Chemotherapy-induced follicle activation and loss in human ovaries. First documentation of the "Burn-Out" effect in clinical cases.

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Introduction

- Infertility and premature ovarian failure are considered to be among the most significant long-term adverse effects of exposure to cytotoxic drug treatments in young women.

- The degree of ovarian damage correlates with the chemotherapy agent of choice in a dose dependent manner

Probability of POI following Bone Marrow Transplantation

	No.	Age	POI
Sanders JE. 1996	73	mean 38	99%
Teinturier C. 1998	21	2 - 17	72%
Thibaud E. 1998	31	3.2 - 17	80%
Meirow D. 1999	63	mean 29	79%
Grigg A. 2000	19	mean 30	100%
Jadoul P. 2011	35	mean 9.8	56% (Very low AMH 85%)
Blumenfeld Z. 2012	36	mean 30.5	89%

Ovarian failure risk -very high

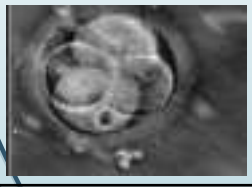
Modified from Meirow D. et al. Clin. Obstet. Gynecol. 2010

Current options for Fertility Preservation

LIMITATIONS-

- Age.
- Time available before chemotherapy.
- Invasive treatments.

Embryo freezing



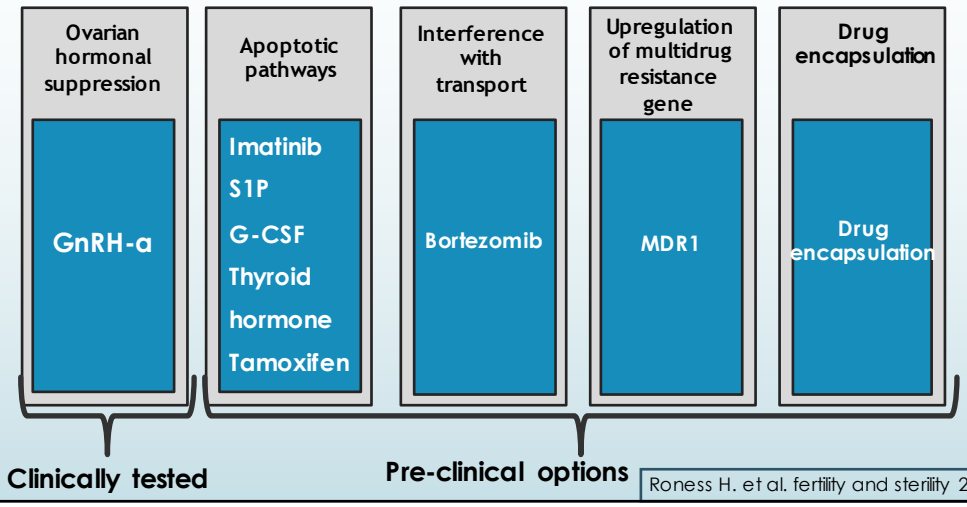
Oocyte freezing

Ovarian tissue

Why pharmacological prevention?

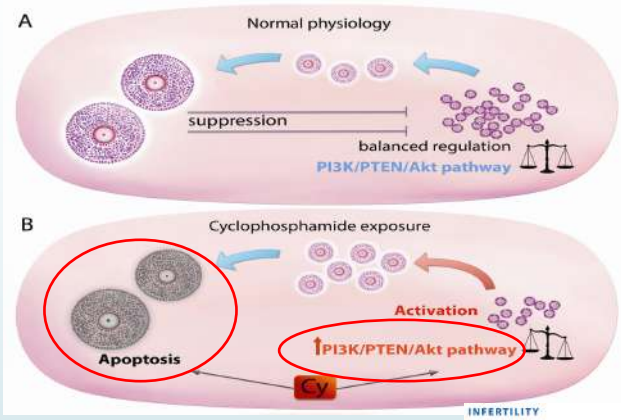
- Suitable for patients of all ages and life stages.
- Cost.
- Can be used when invasive techniques can not be used.
- Can be used in addition to invasive fertility preservation methods- maximizing future fertility.

Protecting agents - Overview



Roness H. et al. fertility and sterility 2016

The "Burn-Out" mechanism



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INFERTILITY

Cyclophosphamide Triggers Follicle Activation and "Burnout"; AS101 Prevents Follicle Loss and Preserves Fertility

Lital Kalich-Philosoph,[1,2*] Hadassa Roness,[1*] Alon Carmely,[1,2] Michal Fishel-Bartal,[1,2] Hagai Ligumsky,[3,4] Shoshana Paglin,[1] Ido Wolf,[3,4] Hannah Kanety,[5] Benjamin Sredni,[2*] Dror Meirow[1,3*†]

PLoS One. 2015 Dec 14;10(12):e0144245. doi: 10.1371/journal.pone.0144245. eCollection 2015.

Cisplatin Induces Overactivation of the Dormant Primordial Follicle through PTEN/AKT/FOXO3a Pathway which Leads to Loss of Ovarian Reserve in Mice.

Chang EM[1], Lim E[2], Yoon S[1,2], Jeong K[3], Bae S[2], Lee DR[1,2], Yoon TK[1], Choi Y[2], Lee WS[1].

Int J Mol Sci. 2016 May 30;17(6). pii: E836. doi: 10.3390/ijms17060836.

Follicle Loss and Apoptosis in Cyclophosphamide-Treated Mice: What's the Matter?

Chen XY[1,2,3], Xia HX[4], Guan HY[5,6,7], Li B[8], Zhang W[9].

Reprod Biomed Online. 2017 Jan;34(1):104-114. doi: 10.1016/j.rbmo.2016.10.005. Epub 2016 Oct 17.

Short-term exposure of human ovarian follicles to cyclophosphamide metabolites seems to promote follicular activation in vitro.

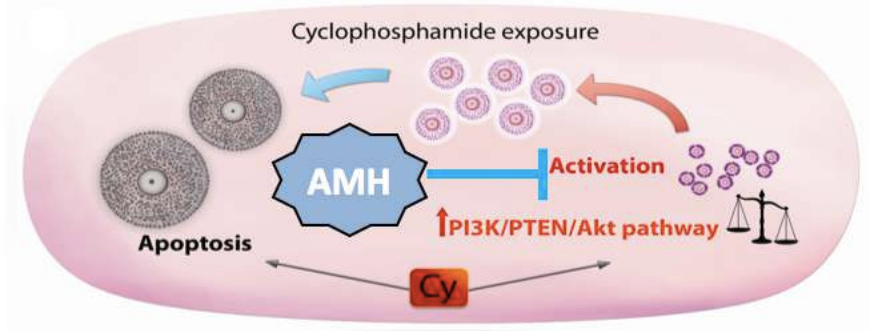
Lande Y[1], Fisch B[1], Tsur A[2], Farhi J[3], Prag-Rosenberg R[1], Ben-Haroush A[1], Kessler-Icekson G[4], Zahalka MA[4], Ludeman SM[5], Abir R[6].

AMH/MIS as a contraceptive that protects the ovarian reserve during chemotherapy

Motohiro Kano[a,b], Amanda E. Sosulski[a,b], LiHua Zhang[a,b], Hatice D. Saatcioglu[a,b], Dan Wang[c], Nicholas Nagykery[a,b], Mary E. Sabatini[d], Guangping Gao[c], Patricia K. Donahoe[a,b,1], and David Pépin[a,b,1]

Potential pharmacological agent: Anti Mullerian Hormone (AMH)

- Cy causes loss of AMH
- Replacement of negative regulation via AMH reduces follicle activation and loss - protecting the ovarian reserve



Study aim-

To study whether the 'Burn-out' mechanism of chemotherapy-induced dormant follicle activation also applies in human ovaries in clinical cases ***in-vivo***.

Material and methods

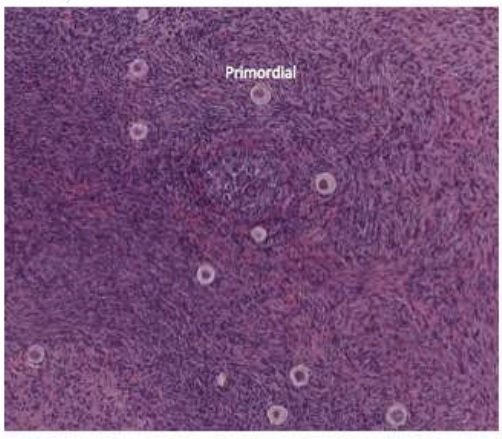
- **Study group-** women who stored ovarian tissue in order to preserve fertility following chemotherapy protocols containing alkylating agents up to 6 months prior to tissue harvesting.

- **Control group-** women with a known malignancy that stored ovarian tissue in order to preserve fertility and were not previously exposed to chemotherapy and were matched by age in a 1 case to 2 controls fashion.

- Histopathological processing on fresh tissue- fixation in buffered formaldehyde, paraffin-embedding, serial sectioning (3.5-µm thick sections) and H&E staining.
- The slides were scanned by automated microscope to create digital images.
- Histologic evaluation by a certified pathologist using a light microscope and independently by two additional researches using the digital images.
- All ovaries were evaluated in at least 3 sections, 5 sections apart one from the other.

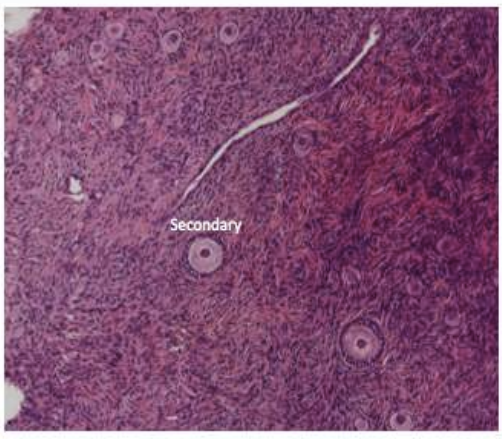
Control

A 20 YO woman without chemotherapy treatment



Study

A 30 YO woman 3 month after CHOP regiment



Statistical Analysis

- Intra Class Correlation (ICC) was calculated in order to assess inter-observer reliability among the 3 different observers.

- Linear mixed models were used to assess the effect of chemotherapy in primordial, growing (primary plus secondary) and proportion of growing [growing / (primordial + growing)] follicles.

Results

STUDY GROUP- 20 women

Average age 27.9

Study group diagnosis-

- 14 - Non-Hodgkin's lymphoma
- 4- Hodgkin's lymphoma
- 2- Breast carcinoma

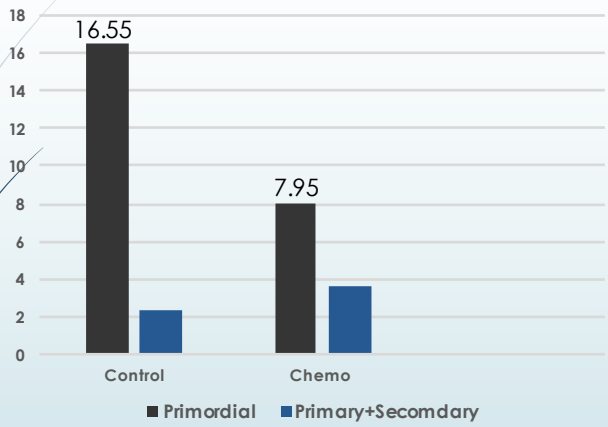
CONTROL GROUP- 40 women

Average age 28.5

Control group diagnosis-

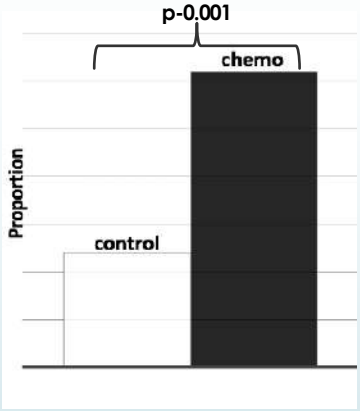
- 12 - Breast carcinoma
- 10 - Hodgkin's lymphoma
- 6 - Non-Hodgkin's lymphoma
- 4 - Ewing sarcoma
- 4 - Cervical malignancy
- 2 - Colon carcinoma
- 2 - Acute myeloid leukemia.

Follicle count



Proportion

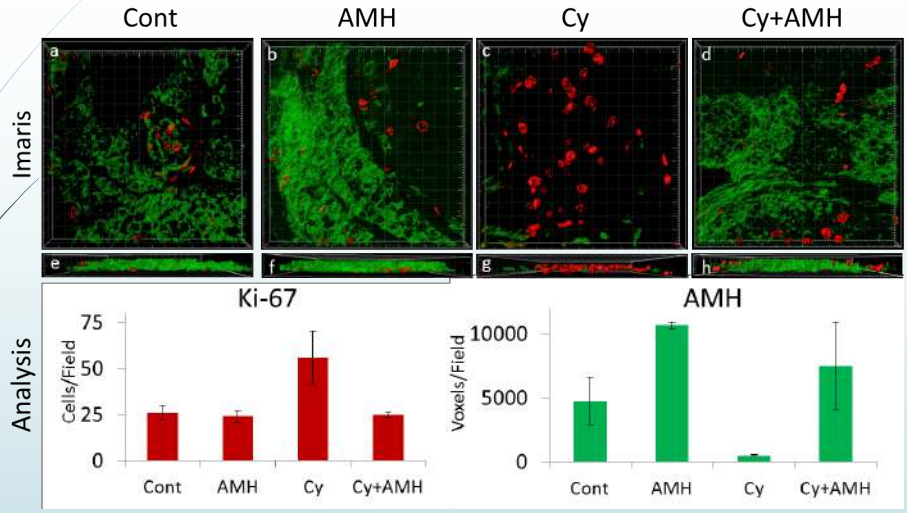
[growing / (primordial + growing)]



High reliability between all the examiners was noted (alpha-0.993).

rAMH Reduces Chemo-Induced Follicle Loss

in-vivo in mice



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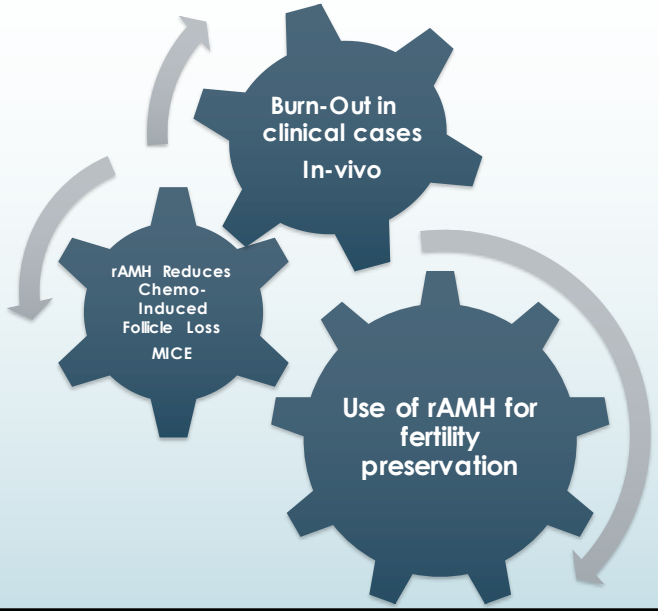
CAN WE STOP THE CLOCK?



THANK YOU FOR YOUR ATTENTION

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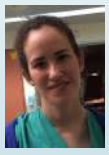
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