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Fertility Preservation in South Africa

Dr Chris Venter
Reproductive Medicine Specialist

From a National Strategy to Clinical practice



Fertility Preservation





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” we should remember that
good fortune often happens
when opportunity meets
with preparation ”

Thomas A Edison



Fertility Preservation



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Why Fertility Preservation?

- Advancement in therapeutics and earlier detection of cancer has led to a 90 % survival rate in people with cancer in their reproductive years.
- Childhood cancer survivors increased from 10 to 90%.
- New advancements in vitrification technologies has improved the success rates of stored gametes.
- ASCO and ESMO, Committee Guidelines stipulate should be standard practice.
- Good evidence that fertility preservation gives hope, improves survivorship.
- Alternatives: Accept, egg donation, surrogacy or adopt.



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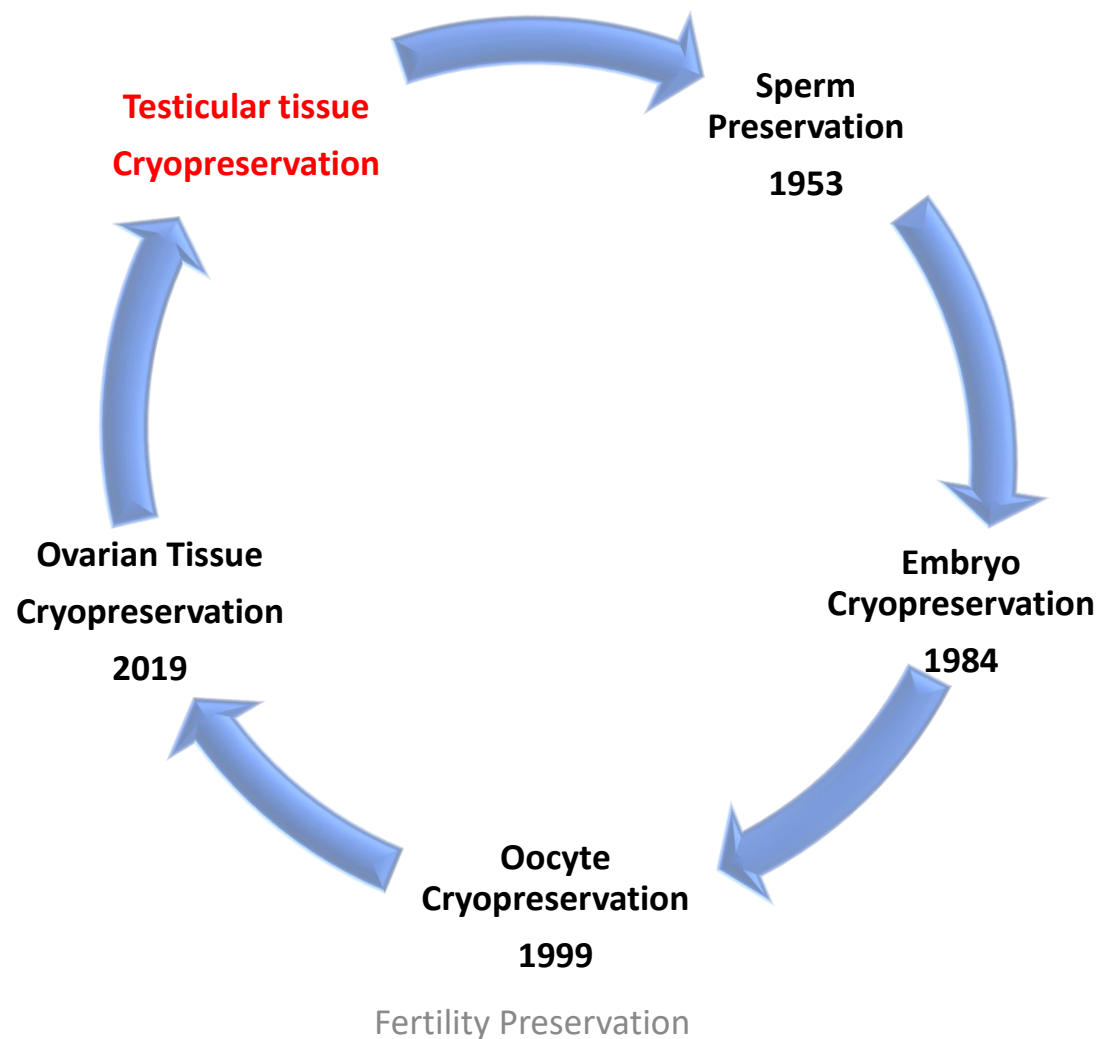
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Evolution of cryo-preservation





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Oncofertility Consortium Global Partners Network



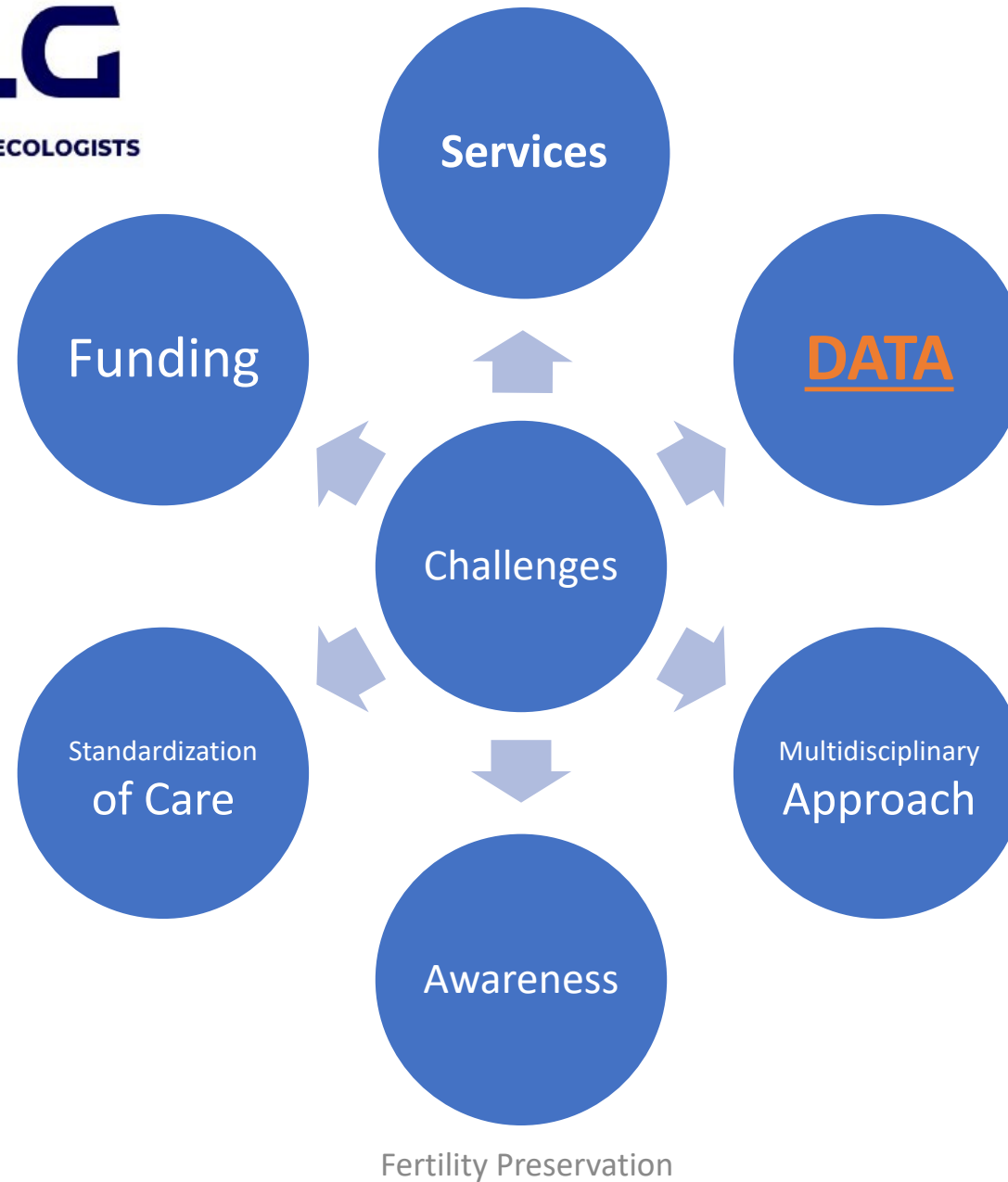
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Fertility Preservation



Data

- ANARA Registry

From 2018 includes FP

From 2021 includes extended FP: Male,
Female (OTC, Oocytes, Embryo)

- South African Cancer Registry

Female Cancers: 12- 40 Yr

2018





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South African Cancer Registry

Female (12-40yrs) - 2018	Nr
Bone	54
Brain, CNS	49
Breast	1258
Cervical	1494
Colorectal	161
Hodgkin lymphoma	152
Leukaemia	51
Melanoma	166
Non Hodgkin lymphoma	287
Ovary	84
Total	5278

ANARA Registry

2018 FP procedures

Only included Oocytes preservation

Cancer: 54

Risk of POI: 28

Social: 107

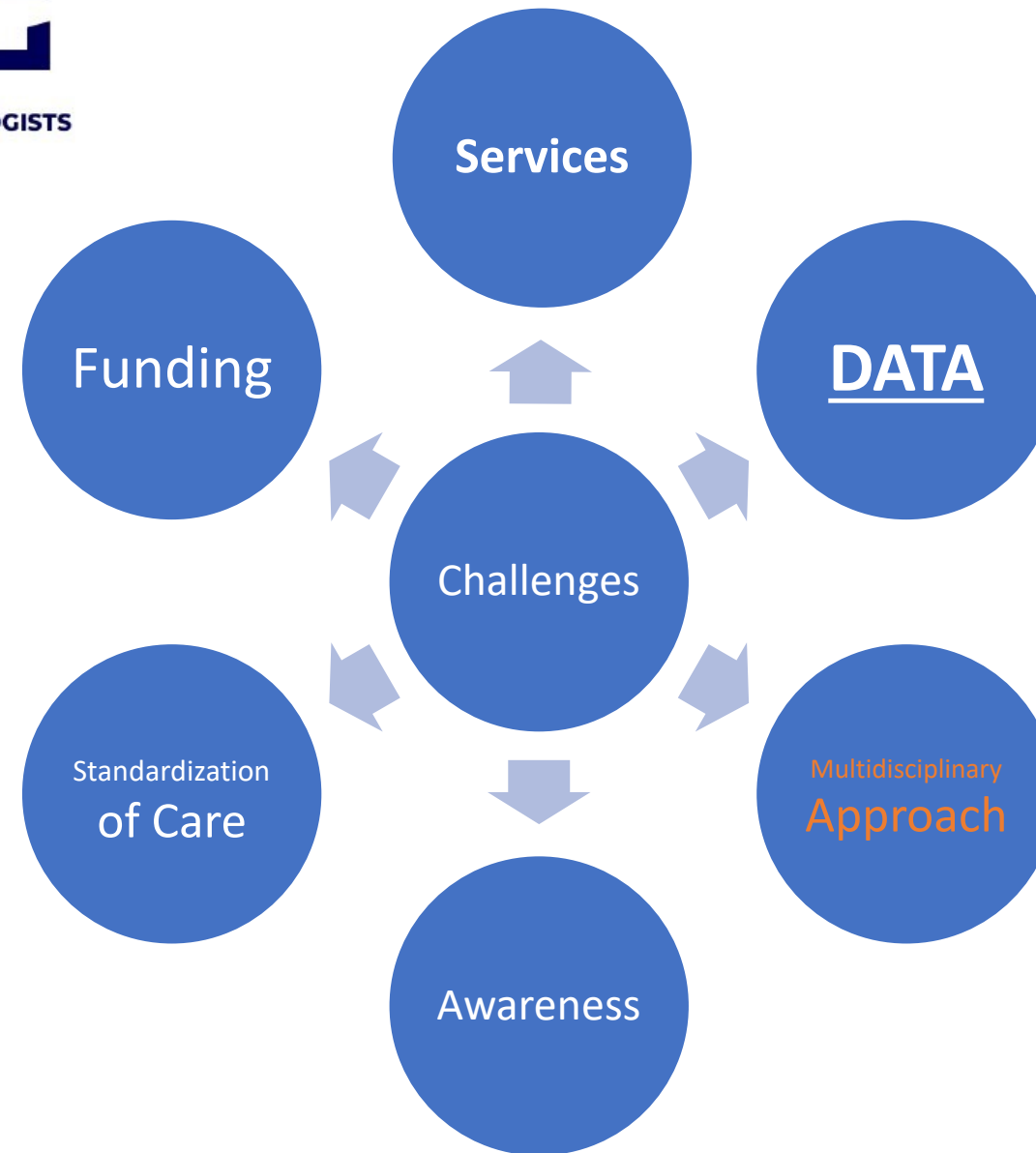
Total : 189

1 % All Cancer patients receives FP



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**Multi - Disciplinary
Approach**



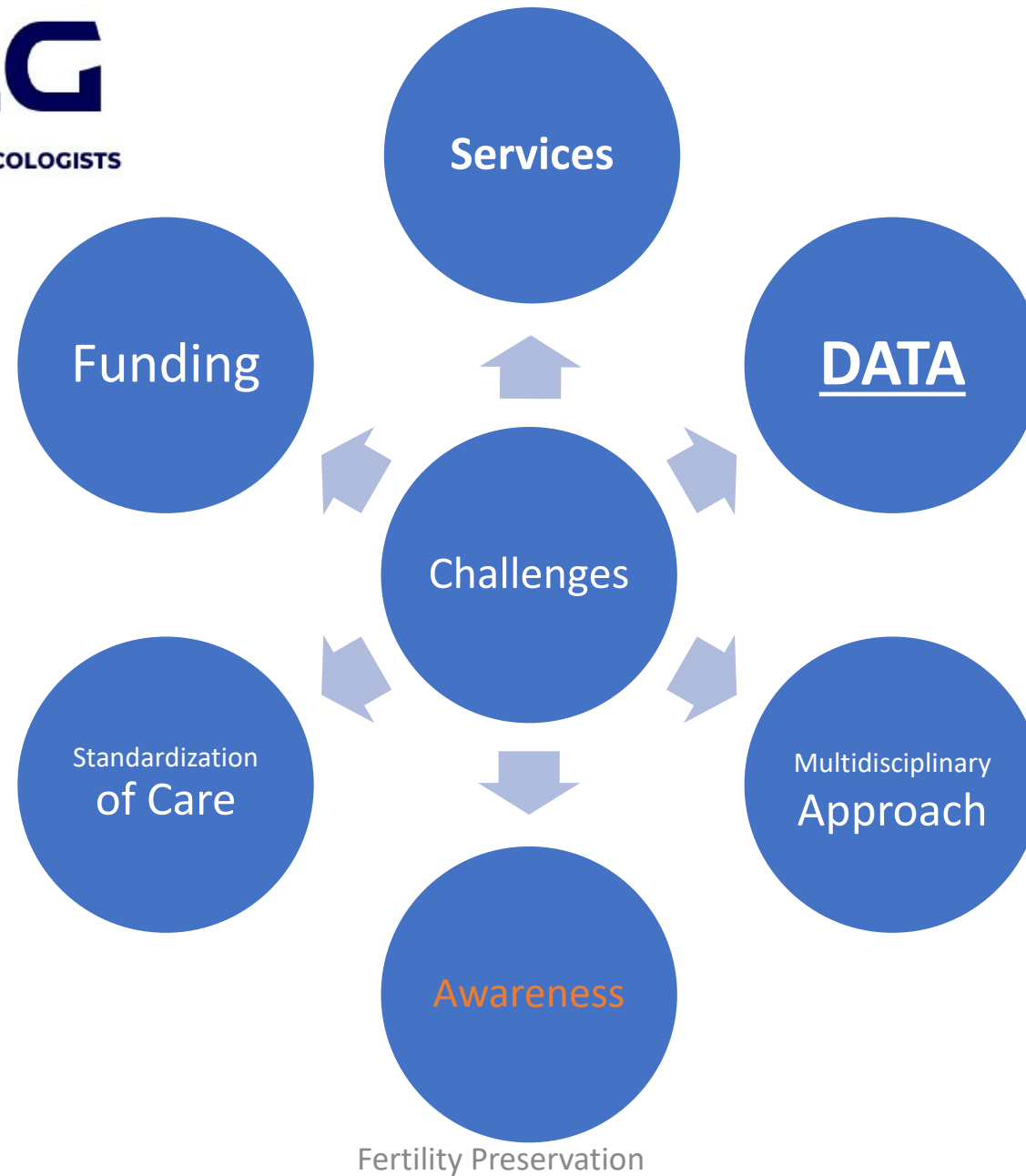
Fertility Preservation

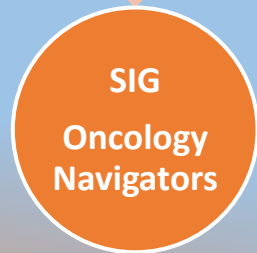
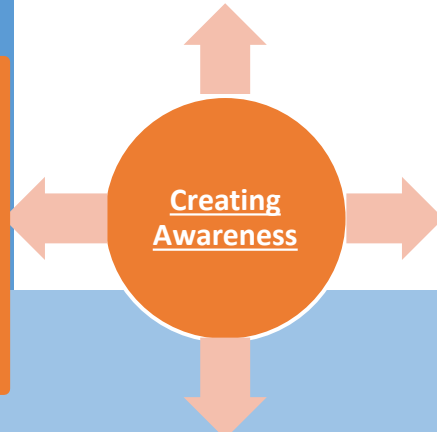
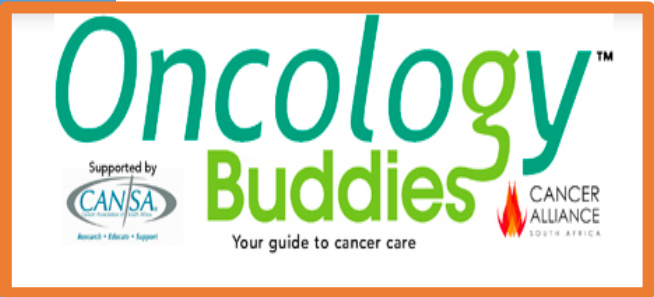




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Standardization of Care

- 3 are Required Operational Practice (ROP)

DEPARTMENT: Clinical Services		Section: Oncofertility
D.2.	Standard Name: Qualifications & Staff Structure: Oncofertility knowledge.	ROP: Yes
Standard Statement / Goal: The fertility specialist must understand the basic principles in fertility preservation specifically related to cancer diagnoses.		

DEPARTMENT: Clinical Services		Section: Oncofertility
D.3.	Standard Name: Processes & Procedures: Cryopreservation competency.	ROP: Yes
Standard Statement / Goal: The procedure of cryopreservation is an essential step in the preservation of a patient's fertility potential.		
Intent: Optimization of future clinical outcomes. Competency in cryopreservation techniques is essential to optimize the chances of achieving a future live birth.		

DEPARTMENT: Clinical Services		Section: Oncofertility
D.7.	Standard Name: Information, Communication & Feedback: Informed consent.	ROP: Yes
Standard Statement / Goal: Consent forms are essential in all Oncofertility procedures and the storage of specimens.		





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FUNDING

Currently out of pocket: reduced fees

15 % population on private health care

85 % in public: fertility care not easily accessible

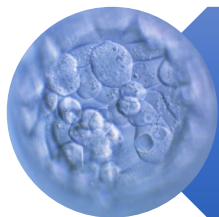
Major Health Care Funder: 2022

Based on following principles:

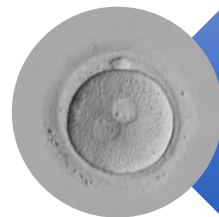
- Need accreditation process - Quality Control
- Need to have accurate data

Others will follow ?

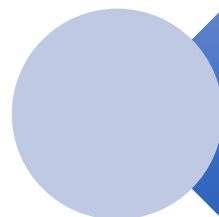
Case Studies



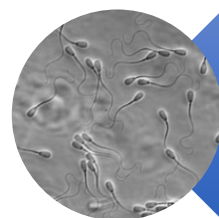
27 yr old female estrogen Positive Breast Cancer



32 yr old Female with Idiopathic Diminished Ovarian reserve



8 yr old Female with Acute Lymphoblastic leukemia



27 yr old Male with Testicular Cancer

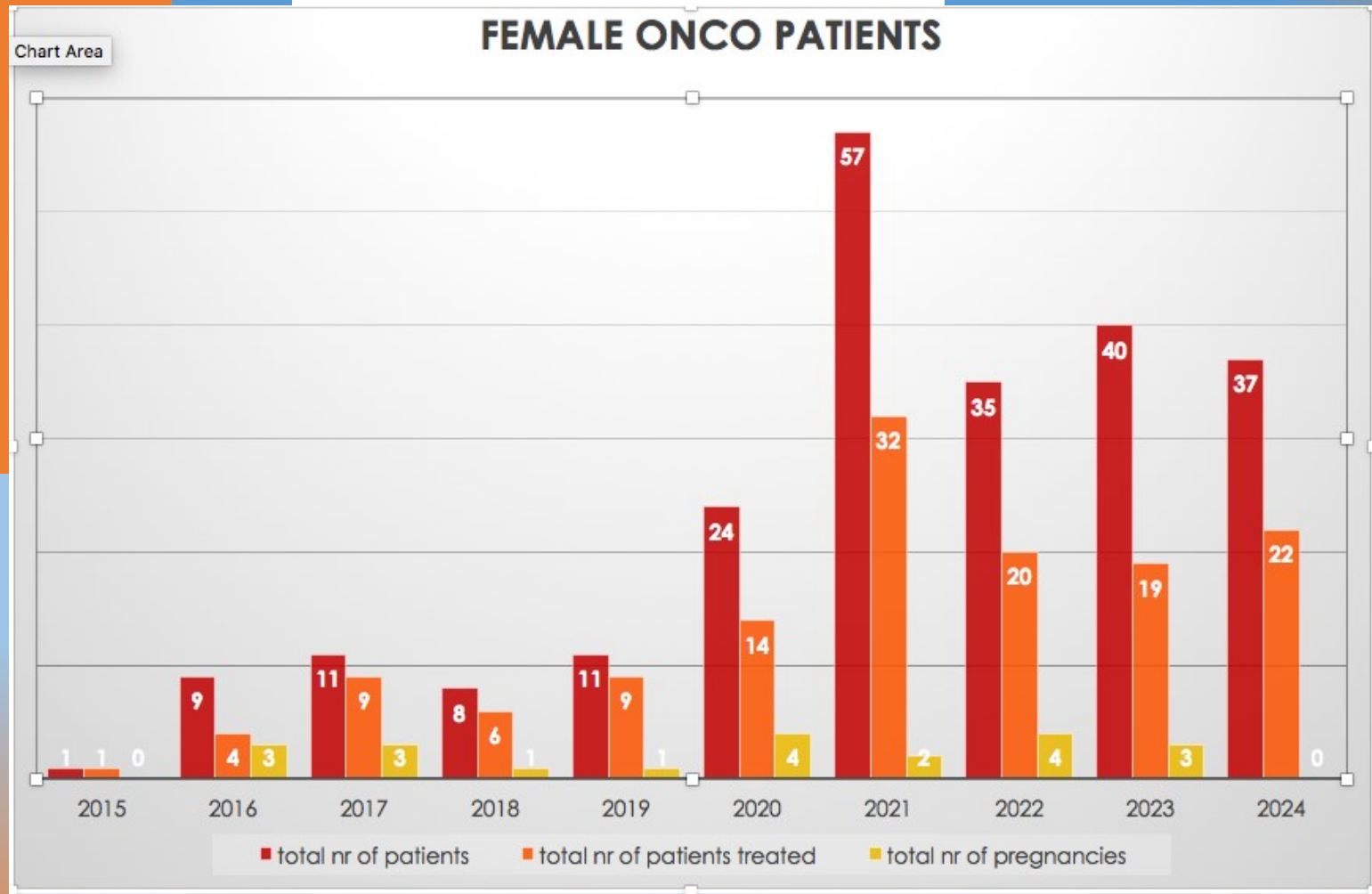
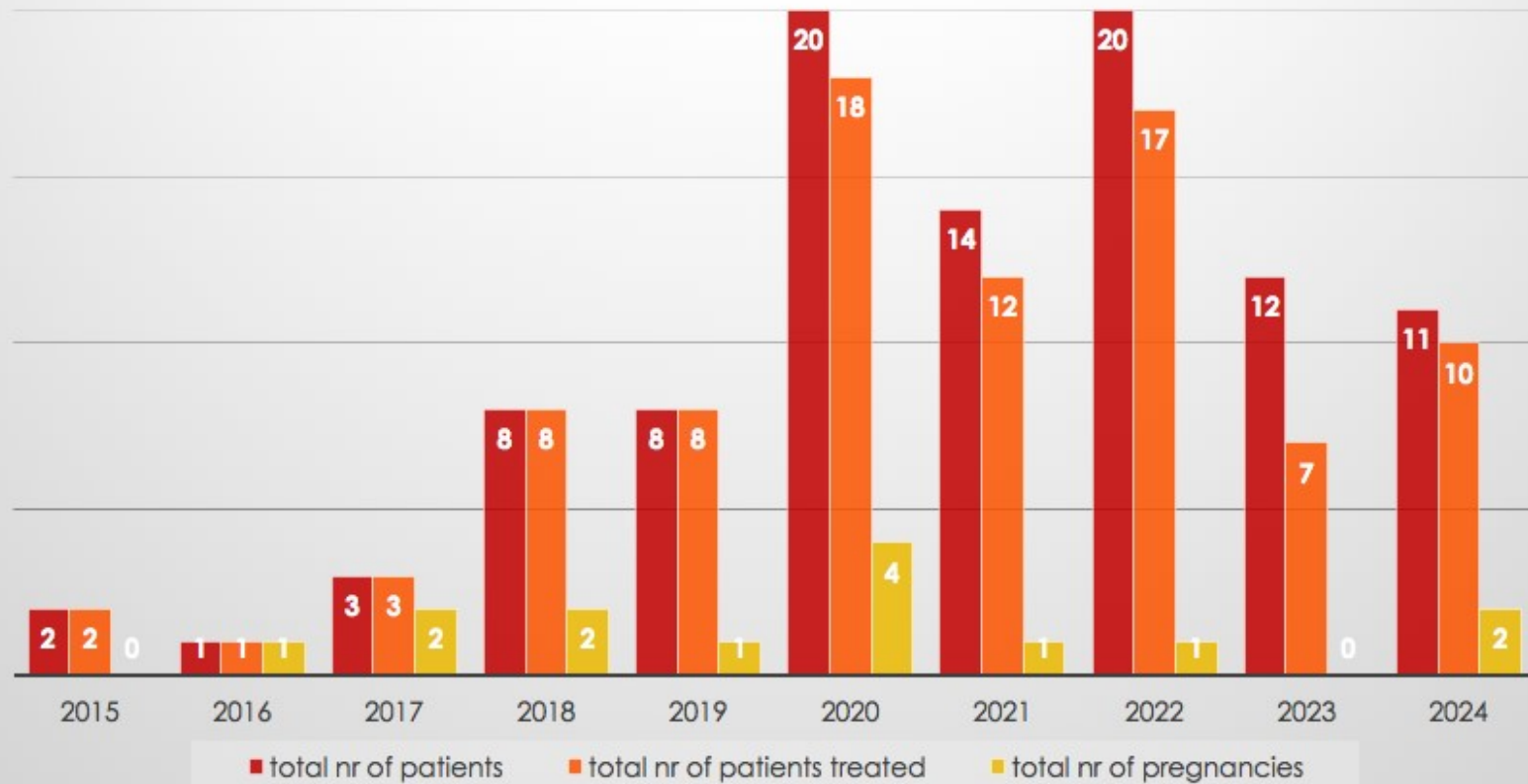


Chart Area

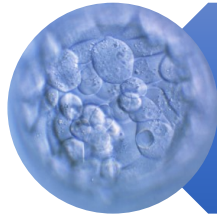
MALE ONCO PATIENTS



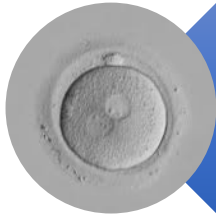


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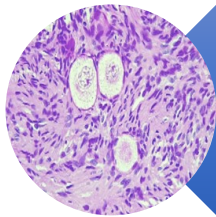
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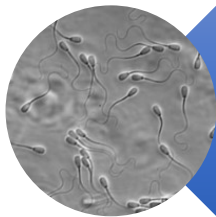
27 yr old female estrogen Positive Breast Cancer



32 yr old Female with Idiopathic Diminished Ovarian reserve



8 yr old Female with Acute Lymphoblastic leukemia



27 yr old Male with Testicular Cancer

Case study 1

- 36 yr old P1G1
- Referred from Oncologist with Stage 3C
- ESTROGEN Positive Breast cancer
- Treatment proposed

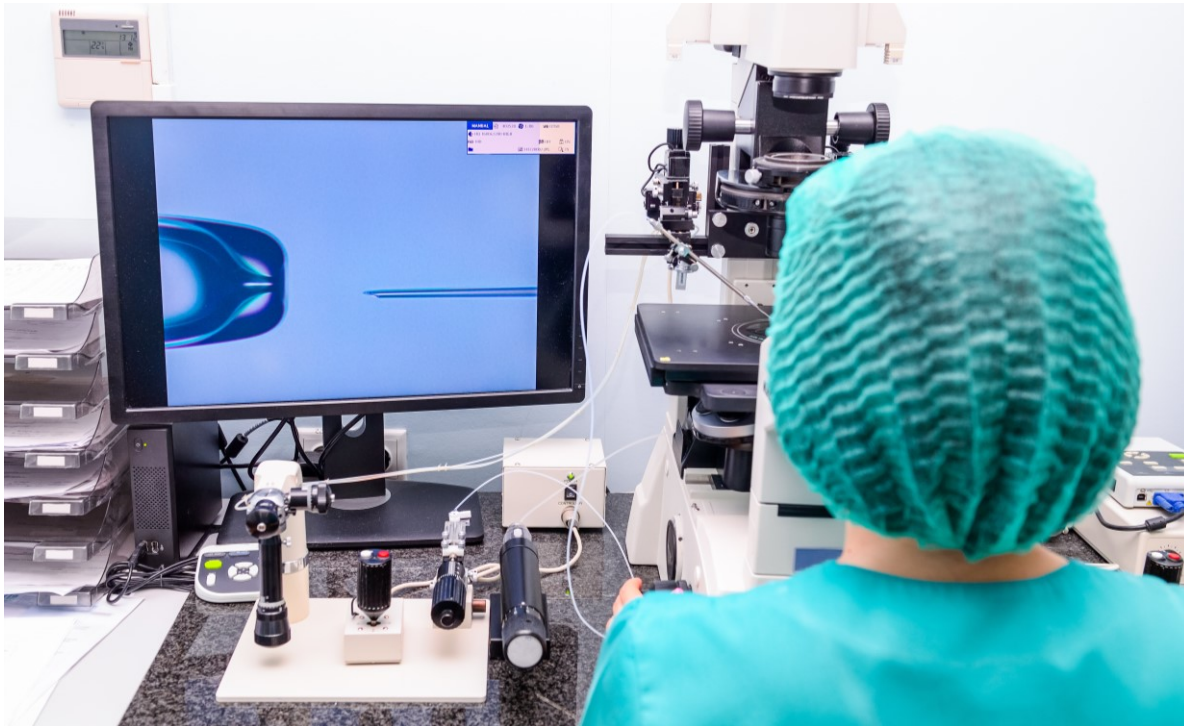
Bilateral mastectomy and node dissection

Adjuvant Chemotherapy



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Current fertility status

Gonadotoxic risk of
Chemo regime

Risk of Cancer treatment
to Fertility

Risk Fertility preservation
to disease progression

Financial Burden

Fertility Preservation



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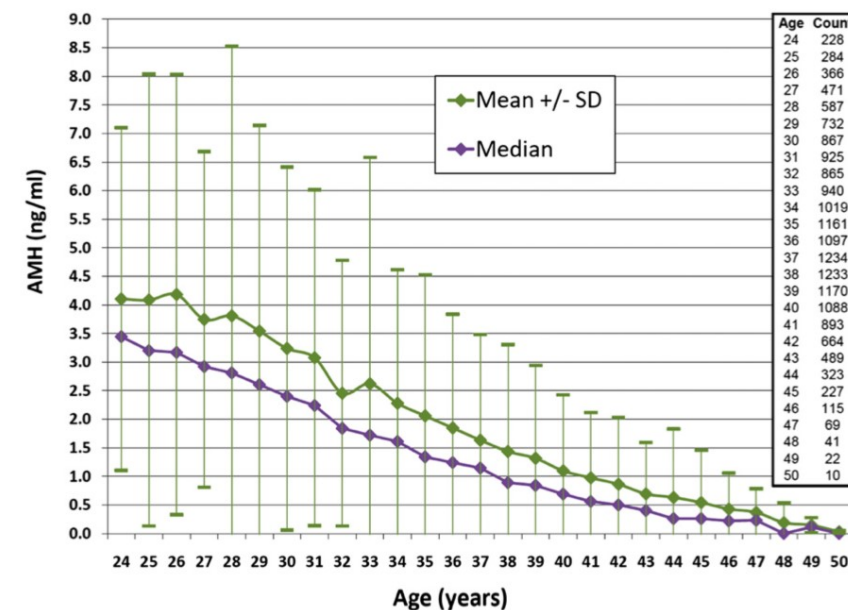
Current fertility reserve



- ESHRE guideline: female fertility preservation
- AMH (anti müllerian hormone)
- Antral Follicle Count

Human Reproduction 2020.

Fertility Preservation



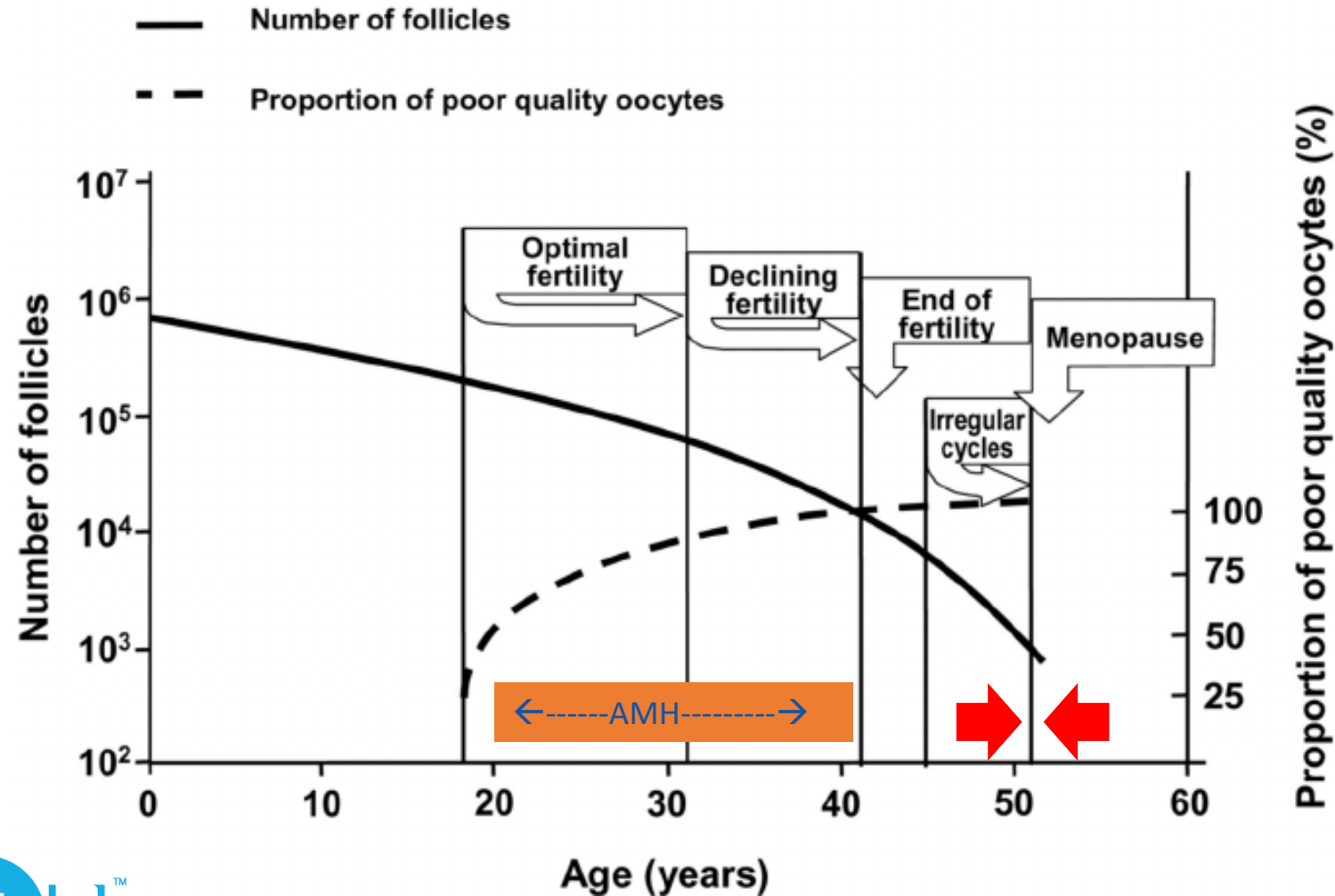
Seifer. Age-specific AMH values for U.S. clinics. Fertil Steril 2011.



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New Biomarkers



AMH

- Poor predictor of short-term chance to conceive
- Good predictor of the age of menopause
- Good predictor of reproductive lifespan



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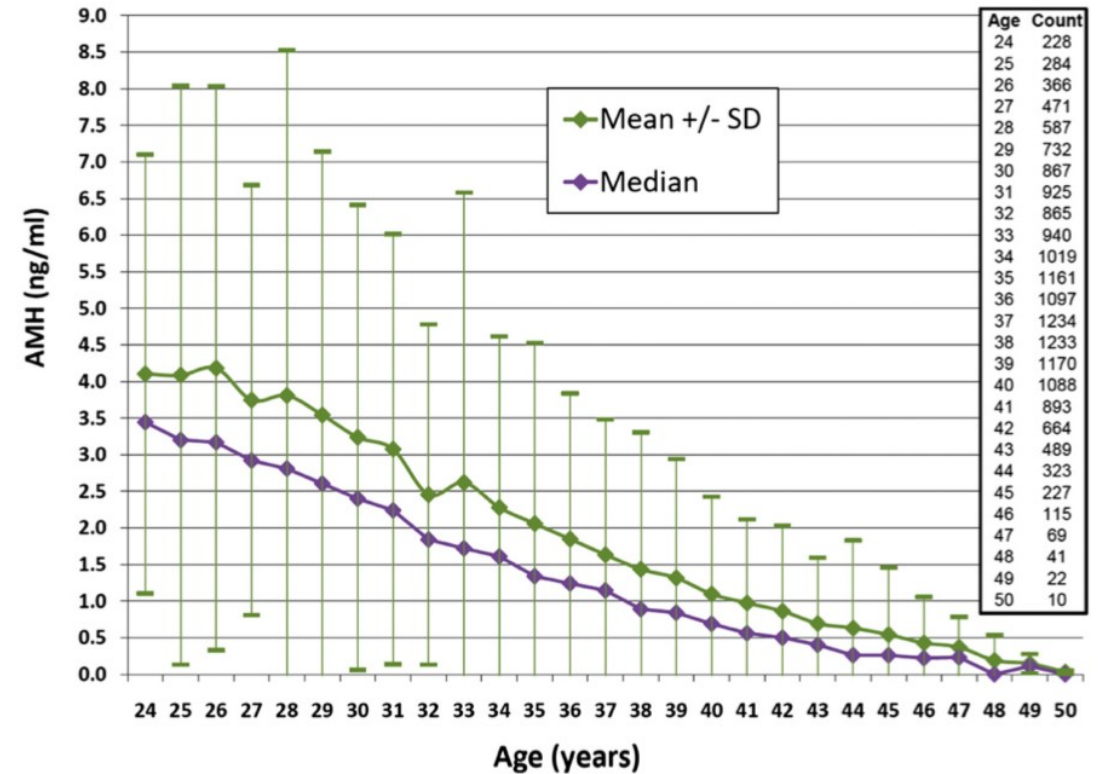
Current fertility reserve

AMH = 0,8

Antral Follicle Count = 5



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Seifer. Age-specific AMH values for U.S. clinics. Fertil Steril 2011.

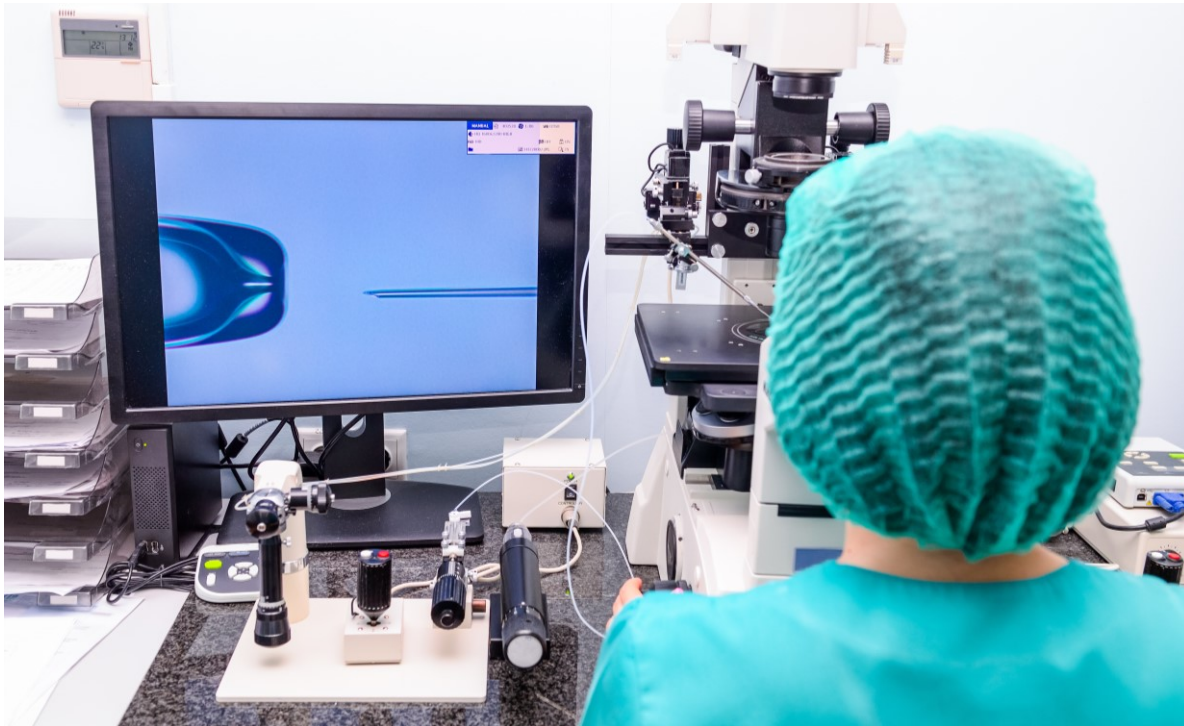


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Current fertility status

Gonadotoxic risk of
Chemo regime

Risk of Cancer
treatment to Fertility

Risk Fertility preservation
to disease progression

Financial Burden

Fertility Preservation



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Gonadotoxic risk of Chemo regime



SPECIAL ARTICLE

Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines[†]

M. Lambertini^{1,2}, F. A. Peccatori³, I. Demeestere⁴, F. Amant^{5,6}, C. Wyns⁷, J.-B. Stukenborg⁸, S. Paluch-Shimon⁹, M. J. Halaska¹⁰, C. Uzan¹¹, J. Meissner¹², M. von Wolff¹³, R. A. Anderson¹⁴ & K. Jordan¹², on behalf of the ESMO Guidelines Committee*



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Table 3. Risks of treatment-related amenorrhoea in female patients^a

Degree of risk	Treatment type/regimen	Comments
High risk (>80%)	Haematopoietic stem cell transplantation (especially alkylating agent-based myeloablative conditioning with cyclophosphamide, busulfan, melphalan or total body RT)	
	EBRT >6 Gy to a field including the ovaries	
	6 cycles of CMF, CEF, CAF or TAC in women of ≥40 years	Significant decline in AMH levels after treatment Early menopause
	6–8 cycles of escalated BEACOPP in women of ≥30 years	Significant decline in AMH levels after treatment Early menopause
Intermediate risk (20%–80%)	6 cycles of CMF, CEF, CAF or TAC in women of 30–39 years	Significant decline in AMH levels after treatment Early menopause
	4 cycles of AC in women of ≥40 years	Significant decline in AMH levels after treatment
	4 cycles of AC/EC → taxane	Significant decline in AMH levels after treatment
	4 cycles of dd (F)EC → dd taxane	
	6–8 cycles of escalated BEACOPP in women of <30 years	Significant decline in AMH levels after treatment
	6 cycles of CHOP in women of ≥35 years	Early menopause
	6 cycles of DA-EPOCH in women of ≥35 years	Significant decline in AMH levels after treatment
	FOLFOX in women of ≥40 years	
Low risk (<20%)	6 cycles of CMF, CEF, CAF or TAC in women of <30 years	Significant decline in AMH levels after treatment Early menopause
	4 cycles of AC in women of <40 years	Significant decline in AMH levels after treatment
	2 cycles of escalated BEACOPP	Significant decline in AMH levels after treatment
	ABVD	Insignificant decline in AMH levels after treatment
	6 cycles of CHOP in women of <35 years	Early menopause
	6 cycles of DA-EPOCH in women of <35 years	Significant decline in AMH levels after treatment
	AML therapy (anthracycline/cytarabine)	Insignificant decline in AMH levels after treatment
	ALL therapy (multi-agent)	Insignificant decline in AMH levels after treatment
	Multi-agent ChT for osteosarcoma (doxorubicin, cisplatin, methotrexate, ifosfamide) in women of <35 years	
	Multi-agent ChT for Ewing's sarcoma (doxorubicin, vincristine, dactinomycin, cyclophosphamide, ifosfamide, etoposide) in women of <35 years	
	FOLFOX in women of ≤40 years	
	Antimetabolites and vinca alkaloids	
	BEP or EP in women of <30 years	
	Radioactive iodine (I-131)	Decline in AMH levels after treatment
	Bevacizumab	
Unknown risk	Platinum- and taxane-based ChT	
	Most targeted therapies (including monoclonal antibodies and small molecules)	
	Immunotherapy	

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AC, doxorubicin, cyclophosphamide; ALL, acute lymphoid leukaemia; AMH, anti-Müllerian hormone; AML, acute myeloid leukaemia; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine; BEP, bleomycin, etoposide, cisplatin; CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ChT, chemotherapy; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; DA-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; dd, dose dense; EBRT, external beam radiotherapy; EC, epirubicin, cyclophosphamide; EP, etoposide, cisplatin; F, fluorouracil; FOLFOX, folinic acid, 5-fluorouracil, oxaliplatin; Gy, Gray; RT, radiotherapy; TAC, docetaxel, doxorubicin, cyclophosphamide.

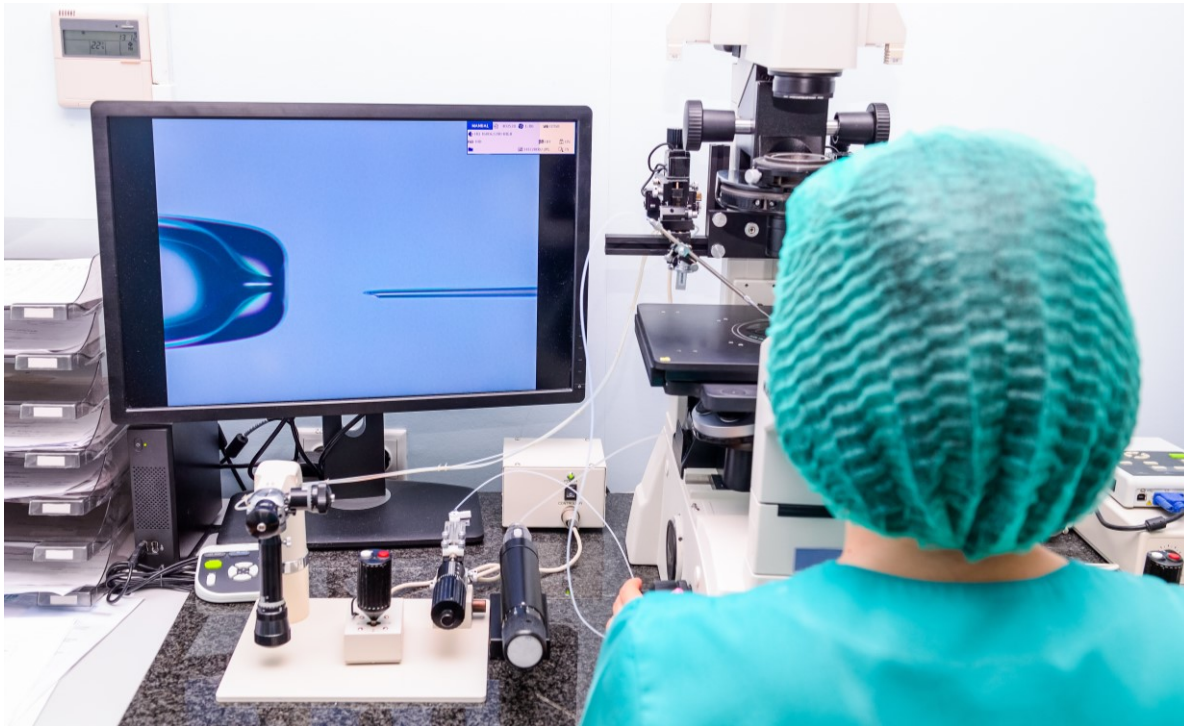
^a Adapted from Lee et al.¹⁰ Table contains examples and is not a complete list.





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Current fertility status

Gonadotoxic risk of
Chemo regime

Risk of Cancer treatment
to Fertility

Risk Fertility preservation
to disease progression

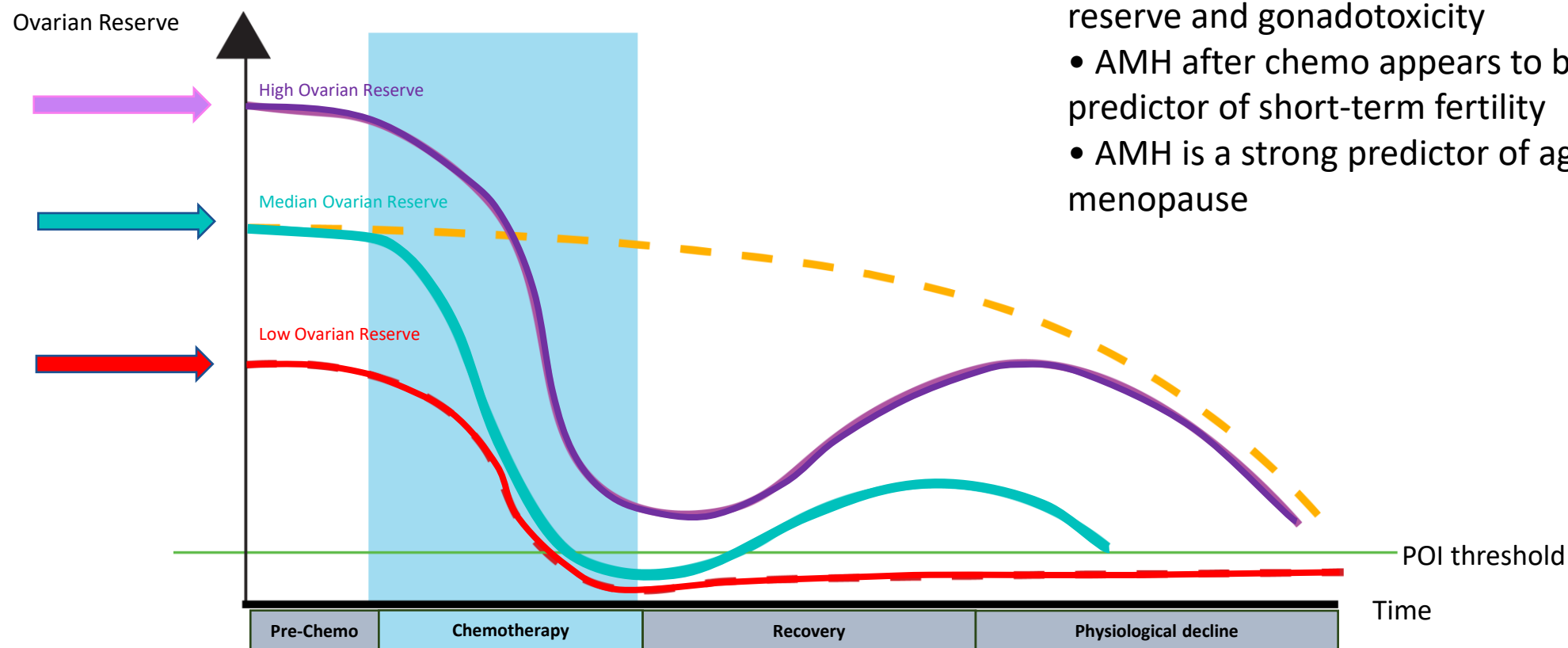
Financial Burden

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Infertility related to follicle depletion in cancer patients

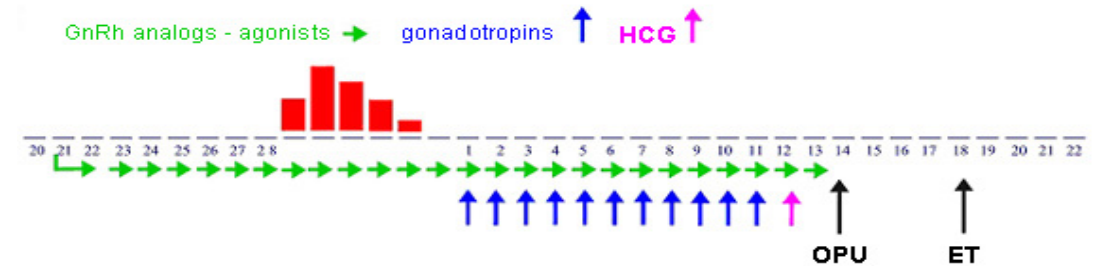


- Recovery depends on age, ovarian reserve and gonadotoxicity
- AMH after chemo appears to be a weak predictor of short-term fertility
- AMH is a strong predictor of age at menopause



Case study 1 Management

- Random start stimulation



- Reproductive Outcome:
 - 15 met II oocytes, 9 fert , 2 X Blastocysts
 - Trophectoderm Biopsy
 - 2/2 euploid
 - Potential to test for BRCA-gene mutation

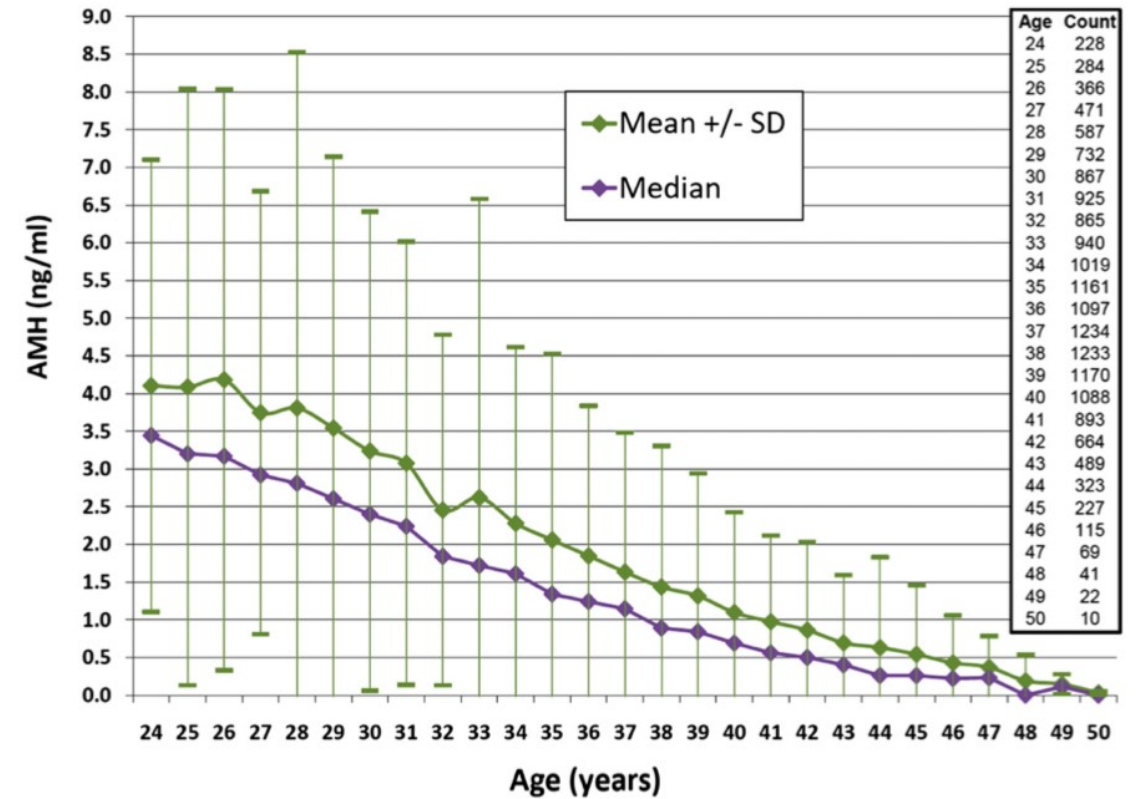


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Post chemo

- 3 YEARS LATER
- AMH= <0,01
- FSH =20



Seifer. Age-specific AMH values for U.S. clinics. Fertil Steril 2011.

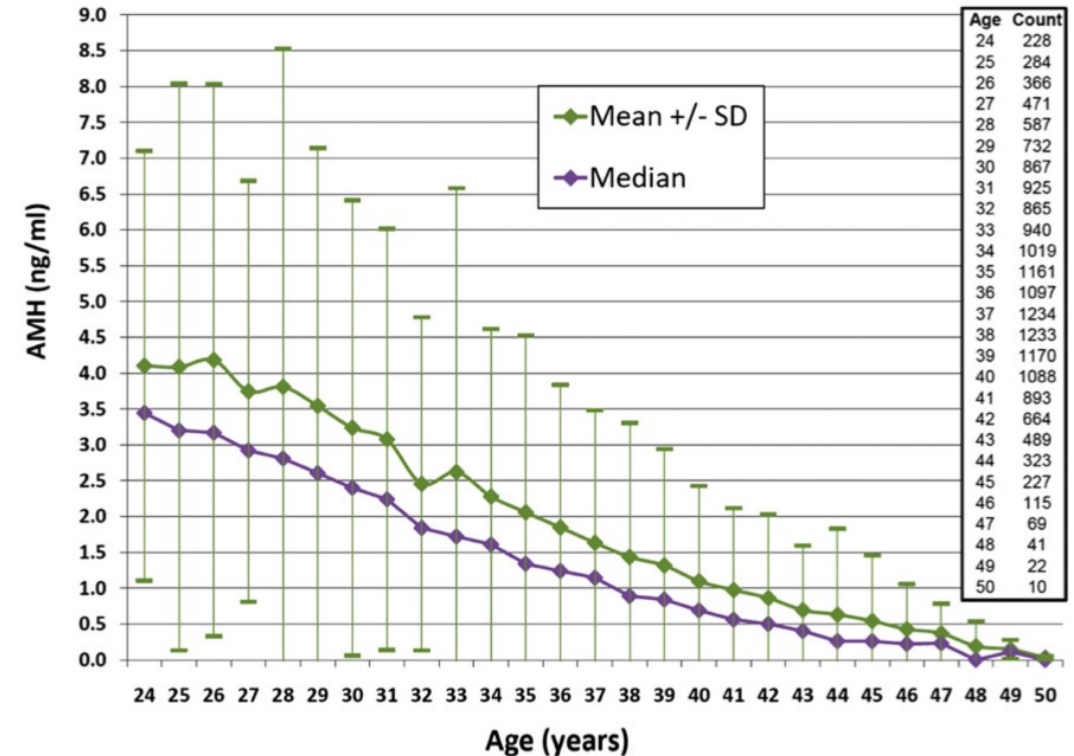


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Case study 2

- 34 yr old single female present for a fertility check
- Considering Elective egg freezing
- AFC = 3+2 : AMH = 0,7
- No risk factors for DOR.
- **Premature Ovarian aging**
- Strongly Recommended →
- Oocyte Cryopreservation



Seifer. Age-specific AMH values for U.S. clinics. Fertil Steril 2011.

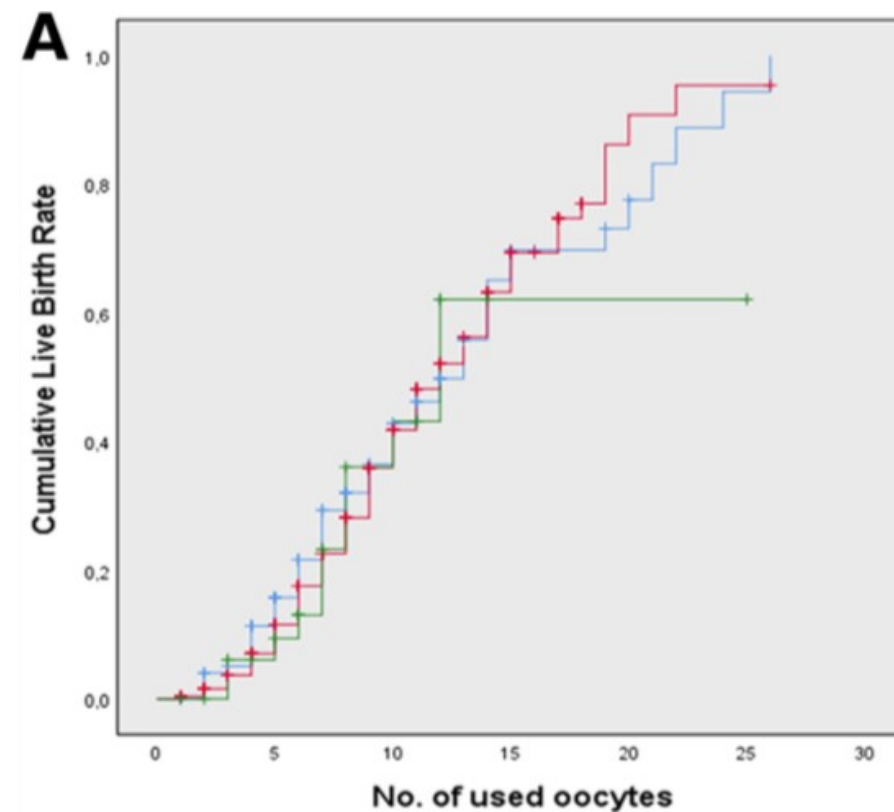
What are the quality of
my oocytes?

AND

- How many oocytes do I need?

Quality of my oocytes?

- Determined by age and Number of oocytes.
 - Cobo et al. Fertility and Sterility 2021
- Younger than 35 Yrs
- Confounding factors
 - Cancer
 - Endometriosis





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Oocyte vitrification for fertility preservation for both medical and nonmedical reasons

Ana Cobo, Ph.D.,^a Juan Antonio García-Velasco, M.D.,^b José Remohí, M.D.,^a and Antonio Pellicer, M.D.^a

^a IVIRMA Valencia, Valencia, Spain, and ^b IVIRMA Madrid and Universidad Rey Juan Carlos, Madrid, Spain

*Fertility and Sterility® Vol. 115, No. 5, May 2021



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Cumulative Live Birth rate and nr of embryos Younger than 35 yrs

EFP	
n = 123	
No. of oocytes	CLBR (95% CI)
3	5.1 (0.7–9.4)
5	15.8 (8.4–23.1)
8	32.0 (22.1–41.9)
10	42.8 (31.7–53.9)
15	69.8 (57.4–82.2)
20	77.6 (64.4–90.9)
24	94.4 (84.3–100.4)

4

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18

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Case study 2 outcome

- 39 yr
- Husband: normal semen analysis
- AMH= 0,03
- Irregular menstrual cycles
- ICSI: 18 oocytes → Fertilized → 4x day 5 blastocyst → 2 blast transferred → 2 PGT-a
- Conceived → singleton pregnancy-
→ Delivered a healthy boy



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Case study 3

- 8 yr old female
- Referred from Oncologist with Acute Lymphoblastic Leukemia
- She had Induction chemo
- Now in remission
- Work up for Miëlo-ablative Chemo
- Very High Risk for becoming Sterile





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Ovarian Tissue Cryopreservation

- Indicated in cancers where there NO time in delaying chemotherapy (ALL)
- Can be performed immediately without delaying start of oncology treatment
- Only proven fertility preservation option in prepubertal females
- - However**
 - Could potentially re-transplant cancer cells.
 - Still regarded as EXPERIMENTAL in South Africa and the US and if patients do opt for this option it should be done under full consent stating the experimental nature of this procedure



Fertility Preservation

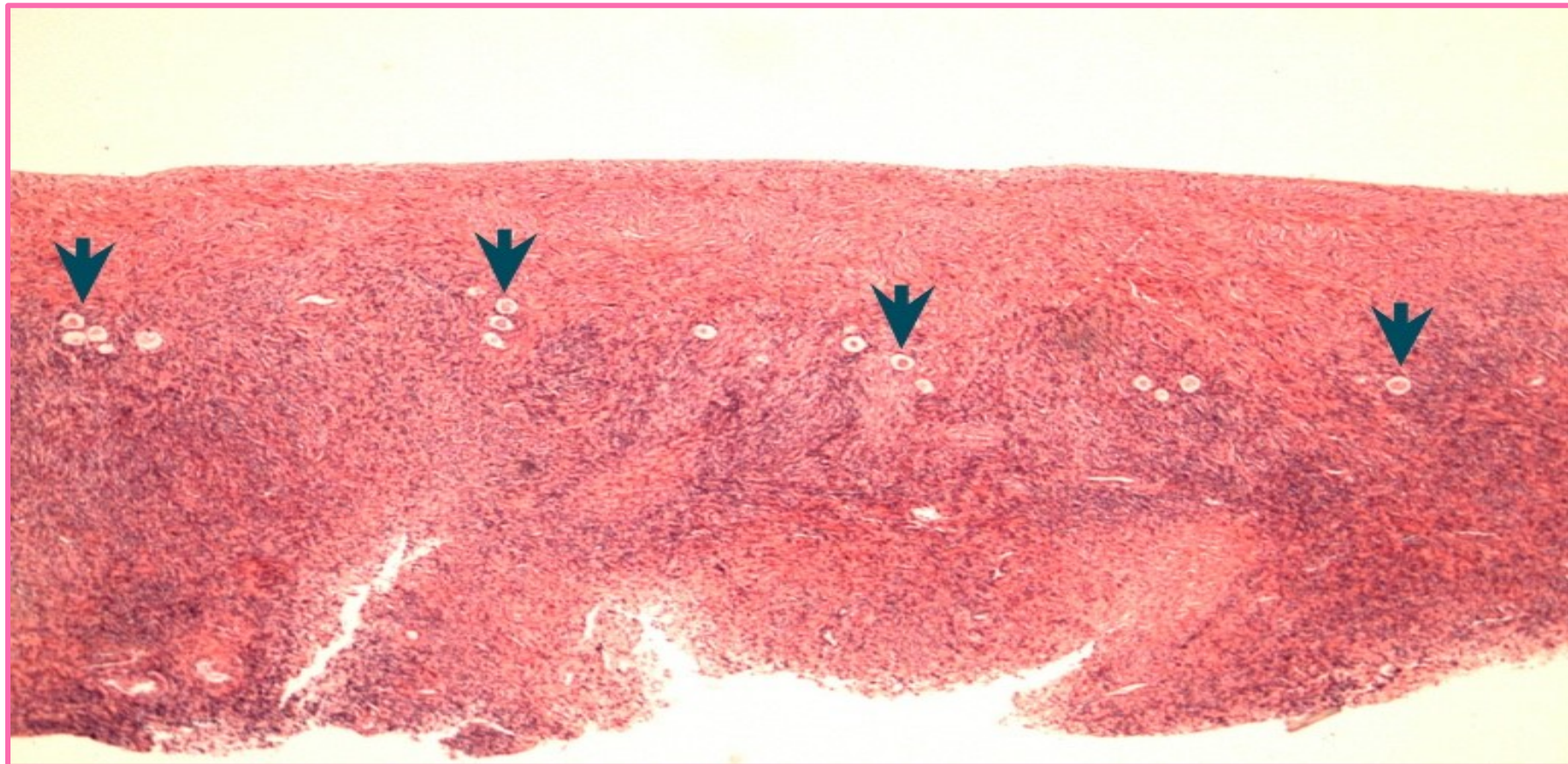




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Ovarian Cortex



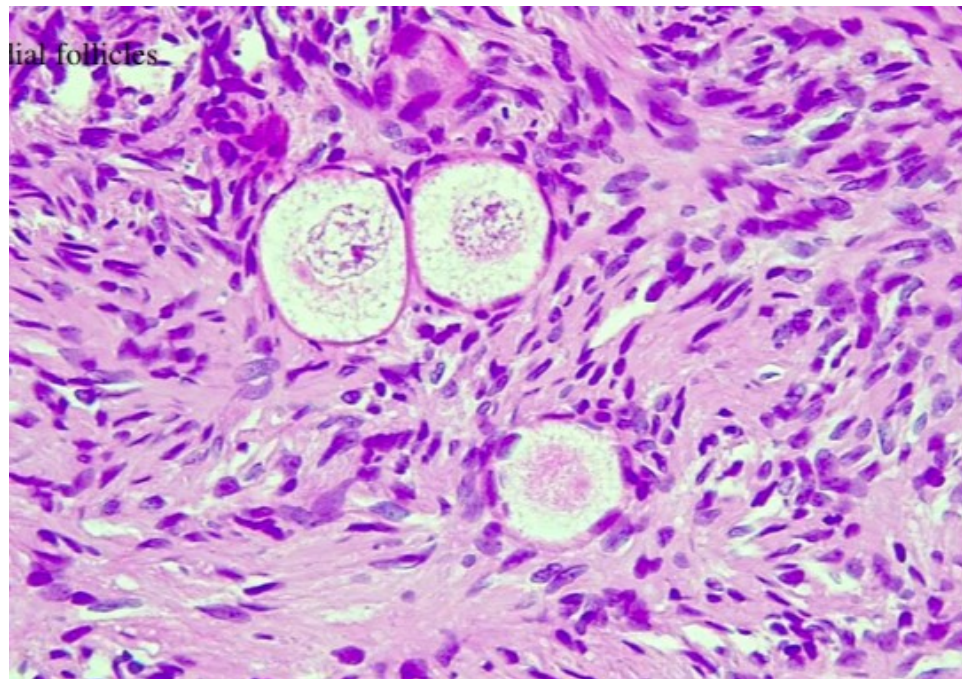
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Ovarian Tissue Cryopreservation

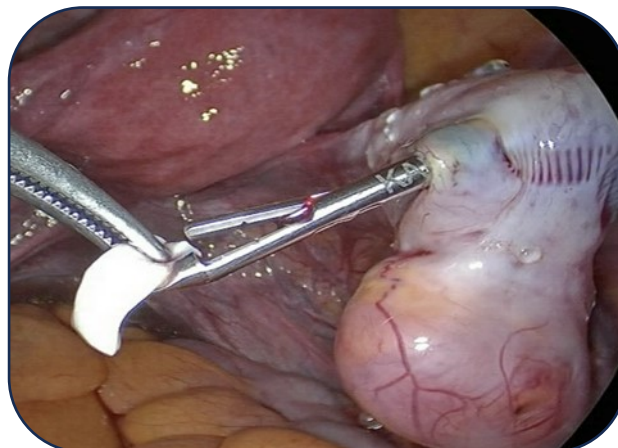
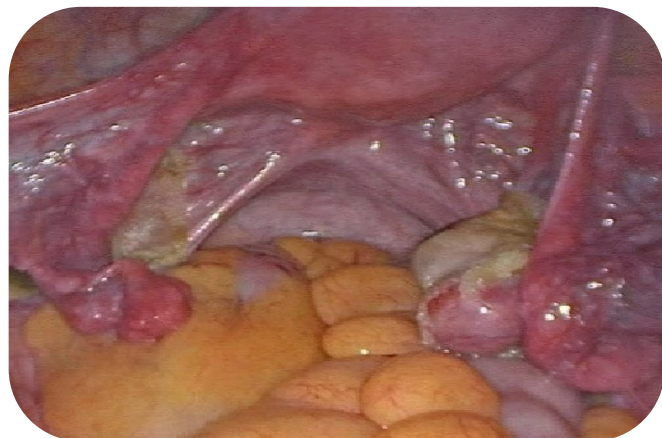
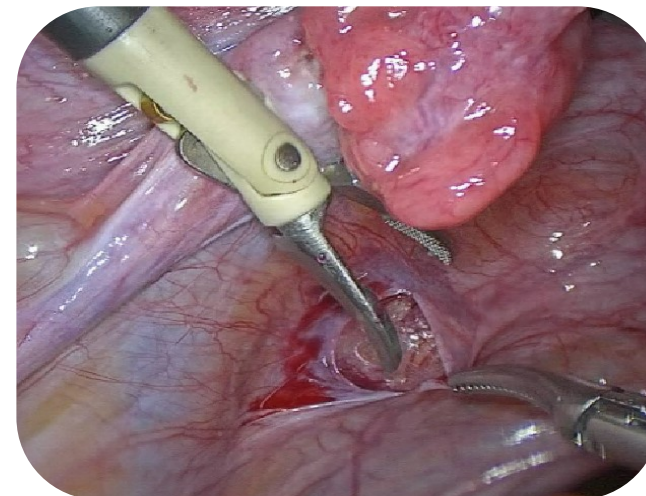
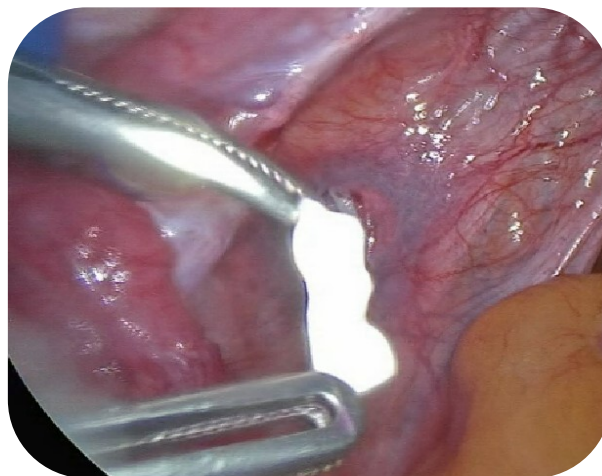
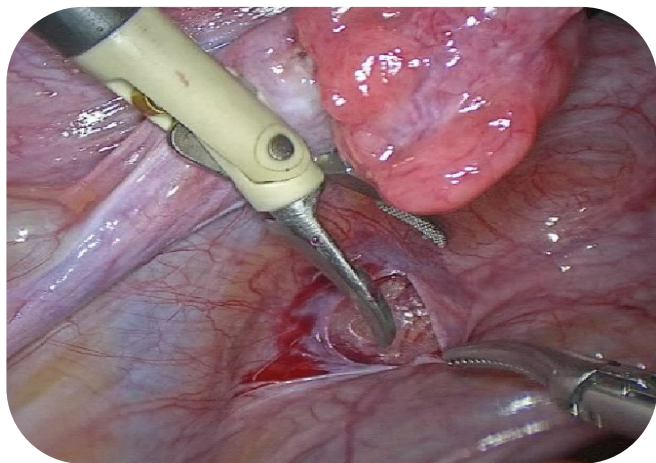


75 PRIMORDIAL FOLLICLES PER HPF



- One ovary dissected
- 14 ovarian strips

Orthotopic Autologous Re-implantation of ovarian Tissue



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Oocyte vitrification versus ovarian cortex transplantation in fertility preservation for adult women undergoing gonadotoxic treatments: a prospective cohort study

Cesar Diaz-Garcia, M.D.,^{a,b,c} Javier Domingo, M.D.,^d Juan Antonio Garcia-Velasco, M.D.,^{e,f}
Sonia Herraiz, Ph.D.,^{b,g} Vicente Mirabet, Ph.D.,^h Ignacio Iniesta, B.Sc.,^b Ana Cobo, Ph.D.,ⁱ José Remohí, M.D.,^{c,j}
and Antonio Pellicer, M.D.^{b,c,j}

- Period 2005-2015
- 1025 OV vs 800 OTC
- Age 31,7 vs 28,2; Mean 5yrs before utilization, 7 % of patients.
- OV= 49 pt – 40,8 % PR : OTC= 44 pt – 33% of which 15 % achieved a spontaneous pregnancy.
-

Conclusion

Both methods effective in fertility preservation.



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Case study 4

27 yr old male

Self Referral ;

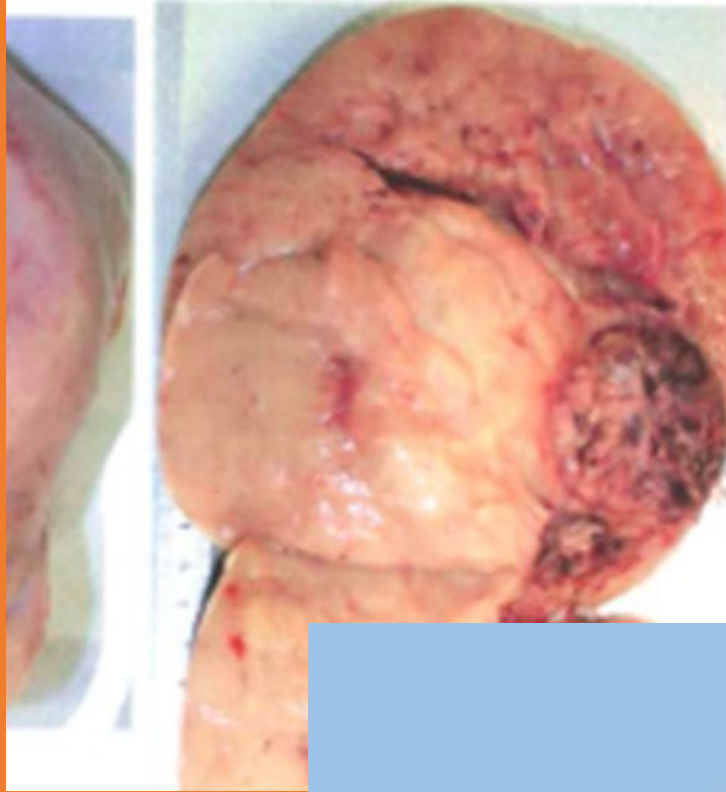
Orchidectomy as a newborn due
to embryological tumor

Now booked for Orchidectomy for
a **Right Testicular Germ Cell tumor**



Fertility Preservation





Case study 4 Management

- Bi-valve of the testis
- Occasional twitching and motile sperm observed
- 5 per HPF
- 5 vials stored



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Case study 4 Management

- Following Year – Married – ICSI
- 35 Oocyte retrieved
- 9 Embryos
- 5/9 Euploid
- Transfer in 2025



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Conclude

The Three arms of Oncofertility are:

- **Multidisciplinary team** approach

Cases are usually complex, and each case should be seen on its own merit

- **Altruism**
- **Inclusivity**
- Reproductive vitrification techniques has evolved and is effective
- We should actively counsel patients at risk
- There is still no guarantees to live birth, and that fertility preservation should be seen as an insurance to boost a patient's chances in achieving a biological child.

THANK YOU

Dr Chris Venter