SPONTANEOUS RECOVERY OF FERTILITY AND OVARIAN FUNCTION AFTER CANCER TREATMENT

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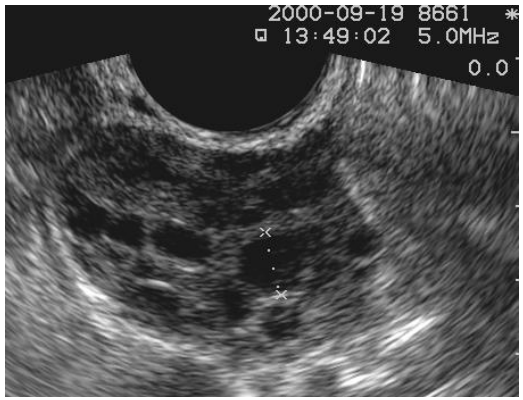
SFOG-veckan, Varberg, 2014

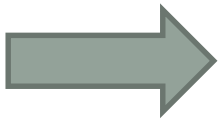
Cancer treatment has detrimental effects on the ovary

- Applies both for chemotherapy and radiation therapy
- Negative effects probably on both the oocyte and the granulosa cells
- Highest risk when treated with ***alkylating agents***, ***TBI*** or ***abdominal radiation***

Before chemo

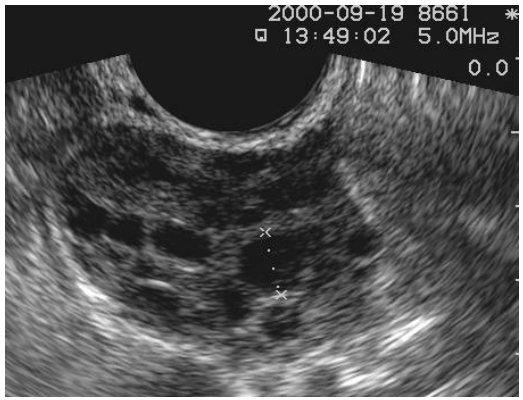
After chemo

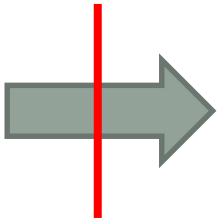




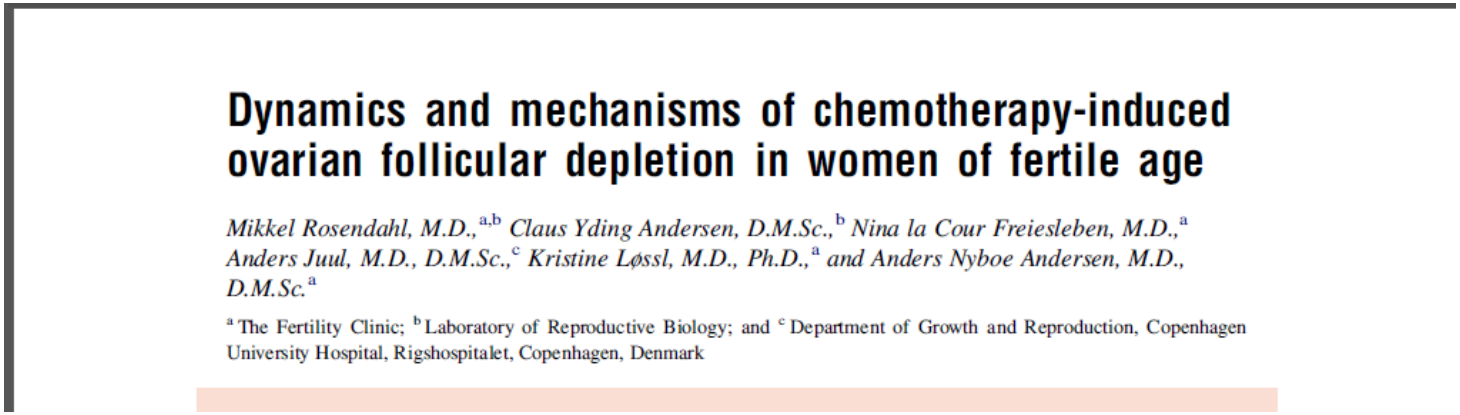
Before chemo

After chemo





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

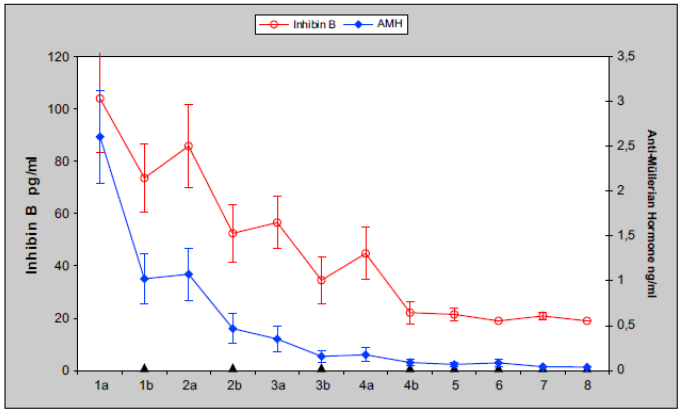
AFC, AMH, FSH and Inhibin B

During chemotherapy

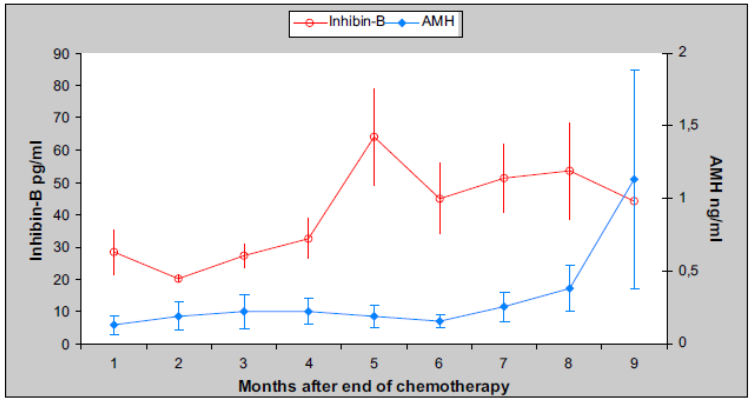
After chemotherapy

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

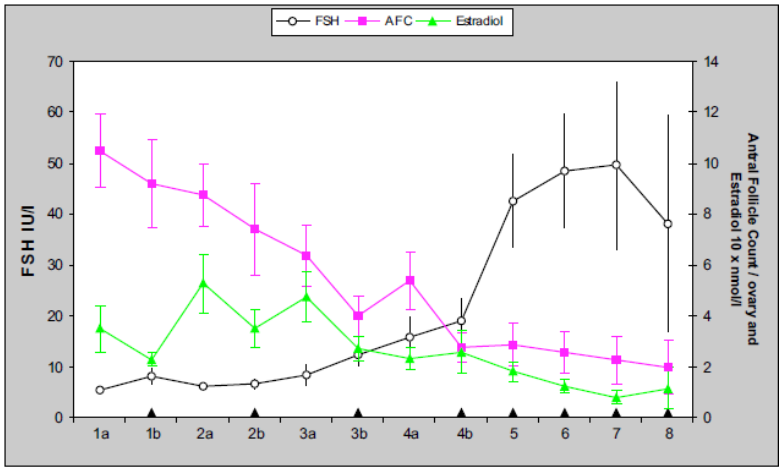
A

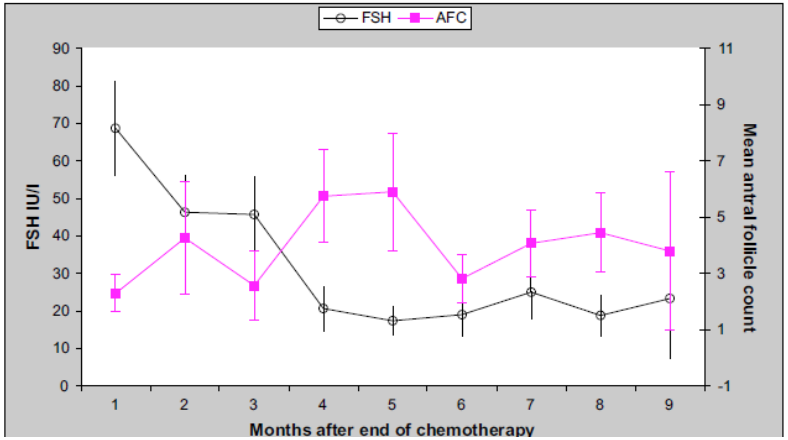


Ovarian function during the recovery period after the end of chemotherapy. Mean levels (± SEM).



B



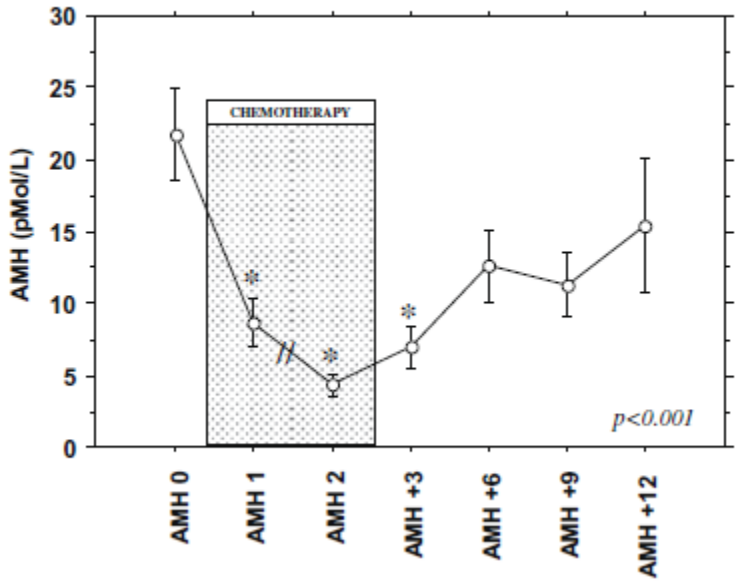


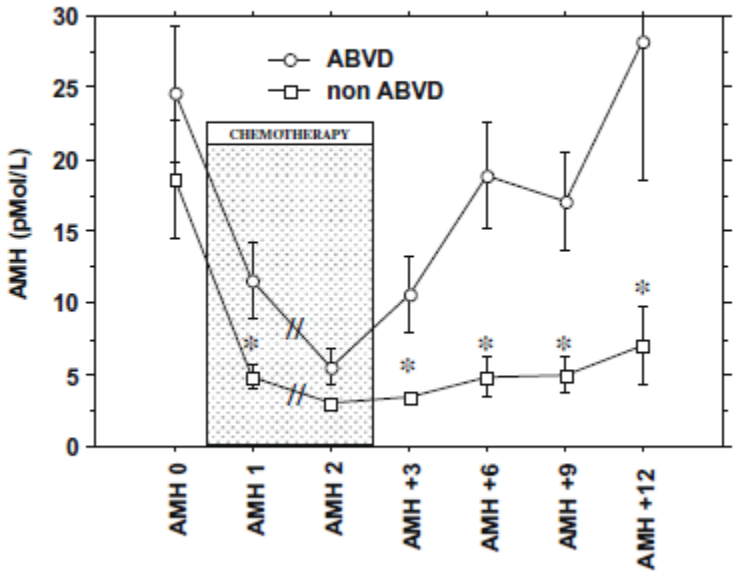
Anti-Müllerian hormone follow-up in young women treated by chemotherapy for lymphoma: preliminary results

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 2





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doi: 10.1210/jc.2003-030352

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**

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

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%)*

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%)*

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 *(57%)*
Oligomenorrhea (n)	5 *(> 35 days)*
Oral contraception (n)	10
Pregnant (n)	5
Menopause (n)	3 *(6%)*

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 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

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

- > 18 years at time of study inclusion
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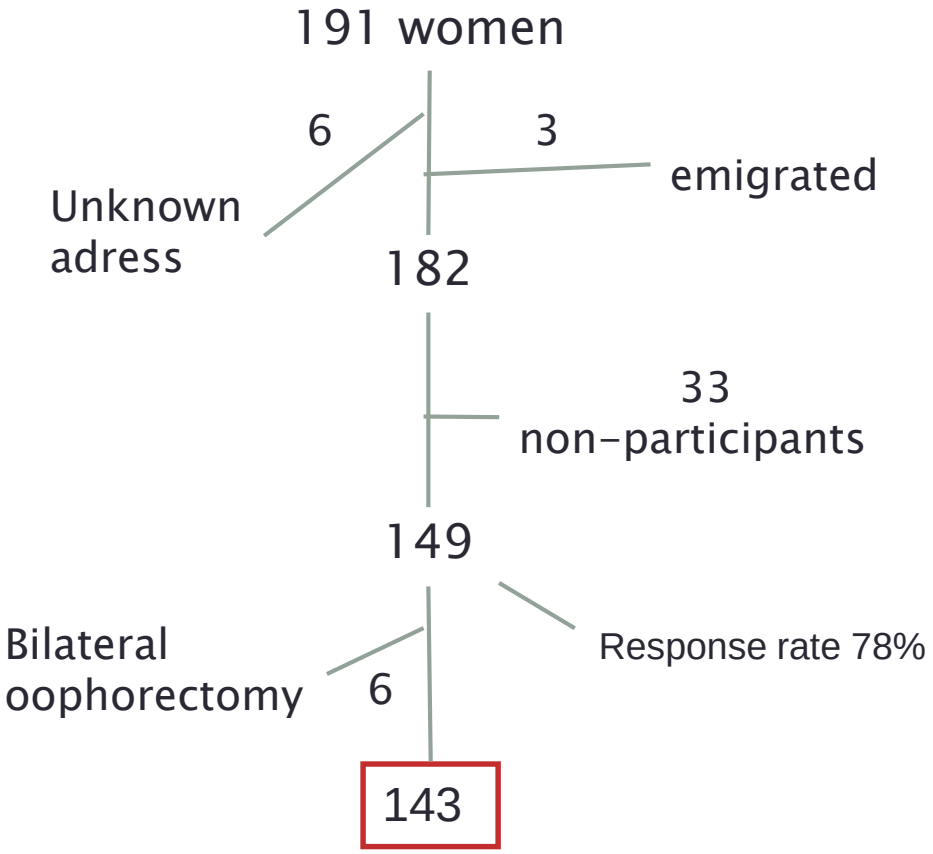
- Flowchart of cohort



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]

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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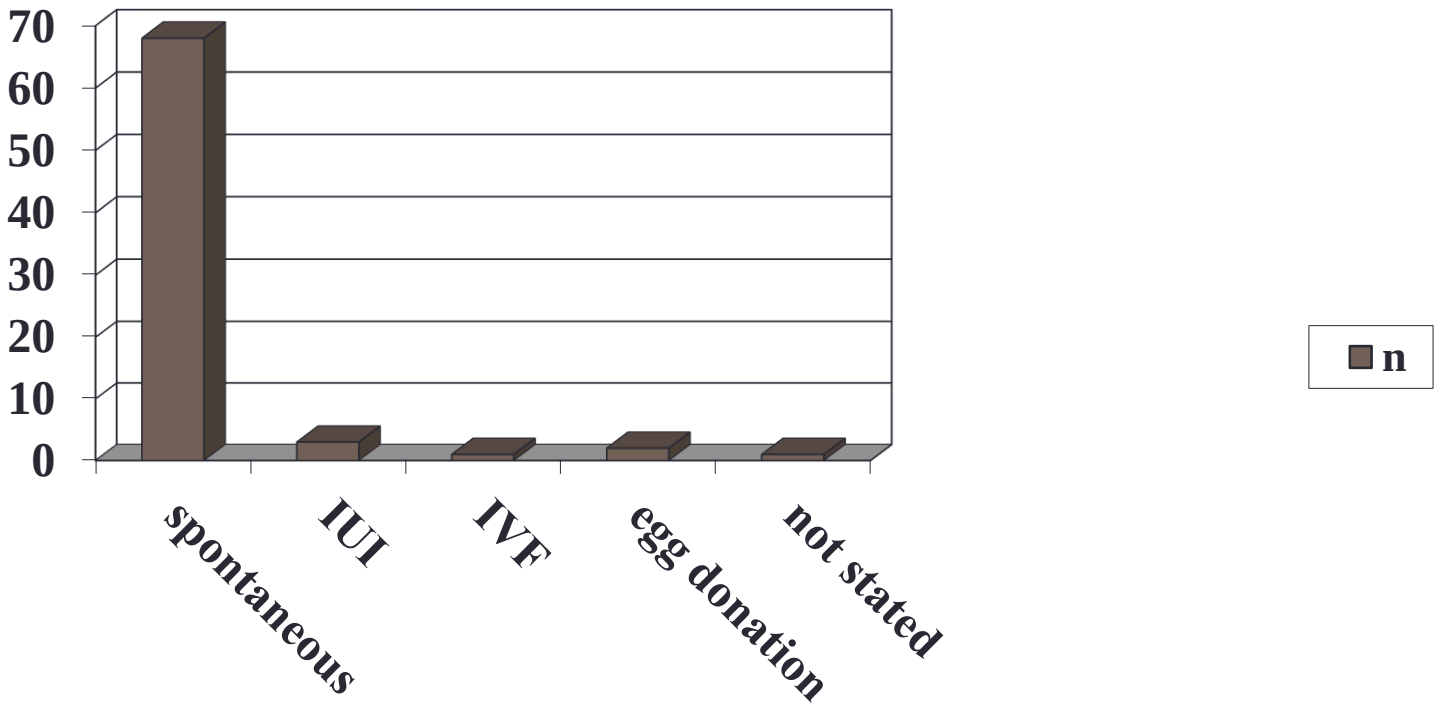
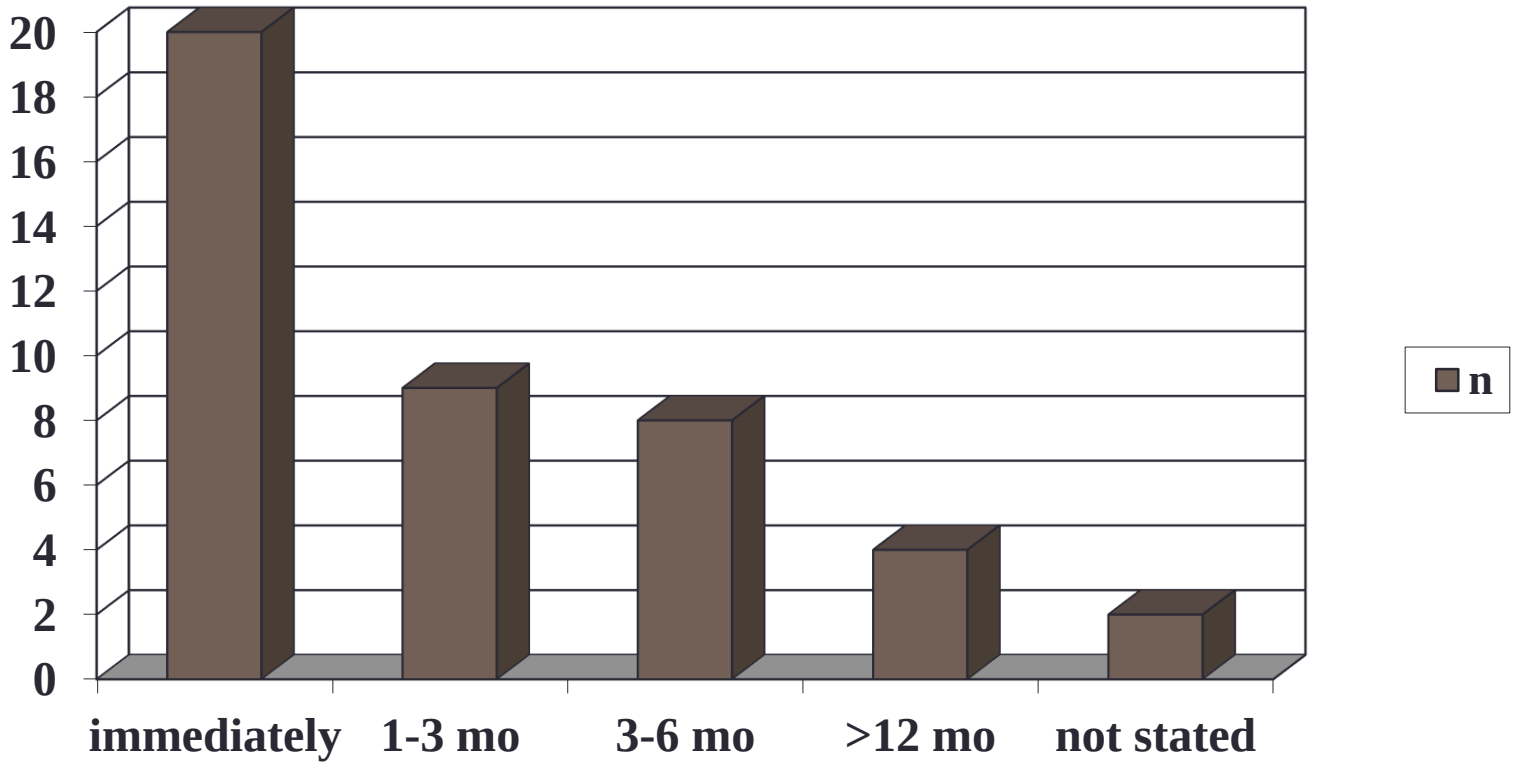
Pregnancies

- < Cryopreservation
  - 50/143 (35%) women had been pregnant before treatment → 38 children born to 31 women
- > Cryopreservation
  - 48/143 (34%) women became pregnant after treatment → 47 children born to 36 women
  - These 48 women shared a total of 75 pregnancies

Origin of 75 pregnancies



Time to pregnancy in 42 spontaneously pregnant women



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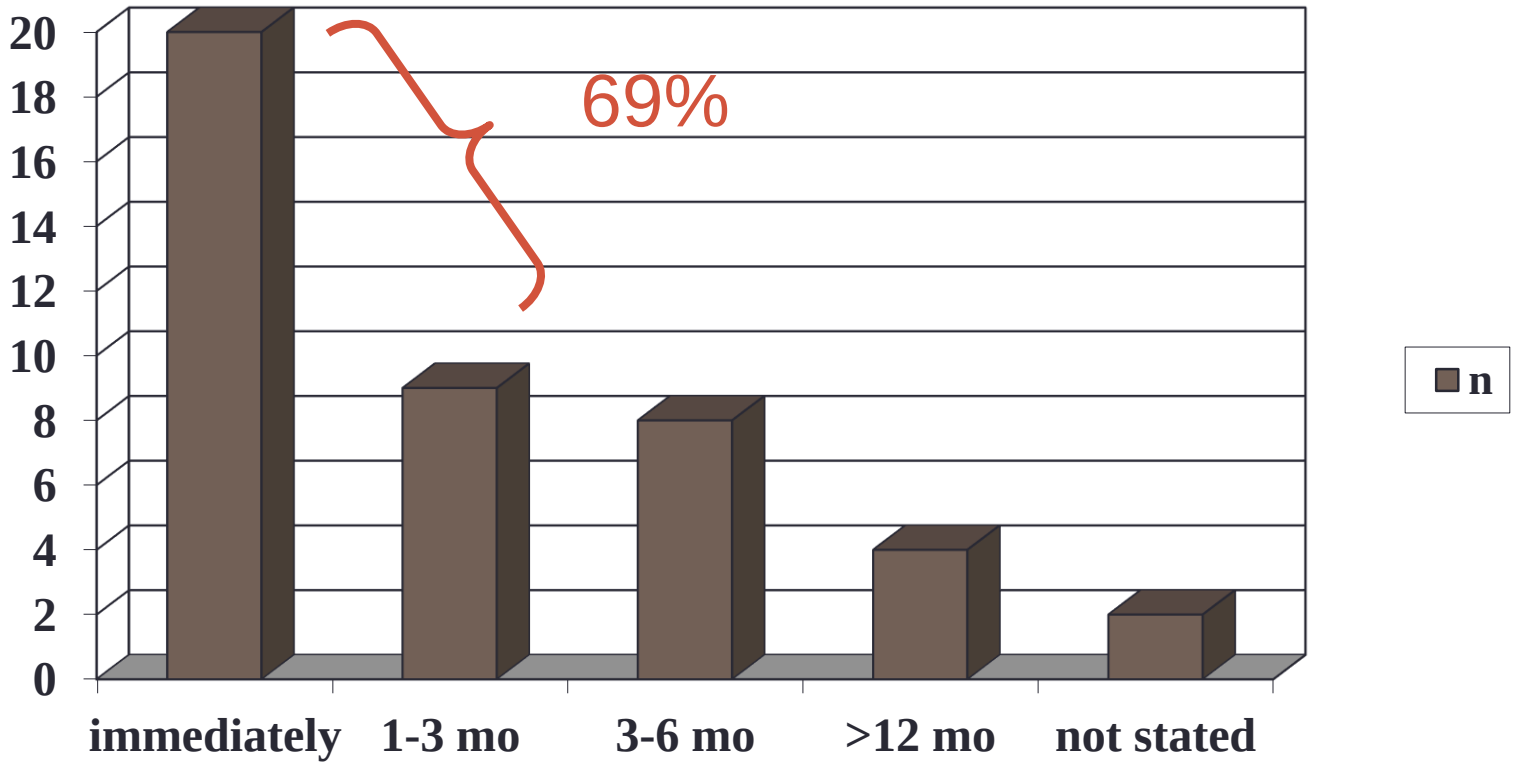
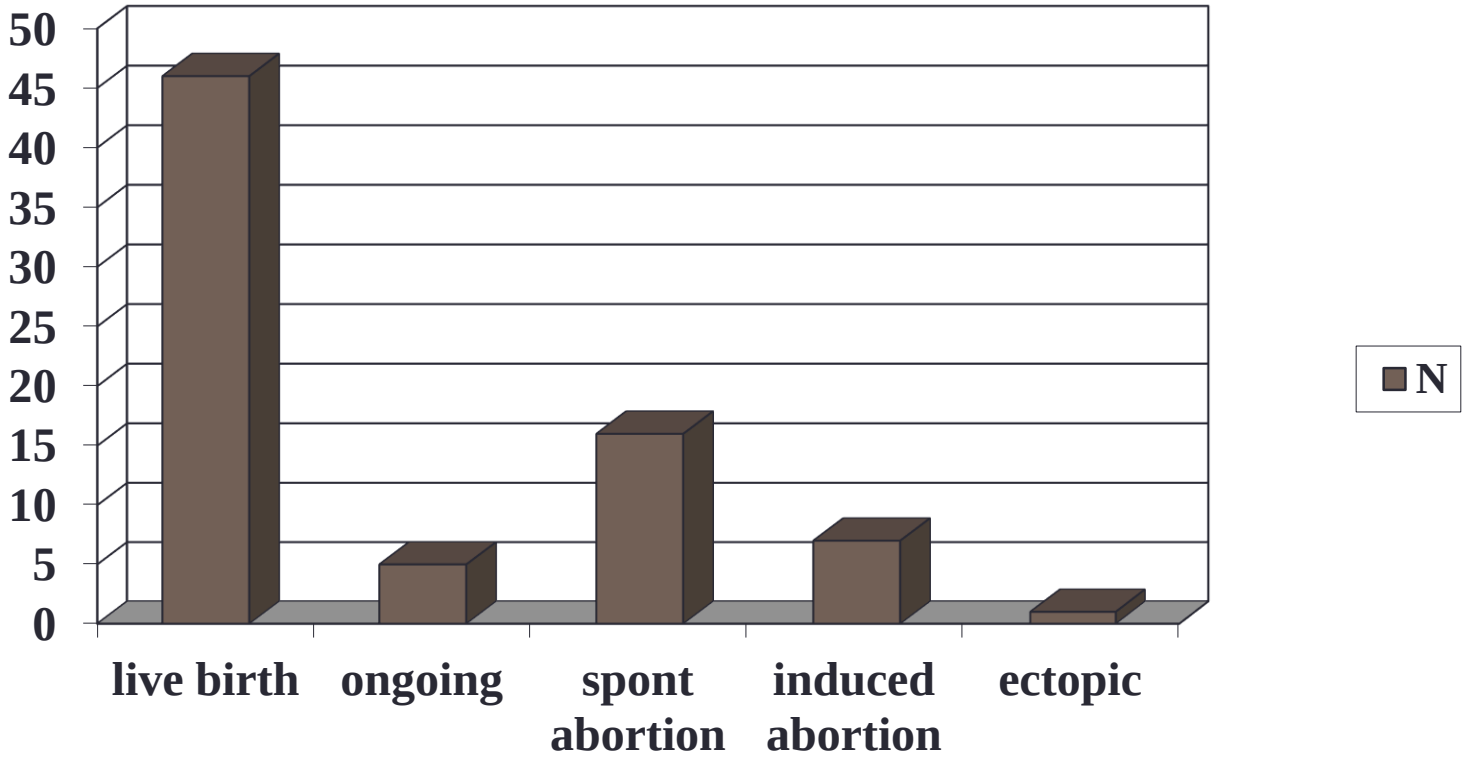


Outcome of 75 pregnancies



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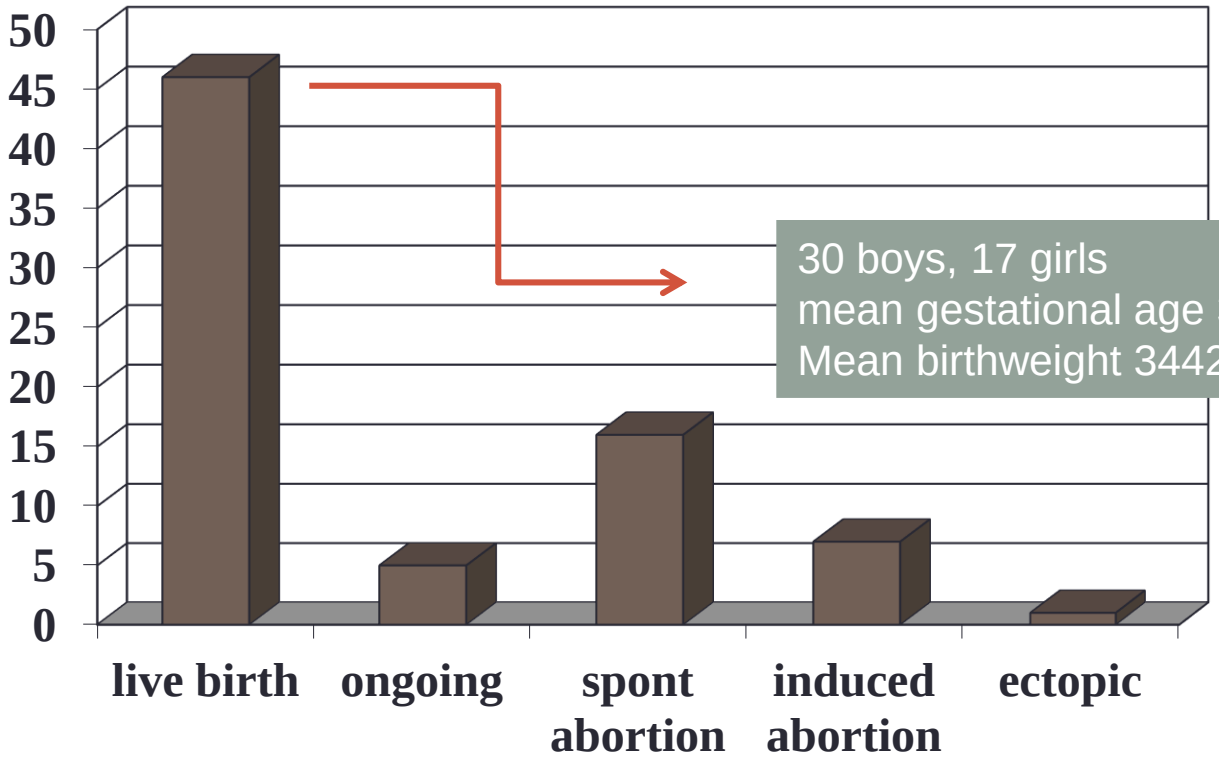

30 boys, 17 girls
mean gestational age 38½ weeks [32-42]
Mean birthweight 3442g [1942-4800]

Conclusion

- Fertility after cancer
  - Chemotherapy doesn’t necessarily destroy the ovarian function
  - Those who do regain ovarian function seem to be able to become pregnant as easily as the background population – even though they only have one ovary
  - Childhood cancer survivors with an intact ovarian function in their mid-20’s seem to also have an intact ovarian function in their mid-30’s

Thank you for your attention

Also thanks to:

Prof. Claus Yding Andersen
Dr. Tine Greve
Prof. Anders Nyboe Andersen
Prof. Erik Ernst
Dr. Anne Loft

Dr. Mikkel Rosendahl