

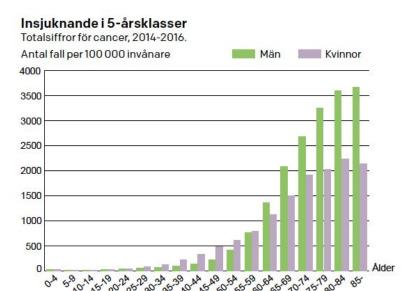


Fertilitetsbevarande åtgärder

KENNY RODRIGUEZ-WALLBERG

PROFESSOR,
ÖVERLÄKARE
Dept Onkologi-Patologi
Karolinska Institutet
Ansvarig för programmet
för fertilitetsbevarande
åtgärder
Dept Reproduktivmedicin
Karolinska Universitets
Sjukhuset, Stockholm





In the youngest groups 3 of 4 will be cured and will become long-term survivors, but many of them will become infertile



Old experiences with a new focus



Bone Marrow Transplant. 1998 Feb;21(3):287-90.

Ovarian function after BMT during childhood.

Thibaud E, Rodriguez-Macias K, Trivin C, Espérou H, Michon J, Brauner R. Pediatric Endocrinology Unit, Université Paris V and Hopital Necker-Enfants Malades, France.

Ovarian function in 31 girls (13.4 y, 11.7-18.6) after BMT (10.3 y, 3.2-17.5)

- Only chemotherapy (N=8), Chemotherapy and TBL 1∠ Gy fractioned (N=9) or TU Gy single dosis (N=7); 5 or 6 Gy single thorax-abd (N=7)
- No breast development (N=14), no puberty progress (N= 2)
- 4 girls with menarche stopped menstrual cycles after BMT
- At the last control (16.3 y,12.1-21.6), gonadotropins were a menopausal levels in 29 girls 23 were amenorrhoic, 2 menstruated

Only 6 girls had ovarian function, 3 were younger, received only chemo without busulfan





Facts and Development



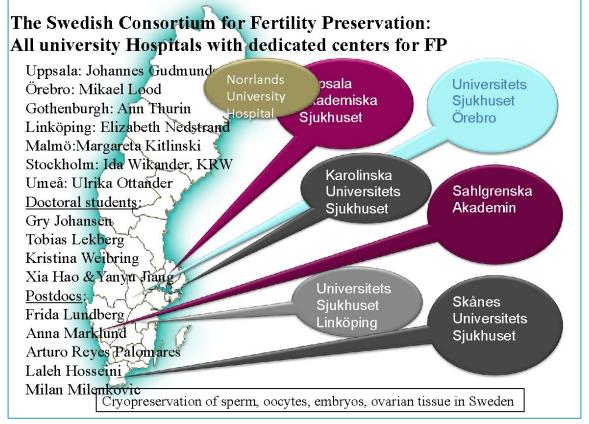
Rodriguez-Wallberg, 2019 Acta Obstet Gynecol Scand





Establishment of programs for fertility preservation at all Swedish university hospitals

COLLABORATION



If the treatment includes:

The following options should be considered:

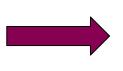




Cancer surgery

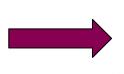
Fertility-sparing surgery preserving gonads.

Preservation of the uterus in females. Use of cryopreservation may also be considered prior to surgery if the risk of gonadal damage is high



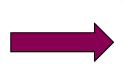
Radiation therapy to pelvic organs and gonads Shielding aiming at reducing damage of reproductive organs and surgical ovarian transposition

Use of cryopreservation may also be considered prior to radiotherapy



Cytotoxic treatment with high risk of gonadal damage

Use of cryopreservation methods such as sperm banking for males, freezing of embryos and oocytes for females and gonadal tissue freezing



Hormone therapy for estrogensensitive breast cancer

Cryopreservation may be considered in women >33 years of age when a 5-year tamoxifen treatment is planned and >28 years of age if a 10-course (ATLAS) is planned, as natural fertility diminishes with age.

Rodriguez-Wallberg and Oktay. Fertility preservation during cancer treatment: clinical guidelines. Cancer Management and Research, 2014



FERTILITY PRESERVATION IN THE NORDIC

AOGS ORIGINAL RESEARCH ARTICLE

Ovarian tissue cryopreservation and transplantation among alternatives for fertility preservation in the Nordic countries – compilation of 20 years of multicenter experience

KENNY A. RODRIGUEZ-WALLBERG^{1,2}, TOM TANBO³, HELENA TINKANEN⁴, ANN THURIN-KJELLBERG⁵, ELIZABETH NEDSTRAND⁶, MARGARETA LACZNA KITLINSKI⁷, KIRSTEN T. MACKLON⁸, ERIK ERNST⁹, JENS FEDDER¹⁰, AILA TIITINEN¹¹, LAURE MORIN-PAPUNEN¹², SNORRI EINARSSON¹³, VARPU JOKIMAA¹⁴, MARITTA HIPPELÄINEN¹⁵, MIKAEL LOOD¹⁶, JOHANNES GUDMUNDSSON¹⁷, JAN I. OLOFSSON^{1,18} & CLAUS YDING ANDERSEN^{8,19}

Acta Obstet Gynecol Scand 2016 June, 95(9):1015-26

Existing programs for fertility preservation at nearly all University Hospital-based Reproductive Medicine centres:

Reported cases: Denmark 822, Sweden 457, Norway 164, Finland 145;

In total: 46 women had tissue transplanted resulting in 17 live births (27%)





"Att få bli förälder är för många människor grundläggande för meningsfullheten med livet"

Assisterad befruktning – etiska aspekter: Statens medicinsk-etiska råd, Smer rapport 2013:1 http://www.smer.se/

K. Rodriguez-Wallberg



HOW OUR PROGRAM STARTED

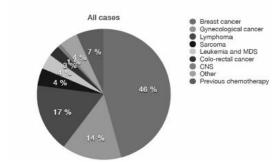
- A CLINICAL PROGRAM FOR FERTILITY PRESERVATION FOR MALES SINCE 1980'S
- A CLINICAL PROGRAM FOR FEMALES FOR FERTILITY SPARING SURGERY
- A DEVELOPED REPRODUCTIVE MEDICINE CENTRE AT A TEACHING HOSPITAL - CRYOPRESERVATION METHODS
- DEDICATED RESEARCHERS
 Outi Hovatta, Julius Hreinsson, Victoria Keros, Mona Sheiki

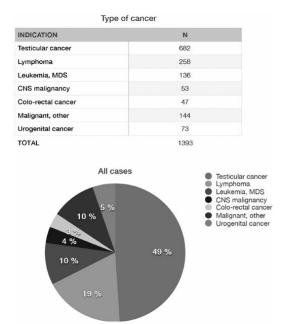




10

INDICATION	N
Breast cancer	390
Gynecological cancer	123
Lymphoma	144
Sarcoma	37
Leukemia and MDS	32
Colo-rectal cancer	23
CNS	8
Other	38
Previous chemotherapy	57
TOTAL	852





Cancer diagnoses in the clinical cohort of women (left panel) and men (right panel) that have undergone fertility preservation at Karolinska University Hospital 1988-2018. *From: Rodriguez-Wallberg et al.*Fertility Preservation for young adults, adolescents and children with cancer. Upsala Journal of Medical Sciences 2020; May; 125(2):112-120.





TO OBTAIN EGGS

- HORMONAL STIMULATION
- TIME AND EXAMS INCLUDING REPEATED TRANSVAGINAL ULTRASOUND
- EGG RETRIEVAL
- TWO WEEKS TIME IS USUALLY REQUIRED
- OVARIAN TISSUE

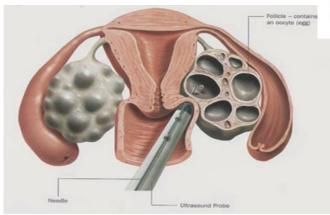
TO OBTAIN SPERMS



A SINGLE SAMPLE BY MASTURBATION IS USUALLY SUFFICIENT





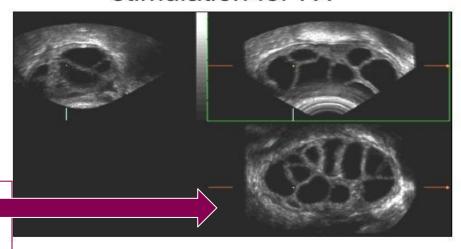


Supraphysiological systemic estrogen levels

Risk of Ovarian

Hyperstimulation syndrome

Ovarian follicles after 6-days FSHstimulation for IVF

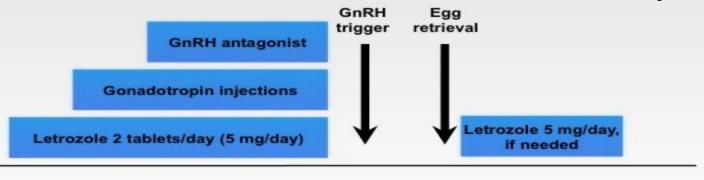




Patient information

Ovarian stimulation using letrozole alongside gonadotropins

Estradiol levels maintained within levels of a normal cycle



Cycle days 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20



Oktay, Türkçüoğlu & Rodriguez-Wallberg, RBMO 2010







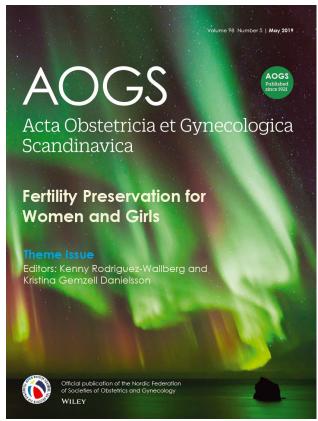


A prospective study of women and girls undergoing fertility preservation due to oncologic and non-oncologic indications in Sweden - Trends in patients' choices and benefit of the chosen methods after long-term follow-up

Kenny A. Rodriguez-Wallberg ⋈, Anna Marklund, Frida Lundberg, Ida Wikander, Milan Milenkovic, Amandine Anastacio, Fotios Sergouniotis, Kjell Wånggren, Jeanette Ekengren, Tekla Lind, Birgit Borgström

First published: 05 February 2019





2024-04-14 K. Rodriguez-Wallberg

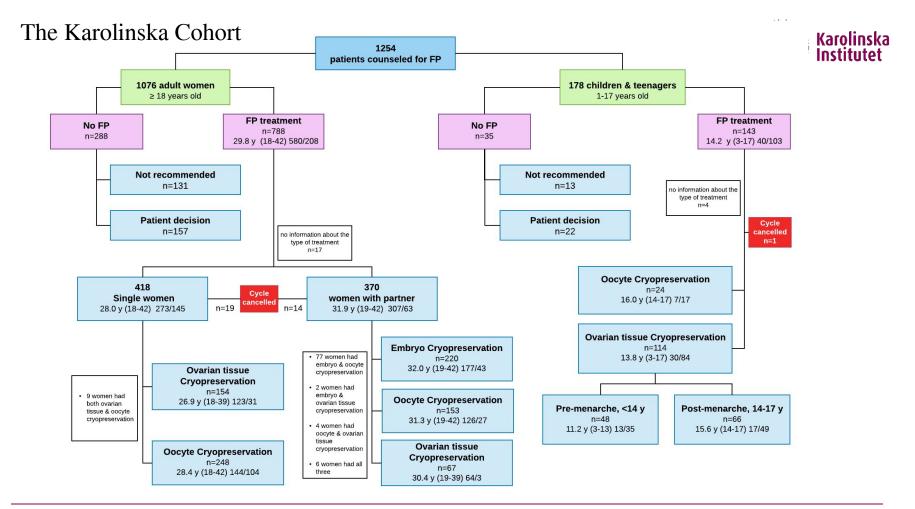


Table 1	Adult Women (≥18y) (N=1076)		
Age - Mean ± SD (range)	30.0 ± 6.1 (18–43)	14.2 ± 2.8 (1–17)	27.8 ± 8.0 (1–43)
Malignant diseases	798 (74.1)	54 (30.3)	852 (67.9)
Breast carreer	336 (36.2)		330 (31.1)
Gynecological cancer	121 (11.2)	2 (1.1)	123 (9.8)
Cervical cancer	78 (7.2)		78 (6.2)
Ovarian cancer	37 (3.4)	2 (1.1)	39 (3.1)
Uterine/endometrial cancer	6 (0.6)		6 (0.5)
Lymphoma	133 (12.4)	11 (6.2)	144 (11.5)
Hodgkin's lymphoma	93 (8.6)	9 (5.1)	102 (8.1)
Other lymphoma	40 (3.7)	2 (1.1)	42 (3.3)
Sarcoma	29 (2.7)	8 (4.5)	37 (3.0)
Ewing's sarcoma	9 (0.9)	3 (1.7)	13 (1.0)
Other sarcoma	19 (1.8)	5 (2.8)	24 (1.9)
Leukaemia and MDS	19 (1.8)	13 (7.3)	32 (2.6)
Colon/rectal cancer	22 (2.0)	1 (0.6)	23 (1.8)
Neurological cancer	8 (0.7)		8 (0.6)
Thyroid cancer	6 (0.6)	1 (0.6)	7 (0.6)
Salivary gland/lingual cancer	4 (0.4)		4 (0.3)
Lung cancer	4 (0.4)		4 (0.3)
Other malignancies	22 (2.0)	1 (0.6)	23 (1.8)
Previous chemotherapy	40 (3.7)	17 (9.6)	57 (4.5)
Benign indications	278 (25.8)	124 (69.7)	402 (32.1)
Genetic predisposition to POI	17 (1.6)	76 (42.7)	93 (7.4)
Turner's syndrome	16 (1.5)	74 (41.1)	90 (7.2)
Galactosemia and other	1 (0.1)	2 (1.1)	3 (0.2)
Gynecologic benign	51 (4.7)	9 (5.1)	60 (4.8)
Impending ovarian failure	16 (1.5)	8 (4.5)	24 (1.9)
Endometriosis	15 (1.4)		15 (1.2)
Uterine, benign	13 (1.2)		13 (1.0)
Ovarian, benign	7 (0.7)	1 (0.6)	8 (0.6)
Autoimmune diseases	34 (3.2)	1 (0.6)	35 (2.8)
Vacaulitia	0.(0.0)		0 (0.7)



Diagnoses in the cohort of women and girls referred for Fertility Preservation (FP) at Karolinska University

Rodriguez-Wallberg et al., AOGS 2019





IN THE KAROLINSKA COHORT:

- •EFFICACY: Utilization rates were 29%, 8% and 5% for embryos, oocytes and ovarian tissue with pregnancy rates of 66%, 54% and 25%, and live birth rates of 54%, 46% and 7%, respectively.
- •EFFICACY: The pregnancy rate was similar but the live birth rate was higher in women with benign vs malign indication for FP (47% vs 21%, p=0.002)





CHILDREN AND TEENAGERS IN THE KAROLINSKA COHORT:

- •Girls and teenagers: 178 of 1254 cases
- Ovarian tissue cryopreservation: 114 cases (13.8 years, range 3-17)
- Oocyte cryopreservation 24 cases (16 years, range 14-17)
- CLINICAL DEVELOPMENTS: An increasing number of young teenagers has elected to undergo hormonal stimulation and egg retrieval



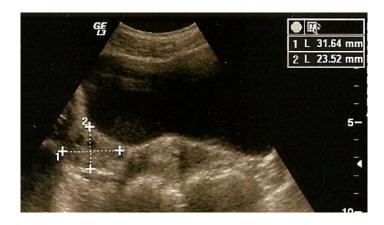


OVARIAN STIMULATION IN VERY YOUNG

GIRLS? A fourteen year-old with Turner's mosaicism.

Abdominal ultrasound under COH

Oktay, Rodriguez-Wallberg & Sahin, Fertil Steril 2010





K. Rodriguez-Wallberg

A fourteen year-old with Turner's mosaicism. Vaginal ultrasound at the time of egg retrieval





Oktay, Rodriguez-Wallberg & Sahin, Fertil Steril 2010





COUNSELING OF GIRLS AND TEENAGERS

- Counseling by a pediatrician and a reproductive medicine specialist
- Written age-adapted information in two versions (older and younger children) + Information to parents and consent forms
- The possibility to undergo fertility preservation later on is also discussed, as well as scenarios in case fertility preservation is not possible or not desired – egg donor treatments and adoption as alternatives



A Prospective Study on Fertility Preservation in Prepubertal and Adolescent Girls Undergoing Hematological Stem Cell Transplantation

Ida Wikander¹, Frida E. Lundberg², Hanna Nilsson², Birgit Borgström² and Kenny A. Rodriguez-Wallberg^{1,2*}

Frontiers in Oncology, June 2021

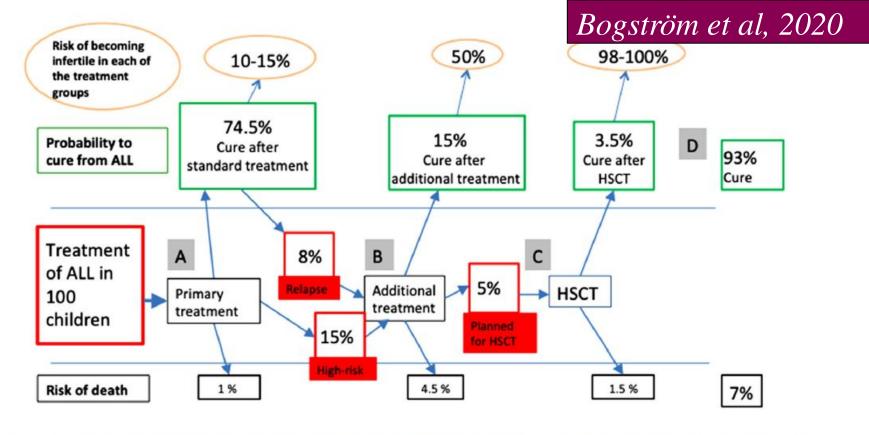


FIGURE 1 Possible timepoints (A-D) for fertility preservation of children presenting with acute lymphocytic leukemia (ALL). The grayboxes (A-D) indicate possible timepoints for the feasibility of fertility preservation in children undergoing treatment for ALL. The proportion of individuals in each box are approximated, according to current data from the Nordic Society for Pediatric Hematology and Oncology (NOPHO) ALL 2008 Protocol for Childhood Acute Lymphoblastic Leukemia. Predicted overall survival at follow-up is about 93%. HSCT, hematopoietic stem cell transplantation



/haematologica.org/index





Vol. 106 No. 10 (2021): October, 2021 > Successful pregnancies after transplantation of ovarian...

CASE REPORTS

Successful pregnancies after transplantation of ovarian tissue retrieved and cryopreserved at time of childhood acute lymphoblastic leukemia – A case report

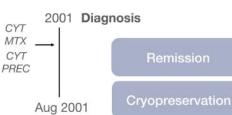
Kenny A. Rodriguez-Wallberg, Milan Milenkovic, Kiriaki Papaikonomou, Victoria Keros.

Britt Gustafsson. Fotios Sergouniotis. Ida Wikander, Ronak Perot, Birgit Borgström. Per Ljungman.

Gisela Barbany.

Vol. 106 No. 10 (2021): October, 2021 https://doi.org/10.3324/haematol.2021.278828

Treatment with cytarabine prednisolone p.o., cytarabine i.v., vincristine i.v., doxorubicin i.v. and methotrexate i.th. (NOPHO ALL 2000 High Risk Protocol)



Philadelphia positive, high risk ALL diagnosis

Complete remission demonstrated by absence of blasts in the bone marrow from ilia crest biopsy and negative lumbar puncture.

Cryopreservation. 1/2 right ovary. Follicle density of 182 follicles/mm² and absence of malignant cells confirmed on histology of one piece of ovarian tissue.





The patient requested ovarian tissue transplantation in 2016:

- No molecular investigations at time of leukemia dignosis
- •Frozen blood cells taken at diagnosis 2001 at the research biobank
- •The cells were used to establish that the patient's leukemic cells harbored the BCR-ABL minor fusion transcript
- Thereafter the transcript was investigated in thawed ovarian tissue pieces
- 15% of tissue used for diagnosis 80 independent PCR reactions





Safety aspects of OTT

- Sensitive molecular methods to detect unique markers present in the blast cells, such as the fusion transcript identified in this case
- The patient was in complete remission in the bone marrow at time of ovarian tissue retrieval
- Very low likelihood to transmit leukemia
- The allogeneic HCST should ensure surveillance to elliminate potential small amounts of leukemic cells potentially introduced with the OTT





1st transplantation Nov 2017 27 tissue pieces transplanted

Menstrual cycles after 85 days, FSH decreased Feb 2018

4 COS attempts, one oocyte obtained, not fertilized

2nd transplantation Nov 2018 19 pieces Menstruation after 86 days

COS resulted in one oocyte retrieved, fertilized, a 4-cells embryo transferred Delivery Nov 2019 + Pregnancy Delivery Aug 2021

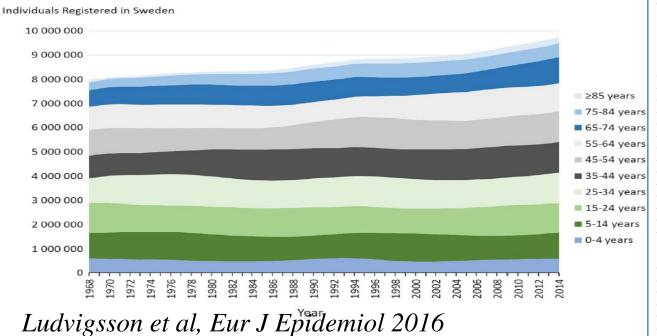




WHAT IS THE SAFETY OF THESE TREATMENTS AIMED AT FREEZING EGGS OR EMBRYOS?

Use of Registered data

The Swedish Total Population Registers and Healthcare Registers



Unique identifiers (PIN)

Births
Deaths
Disease codes
Intervention codes
Link to parents/
Link to offspring
Follow-up

EXCELLENT MEDICAL RESEARCH TOOL

Women with breast cancer who underwent fertility preservation (exposed) were linked to the SBCR using each individual's unique number

n = 202

Control women
(unexposed to fertility
preservation and matched
for age at breast cancer
diagnosis) were identified
from the SBCR



Women referred from other healthcare regions or non-Swedish citizens who were not in the Swedish Cancer Registry

6 excluded

Women who had had previous breast cancer or who presented with relapse at the time of fertility preservation

3 excluded

Women with bilateral breast cancer or stage T4 cancer

4 excluded

Total number of exposed women available for matching

n = 189

BREAST CANCER

Design of a matched cohort study 1997-2013

n = 378

Q: How to get controls?

A: Stockholm Breast Cancer Registry SBCR

<u>Rodriguez-Wallberg et al.</u>

Breast Cancer Res Treat 2018

Table 2 A comparison of the incidence of relapse in exposed women with breast cancer who had undergone fertility preservation and that in women who had not been exposed to fertility preservation (n = 534)

	Model 12 IRR (95% CI)	Model 2 ^b IRR (95% CI)	Model 3 ^c IRR (95% CI)	Model 4 ^d IRR (95% CI)
Fertility preservation				
No fertility preservation n=378	1.00 (reference) ^e	1.00 (reference) ^e	1.00 (reference) ^a	1.00 (reference)
Fertility preservation that does not	0.80 (0.40-1.60)	0.82 (0.41-1.64)	0.75 (0.37-1.50)	0.83 (0.42-1.67)
require hormonal stimulation Fertility preservation that requires The- monal stimulation	0.59 (0.34-1.04)	0.65 (0.37–1.15)	0.67 (0.38–1.19)	0.66 (0.37–1.17)
Period of diagnosis n=188				
1997-2002	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2003-2007	0.50 (0.33-0.76)	0.53 (0.35-0.80)	0.52 (0.34-0.79)	0.52 (0.35-0.79)
2008-2013	0.32 (0.18-0.54)	0.33 (0.19-0.56)	0.30 (0.17-0.53)	0.34 (0.19-0.58)
Tumor size				
ТО		0.20 (0.03-1.47)	0.20 (0.03-1.47)	0.19 (0.03-1.40)
TIS		_	200000000000000000000000000000000000000	
1 (≤ 20 mm)		1.00 (reference)	1.00 (reference)	1.00 (reference)
II (21-50 mm)		1.47 (1.00-2.17)	1.22 (0.79-1.87)	1.53 (1.03-2.29)
III (> 50 mm)		1.34 (0.74-2.42)	0.86 (0.43-1.73)	1.42 (0.77-2.60)
Lymph nodes				
0		1.00 (reference)	1.00 (reference)	1.00 (reference)
1-3		1.73 (1.14-2.62)	1.71 (1.12-2.60)	2.00 (1.26-3.18)
> 3		2.45 (1.55-3.87)	2.25 (1.40-3.62)	2.91 (1.73-4.90)
Receptors				
ER+			1.00 (reference)	1.00 (reference)
ER-			1.01 (0.68-1.49)	1.12 (0.75-1.69)
Neoadjuvant treatment				
No			1.00 (Reference)	-
Yes			1.85 (1.13-3.04)	
Chemotherapy				
No				1.00 (reference)
Yes				0.64 (0.37-1.12)

CI confidence interval, IRR incidence rate ratio, ER estrogen receptor

Rodriguez-Wallberg et al.

Breast Cancer Res Treat 2018



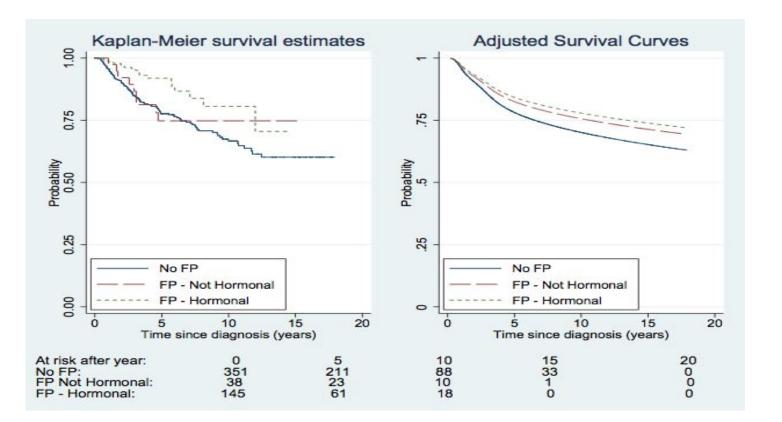
Adjusted for age at diagnosis (using a restricted cubic spline with 4 degrees of freedom) and the calendar period of the diagnosis

^bFurther adjusted for tumor size and the number of involved lymph nodes

^cFurther adjusted for estrogen receptor status and neoadjuvant treatment

^dAdjusted for chemotherapy treatment (pre- or postoperative)

^oEvidence for the proportional hazard assumption





Rodriguez-Wallberg et al. **Breast Cancer Res Treat 2018** Feb; 167(3):761769. **Safety of fertility preservation in breast cancer in a register-based matched cohort study**



Human Reproduction, Vol.35, No.4, pp. 929–938, 2020

Advance Access Publication on April 21, 2020 doi:10.1093/humrep/deaa029

human reproduction ORIGINAL ARTICLE Reproductive endocrinology

Efficacy and safety of controlled ovarian stimulation using GnRH antagonist protocols for emergency fertility preservation in young women with breast cancer—a prospective nationwide Swedish multicenter study

Anna Marklund^{1,2}, Sandra Eloranta³, Ida Wikander⁴, Margareta Laczna Kitlinski⁵, Mikael Lood⁶, Elizabeth Nedstrand⁷, Ann Thurin-Kjellberg⁸, Pu Zhang⁹, Jonas Bergh^{1,10}, and Kenny A. Rodriguez-Wallberg^{1,4,11,*}





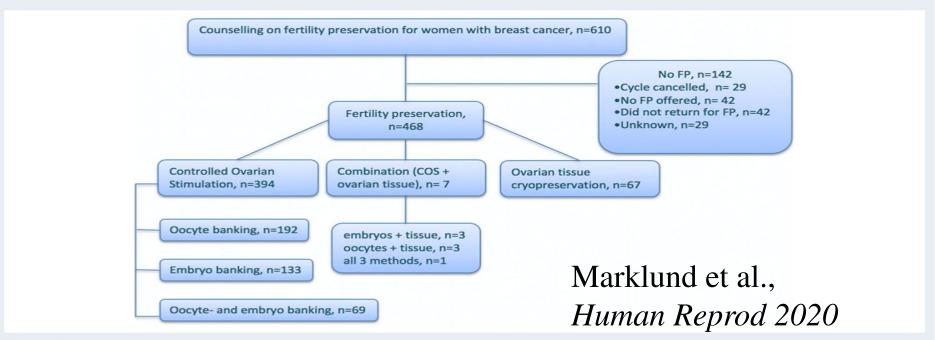


Figure | A flowchart of women with BC who were counseled on FP options at six Swedish university hospitals between | January 1995 and 30 June 2017.

WIDER IMPLICATIONS OF THE FINDINGS:

The results of our study support the premise that recently introduced potential 2024-04-14

Table II Comparison of outcomes of COS with and without letrozole.

Cycle outcomes	COS treatments in antagonist protocols, n = 380				Letrozole-based protocols, n = 224				
	Letrozole	No Letrozole	P-value*	Conventional start				hCG trigger	
Number of cycles	224	156		179	201		96	128	
Days of ovarian stimulation	10.5	11.0		10.5	10.9	0.053	10.7	10.4	
Range	5-18	7-17	0.03	5-17	5-18		6-18	5-18	0.34
Unknown	2	0		1	1		0	2	
Total dose of gonadotropins	2330	2064	0.004	2066	2359	0.001	2379	2294	0.51
(IU)	500-6750	800-5400		500-5550	750-6750		1050-6750	500-5850	
Range									
Oocytes retrieved	12.32	12.21	0.917	12.3	12.2	0.79	13.66	11.32	0.027
Range	0-55	0-52		0-55	0-52		0-55	0-44	
Mature oocytes ^a	8.45	8.52	0.941	9.1	7.9	0.197	9.3	7.6	
Range	0-46	0-24		0-44	0-23		0-44	0–26	0.14
Unknown	5	8		7	6		1	4	
Mature oocytes/total oocytes ratio ^a	0.71	0.79	0.037	0.76	0.70	0.078	0.74	0.68	0.106
osi	6.48	7.19	0.193	7.29	6.31	0.045	6.65	6.35	0.693
Range	0-45.8	0-31.1		0-45.83	0-22.88			0–26	
Oocytes cryopreserved ^a	9.7	10.0	0.81	10.6	8.97	0.067	10.4	9.1	0.252
Range	0-40	1-27		0-40	0-24		0-40	0–28	
Fertilization rate (%) ^b	0.64	0.63	0.89	0.66	0.62	0.276	0.69	0.60	0.28
Embryos cryopreserved ^b	4.0	5.3	0.075	4.75	4.78	0.922	5.5	3.0	0.003
Range	0-11	0-29		0–16	0-29		0-11	0–9	



WIDER IMPLICATIONS OF THE FINDINGS:

The results of our study support the premise that recently introduced potential improvements to COS-protocols for FP in women with BC are efficacious and safe Marklund et al., Human Reprod 2020



Research

JAMA Oncology | Original Investigation

Reproductive Outcomes After Breast Cancer in Women With vs Without Fertility Preservation

Anna Marklund, MD; Frida E. Lundberg, PhD; Sandra Eloranta, PhD; Elham Hedayati, MD, PhD; Karin Pettersson, MD, PhD; Kenny A. Rodriguez-Wallberg, MD, PhD

Nov 17 2020

Fertility preservation was effective and safe





Johansen et al. BMC Cancer (2020) 20:1009 https://doi.org/10.1186/s12885-020-07511-y

BMC Cancer

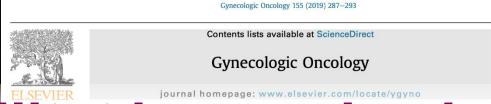
RESEARCH ARTICLE

Open Access

A Swedish Nationwide prospective study of oncological and reproductive outcome following fertility-sparing surgery for treatment of early stage epithelial ovarian cancer in young women

Gry Johansen^{1,2}, Pernilla Dahm-Kähler^{3,4}, Christian Staf⁶, Angelique Flöter Rådestad⁶ and Kenny A. Rodriquez-Wallberg^{1,7*}

Fertilitetssparande kirurgi vid äggstockscancer hos unga kvinnor?



Naturlig fertilitet bevarad och inga skillnader i överlevnad

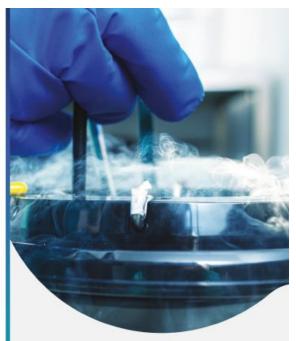
European Society of Human Reproduction and Embryology





w.eshre.eu/guidelin





Female Fertility Preservation

Guideline of the European Society of Human Reproduction and Embryology

2020

ESHRE Female Fertility Preservation Guideline Development Group



78 recommendations:

- Organization of care
- Information provision and support
- Pre-FP assessment
- FP interventions
- After treatment care
- Ongoing developments



Guideline group on Female Fertility Preservation

K. Rodriguez-Wallberg

























