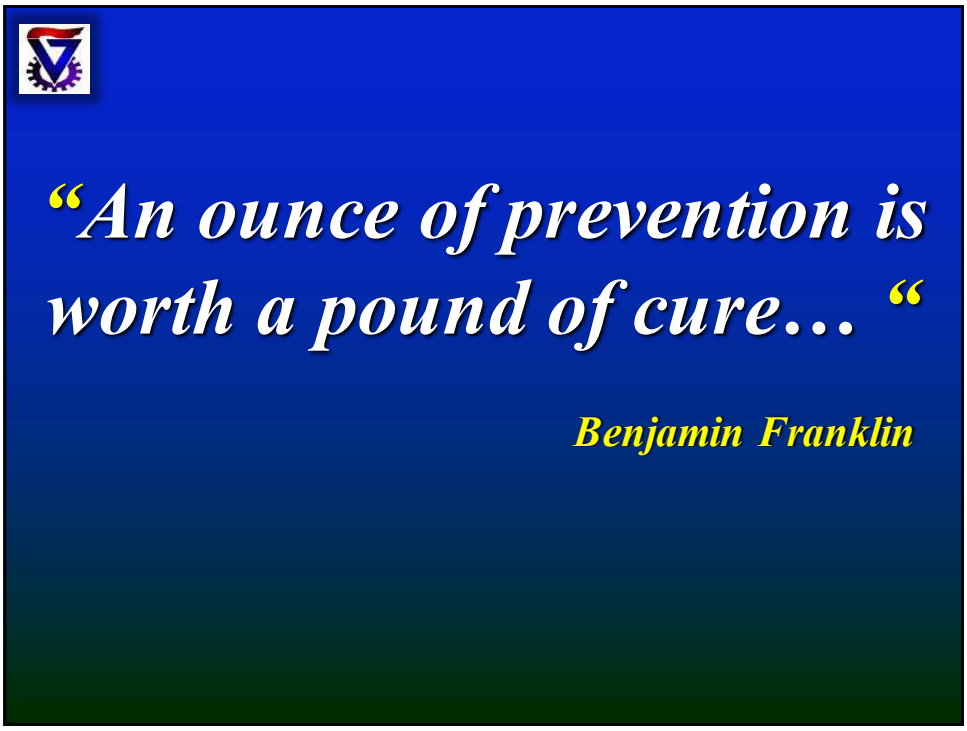
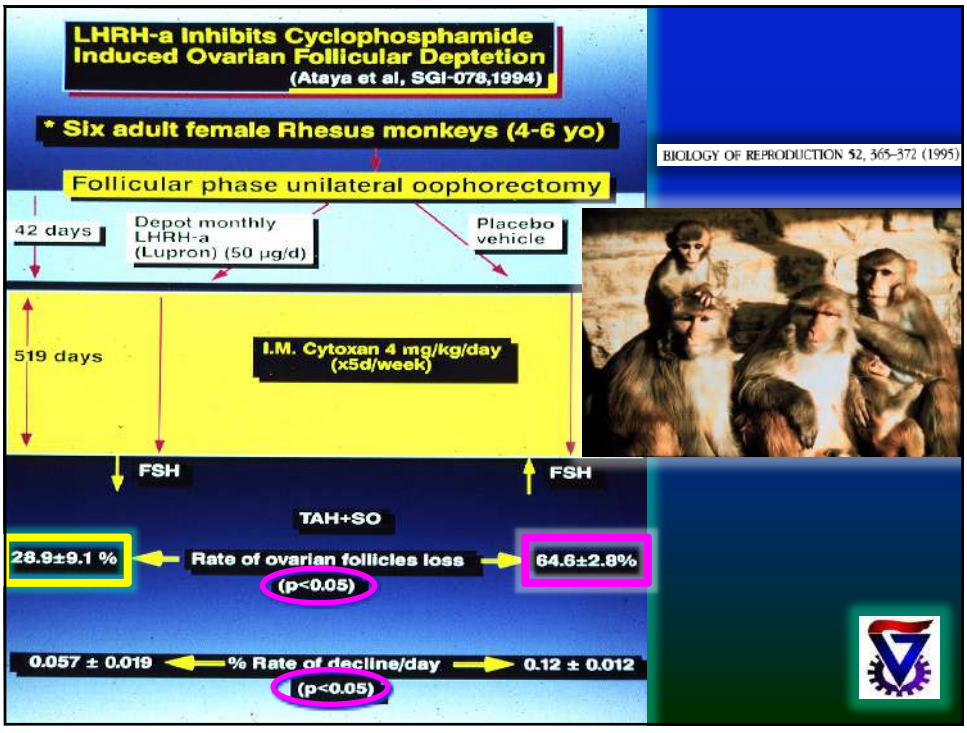
Disclosure
No conflicts of interest to disclose


"An ounce of prevention is worth a pound of cure… "
Benjamin Franklin

Is it helpful?



Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies

M. Lambertini[1], M. Ceppi[2], F. Poggio[1], F. A. Peccatori[3], H. A. Azim Jr[4], D. Ugolini[5], P. Pronzato[1], S. Loibl[6,7], H. C. F. Moore[8], A. H. Partridge[9], P. Bruzzi[2] & L. Del Mastro[10*]

Ann Oncol. ***2015***.

- ***12 RCTs*** including ***1231 patients***. LHRHa was associated with a ***significant reduced risk of POF*** (OR 0.36, 95% CI 0.23–0.57; ***P<0.001***), yet with significant heterogeneity). In 8 studies reporting ***amenorrhea*** rates 1 year after chemotherapy, LHRHa reduced it (OR 0.55, 95% CI 0.41–0.73, ***P<0.001***) without heterogeneity.
- In five studies reporting ***pregnancies***, more patients treated with LHRHa achieved pregnancy (33 ***vs*** 19 women; OR 1.83, 95% CI 1.02–3.28, ***P=0.041***; P heterogeneity =0.629). In three studies reporting DFS, no difference was observed (HR 1.00, ***P=0.939***).

- ***Conclusion***: ***Ovarian suppression with LHRHa reduces POF, increases pregnancy rate, without negative consequence on prognosis.***

Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies

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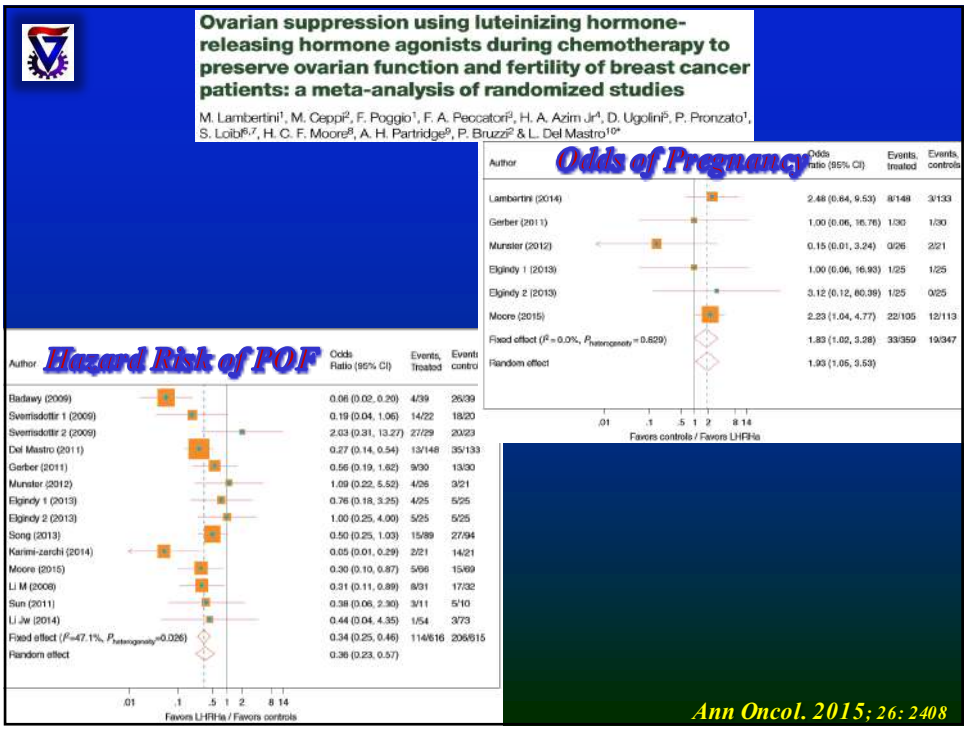

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Annals of Oncology 2015

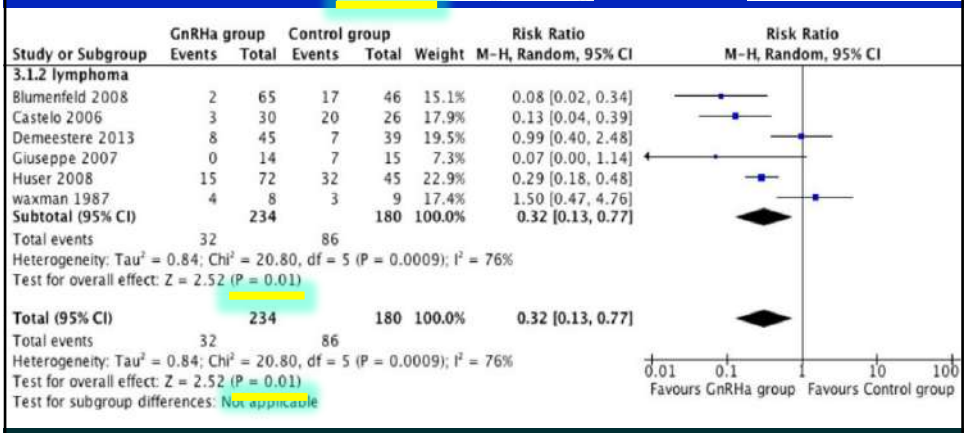
	No. studies	No. patients	Result LHRHa vs control	P value	I^2
Premature Ovarian Failure	12	1,231	18.5% vs 33.5% OR=0.36	<0.001	47.1%
One-year Amenorrhea	8	882	31.0% vs 42.9% OR=0.55	<0.001	0.0%
Patients with Pregnancy	5	706	33 vs 19 OR=1.83	0.041	0.0%
Disease-Free Survival Events	3	626	19.5% vs 18.8% HR=1.00	0.939	68.0%

- "***Conclusion***: "ovarian suppression with LHRHa during chemotherapy is associated with a ***reduced risk of POF*** and seems to ***increase pregnancy rate*** in young breast cancer patients, with ***no negative impact on prognosis***".
- "…useful and safe not only in HR-negative breast cancer, but also in ***HR-positive*** tumors, (2/3 of breast cancer in young women)."

GnRHa for Preservation of Ovarian Function during Chemotherapy in Lymphoma Patients of Reproductive Age: A Summary Based on 434 Patients

Zhang Y et al,

GnRH May Preserve Ovarian Function | PLOS ONE | www.plosone.org | November 2013 | Volume 8 | Issue 11



Forest plots showing POF rate of eligible studies comparing GnRHa + chemotherapy vs chemotherapy alone

Conte & Del Mastro. Minerva Ginecol 2017;69:350

TABLE I.—*Features of main randomized clinical trials on ovarian suppression with LHRHa during chemotherapy.*

Study	Patients (N.)	Median age	Type of cancer	Study arms	Primary endpoint	POF definition	Results
Badawy *et al.*[9] 2009	80	21	Breast cancer	FAC+goserelin *vs.* FAC	No spontaneous ovulation	8 months	Favors CT+LHRHa
Sverrisdottir *et al.*[10] 2009	94	45	Breast cancer	CMF±tamoxifen + goserelin *vs.* CMF±tamoxifen	No menses	36 months	Favors CT+LHRHa
Gerber *et al.*[11] 2011	60	37	Breast cancer only HR-	CT+goserelin *vs.* CT	No menses	6 months	Do not favor LHRHa+CT
Munster *et al.*[13] 2012	47	43	Breast cancer	CT+triptorelin *vs.* CT	No menses	2 years	Do not favor LHRHa+CT
Eligindy *et al.*[14] 2013	93	18-40 y	Breast cancer only HR-	CT+triptorelin±GnRH antagonist *vs.* CT alone	No menses	12 months	Do not favor LHRHa+CT
Song *et al.*[15] 2013	183	42	Breast cancer	NR	No menses and postmenopausal levels of FSH and E2	12 months	Favors LHRHa+CT
Karimi-Zarchi *et al.*[16] 2014	42	35	Breast cancer only HR-	Diphereline+CR *vs.* CT	No menses	6 months	Favors LHRHa+CT
Del Mastro *et al.*[12] 2011	281	39	Breast cancer	Triptorelin+CT *vs.* CT	No menses and postmenopausal levels of FSH and E2	12 months	Favors LHRHa+CT
Lambertini *et al.*[21] 2015 (update of Del Mastro *et al.*)]	246	39	Breast cancer	Triptorelin+CT *vs.* CT	Menses resumption	7 years	Favors LHRHa+CT
Moore *et al.*[17] 2015	218	38	Breast cancer only HR-	Goserelin+CT *vs.* CT	Amenorrhea for the prior 6 months and postmenopausal levels of FS	24 months	Favors LHRHa+CT
Sun *et al.*[18] 2011	NR	33	Breast cancer	Goserelin+CT *vs.* CT	No menses	12 months	Favors LHRHa+CT
Li M *et al.*[20] 2008	63	NR	Breast cancer	Goserelin+CT *vs.* CT	No menses	12 months	Favors LHRHa+CT
LI JW *et al.*[19] 2014	216	38	Breast cancer	Goserelin+CT *vs.* CT	No menses and postmenopausal levels of FSH	12 months	Favors LHRHa+CT

Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy induced premature ovarian failure in premenopausal women (Review)

2011;CD008018

Chen H, Li J, Cui T, Hu L

Main results

Included studies in this review showed that intramuscular/subcutaneous administration of GnRH agonists was effective in protecting menstruation and ovulation after chemotherapy (resumed menses: RR 1.90, 95% CI 1.30 to 2.79; amenorrhoea: RR 0.08, 95% CI 0.01 to 0.58; ovulation: RR 2.70, 95% CI 1.52 to 4.79), whereas intranasal administration of GnRH agonists had no protective effect on ovaries (resumed menses: RR 0.75, 95% CI 0.33 to 1.72; ovulation: RR 1.13, 95% CI 0.20 to 6.24). Pregnancy rates were not significantly different between groups (intramuscular/subcutaneous GnRH agonist: RR 0.21, 95% CI 0.01 to 4.09; intranasal GnRH agonist: RR 0.41, 95% CI 0.02 to 8.84). Ultrasound antral follicular count (AFC) was not significantly different between groups (SMD 1.11, 95% CI 0.32 to 1.90).

Authors' conclusions

The use of GnRH agonists should be considered in women of reproductive age receiving chemotherapy. Intramuscular or subcutaneous GnRH analogues seem to be effective in protecting ovaries during chemotherapy and should be given before or during treatment, although no significant difference in pregnancy rates was seen.

THE COCHRANE COLLABORATION®

Original Investigation

Gonadotropin-Releasing Hormone Agonists for Ovarian Function Preservation in Premenopausal Women Undergoing Chemotherapy for Early-Stage Breast Cancer

A Systematic Review and Meta-analysis *Munhoz et al; 2016:2*

JAMA Oncology

RESULTS Seven studies were included in this analysis, totaling 1047 randomized patients and 856 evaluable patients. The use of GnRHa was associated with a higher rate of recovery of regular menses after 6 months (odds ratio [OR], 2.41; 95% CI, 1.40-4.15; *P* = .002) and at least 12 months (OR, 1.85; 95% CI, 1.33-2.59; *P* < .001) following the last chemotherapy cycle. The use of GnRHa was also associated with a higher number of pregnancies (OR, 1.85; 95% CI, 1.02-3.36; *P* = .04), although this outcome was not uniformly reported and fertility or rate of pregnancy was not the primary outcome in any of the trials.

CONCLUSIONS AND RELEVANCE Gonadotropin-releasing hormone agonists given with chemotherapy was associated with increased rates of recovery of regular menses in this meta-analysis. Evidence was insufficient to assess outcomes related to GnRHa and ovarian function and fertility and needs further investigation.

JAMA Oncol

Factors associated with ovarian function recovery after chemotherapy for breast cancer: a systematic review & meta-analysis

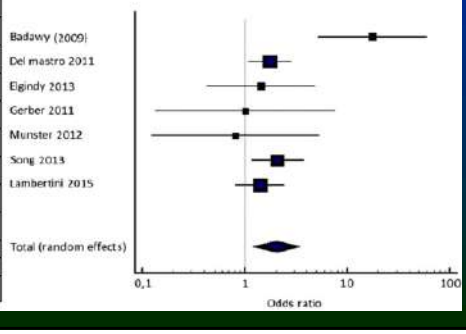
Silva et al, 2016

human reproduction META-ANALYSIS

- Metaanalysis of 15 studies.
- Younger age (≤40 years) and exposure to GnRHa were positively associated with menses recovery (***OR 6*** and ***2.03***, respectively).

	GnRH agonist		Control		Odds Ratio (OR) 95% (CI)
	Events	Total	Events	Total	
Badawy et al, 2009	35	39	13	39	17.50 (5.11-59.88)
Del Mastro et al, 2011	88	139	60	121	1.75 (1.07-2.88)
Elgindy et al, 2013	41	46	40	47	1.44 (0.42-4.90)
Gerber et al, 2011	28	30	28	30	1.00 (0.13-7.60)
Munster et al, 2012	23	26	19	21	0.81 (0.12-5.34)
Song et al, 2013	53	89	39	94	2.08 (1.15-3.74)
Lambertini et al, 2015	116	148	96	133	1.40 (0.81-2.41)
Total		517		485	2.03 (1.18 to 3.47)
Total Events	384		295		
Heterogeneity (I^2)	60.91 (p = [illegible])				
Test for overall effect	Z = 2.5[illegible] (p = 0.01)				

GnRH agonist exposure and menses recovery



Role of LHRH-a (Triptorelin) in Preserving Ovarian Function during Chemotx. for Early Breast Ca. patients: Results of a Multicenter Phase III Trial (*Gruppo Italiano Mammella*)

Del Mastro et al. JAMA. 2011;306:269

- Stage I-III; premenopausal; age 18-45; ***HR +*** or **-**. Years: 2003-8;
- ***Arm A: 133pts, Chemotx. alone; Arm B: 148pts, CT+GnRHa.***
- Comparable age and cumulative Cyclophosphamide.
- **POF** *(1 year)* - **32.3% in arm A** & **13.5% in arm B** (***P = 0.0002***), with a 19% absolute reduction (95% CI 8-29).
- Menstrual activity/ premenopausal E_2 levels - 58% in arm A *vs* 77% in arm B (***P = 0.006***).
- Logistic regression analysis: LHRH-a was independently associated with a higher probability of COF preservation (***P = 0.001***).

- ***Conclusion: Temporary ovarian suppression with LHRH-a during CTX is associated with a significant increase in COF preservation.***

Is it SAFE?

Ovarian Suppression With Triptorelin During Adjuvant Breast Cancer Chemotherapy and Long-term Ovarian Function, Pregnancies, and Disease-Free Survival: A Randomized Clinical Trial.

Lambertini et al. JAMA 2015; 314.

- Median follow-up **7.3 years**.
- The 5-year cumulative menstrual resumption was 72.6% (95% CI, 65.7%-80.3%) among the 148 patients in the LHRHa group and 64.0% (95% CI, 56.2%-72.8%) among the 133 patients in the control group (age-adjusted HR, 1.48 [95% CI, 1.12-1.95]; **P = 0 .006**.
- **CONCLUSIONS:** Among premenopausal women with **HR+** or **HR-** breast cancer, concurrent administration of GnRHa and chemotherapy, *vs*. chemotherapy alone, was associated with **higher long-term ovarian function recovery**. There was **no difference in DFS.**

ASCO

Goserelin for Ovarian Protection during Breast-Cancer Adjuvant Chemotherapy

The NEW ENGLAND JOURNAL of MEDICINE

Moore HC et al; SWOG/POEMS Cancer Research Group

- **Methods:** Randomly assigned **257** premenopausal women with HR- breast cancer to chemotherapy with/without GnRHa.
- **Results:** Among 135 with complete primary end-point data, the **POF** rate was **8%** in GnRHa group *vs* **22%** in controls (**OR 0.30; 95% CI, 0.09-0.97**; **P=0.04**).
- **Pregnancy** rate higher in the GnRHa group (**21% vs. 11%, P=0.03**).
- The GnRHa group also had **improved disease-free survival** (**P=0.04**) and **overall survival** (**P=0.05**).
- **Conclusions:** GnRHa protect against POF, reducing the risk of early menopause and improving fertility.

(NCI; POEMS/S0230 Clinical Trials.gov number, NCT00068601)

N Engl J Med 2015;372:923-32

Gonadotrophin Releasing Hormone Analogues for Ovarian Function Preservation in Young Females Undergoing Chemotherapy

Bansal et al. *Asian Pac J Cancer Prev. 2014;15:2185*

In our study, the use of GnRHa is associated with 99% increase in the rate of ovarian preservation and 45% increase in the rate of pregnancy, compared to those who donot receive GnRHa along with chemotherapy.

Asian Pac J Cancer Prev, **15 (5)**, 2185-2190

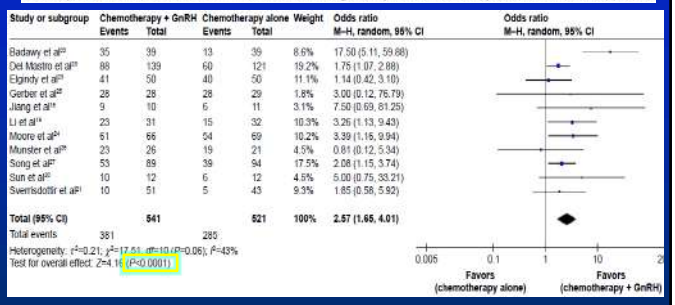
Utility of GnRHa for prevention of chemotherapy-induced ovarian damage in premenopausal women with breast cancer: a systematic review and meta-analysis

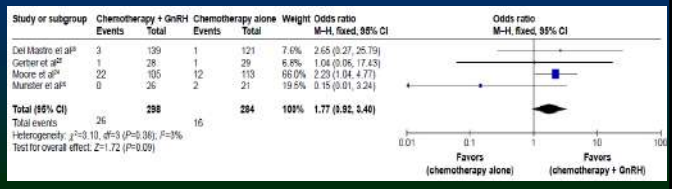
Shen et al; Onco Targets & Therapy. 2015:8

Results: 11 RCTs with 1,062 participants.
A significantly greater number of women treated with GnRHa experienced spontaneous resumption of menses after the adjuvant chemotherapy, yielding a pooled OR= 2.57 (95%CI= 1.65-4.01)
P<0.0001

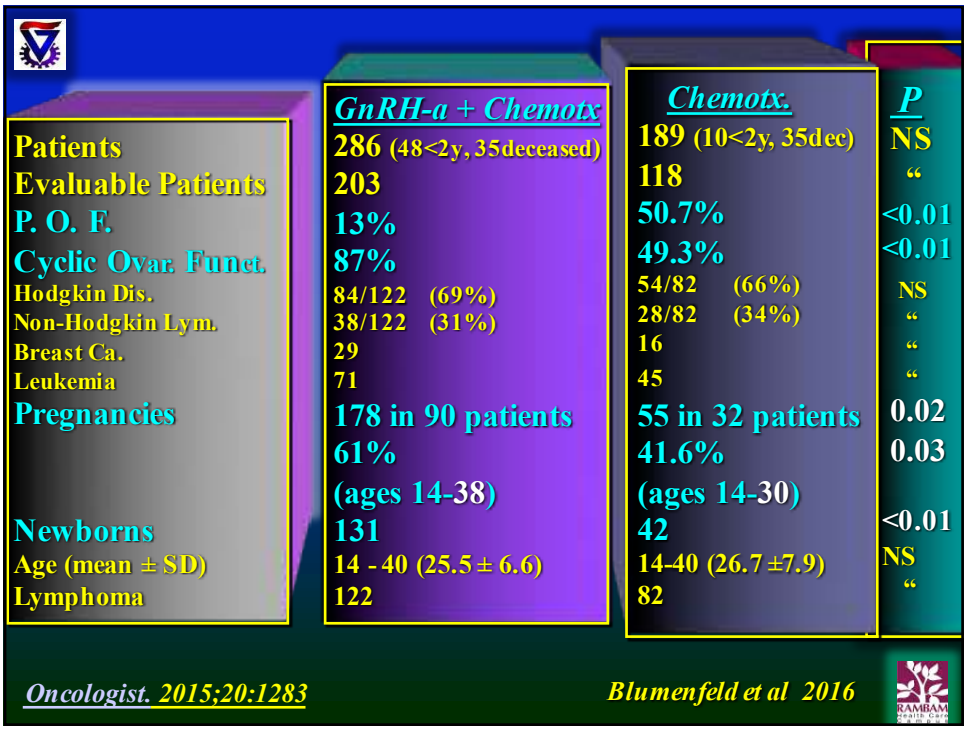
Conclusion: GnRHa co-treatment plays a beneficial role in resumption of ovarian function.

Forest plot of the rate of resumed menses for GnRH agonists plus chemotherapy versus chemotherapy alone





rate of spontaneous pregnancy



Results - Summary

- 87% in the GnRHa group resumed cyclic ovarian function [COF], *vs* only 50% of the controls, and the rest suffered POF (***P=0.003***)
- 61% of the survivors in the GnRHa group ***conceived***, vs 42% of the controls (***P=0.033***)
- ***Spontaneous pregnancies*** occurred in **58%** of the survivors in the GnRHa group [up to 6 pregnancies/patient], vs **34.9%** of the controls [up to 4/patient], (***P=0.006***)
- The age at chemotherapy, of those who spontaneously conceived was **14-38** in the GnRHa group, *vs.* **14-30** y. in the control group, suggesting a possible prolongation of the ***"Fertile window"*** by almost 10 years!

Results

	GnRH-a + Chemotx	Chemotx.	P
Patients	286 (45<2y, 35dec)	189 (10<2y, 35dec)	NS
Evaluable Patients	145	72	"
Age (mean ± SD)	14 - 40 (25.5 ± 6.6)	14-40 (26.7 ±7.9)	NS
Hodgkin Dis.	84/122 (69%)	54/82 (66%)	"
Non-Hodgkin Lym.	38/122 (31%)	28/82 (34%)	"
Breast Ca.	29	16	"
Leukemia	71	45	"
P. O. F.	13%	51%	<0.01
Cyclic Ovar. Funct.	87%	49%	"
Pregnancies	178 in 90 patients	55 in 32 patients	<0.03
	61%	42%	<0.02
Spontaneous preg.	58%	35%	0.006
Age at chemotx.	14-38	ages 14-30	
Newborns/Gestations	131/178 (73.5%)	42/55(74.5%)	NS

Temporary Ovarian Suppression With Gonadotropin-Releasing Hormone Agonist During Chemotherapy for Fertility Preservation: Toward the End of the Debate? DelMastro & Lambertini

The Oncologist 2015;20:1233

- In a prospective study (London, UK), of 125 consecutive breast ca. patients undergoing concurrent GnRHa and chemotherapy, 104 (84%) recovered menstruation *[Wong et al, Ann Oncol,2013].* 42 (74%) attempted pregnancy, and 30 of those, ***71% conceived***.

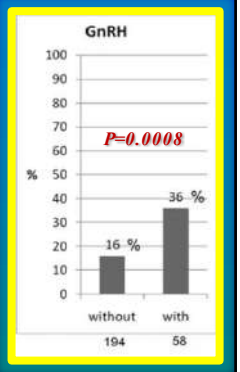
- ***High pregnancy rates after GnRHa cotreatment:***
  - ***Europe***: Wong *et al.* study, ***71%*** conceived *[**Ann Oncol**,2013].* ***UK***
  - ***America***: POEMS-SWOG study, ***88%*** conceived *[Moore, **NEJM** 2015].* ***USA***
  - ***Asia***: Blumenfeld *et al.* study, ***61%*** conceived. *[**Oncologist** 2015].* ***Israel***

- ***Conclusion***: "***temporary ovarian suppression with GnRHa during chemotherapy might be considered a reliable strategy not only to preserve ovarian function but also to increase the likelihood of becoming pregnant ...***"

Fertility and gonadal function in female survivors after treatment of early unfavorable Hodgkin lymphoma (HL) within the German Hodgkin Study Group HD14 trial

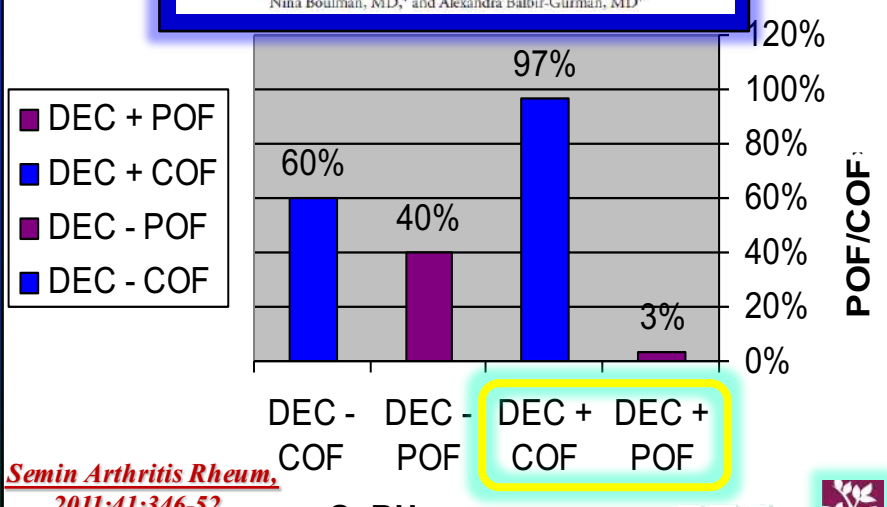
Behringer et al. Ann Oncol. 2012; 23

- "…the use of GnRHa during chemotherapy …significantly increased the probability to become ***pregnant***. ***[OR=12.87]*** (***P=0.0008***) "
- "…the multivariate analysis in the present study reveals that the use of GnRHa during therapy is a strong, independent, and highly significant predictor of pregnancies."
- " We thereby adjusted our analysis to a high degree and nevertheless found surprisingly strong (***OR > 12***) evidence supporting the prophylactic use of GnRHa in early unfavorable HL."



Gonadotropin Releasing Hormone Agonists May Minimize Cyclophosphamide Associated Gonadotoxicity in SLE and Autoimmune Diseases

Zeev Blumenfeld, MD,* Or Mischari,* Naomi Schultz, RN,† Nina Boulman, MD,‡ and Alexandra Balbir-Gurman, MD†



Semin Arthritis Rheum, 2011;41:346-52

Combined Studies on GnRH-a in SLE/Autoimmune Dis.					
Authors	**Age years**	**Disease**	**Cumulative CTX dose**	**GnRHa + POF**	**GnRHa – POF**
Somers McCune US-2005	24 ± 4	SLE	13 ± 7 g	1/20 (5%)	6/20 (30%)
Liang, 2008 China	35.3±2.4 [30-39]	SLE	? g	3/28 (11%)	-
Manger 2006 Germany	30-40	SLE	? g	-	60%
Blumenfeld 2011	17-39	SLE, RA,SS, MCTD, GN	9.5 ± 4.4 g	1/31 (3.3%)	5/11 (45%)
Pereyra-2010 Argentina		SLE		0/15 (0%)	6/10 (60%)
Henes et al. 2012 ,Fertiprotekt	25±6	SLE	? g	?/63	?/5
TOTAL	**17-40**	**CTD**	**8-20g**	**5/94 (5.3%)**	**17/41 (41.5%)**

Spontaneous pregnancy and normal delivery after repeated autologous bone marrow transplantation and GnRH agonist treatment *Hum Reprod 2007; 22*

- At age of 14.5 treated with CHOP/GnRHa CR for NHL.
- At 15.5y - recurrence, ***aggressive chemotx*** & GnRHa → ***BMT***.
- ***Spontaneous pregnancy***, age 24, → miscarriage.
- ***Spontaneous pregnancy***, age 24, → normal development and fetal sonographic screenings at 15 & 23 weeks' gestation.
- At 26 wks - recurrence→ Chemotherapy→ IUGR→ IUFD.
- Consolidation ***aggressive chemotherapy*** & GnRHa→ ***BMT***. Request for Ovarian cryopreservation or IVF denied.
- Age 28→ ***Spontaneous pregnancy,→ Nl. Term delivery, Apgar: 9/10*** *[8,2006]*
- **Age 30→ *Spontaneous pregnancy,→ Nl delivery,*** *[9.2008].*
- Age 33→ ***Spontaneous pregnancy,→ Nl delivery,*** *[2011].*

Zeev Blumenfeld, Myriam Ben Arush and Tsila Zuckerman

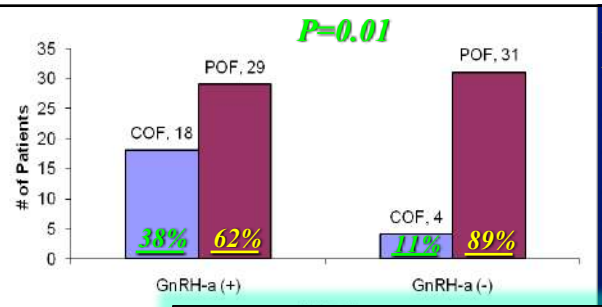
RAMBAM

Pregnancies after BMT?

Pregnancy after BMT in Hematological Malignancies

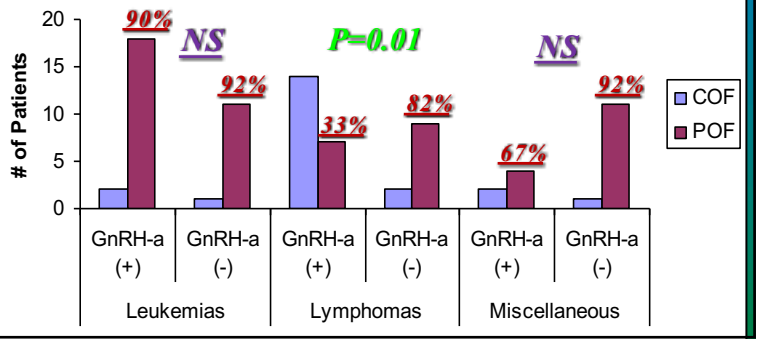
- A large survey of fertility after stem cell transplantation (SCT) in the 229 centers of the European Group for BMT, investigated conceptions after 19,412 allogeneic & 17,950 autologous transplant patients. *(Salooja. Lancet 2001;358).*
- Only 0.6% of patients conceived after ONE SCT.
- Report on a 4 y.o. patient treated by allogeneic BMT (after conditioning regimen containing Busulfan & Cyclophosphamide who had four successful pregnancies without any reproductive assistance. *[Remérand et al. J Inherit Metab Dis. 2009, 32:S111]*

Four successful pregnancies in a patient with mucopolysaccharidosis type I treated by allogeneic bone marrow transplantation



Blumenfeld Z, Patel B, Leiba R, Zuckerman T. GnRHa may minimize POF in young women undergoing autologous stem cell transplantation. Fertil Steril. 2012;98:1266.

- Best new investigator poster. SGI annual meeting, March 2011.



Cancer and fertility preservation: recommendations from two international expert meetings

Matteo Lambertini, Lucia Del Mastro, MC. Pescio, Claus Y. Andersen, HA. Azim, Fedro A. Peccatori, M Costa, A Revelli, F Salvagno, A Gennari, FM Ubaldi, GB La Sala, C De Stefano, W. Hamish Wallace, Ann H Partridge, & P Anserini.

- The 2015 St. Gallen International Expert Consensus panel & the National Comprehensive Cancer Network (NCCN) guidelines: "LHRH agonist therapy during chemotherapy proved effective to protect against POF and preserve fertility…"

  [Annals of Oncology 2015;26:1533]

- ***Recommendation 10***: Ovarian suppression with LHRHa during chemotherapy should be considered a reliable strategy to preserve ovarian function and fertility, at least in breast cancer patients, given the availability of new data suggesting both the safety and the efficacy of the procedure…

  (***I, A***) *[BMC Medicine 2016;14:1]*

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[Annals of Oncology 26: 1533, 2015]

- ***Recommendation 10 (NCCN)***: Ovarian suppression with LHRHa during chemotherapy should be considered a reliable strategy to preserve ovarian function and fertility, at least in breast cancer patients, given the availability of new data suggesting both the safety and the efficacy of the procedure… (***I, A***)

[BMC Medicine (2016)14:1]

Table 1 Levels of evidence and grades of recommendation (according to the ESMO Clinical Practice Guidelines for fertility preservation in cancer patients [11])

Levels of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grade of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Lambertini et al. BMC Medicine (2016) 14:1

Levels of evidence & grades of recommendation ESMO Clinical Practice

Lambertini et al. BMC Medicine (2016) 14:1

Temporary ovarian suppression during chemotherapy to preserve ovarian function and fertility in breast cancer patients: A GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology

Lambertini M, Cinquini M, Moschetti I, Peccatori FA, Anserini P, Valenzano Menada M, Tomirotti M, Del Mastro L.

EJC 2017 EUROPEAN JOURNAL OF CANCER

- Following the availability of new data on this controversial topic, the Panel of the Italian Association of Medical Oncology (AIOM) Clinical Practice Guideline on fertility preservation in cancer patients decided to apply the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology around the relevant and current question on the clinical utility of temporary ovarian suppression with LHRHa during chemotherapy as a strategy to preserve ovarian function and fertility in breast cancer patients.

- According to the GRADE evaluation, the result was a strong positive recommendation in favour of using LHRHa to preserve ovarian function and fertility in breast cancer patients.

Eur J Cancer. 2017;71:25

EJC 2017 EUROPEAN JOURNAL OF CANCER

Current guidelines on the use of temporary ovarian suppression with LHRHa during chemotherapy in preventing treatment-related premature ovarian failure and fertility in breast cancer patients.

Guidelines	Year	Recommendations
ASCO [4]	2013	Insufficient evidence regarding the effectiveness of LHRHa and other means of ovarian suppression in fertility preservation. LHRHa should not be relied upon as a fertility preservation method.
ESMO [5]	2013	The use of LHRHa concomitantly with chemotherapy should not be regarded as a reliable means of preserving fertility. Data on long-term ovarian function and pregnancy rates are warranted.
St. Gallen [25]	2015	LHRHa therapy during chemotherapy proved effective to protect against premature ovarian failure and preserve fertility in young women undergoing chemotherapy. Hence, the Panel strongly supports the use of LHRHa during chemotherapy for hormone receptor-negative disease to preserve ovarian function and fertility.
NCCN [26]	2016	Ovarian suppression with LHRHa administered during adjuvant chemotherapy in pre-menopausal women with hormone receptor-negative disease may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhoea.
BCY2 [6]	2016	The most recent data suggested a protective ovarian effect of LHRHa in both patients with hormone receptor-positive and -negative disease with no signal for harm from a breast cancer recurrence standpoint. The BCY2 Panel therefore agreed this strategy can be discussed with patients interested in potentially preserving fertility and/or ovarian function.
AIOM	2016	Temporary ovarian suppression with LHRHa during chemotherapy should be recommended to all pre-menopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation.

Abbreviations: LHRHa, luteinising hormone-releasing hormone analogues; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; BCY2, International Consensus Conference for Breast Cancer in Young Women; AIOM, Italian Association of Medical Oncology.

M. Lambertini et al. / European Journal of Cancer 71 (2017) 25–33

Second international consensus guidelines for breast cancer in women (BCY2)

Paluch-Shimon et al. Breast 2016; 26: 87-99

GnRH agonists & ovarian function preservation

The effectiveness of GnRH agonists to preserve ovarian function in women receiving chemotherapy, thus reducing the risk of early menopause and increasing the chances for future fertility, has not yet been fully elucidated. Despite limitations in study design and statistical power, the most recent randomized controlled trials suggest a protective ovarian effect in both HR+ and HR− patients and no signal for harm from a breast cancer recurrence standpoint [75,76]. A recent meta-analysis supports these findings [77]. The BCY2 panel therefore agreed this strategy can be discussed with patients interested in potentially preserving fertility and/or ovarian function.

ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3)

The Breast 2017

Shani Paluch-Shimon [a, 1], Olivia Pagani [b, 1], Ann H. Partridge [c], Omalkhair Abulkhair [d], Maria-João Cardoso [e], Rebecca Alexandra Dent [f], Karen Gelmon [g], Oreste Gentilini [h], Nadia Harbeck [i], Anita Margulies [j], Dror Meirow [a], Giancarlo Pruneri [l], Elzbieta Senkus [m], Tanja Spanic [n], Medha Sutliff [o], Luzia Travado [e], Fedro Peccatori [k, 2], Fatima Cardoso [e, *, 2]

4.2.4. GnRH agonists & ovarian function preservation

GnRH agonists appear to preserve ovarian function in women receiving chemotherapy [63–65], reducing the risk of early menopause and increasing the chances for future fertility, and should be discussed as an option with all patients interested in potentially preserving fertility and/or ovarian function who are candidates for chemotherapy, irrespective of tumor subtype.

The use of GnRH analogue concomitant with adjuvant CT should be discussed on a case by case basis to preserve ovarian function and possibly fertility IB

Levels of evidence grading system [26].

Grade of Recommendation/Description	Benefit vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation

GnRHa debate

Why?

GnRHa in female patients undergoing hematopoietic SCT

Cima et al, Endocrine Connections. 2017; 6: 162

Reference	Endpoint	No. of patients	Results GnRHa vs control	P value
Pro				
Lambertini, 2015	POF	1231	18.5% vs 33.5%, OR=0.36	<0.001
	1-year Amenorrhea	882	31% vs 42.9%, OR=0.55	<0.001
	PR	706	33 vs 9, OR=1.83	0.041
	DFS	626	19.5% vs 18.8%, HR=1.00	0.939
Shen, 2015	POF	1064	OR 2.57, 95% CI 1.65–4.01	0.0001
	PR		OR 0.177; 95% CI=0.92, 1.40	0.09
Del Mastro, 2014	POF	765	OR=0.43; 95% CI: 0.22–0.84	0.013
Sun, 2014	POF	621	9.66% vs 26.67%, RR of 0.45, 95% CI 0.22–0.92	0.02
Yang, 2013	POF	528	RR of 0.40, 95% CI 0.21–0.75	
	RM		RR=1.31, 95% CI 0.93–1.85	
	PR		RR=0.96, 95% CI 0.20–4.56	
Wang, 2013	RM	677	OR 2.681; 95% CI, 1.169–6.146	
Chen, 2011	RM		RR 1.90, 95% CI 1.30–2.79	
	Amenorrhea		RR 0.08, 95% CI 0.01–0.58	
	Ovulation		RR 2.70, 95% CI 1.52–4.79	
	PR		RR 0.21, 95% CI 0.01–4.09	
Bedaiwy, 2011	RM	340	57.22% vs 35.22%	0.03
			OR 3.46; 95% CI, 1.13–10.57	
	Spontaneous Ovulation	98	60.41% vs 22%	0.0002
			OR 5.70; 95% CI, 2.29–14.20	
Munhoz, 2016	RM 6 months	856	OR=2.41; 95% CI 1.40–4.15	0.002
	RM 12 months	778	OR 1.85; 95% CI 1.33–2.59	0.0003
	PR	218	OR 1.85; 95% CI 1.02–3.36	0.04
Contra				
Elgindy, 2015	RM	907	68.4% vs 59.9%, RR 1.12, 95% CI 0.99–1.27	0.7
	PR		RR 1.63, 95% CI 0.94–2.82	

CI, confidence interval; DFS, disease-free survival; OR, odds ratio; POF, premature ovarian failure; PR, pregnancy rate; RCT, randomized clinical trials; RM, resumption of menses; RR, relative risk.

Meta-analyses of RCT

Protecting Ovaries During Chemotherapy Through Gonad Suppression: A Systematic Review and Meta-analysis.

Elgindy et al. Obstet Gynecol. 2015.

No protection.

- ***Letters to the Editor***: This metaanalysis has been criticized by the two leading groups in fertility preservation in breast cancer:
  - Lambertini M, ...Del Mastro L. *Ob.Gyn. 2015;126:901.*
  - Falcone T, … Moore HC. *Ob.Gyn. 2015;126:899.*

Why is the discrepancy ?

- "Elgindy *et al*, have ***assigned lower weight to the two large, RCT (NEJM & JAMA) and excluded RCT's in support of GnRHa, with a possible consequent underestimate of the beneficial effect*** of the GnRHa cotreatment."
- The reservations raised by these two groups of investigators concluded that the findings in the negative metaanalysis, ***did not provide sufficient evidence of a risk–benefit analysis that would disclaim the use of GnRHa for fertility preservation***.
- Furthermore…

Gonadotropin-Releasing Hormone Agonist for the Prevention of Chemotherapy-Induced Ovarian Failure in Patients With Lymphoma: 1-Year Follow-Up of a Prospective Randomized Trial Demeestere et al

J Clin Oncol 31:903-909. © 2012

*AMH was higher in the GnRHa group *vs* control (1.4±0.35 *vs* 0.5±0.15ng/mL, respectively; ***P=0.04***).

* Metrorrhagia more frequent in the control group (38.4% *vs* 15.6%, ***P=0.024***).

* ***Conclusion:*** 20% POF in both groups after ***1y*** FU.

"…better ovarian function resumption was observed in the update analysis at ***2 y's"*** by Demeestere *et al*; " the # of patients who totally restored their ovarian function was higher in the GnRHa group (***P = 0.049***) *vs* control."

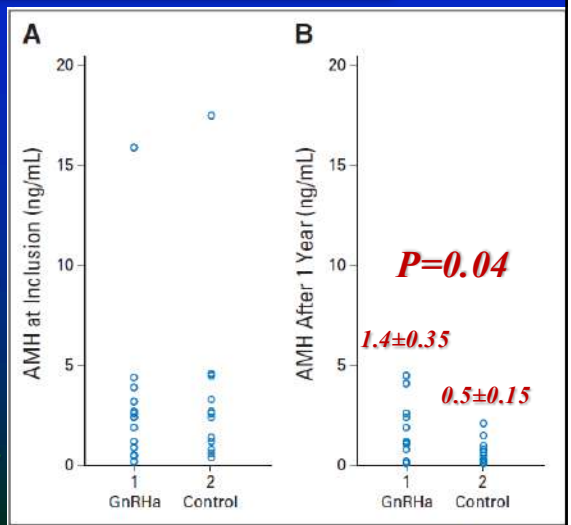


Fig 4. Anti-Müllerian hormone (AMH) values at (A) inclusion and (B) after 1 year of follow-up in the gonadotropin-releasing hormone agonist (GnRHa) and control groups.

Triptorelin to prevent chemotherapy-induced ovarian failure in lymphoma patients: a prospective randomized study

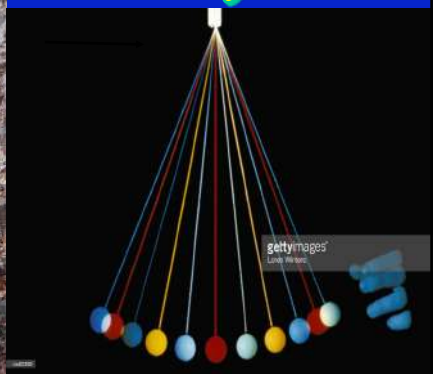
Demeestere et al, (abs.) ISFP meeting, Valencia 2013

However, ***the number of patients who totally restored their ovarian function (FSH≤10 IU/L) was higher in the GnRHa group (P=0.049) confirming results of AMH.***

Conclusion: Triptorelin …has a ***positive effect*** on the ovarian reserve in patients who recovered ovarian function.

No Evidence for the Benefit of Gonadotropin-Releasing Hormone Agonist in Preserving Ovarian Function and Fertility in Lymphoma Survivors Treated With Chemotherapy: Final Long-Term Report of a Prospective Randomized Trial *J Clin Oncol 34. © 2016*

Why ?



The GnRHa Pendulum…

No Evidence for the Benefit of Gonadotropin-Releasing Hormone Agonist in Preserving Ovarian Function and Fertility in Lymphoma Survivors Treated With Chemotherapy: Final Long-Term Report of a Prospective Randomized Trial Demeestere et al

- ***Dropout rate***: **50%**, & **25%** loss of follow-up or data unavailability. Although the original study design "mandated the accrual of ***157*** patients to ensure a power of 80% and a type error I probability of 5%, enrolment was discontinued after the assignment of 129 patients," but only ***63*** patients were evaluated for POF, 31-32 in each arm, in 15 centers (1-3 patients/arm/center).
- Furthermore, ***five pregnancies*** were reported in patients with ***protocol-defined POF*** of "one FSH>40U/L measurement" challenging the accuracy of POF definition, and the resulting conclusions.
- The small number of the evaluated patients [***α error***] may explain the "negative" results after one year, the pendulum swinging to "positive" result at 2 years, and again switching back to negative conclusion at 5 years.

J Clin Oncol 34. © 2016

- Suboptimal compliance in randomized trials is well known to cause negative results.

Romero et al, Am J Ob Gyn. 2017

Cramer JA, Spilker B. Patient compliance in medical practice and clinical trials: Raven Press;1991. 387

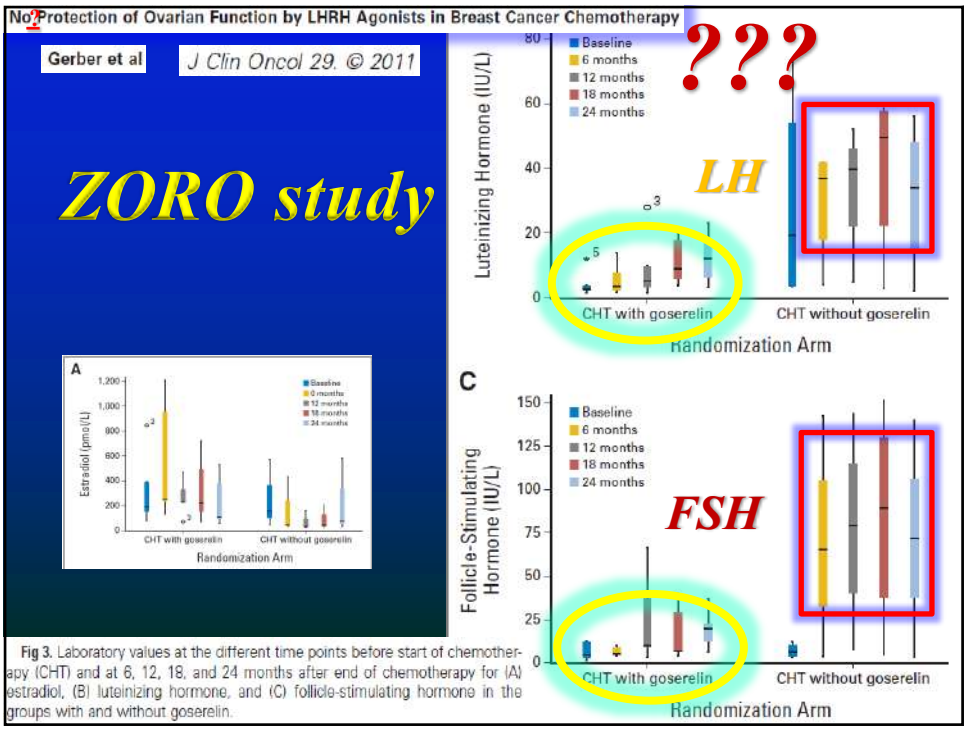


Fig 3. Laboratory values at the different time points before start of chemotherapy (CHT) and at 6, 12, 18, and 24 months after end of chemotherapy for (A) estradiol, (B) luteinizing hormone, and (C) follicle-stimulating hormone in the groups with and without goserelin.

GnRHa for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial.

Leonard…Anderson Ann. Oncol. 2017;28
NEJM Journal Watch, Nov. 3, 2017

- ***Patients & methods***: prospective RCT of 227 stage I-III BC.
- ***Results*: GnRHa reduced the prevalence of *amenorrhoea*** between 12 and 24 months to 22% versus 38% in the control group (***P = 0.015***) and the prevalence of ***POI*** to 18.5% versus 34.8% in the control group (***P = 0.048***). ***FSH was*** lower in all women treated with goserelin at both 12 & 24 m's (***P = 0.027, P = 0.001***, respectively).
- ***Conclusion*: GnRHa reduced the risk of POI…≤40 y's.**

Luteinising hormone releasing hormone agonists (LH-RHa) in premenopausal early breast cancer patients: Current role and future perspectives

Del Mastro et al. Cancer Treatment Reviews (2010)

Why is the discrepancy ?

- ***I.*** A possible explanation of the different results may be the ***different timing*** of ovarian function assessment.
- Since ovarian function resumption may occur up to or more than 24 months after chemotherapy, an ***early assessment*** (6 m's after chemotherapy), may ***underestimate the true effect of GnRHa***.

- ***II.*** In protocols of low gonadotoxicity the needed number in each arm is hundreds of patients …
- ***III.*** Several studies were ***prematurely ended*** before reaching the number calculated for power analysis.

Conclusions

- GnRHa cotreatment preserves ***COF*** & ***FERTILITY*** (pregnancies & deliveries) with similar or improved survival.

- Failure to offer GnRHa cotreatment in addition to cryopreservation of embrya, ova, & ovarian tissue may disadvantage many patients who could benefit such a clinical combination.

- Additionally, GnRHa co-treatment decreases the thrombocytopenia associated menorrhagia, and may have beneficial immune influences.

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- Raya Gendelman, B.Sc.

If you are convinced you are right…

"No one is more hated than he who speaks the truth."

— Plato

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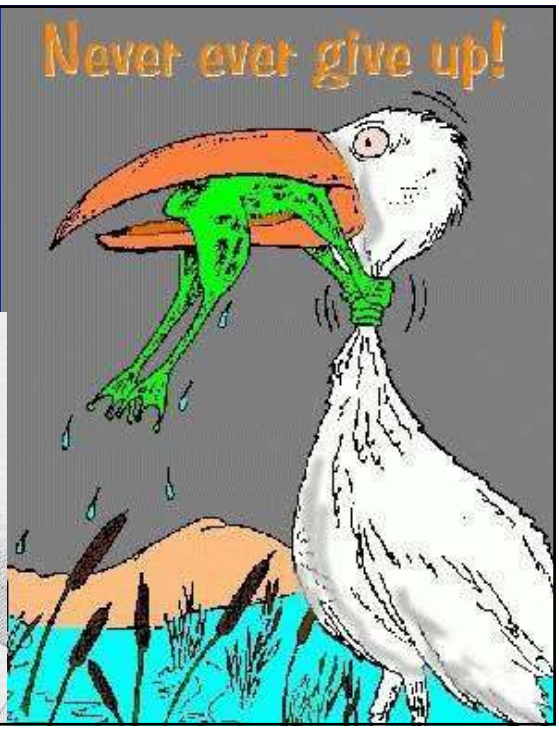


Thank
You


Thank You
Backfire…