Rigshospitalet
The Fertility Clinic

Copenhagen, Denmark

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Spontaneous recovery of ovarian function and fertility after cancer treatment

Kirsten Tryde Macklon, Ph.D.

Do the ovaries always look like this after chemotherapy?

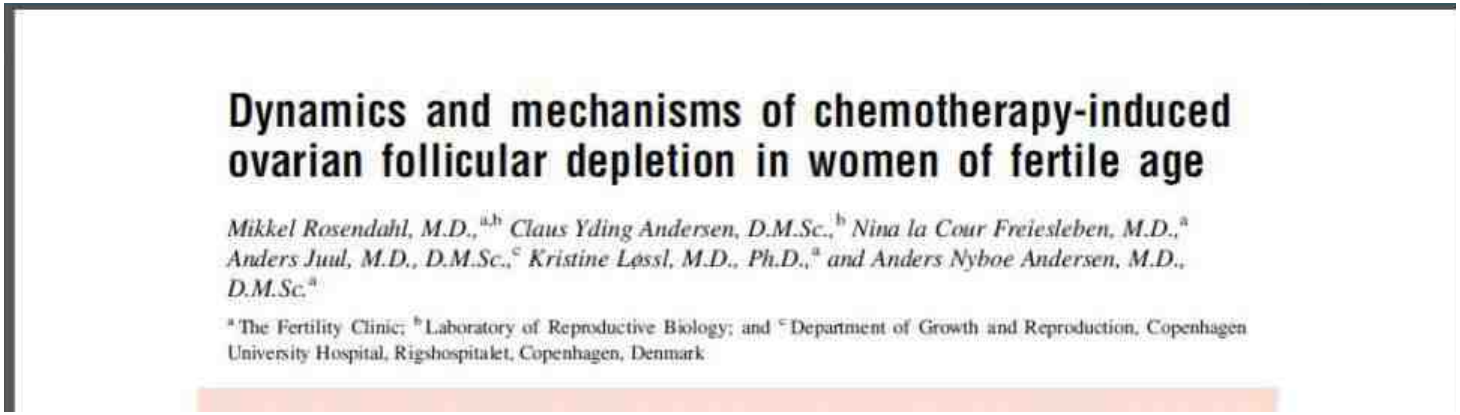
NO

Extent of damage

- Depends on

  - Age of the patient
  - Type of drug; field of radiation
  - Cummulative dose
  - Ovarian reserve of the patient

Acute follicular damage during chemotherapy



Dynamics and mechanisms of chemotherapy-induced ovarian follicular depletion in women of fertile age

Mikkel Rosendahl, M.D.,[a,b] *Claus Yding Andersen, D.M.Sc.,*[b] *Nina la Cour Freiesleben, M.D.,*[a] *Anders Juul, M.D., D.M.Sc.,*[c] *Kristine Løssl, M.D., Ph.D.,*[a] *and Anders Nyboe Andersen, M.D., D.M.Sc.*[a]

[a] The Fertility Clinic; [b] Laboratory of Reproductive Biology; and [c] Department of Growth and Reproduction, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Fertil Steril, 2010

17 women between 19 and 35 years of age
with various cancer diagnoses were followed before,
during and up to 1 year after chemotherapy

AFC, AMH, FSH and Inhibin B

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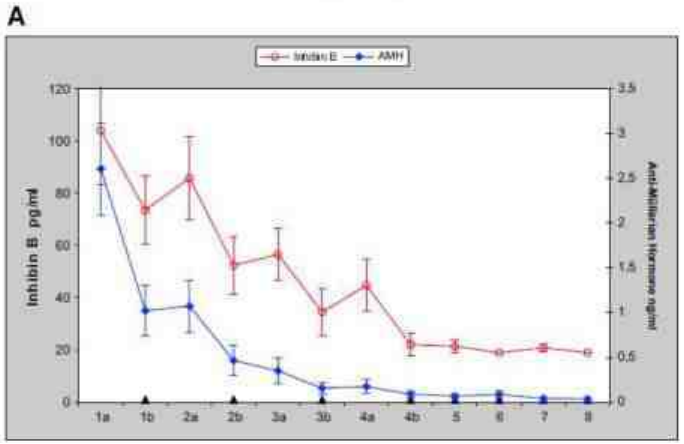
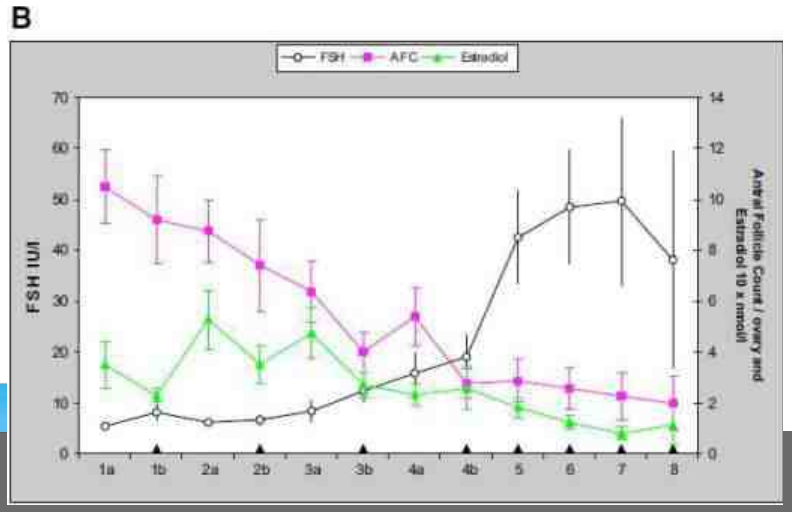
During chemotherapy

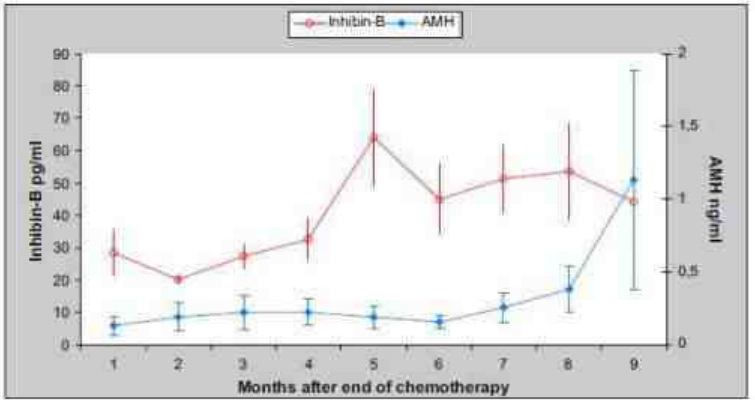
Mean levels (± SEM) of markers of ovarian function during chemotherapy 1–8. **(A)** The day before
after a treatment. *Pyramids* indicate 1 week after a series of chemotherapy.

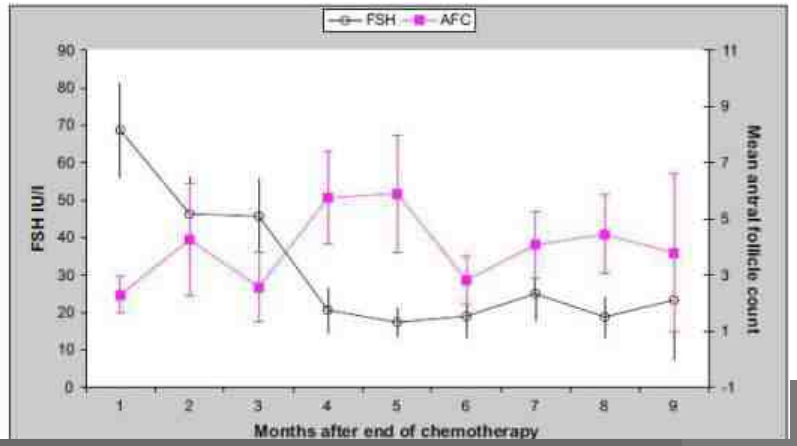




After chemotherapy

Ovarian function during the recovery period after the end of chemotherapy. Mean levels (± SEM).





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Risk of permanent amenorrhoea in women with breast cancer

Petrek, 2006, *J Clin Oncol*

595 women

Median follow-up
45 months

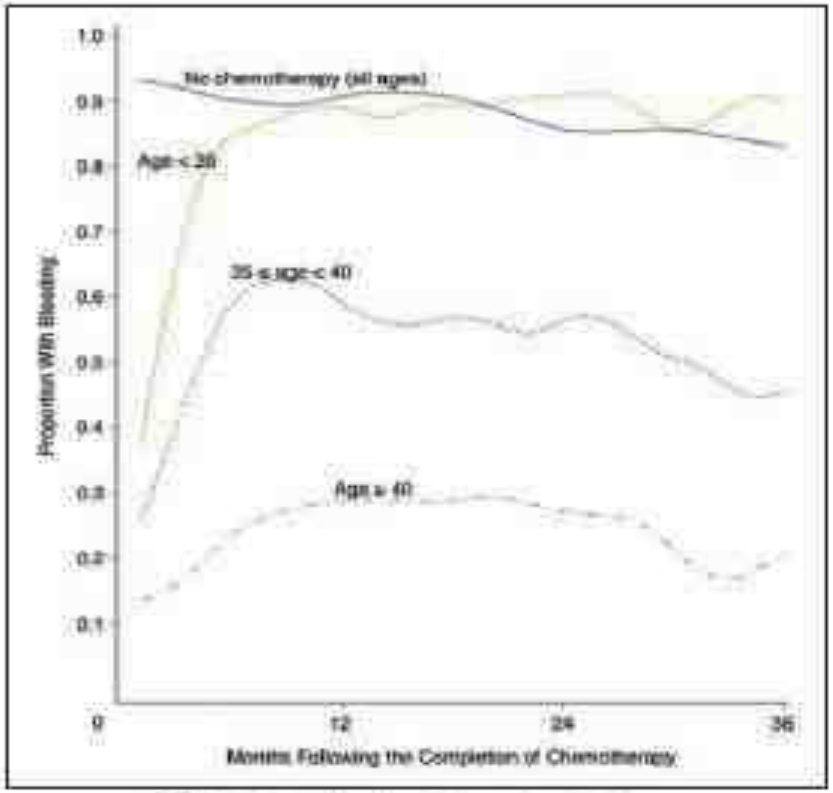

Fig 2. Bleeding after chemotherapy by patient age.

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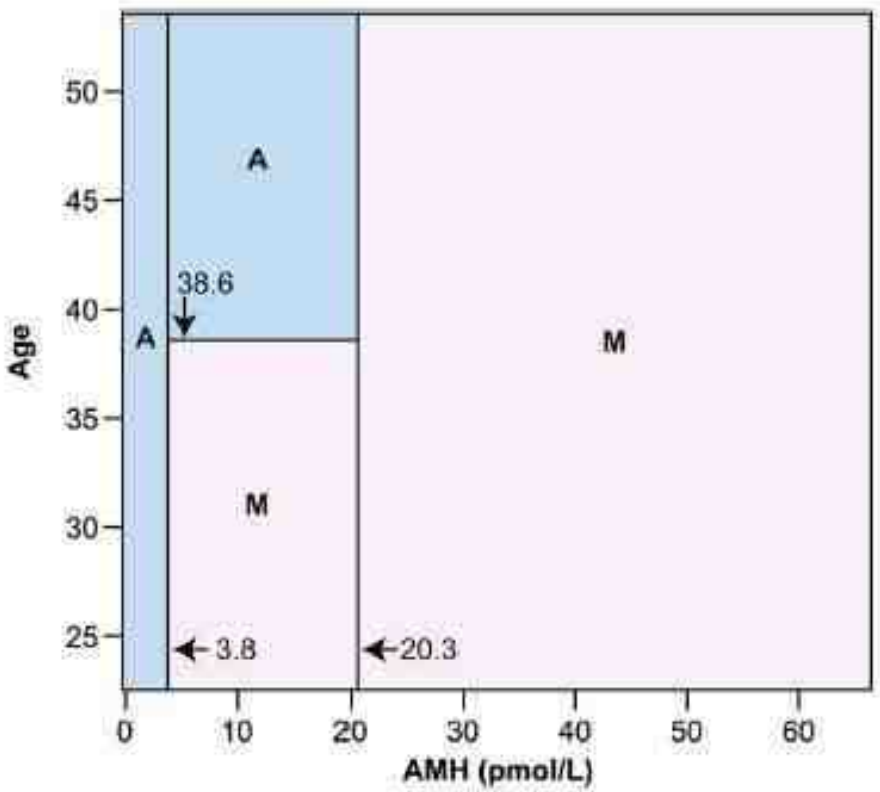
AMH as a predictor of chemotherapy-induced amenorrhoea

Anderson RA, *Eur J Cancer*, 2013



59 women with early breast cancer
2 year follow up

Pretreatment AMH was significantly lower in women with amenorrhoea at 2 years

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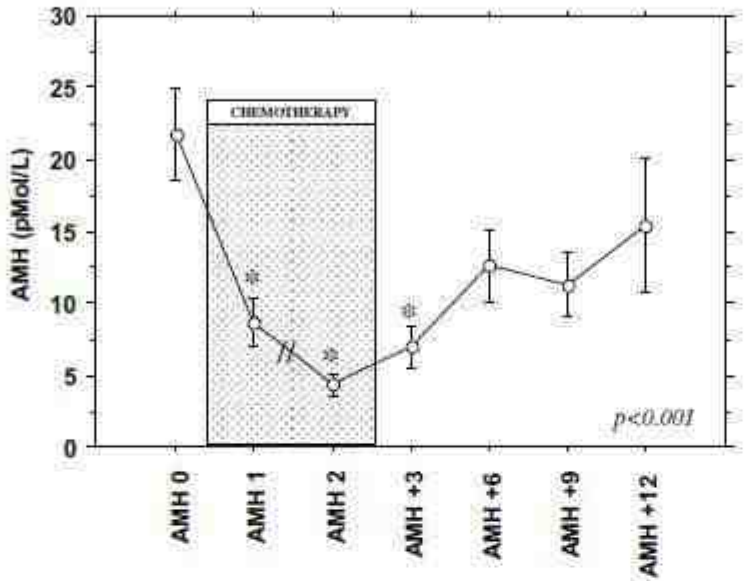
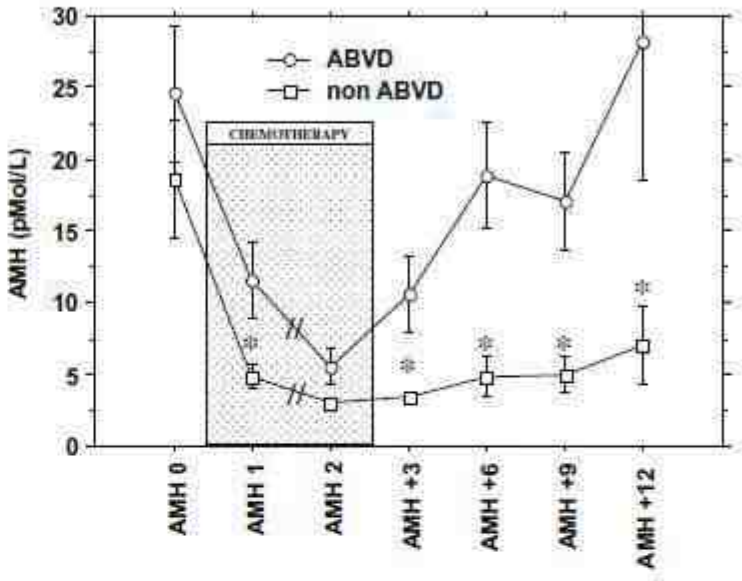
Anti-Müllerian hormone follow-up in young women treated by chemotherapy for lymphoma: preliminary results

Christine Decanter [a,b,*], Franck Morschhauser [b,c], Pascal Pigny [b,d], Catherine Lefebvre [a,b], Cécile Gallo [a,b], Didier Dewailly [a,*]

RBMonline, 2009

AMH follow-up after chemotherapy





Pregnancy after autologous haematopoietic SCT in patients with autoimmune diseases

- Retrospective analysis
- 324 female patients
- 22 pregnancies in 15 patients (4.6 %)
- mean age at transplantation 24 years
- mean age at 1st delivery 32 years

Snarski E, *Bone Marrow Transplant*, 2015

What about fertility in childhood cancer survivors?

0021-972X/03/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 88(11):5307–5314

doi: 10.1210/jc.2003-030302

Reduced Ovarian Function in Long-Term Survivors of Radiation- and Chemotherapy-Treated Childhood Cancer

ELISABETH C. LARSEN, JØRN MÜLLER, KJELD SCHMIEGELOW, CATHERINE RECHNITZER, AND ANDERS NYBOE ANDERSEN

The Fertility Clinic (E.C.L., A.N.A.), the Department of Growth and Reproduction (J.M.), Pediatric Clinic II (K.S., C.R.), Late Effects Clinic (C.R.), and Department of Pediatrics (J.M.), The Juliane Marie Centre, Rigshospitalet, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark

100 female childhood cancer survivors
70 w regular menstrual cycles
Mean age at diagnosis: 5 years (0-15)
Mean age at study: 26 years (19-44)

- **Endocrine and sonographic signs of a reduced ovarian reserve when compared to a control group**

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10 years later
Questions to be answered:

1. How many of the 70 survivors who had regular menstrual cycles 10 years ago have entered menopause ?
2. How many pregnancies and deliveries have they had ?
3. Were the pregnancies achieved spontaneously or after fertility treatment ?
4. What about the ovarian reserve ?

Nielsen SN, RBMonline, 2013

Study population 2010

2001

- 70 survivors with regular menstrual cycles
  - *2 Deceased*
  - *2 Emmigrated*

2010

- 66 Eligible survivors
  - *13 Non-responders*

2010

- 53 Survivors = study population
- *(Participation rate 80.3%)*

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Results 2010

- ***TREATMENT-RELATED AND CLINICAL DATA in 53 survivors***

Age at study inclusion (yr)	35 (28–49)
Chemotherapy (n)	53
Potential ovarian irradiation (n)	11
Regular menstrual cycles (n)	30
Oligomenorrhea (n)	5
Oral contraception (n)	10
Pregnant (n)	5
Menopause (n)	3 *(6%)*

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Results 2010
– *reproductive history among 53 participants*

- At study entry 13 out of 53 survivors had not tried to conceive
- A total of 40 survivors had had 74 pregnancies
- 33 out of 40 (83%) had had at least 1 live birth !

Conclusion I – *10 year follow up*

- Menopause developed in 6%
- Sonographic signs of a diminished ovarian reserve in survivors with regular cycles
- A trend towards lower AMH-levels in the survivors but not significant

Conclusion II – *10 year follow up*

- HOWEVER:
- The majority of survivors who had tried to conceive had given birth to at least 1 child.
  - *If ovarian function of childhood cancer survivors is preserved in the mid-twenties it is likely to persist until the mid-thirties giving a good chance of childbearing.*

Fertility in cancer patients after cryopreservation of one ovary

KT Schmidt [a,b,*], A Nyboe Andersen [a], T Greve [b], E Ernst [c], A Loft [a], C Yding Andersen [b]

[a] *The Fertility Clinic, Copenhagen University Hospital, Rigshospitalet 9, DK-2100 Copenhagen, Denmark;* [b] *The Laboratory of Reproductive Biology, Copenhagen University Hospital, Rigshospitalet, DK-2100 Copenhagen, Denmark;* [c] *The Fertility Clinic, University Hospital of Aarhus, 8200 Skejby, Aarhus, Denmark*

[*] Corresponding author. *E-mail address:* kirsten.tryde.schmidt@rh.regionh.dk (KT Schmidt).

RBMonline; 2013

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Inclusion criteria

- > 18 years at time of study inclusion
- Cryopreservation of an ovary > 2 years ago
- Chemo- or radiation therapy
- One ovary left

Inclusion criteria

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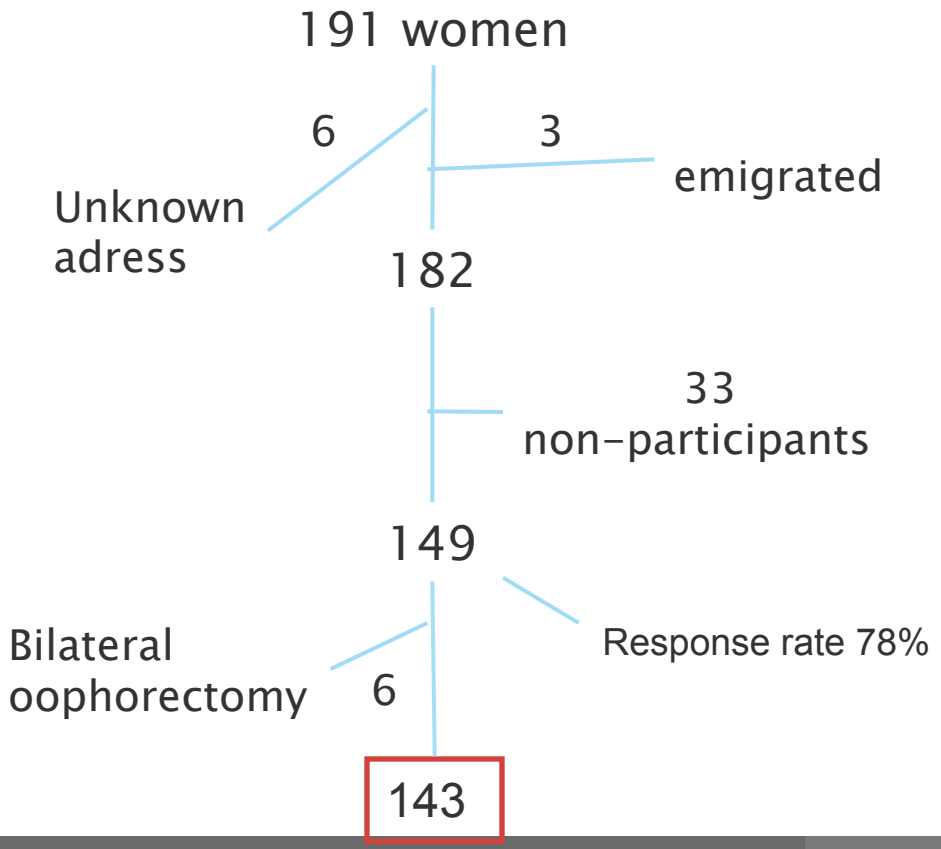
- Flowchart of cohort



Questionnaire

- Treatment
- Menstrual history
- Hormonal anticonception or replacement therapy
- Pregnancies before and after treatment
- Course of pregnancies
- Future pregnancy wish?
- Want to make use of cryopreserved tissue?

Patients

diagnosis	n	Age*, mean [range]	Chemo-therapy, n	Radiation** therapy, n	BMT
Breast	54	30.2 [22-38]	54		
Lymphoma	40	25.2 [16-34]	36		4
Sarcoma	9	18.5 [13-27]	8		1
Leukaemia	15	21.5 [13-31]	3		12
Other Mal	15	25.4 [15-34]	11	4	
Aplastic anemia	3	25 [23-26]			3
Autoimmune	7	23.8 [16-28]	7		

*at time of cryopreservation
**abdominal or spinal

Mean follow-up time 58 months [24-129 mo]

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Results, premature ovarian failure (POF)

	Breast n=54	Lymphoma n=40	Leukaemia n=15	Sarcoma n=9	Auto-Immune n=7	Aplastic Anemia n=3	Others n=15
+POF n (%)	5 (9)	6 (15)	13 (87)	2 (22)	0	1 (33)	3 (20)
÷ POF n (%)	46 (85)	27 (68)	0	5 (56)	5 (71)	2 (67)	11 (73)
Not certain n (%)	3 (6)	7 (17)	2 (13)	2 (22)	2 (29)	0	1 (7)

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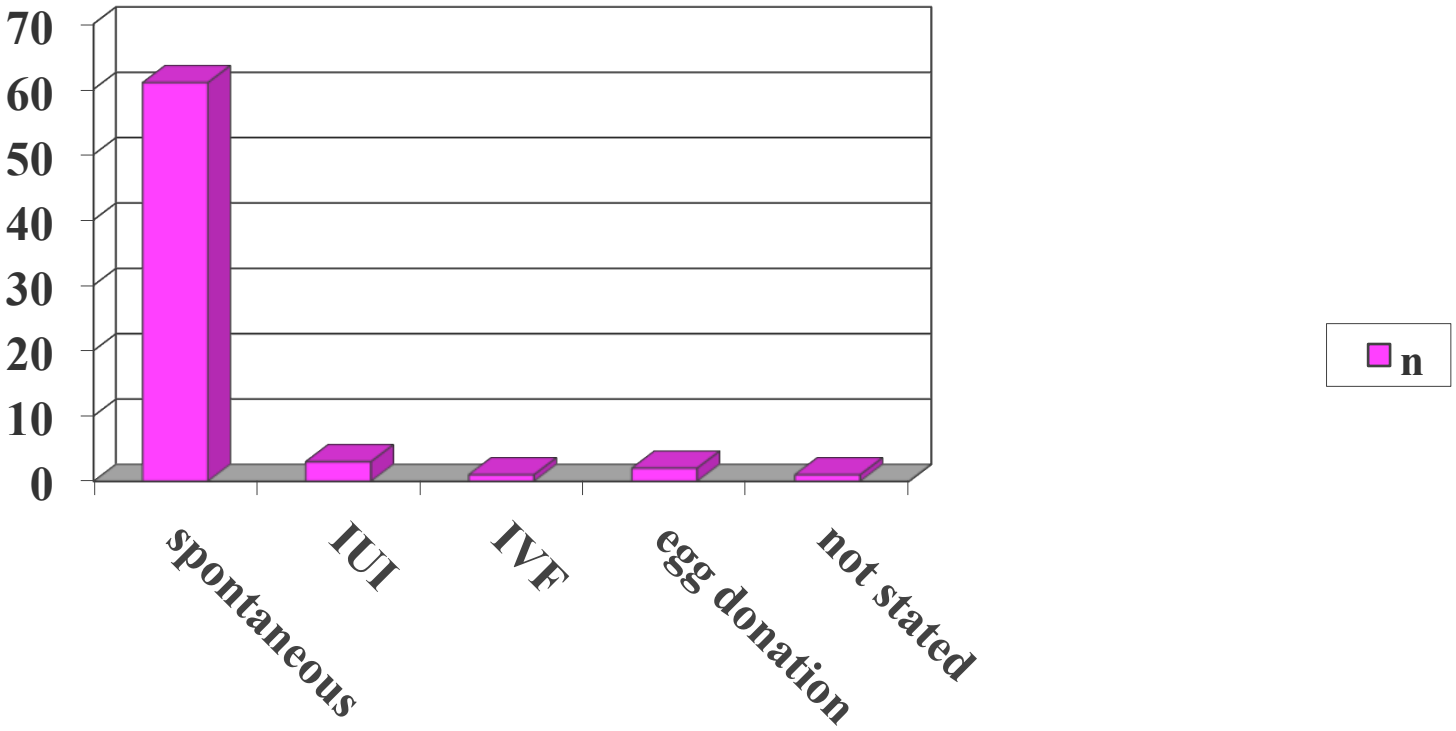
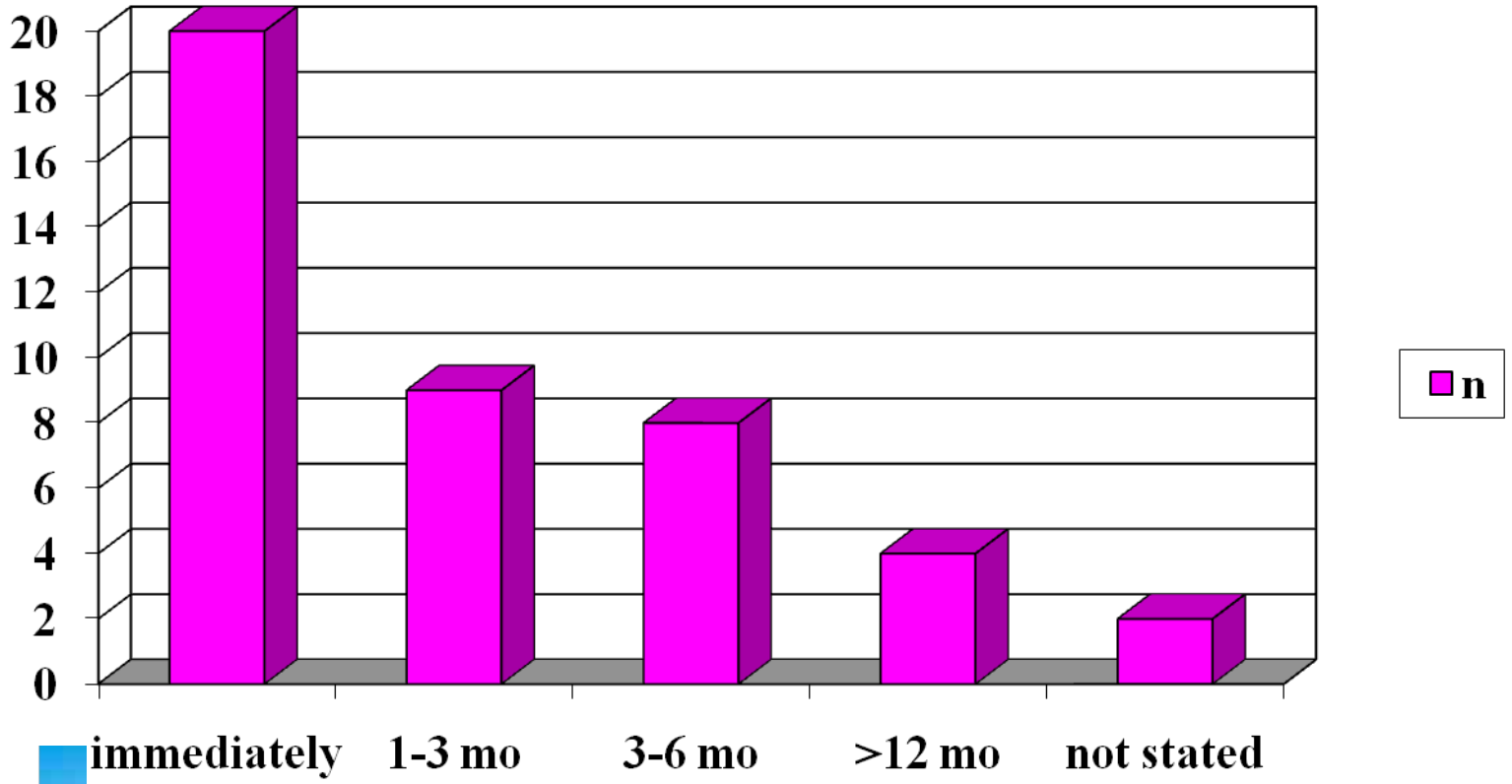
Pregnancies

- < Cryopreservation
  - 50/143 (35%) women had been pregnant before treatment → 38 children born to 31 women
- > Cryopreservation
  - 57/143 (40%) women had a pregnancy wish after treatment → 41 (72%) women obtained a total of 68 pregnancies
  - (Additionally, there were 5 unwanted pregnancies in the group without a pregnancy wish)

Origin of 68 pregnancies



Time to pregnancy in 41 spontaneously pregnant women



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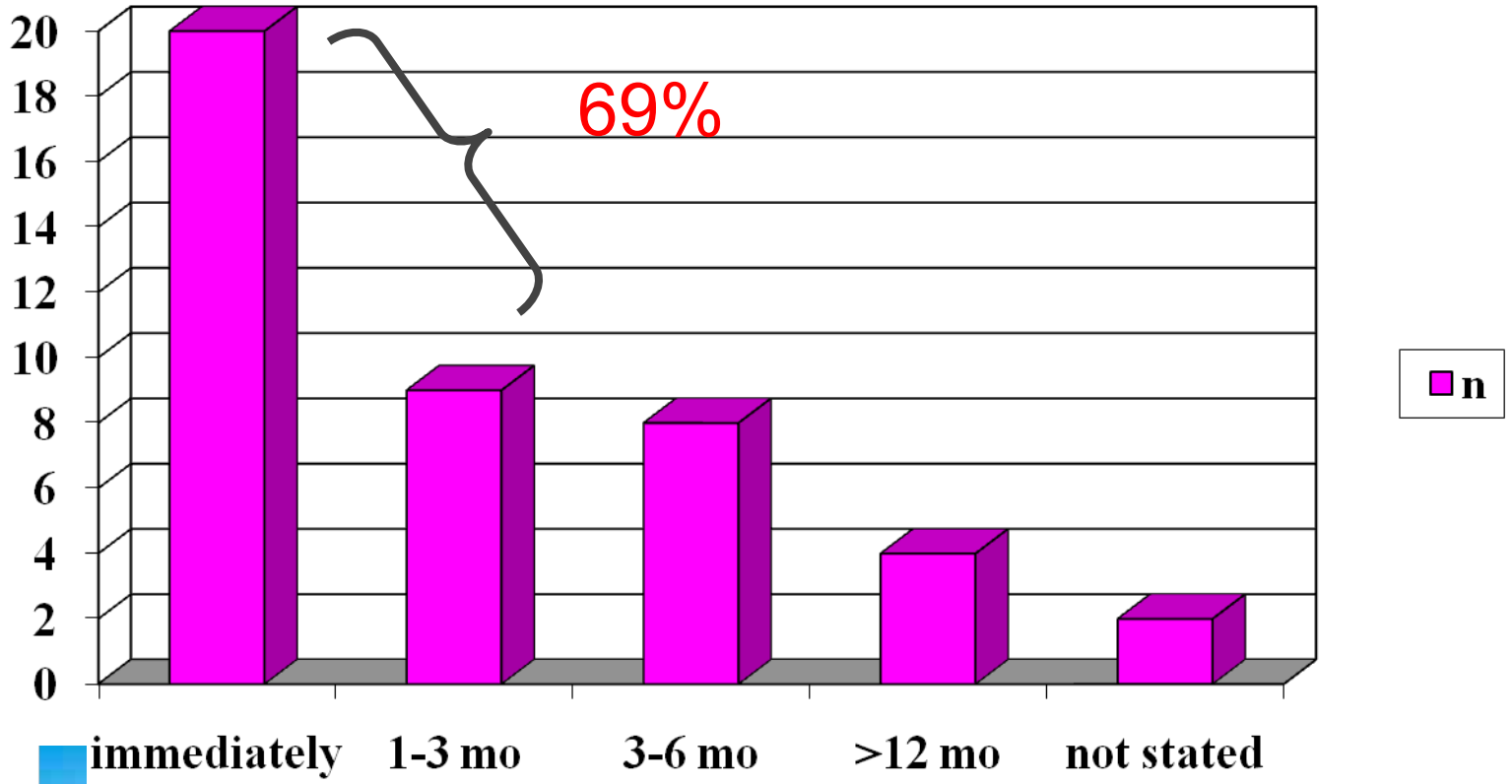
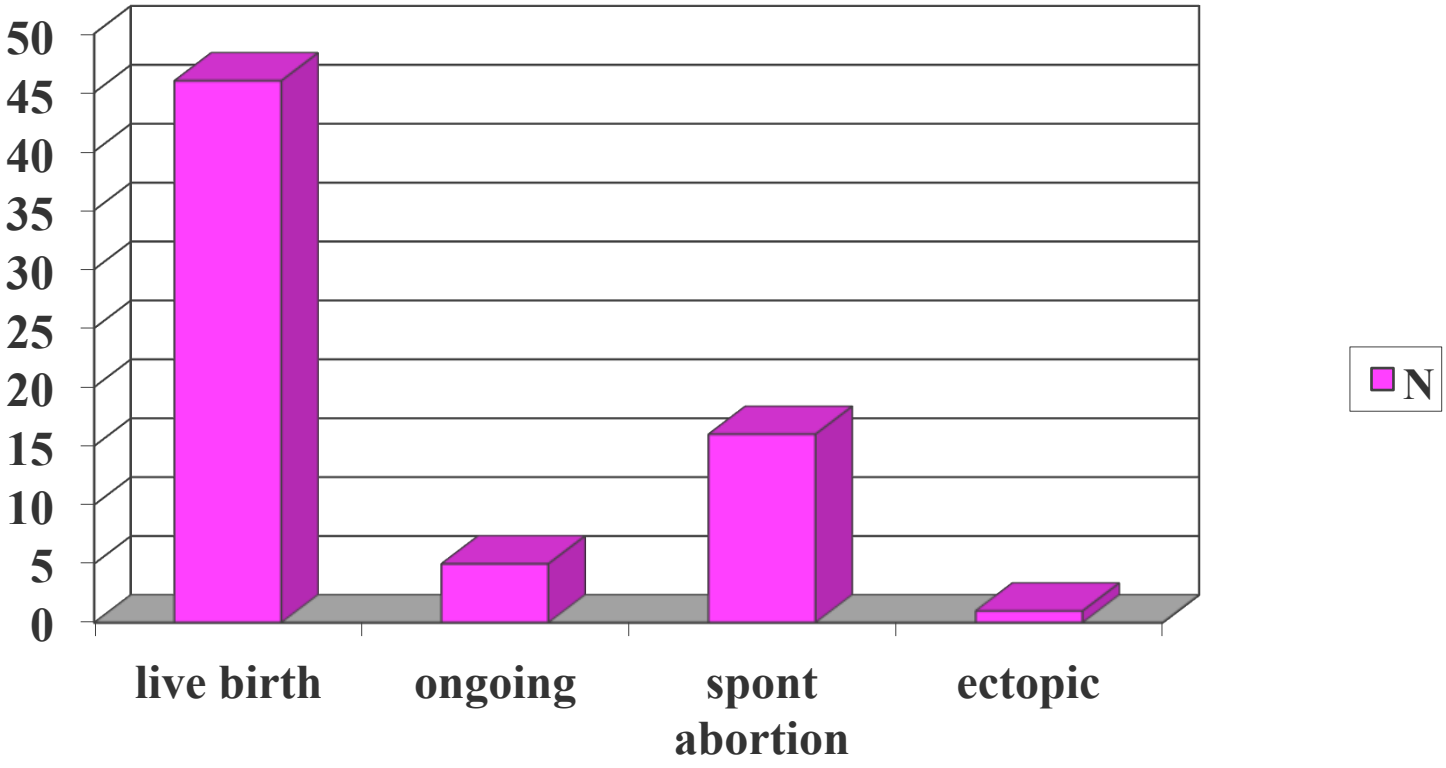


Outcome of 68 pregnancies



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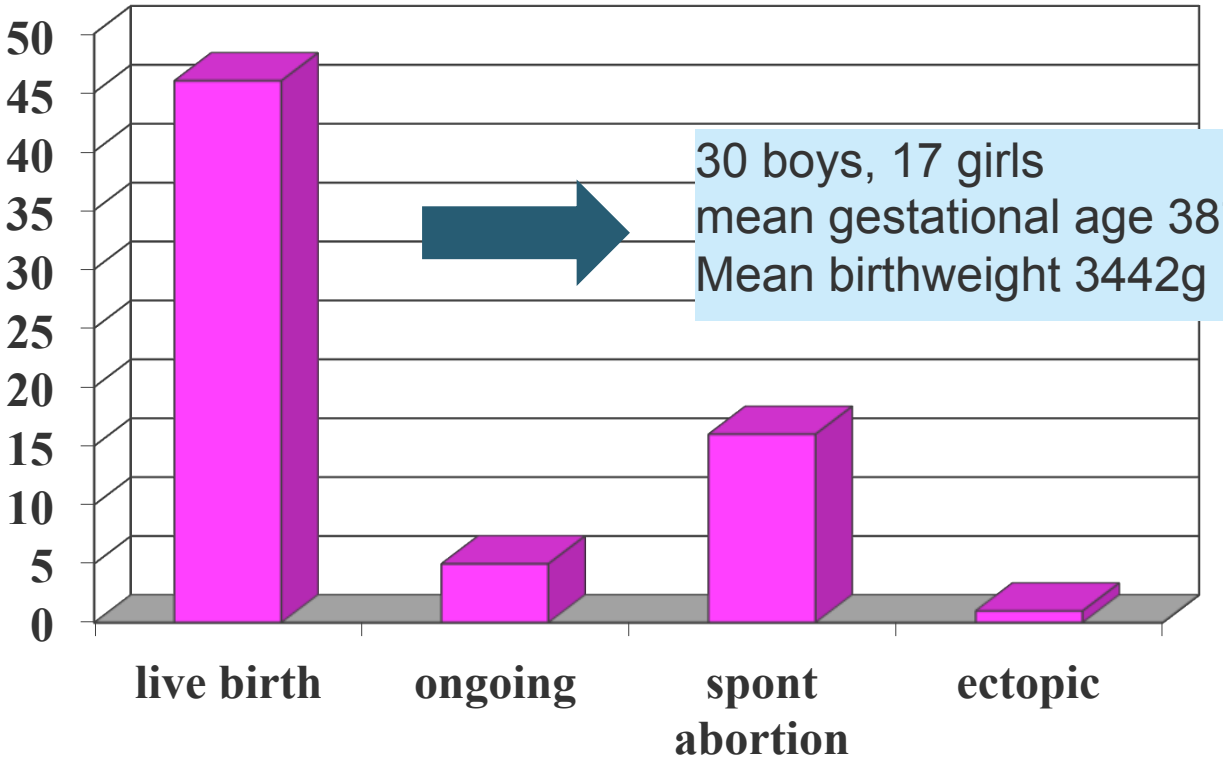

30 boys, 17 girls
mean gestational age 38½ weeks [32-42]
Mean birthweight 3442g [1942-4800]

Conclusion

- It is possible to regain the ovarian function after cancer treatment
- Risk of amenorrhoea depends on pre-treatment AMH and age of the patient and type of protocol used
- Having only one ovary (due to cryopreservation of the other) does not seem to affect the fertility in women with an intact ovarian function post-treatment

Conclusion

- Important when we counsel our patients before chemotherapy

- We need long term follow up studies to assess the risk of premature menopause in women who have received cancer treatment

Thank you for your attention

Also thanks to:

Prof. Claus Yding Andersen
Dr. Elisabeth Larsen
Prof. Anders Nyboe Andersen
Prof. Erik Ernst
Dr. Anne Loft

Dr. Mikkel Rosendahl