



## Fertility preservation in Cancer patients

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### Fertility and Reproduction in Cancer patients

Survival rate following different types of cancer has improved dramatically in the recent years following chemotherapy, resulting in an increasing number of "cancer survivors"

**However, Long-term side-effects:**

- Organ toxicity
- Ovarian failure
- Genetic abnormalities & 2<sup>nd</sup> Malignancy

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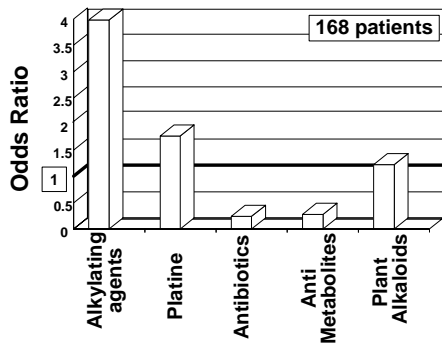
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### Ovarian Failure by Drug Families

Age adjusted Odds ratio exposed vs. unexposed



OR: 1=34%O.F.

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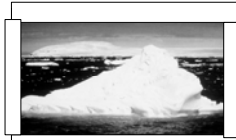
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**Infertility post chemo. and irradiation**

- **Chemotherapy effects are not - "All or None".**  
Ovarian Failure is the tip of the iceberg.



Significant reduction in follicle reserve can be identified in the majority of the patients.

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**Hodgkin's Disease**

Ref.	Treatment	Ovarian failure
Howell & Shalet Review 98	Aggressive treatment	38% - 57%
Meirow 99	Relapse post 1 <sup>st</sup> treatment	32%
Bokemeyer	Infradiaphragmatic Rx.	50%
Brusamolino 2000	Ovarian sparing protocol	<25 - 0% <45 - 30%

Meirow Hum. Reprod. Update 2001

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**Ablative Chemotherapy & Bone Marrow Transplantation**

	No.	Age	% failure
Sanders 96	73	mean 38	99
Teinturier 98	21	2 - 17	72
Thibaud 98	31	3.2 - 17	80
Meirow 99	63	mean 29	79
Grigg 2000	19	mean 30	100

Ovarian failure risk - very high.

Meirow Hum. Reprod. Update 2001

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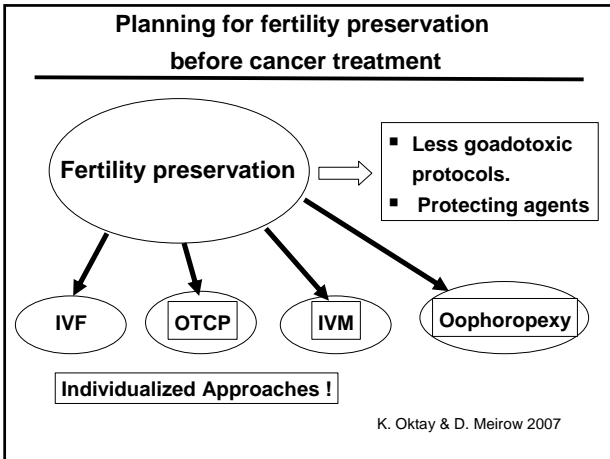
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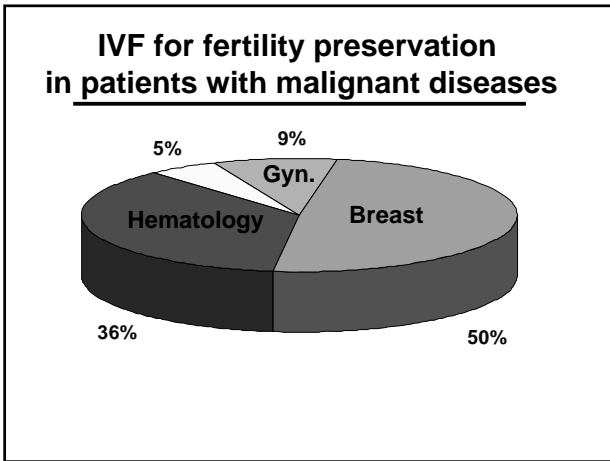
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**Consultation for IVF**

**No previous chemotherapy:**

- Indications
- Time available
- Partner
- Medical status

**IVF post chemotherapy treatments:**

- Ovarian reserve
- Medical status

IVF - 43% of patients with Homatological malignancies had previous chemotherapy.

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### IVF Patients for fertility preservation 2003-2007

Number of patients	65
Number of cycles	70
Age	Mean 30.7
Age range	19-42
Eggs collected	0 -32
Stored Embryos	Mean 6.7

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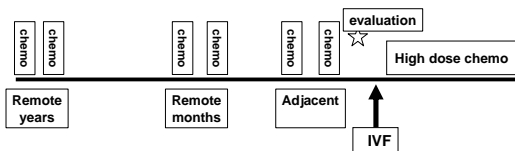
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- Hodgkin's disease – before / post chemotherapy  
> 27 years, high dose chemotherapy.
- Non Hodgkin's lymphoma – post 1<sup>st</sup> line before BMT.
- Acute Leukemia – post 1<sup>st</sup> line before BMT.
- Chronic Myeloid Leukemia – before BMT.
- Multiple Myeloma – before BMT.




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### Ovarian tissue cryo-preservation post recent Chemotherapy

2-3 months post chemotherapy

Disease	Age	IVF Eggs	Biopsy PMF
Non-Hodgkin's D	21	0	++
Hodgkin's D	25	0	+++
Hodgkin's D	25	0	+++

The ovaries are temporarily inactive  
But patients are not sterile.

Meirow et.al. Leukemia Lymphoma 2007

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### Efficacy of in vitro fertilization after chemotherapy.

TABLE 1

IVF outcome in cancer patients during (patients 1–4) or before (patients 5–11) chemotherapy.

Patient	Age (y)	Pathology	Chemotherapy before IVF	E <sub>2</sub> at hCG (pg/mL)	Ampules used	Oocytes	Cryopreserved embryos
1	32	NHL	1 regimen <sup>a</sup>	671	102	6	1
2	22	AML	2 regimens <sup>b</sup>	121	78	0	0
3	26	AML	2 regimens <sup>b</sup>	<10	82	0	0
4	24	ALL	3 regimens <sup>c</sup>	<10	74	0	0
5	31	MA	0	2430	32	10	6
6	24	HL	0	2500	24	13	10
7	26	HL	0	2610	27	25	11
8	33	NHL	0	1202	24	8	5
9	25	BOT	0	6750	104	12	5
10	26	HL	0	1576	34	11	4
11	26	OC II	0	1540	63	9	4

Dolmans et al., Fertil. And Steril. 2005

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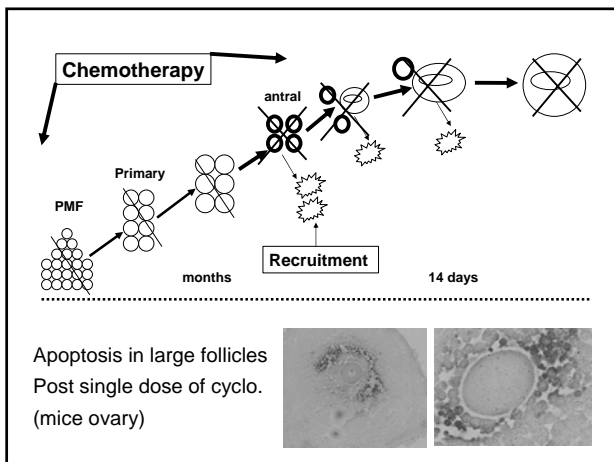
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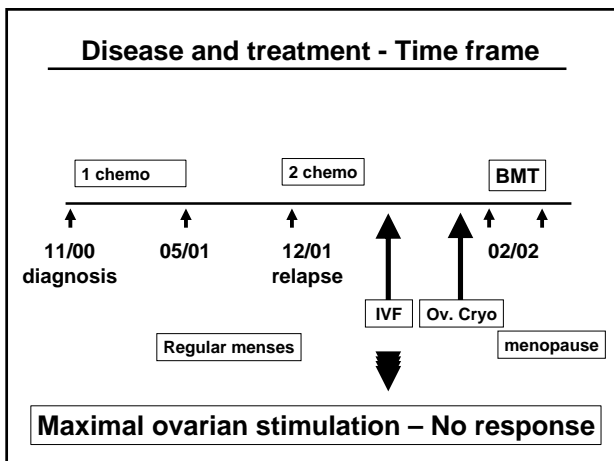
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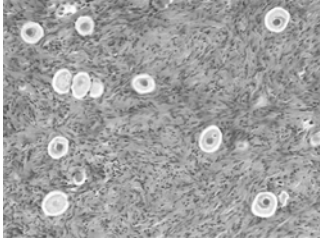
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**Ovarian tissue cryopreservation  
post IVF failure**



> 150 PMF in 0.5 mm<sup>3</sup>

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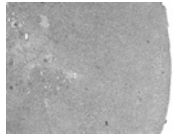
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**Two years following  
Bone Marrow Transplantation**

- Amenorrhea
- FSH (IU/l) 40 -104
- E2 low
- Inhibin B 0
- AMH 0



Ovarian biopsy - atrophy  
(during transplantation)

**Ovarian failure**

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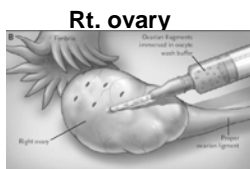
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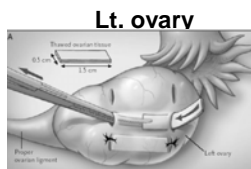
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**Transplantation of Ovarian Tissue**

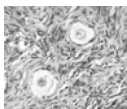
*Technique*



**Rt. ovary**



**Lt. ovary**



Follicles in  
thawed ovarian tissue

THE NEW ENGLAND  
JOURNAL of MEDICINE  
Meirow, Dor 2005

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**IVF attempts post transplantation**

IVF mo post	hMG	FSH IU/L	AMH ng/ml	Inhibin B pg/ml	Follicle Lt Ov	Egg
2	-	57	<0.01	11	-	
3	+	28	<0.01	8	22	-
5	+	20	<0.01	7.6	-	
8	natural	24	5.3	13	20	-
9	Modified natural	8	5.3	89	22	+

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**IVF after chemotherapy**

IVF after remote chemotherapy (>4-6 months)

Response:

- Related to patient's age (not infertile patients).  
Mean age 27 (range 17-35)
- Previous oncology treatment.

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**IVF post high dose chemotherapy**

- Young patients < 32 years old.
- All had high dose chemotherapy.
- All high FSH up to 70 –repeated tests.
- Irregular menstruations – not amenorrhea !
- US- cysts/ follicle, endometrial development.

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### **IVF post high dose chemotherapy**

Natural assisted cycle – 13 cycles 6 patients

- All developed follicles.
- Time for follicle development – very long (19d)  
very short
- Adequate E2.
- Egg retrieval 10/13 77%.
- Fertilization 90%.
- Embryo transfer all.
- Pregnancies 3/6 patients. 3 had normal deliveries.

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High FSH in young patients years post high dose chemotherapy can result in good IVF outcome - If the patient reports on vaginal bleeding.

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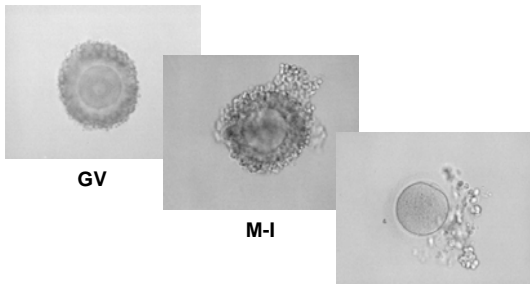
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### **Oocyte maturation**



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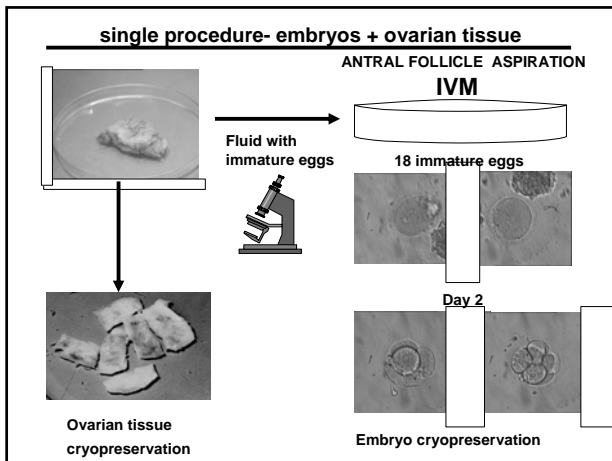
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**Ovarian Cryopreservation and IVM**  
Case-Report

- A single, 37 years old woman.
- Diagnosed with Breast Ca 2 weeks ago.
- Planned for Chemotherapy (AC-T protocol).
- Was admitted for Ovarian Cryopreservation before chemotherapy.
- 21 immature oocytes (GV) were recruited from the ovarian cortex and were incubated in IVM medium for maturation.

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**Ovarian Cryopreservation and IVM**  
Case-Report

- 8 oocytes mature after 24h and another 4 oocytes mature after 48h (Total of 12 oocytes, 57%).
- ICSI was performed on all mature oocytes.
- 7 oocytes were fertilized (F.R.-58%) and developed to embryos.
- All 7 embryos were frozen on D2.

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## IVF in breast cancer patients




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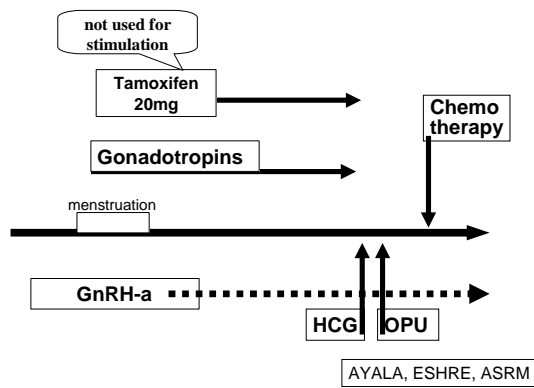
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### Stimulation Protocol




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### Sheba IVF protocol in Breast Cancer patients Undergoing Ovarian Stimulation before Chemotherapy

Number of patients	32
Age	33.5
Tamoxifen protection	28
Conventional stimulation	4
<del>Short protocol</del>	2 canceled cycles !

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**Sheba IVF protocol  
in Breast Cancer patients Undergoing  
Ovarian Stimulation**

	Conventional protocol + Tamoxifen
Number of patients	32
E2 at HCG	1772
No. oocytes	11
Fertilized eggs	7
2pn zygotes	6

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**E2 LEVELS IN PATIENTS  
WITH TAMOXIFEN**

E2 levels -      mean group      2655.18 pmol/l  
                          10<sup>th</sup> percentile      6170.5 pmol/l  
                          Peak                      10,000 pmol/l

FSH levels      Variable

LH levels        Variable

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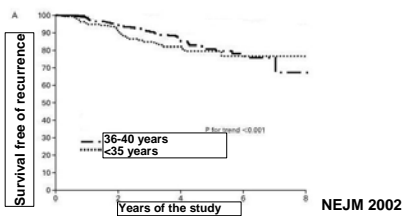
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**Recurrence rate**



**During 5 years of experience  
2 patients (6%) had recurrence of disease**

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**Conclusions**

**The safety of the proposed protocol for IVF:**

- Elevated E2 - short duration.
- E2 levels in IVF comparable with E2 in Tamoxifen adjuvant therapy.
- Conventional stimulation.
- Significant number of eggs.
- Good quality embryos that can give real hope for fertility preservation in breast cancer patients.
- Recurrence of cancer not increased !

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**Results of IVF treatments in cancer patients**

Sheba Medical Center

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**Chemotherapy Administration  
According to Type of Malignancy  
(n=54)**

	Chemotherapy Before Fertility treatment	No Chemotherapy
<b>Breast Cancer</b>	<b>6 (22.2%)</b>	<b>21 (77.8%)</b>
<b>Hematological</b>	<b>10 (58.8%)</b>	<b>7 (41.2%)</b>
<b>Gynecological</b>	<b>3 (37.5%)</b>	<b>5 (62.5%)</b>
<b>Solid Tumors</b>	<b>1 (50%)</b>	<b>1 (50%)</b>
<b>Total</b>	<b>20 (37%)</b>	<b>34 (63%)</b>

Sheba Medical Center

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ART Results With and Without Chemotherapy (CT)			
	After CT	No CT	<u>P-Value</u>
Mean Age	32.1±1.1 (25-44)	31.5±1.8 (23-39)	NS
Estradiol (pg/ml)	960.0±166 (468-1538)	1867.8±217 (463-3945)	0.05<
No. of Eggs	6.0±0.9 (0-15)	11.8±1.4 (0-32)	0.05<
No. of 2PN	4.0±0.7 (0-9)	7.0±1.0 (0-23)	0.05<
Fertilization(%)	59.7±4.1%	60.0±7.1%	NS

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Pregnancies According to Type of Malignancy				
Spontaneous + ART Pregnancies				
	Breast Cancer n=27	Hematological n=17	Gynecological n=8	Solid Tumors n=2
After CT	2	2	2	0
No CT	3	1	0	1
Total(%)	5(18.5)	3(17.6)	2(25)	1(50)

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**Conclusions**

- Ovarian reserve is significantly reduced after chemotherapy treatment even with low risk medications.
- IVF can be successful in young patients after chemotherapy excluding those following BMT.
- Ovarian tissue cryopreservation and/or IVM can be offered when patients require immediate chemotherapy.

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<b>IVF Unit</b> <b>Obstet. &amp; Gynecol. Depart.</b>	
Dor J. Meirov D. Levron J. Bider D. Rabinovici J. Seidman D. Horovitz A. Baum M. Elizur S. Maman E. Mechtinger R.	<b>Hematology Depart.</b> Hardan I. Nagler A.  <b>Pathology Depart.</b> Fridman E.  <b>MRI Unit</b> Kushnir T. Manor D.  <input type="text"/>




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