

Ovarian tissue banking

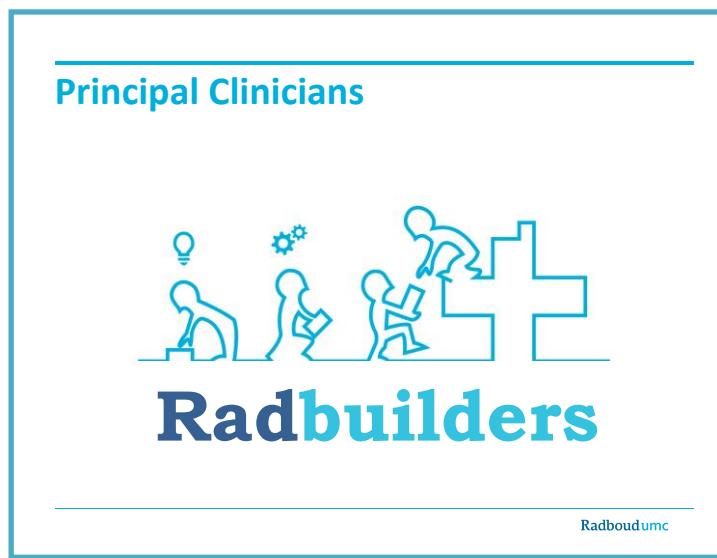
Ina Beerendonk, MD PhD, gynaecologist
Principal Clinician OncoFertility

*Radboud University Nijmegen Medical Centre,
Nijmegen, The Netherlands*

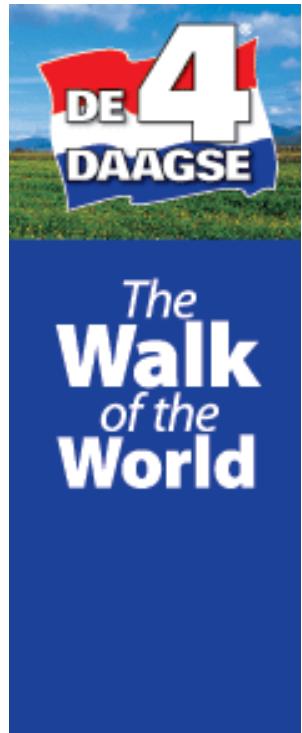


Tomas Schats

Declaration of COI



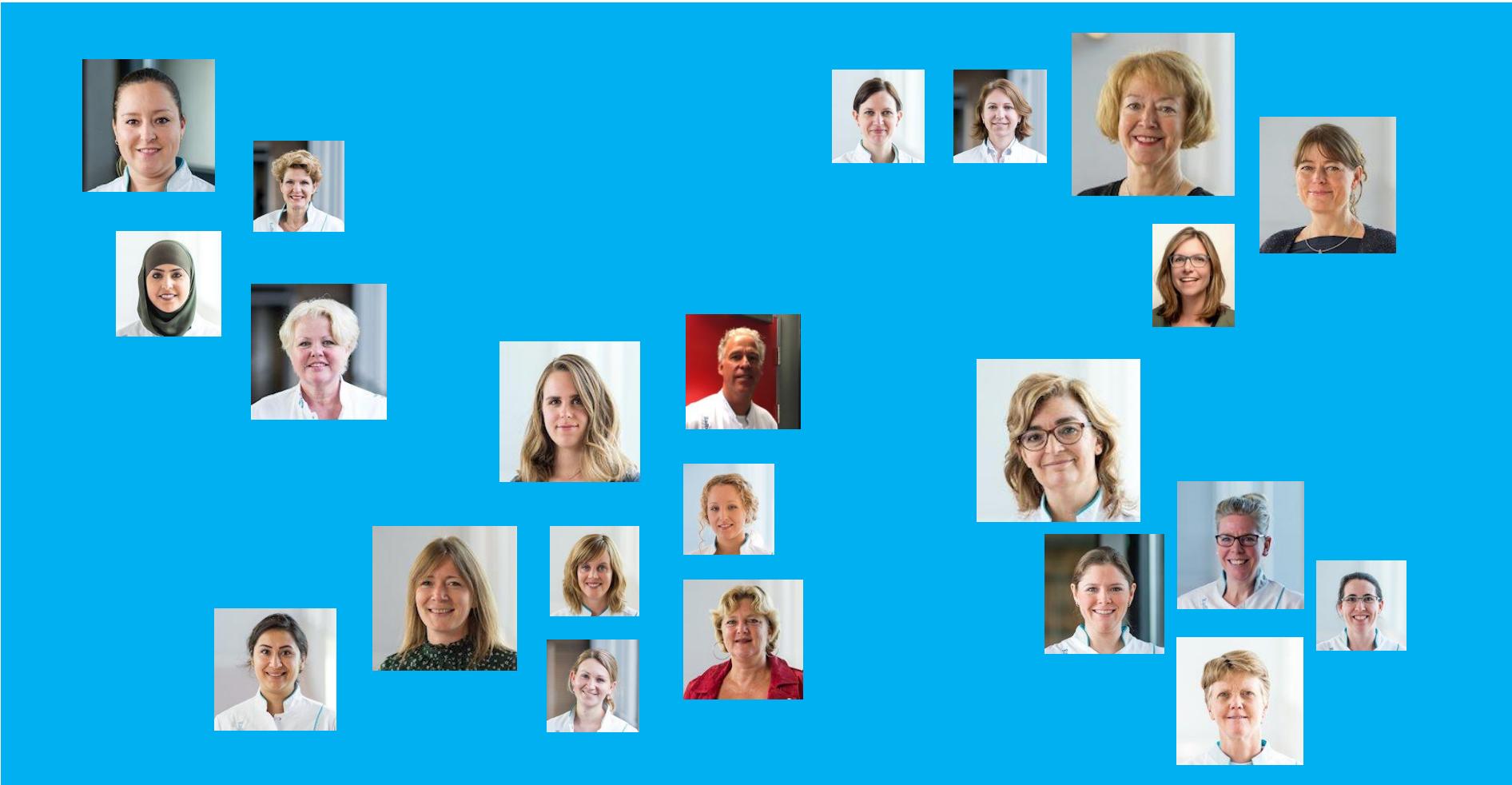






Radboudumc

Team Fertility Preservation



Simon Fishel interview: the man behind ovarian grafting

The news that a British clinic has developed a procedure that can delay the menopause for up to 20 years caused a media storm this month. Turns out the man at the centre of it, fertility expert Simon Fishel, knows all about controversy. Interview by Andrew Anthony



Professor Simon Fishel, 66, photographed at Care Fertility Birmingham
MARK HARRISON

Learning objectives

History

Indications

Obtaining ovarian tissue

Storage

Transplantation

Results

Risks and challenges

Quality assurance and control

History

Brussels april 2004



History

Eerste baby geboren na terugplaatsing eierstokweefsel

20 januari 2016 • PERSBERICHT

Eind 2015 is een vrouw bevallen van een baby die verwekt kon worden dankzij het terugplaatsen van ontdooid eierstokweefsel. De vrouw was onvruchtbaar geworden door een behandeling voor kanker. Dankzij de transplantatie kon zij toch weer zwanger worden. Deze innovatieve behandeling wordt in Nederland alleen in het Leids Universitair Medisch Centrum (LUMC) uitgevoerd en heeft nu voor het eerst geleid tot een doorgaande zwangerschap en de geboorte van een gezond kind.

Het eierstokweefsel werd bij de vrouw weggehaald voordat zij chemotherapie onderging. Artsen verwijderden één van haar eierstokken, waarvan de buitenschil met daarin onrijpe eicellen werd ingevroren. Ruim drie jaar later is het weefsel ontdooid en teruggeplaatst in de achtergebleven eierstok en onder het buikvlies. In het teruggeplaatste weefsel zijn vervolgens weer eicellen gaan rijpen, zegt Lucette van der Westerlaken, hoofd van het IVF-laboratorium van het LUMC. "De vrouw is daarna, met behulp van IVF, zwanger geworden. Na een normaal verlopen zwangerschap kwam in november haar kind ter wereld. Dat is uniek in Nederland, en wereldwijd zijn er pas zestig kinderen geboren na deze behandeling. Ruim 40 kinderen zijn geboren nadat de moeder is behandeld tegen kanker."

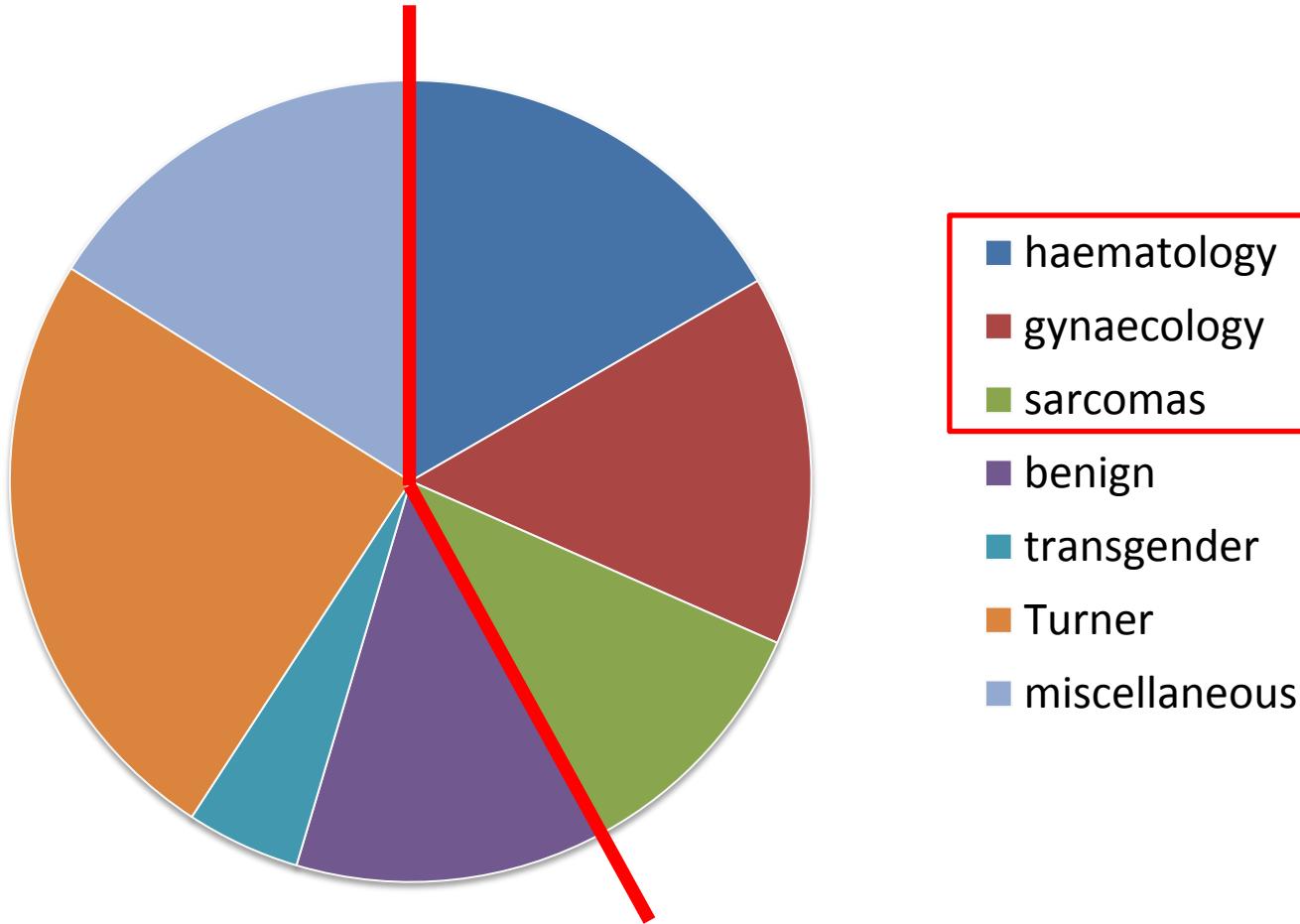
Geen tijd

Jonge vrouwen die voor kanker behandeld moeten worden, kunnen door de chemo- of radiotherapie onvruchtbaar worden. Het invriezen van eicellen kan het mogelijk maken later toch nog een kind te krijgen. Maar als snel met de behandeling moet worden gestart, is er vaak geen tijd voor de hormonale stimulatie van de eierstokken die nodig is om eicellen af te kunnen nemen. "Voor deze vrouwen kan het invriezen en later terugplaatsen van eierstokweefsel een alternatief zijn", zegt gynaecoloog Leoni Louwé. "Er zijn wel een aantal criteria waar de vrouwen aan moeten voldoen, bijvoorbeeld wat betreft de leeftijd en het risico op uitzanding van de kanker naar de eierstok."



Indications

Cryobank Radboudumc



n = 174; of which 104 ≤ 18 jaar

Jan 2019

Indications

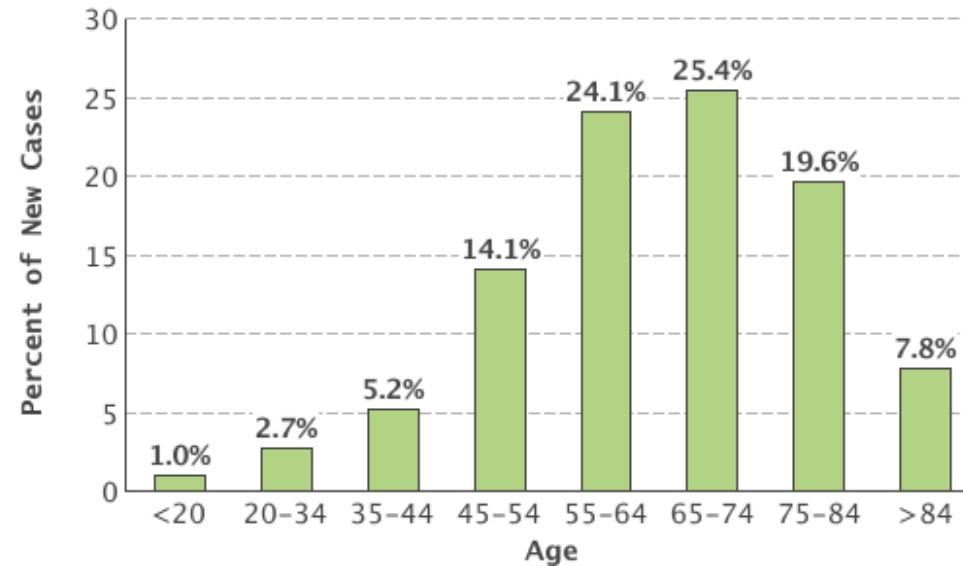
IARC figures about cancer 2018

18.1 million new diagnoses / year

In Europe 276,000 people < 44 y

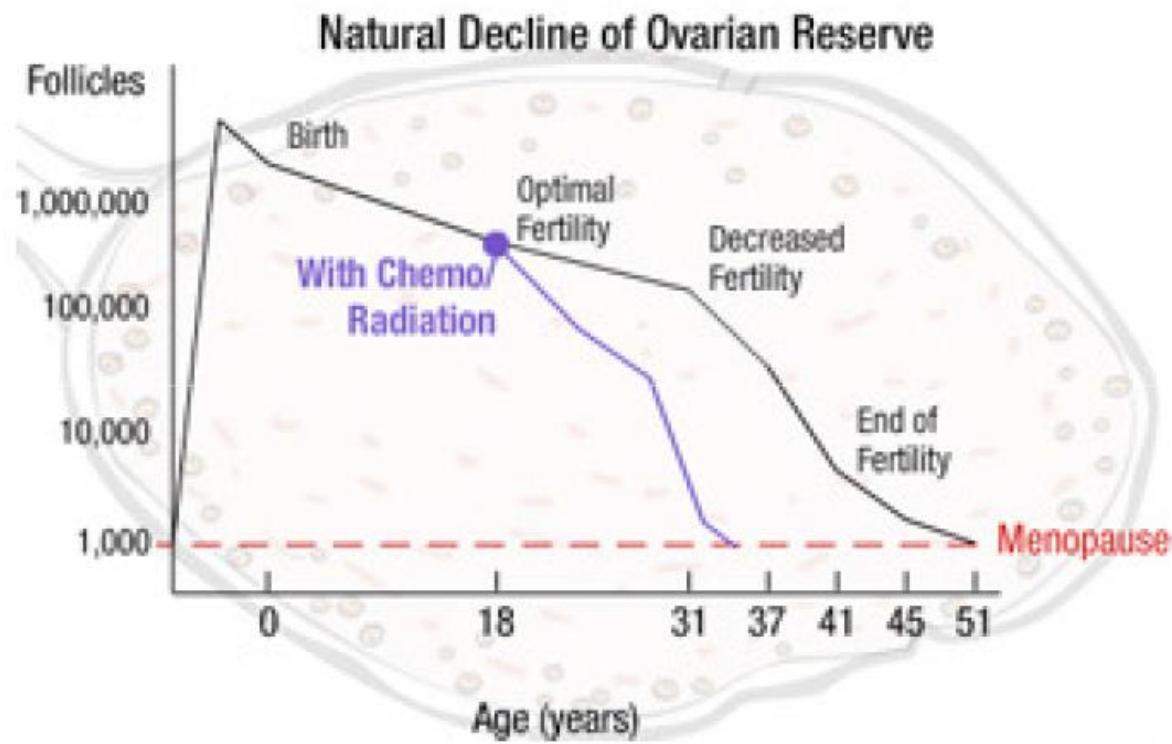
65% females

Source: National Cancer Institute



Indications

Effect of oncological treatment on female fertility



Indications

Gonadotoxicity in survivors of CAYA cancer

Risk on premature ovarian insufficiency

Who needs surveillance?	
Counselling regarding the risk of premature ovarian insufficiency and its implications for future fertility <i>is recommended</i> for survivors treated with:	
• Alkylating agents in general (level A evidence)	Level A ^{9,29-31}
• Cyclophosphamide and procarbazine (level C evidence)	Level A ^{9,30,31}
• Radiotherapy potentially exposing the ovaries (level A evidence)	Level C ³²
POI risk in survivors of CAYA cancer	
Increased risk after alkylating agents v no alkylating agents	No studies
Increased risk after higher alkylating agent dose v lower dose	Level C ³²
Increased risk after cyclophosphamide v no cyclophosphamide	No studies
Increased risk after higher cyclophosphamide dose v lower dose	Level C ³²
Increased risk after procarbazine v no procarbazine	No studies
Increased risk after higher procarbazine dose v lower dose	No studies
Risk after multiple alkylating agents and other chemotherapeutic agents v single alkylating agents	No studies
Risk after other alkylating agents*	No studies
Risk after platinum agents†	No studies
Increased risk after radiotherapy to which ovaries are potentially exposed v no radiotherapy	Level A ^{9,29-35}
Increased risk after higher dose of radiotherapy to which ovaries are potentially exposed v lower dose	Level A ^{30,32-34}
Increased risk after radiotherapy to which ovaries are potentially exposed and alkylating agents v either treatment in the same dose alone	Level C ⁹
Increased risk after treatment at older age v younger age	Level B ^{9,29,35}
Risk after unilateral oophorectomy	No studies

van Dorp et al, 2016 JCO

Indications

Female fertility after cancer

20-50% lower chance of pregnancy

Green 2009, Reulen 2009, Sklar 2006, Madanat 2008, Syse 2007, Cvancarova 2009

Premature ovarian failure (POI)

8% of childhood cancer survivors

19-30% of adult women treated < 40 years

(vs 0.8% general population)

Sklar 2006, De Bruin 2008, Swerdlow 2014, Rosenberg 2013

Indications

Important issue of QOL in young cancer survivors

Letourneau, 2012



Indications

Fertility and FP options in women/girls

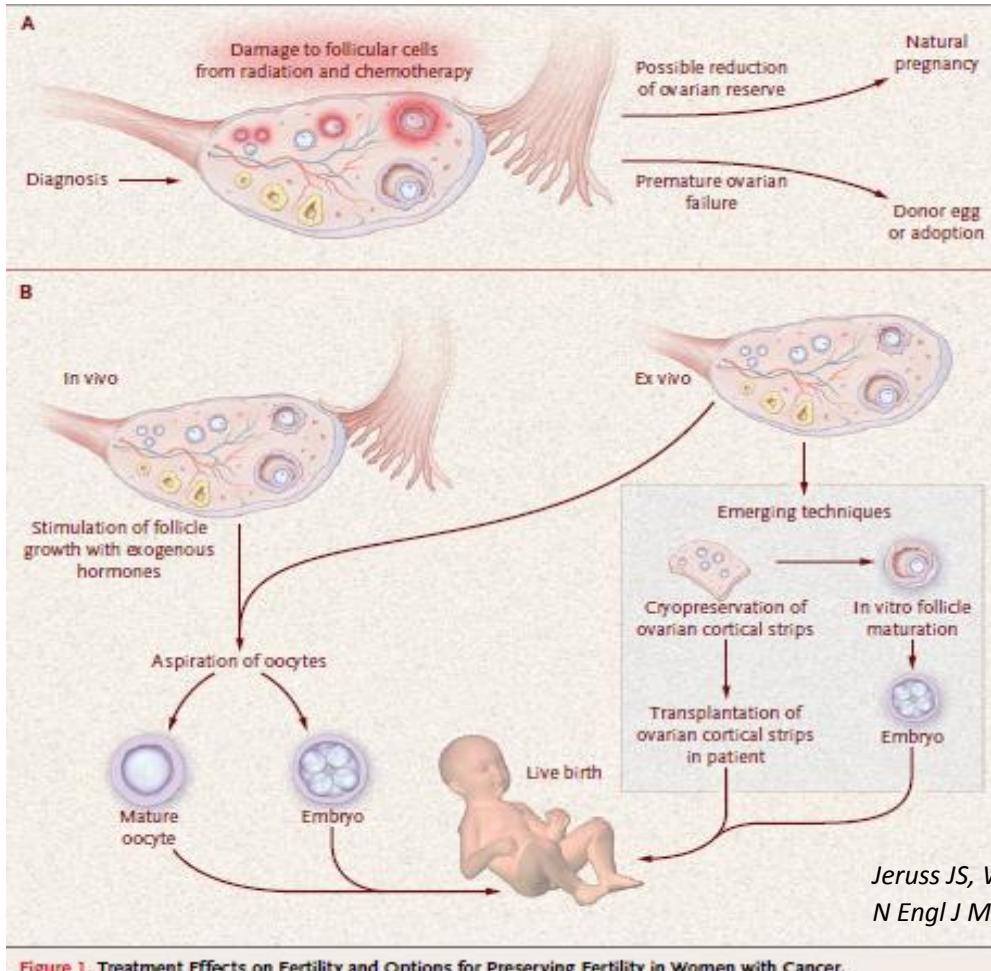


Figure 1. Treatment Effects on Fertility and Options for Preserving Fertility in Women with Cancer.

Indications

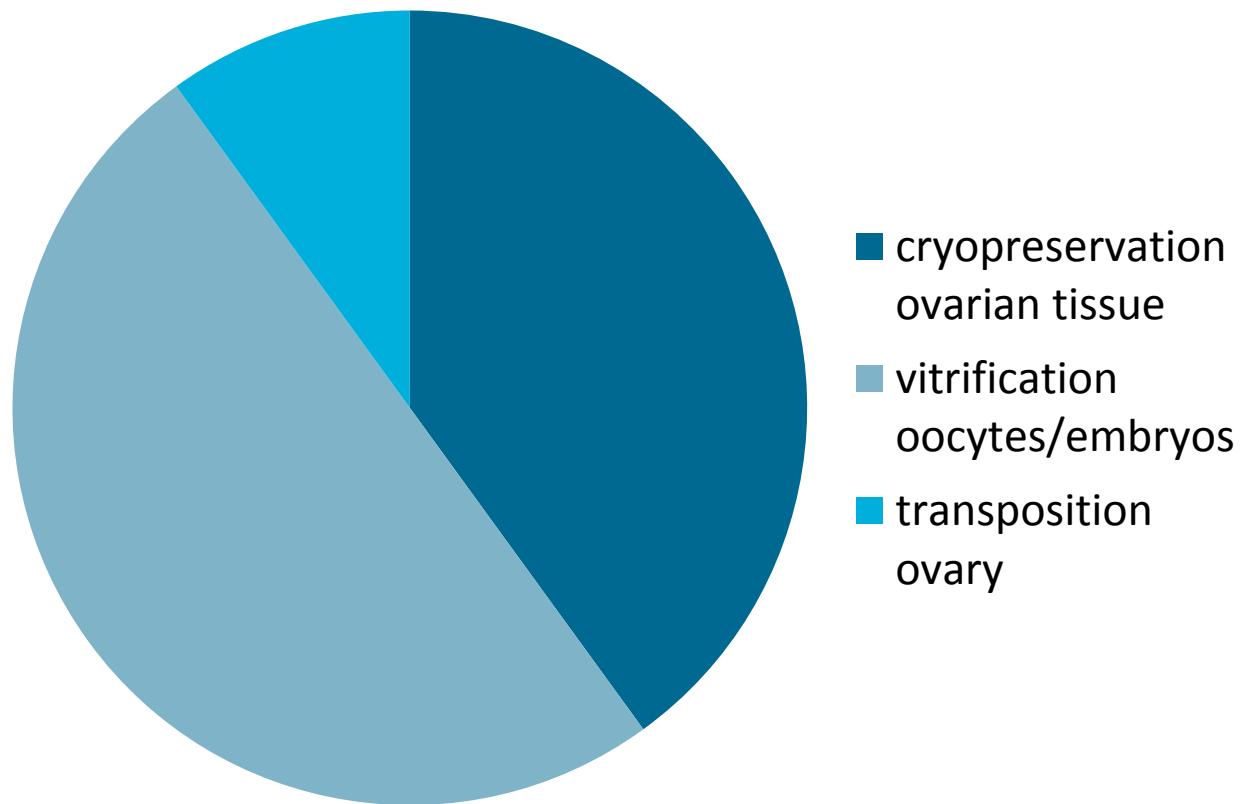
Fertility and FP options in women/girls

Group	Method	Cryopreservation	Treatment	Recipient	Concerns
Women	Hormone stimulation Hormone cycle 2-3 weeks	Zygote or embryo	Embryo transfer	Patient or gestational surrogate	Delay in cancer treatment Hormone injections Availability of appropriate sperm donor
Postpubertal girls	Hormone stimulation Hormone cycle 2-3 weeks	Mature oocyte			
Postpubertal girls Prepubertal girls	Laparoscopic oophorectomy	Cumulus-oocyte complexes Ovarian cortical strips	Ovarian transplantation In vitro follicle maturation and in vitro fertilization or ICSI with embryo transfer	Patient Patient or gestational surrogate	Potential reintroduction of cancer cells Experimental

The diagram illustrates the various methods for fertility preservation in women and girls, categorized by age group and treatment modality. For women, a hormone cycle leads to the stimulation of multiple follicles, resulting in either a zygote or embryo (which can be transferred to the patient or a surrogate) or a mature oocyte (which can be cryopreserved). For postpubertal girls, a hormone cycle leads to the stimulation of individual follicles, resulting in cumulus-oocyte complexes. For prepubertal girls, laparoscopic oophorectomy is performed to remove ovarian cortical strips, which are then cryopreserved. These preserved eggs or ovarian tissue can be used for future treatments such as ovarian transplantation or in vitro fertilization with intracytoplasmic sperm injection (ICSI) followed by embryo transfer.

Indications

Application of fertility preservation



Indications

Inclusion criteria (oncology)

- Good ovarian reserve (< 35 years)
- Use tissue possible before legal age limit
- Probability of POI > 50%
- Infection serology results according to the valid position statement

Dutch guideline for Fertility Preservation in women with cancer, 2016

Indications

Exclusion Criteria (oncology)

- Contraindication for surgical intervention
- High risk of ovarian metastasis
- Genetic predisposition to ovarian carcinoma

Dutch guideline for Fertility Preservation in women with cancer, 2016

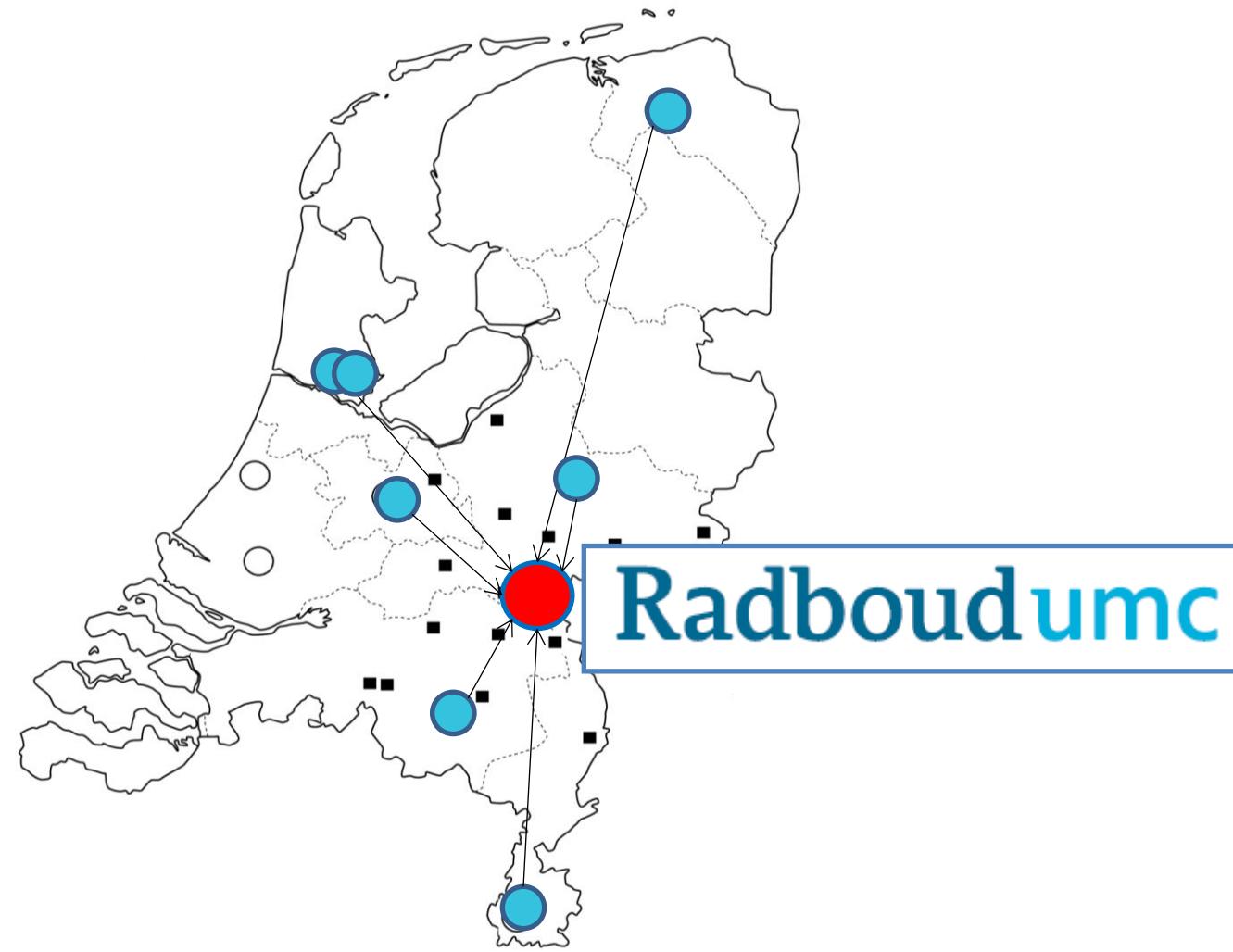
Obtaining

Removal of ovarian tissue



Obtaining

Transportation



Radboudumc

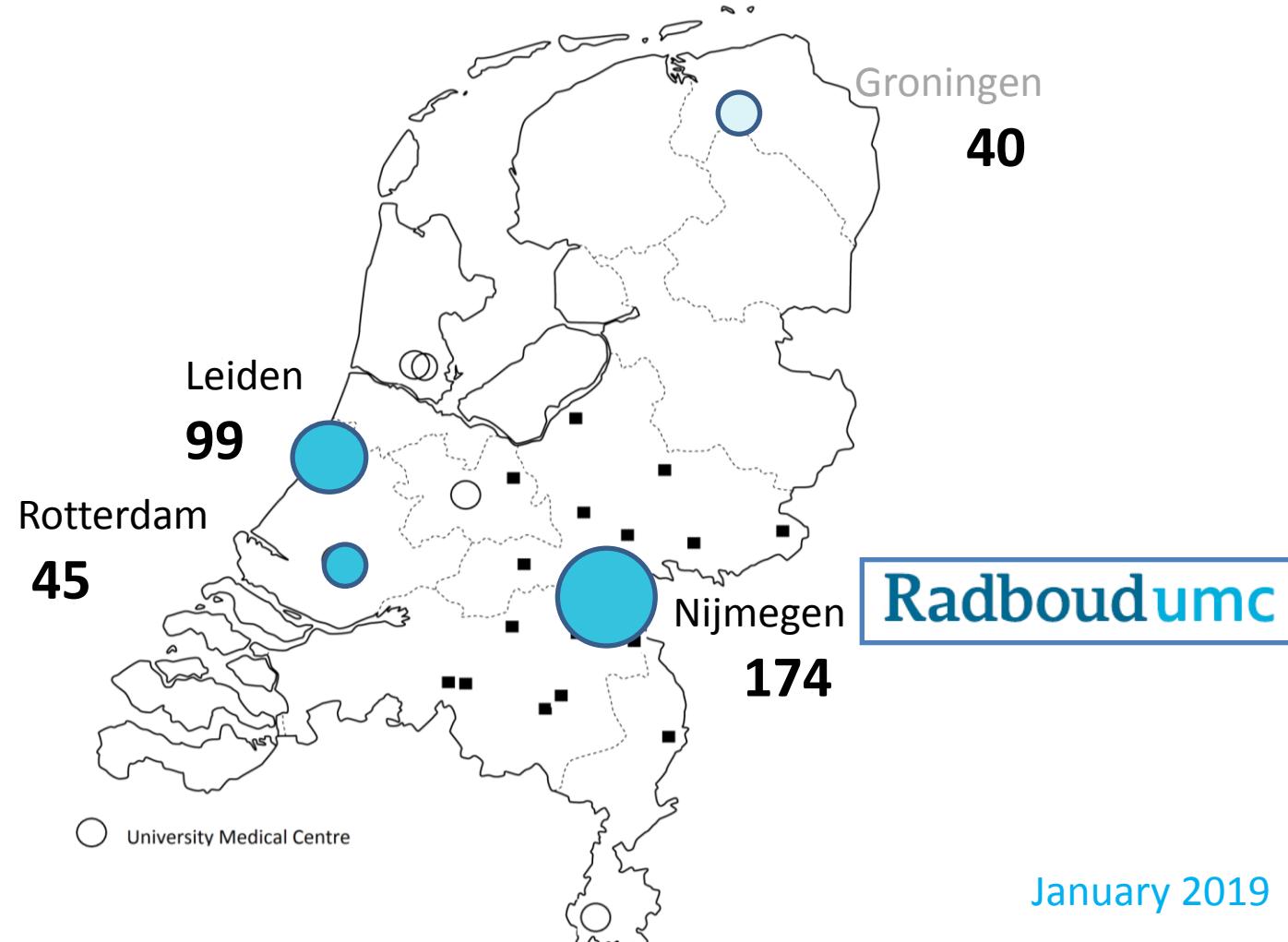
Obtaining

Medical transportation



Storage

Cryobanking ovarian tissue

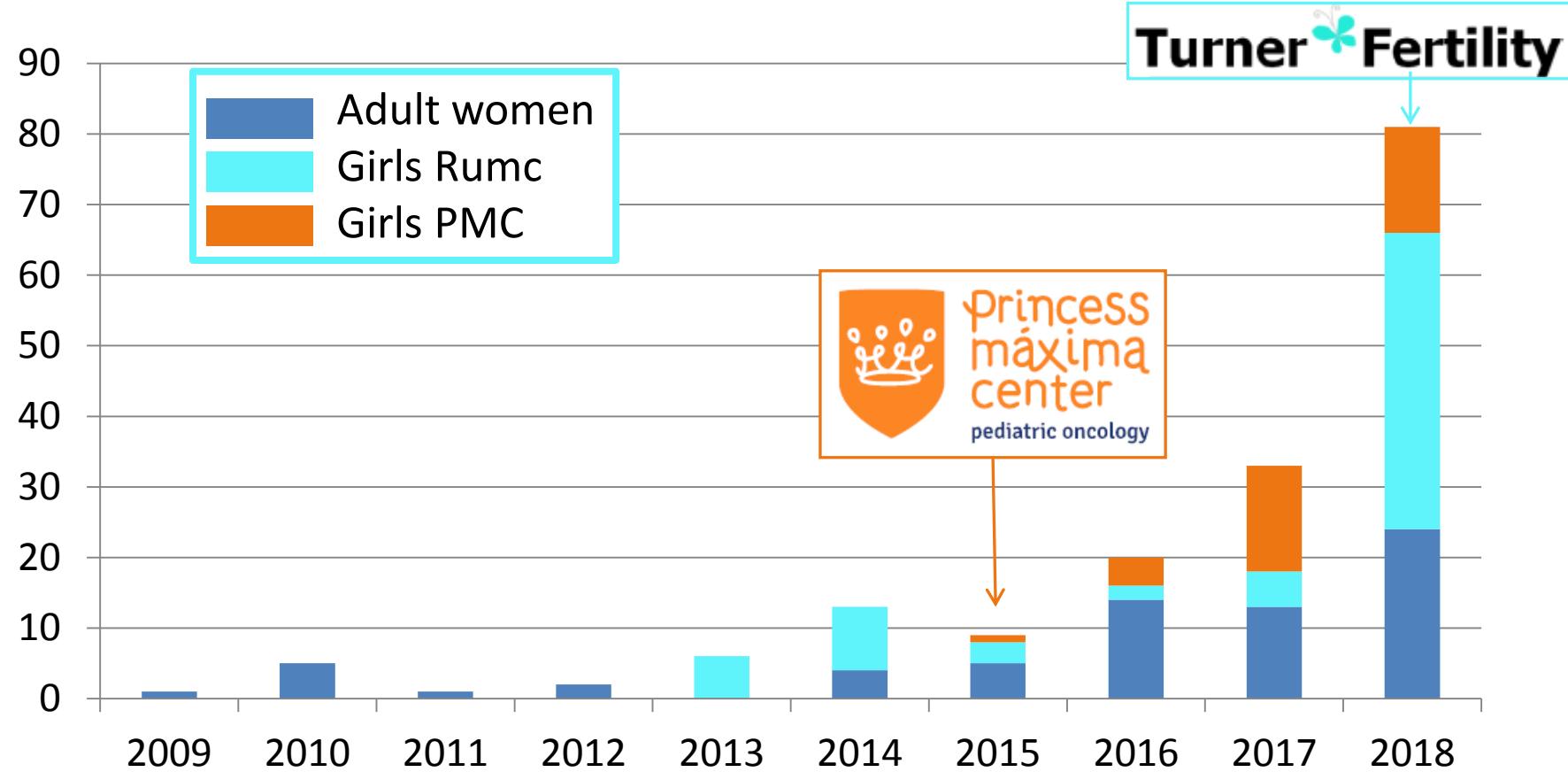


January 2019

Radboudumc

Storage

Development cryobank Radboudumc



Storage

Ovarian tissue banking

Belgium: > 1200 cases in 5 clinics

personal communication, april 2019 Dolmans and Demeestere

The Netherlands: 359 cases in 4 clinics

SIG Fertility Preservation NVOG, jan 2019

FertiPROTEKT: >400 cases per year

Lotz et al, 2019



Storage

Slow freezing vs vitrification

In-vitro results human concerning morphology of tissue, preservation of primordial follicles and estradiol production:

- 1 study vitrification superior *Ref: Keros 2009*
- 3 studies similar *Ref: Zhou 2016, Sanfilippo 2015, Klocke 2015*
- 2 studies slow freezing superior *Ref: Oktem 2011, Dalman 2017*

Storage

Slow freezing vs vitrification

In-vitro results human concerning morphology of tissue, preservation of primordial follicles and estradiol production:

- 1 study vitrification superior *Ref: Keros 2009*
- 3 studies similar *Ref: Zhou 2016, Sanfilippo 2015, Klocke 2015*
- 2 studies slow freezing superior *Ref: Oktem 2011, Dalman 2017*

Results **pregnancies** human:

- No proof that vitrification is superior
- Only 2 live births after vitrification

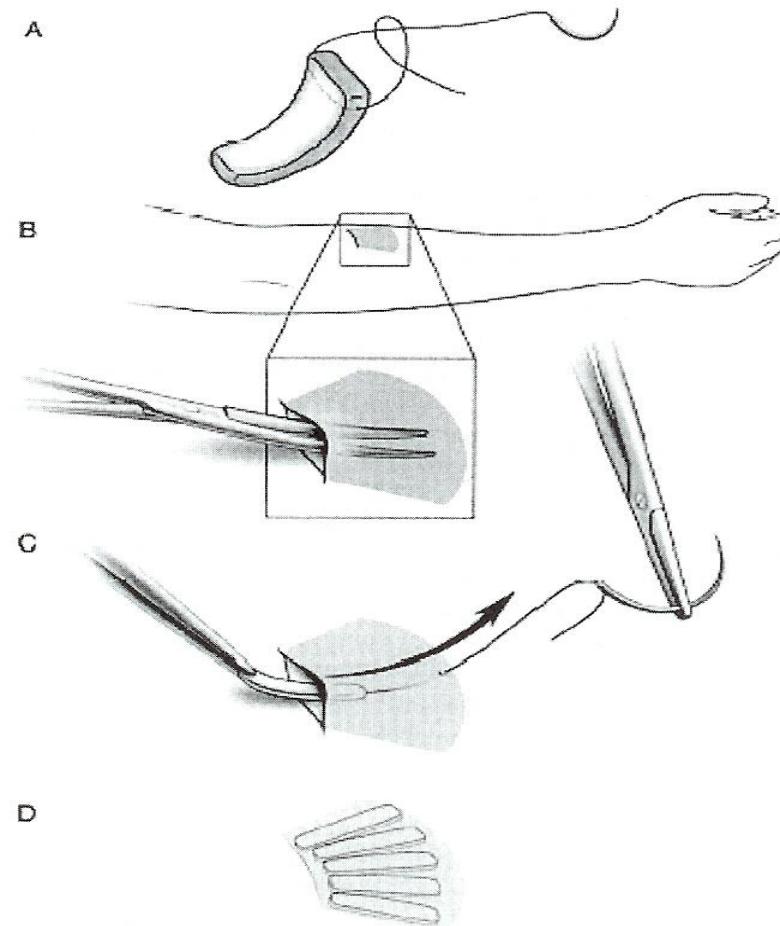
Ref: Suzuki 2015

- Xenografting
- Orthotopic transplantation
- Heterotopic transplantation
- Loss of follicles due to cryopreservation relatively low
- 2/3 loss of follicles due to ischemia following transplantation



Transplantation

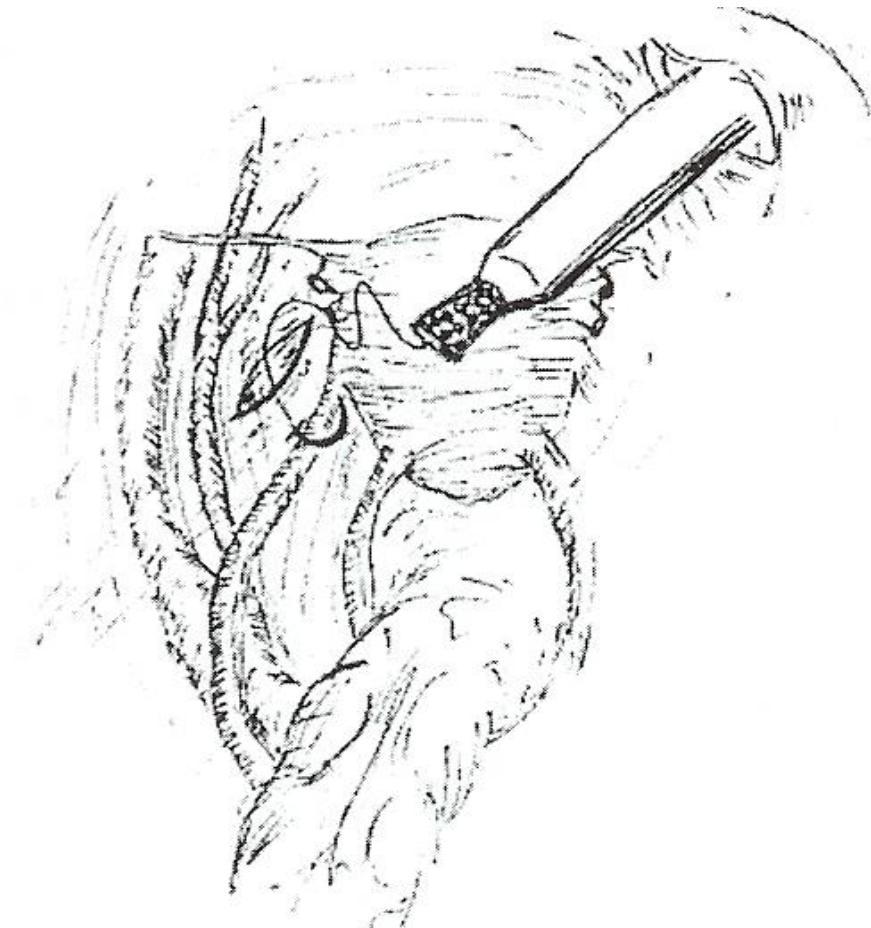
Heterotopic



Oktay et al, 2003

Transplantation

Orthotopic



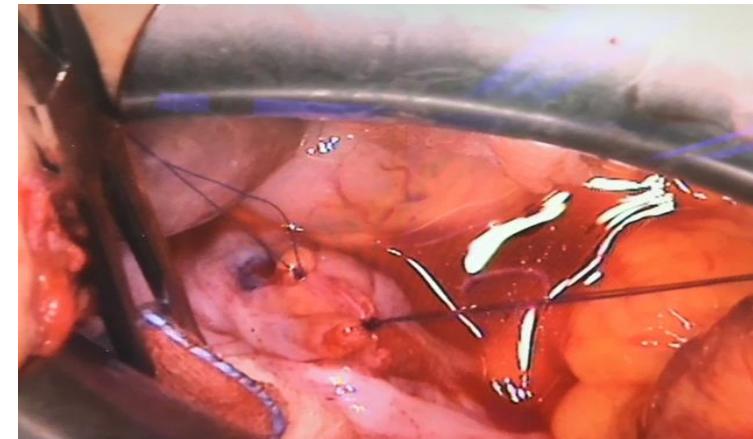
Oktay et al, 2001

Transplantation

Techniques



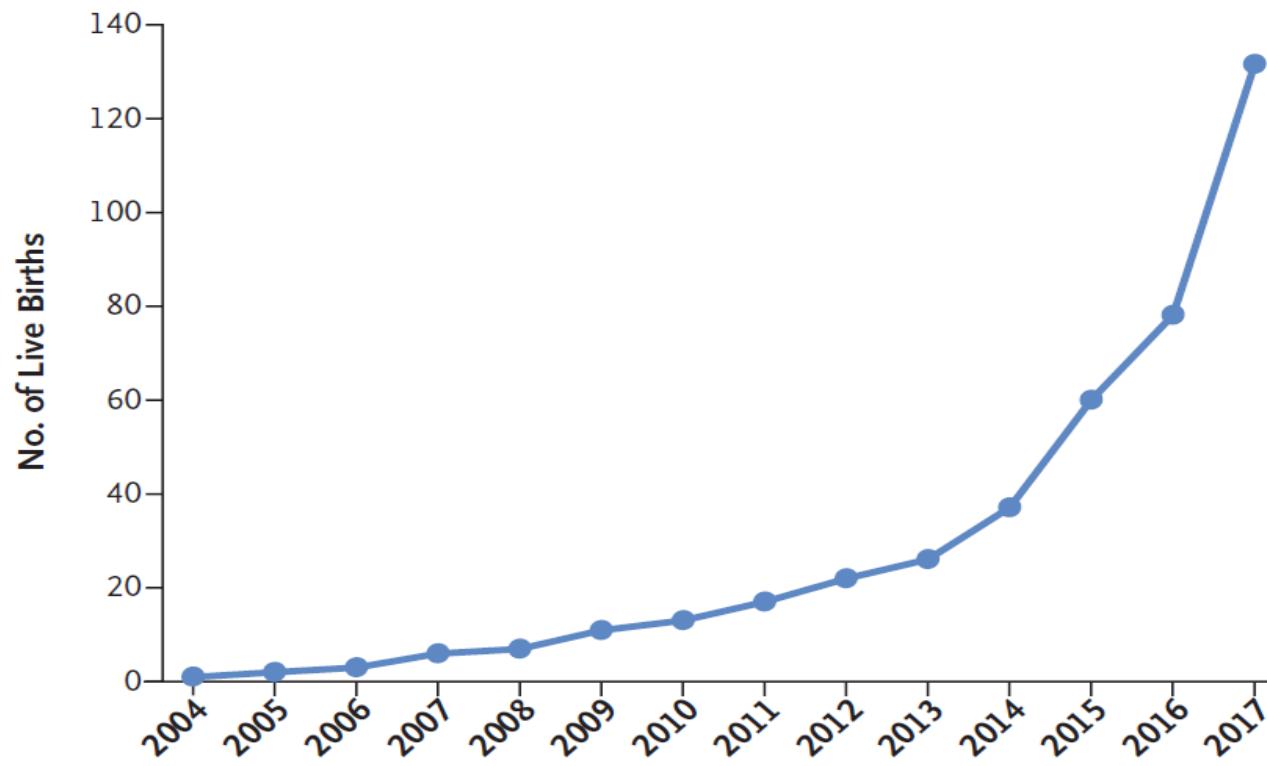
- Optimal vascularisation
- Orthotopic transplantation
- Fixation



Donnez et al, 2018

Results

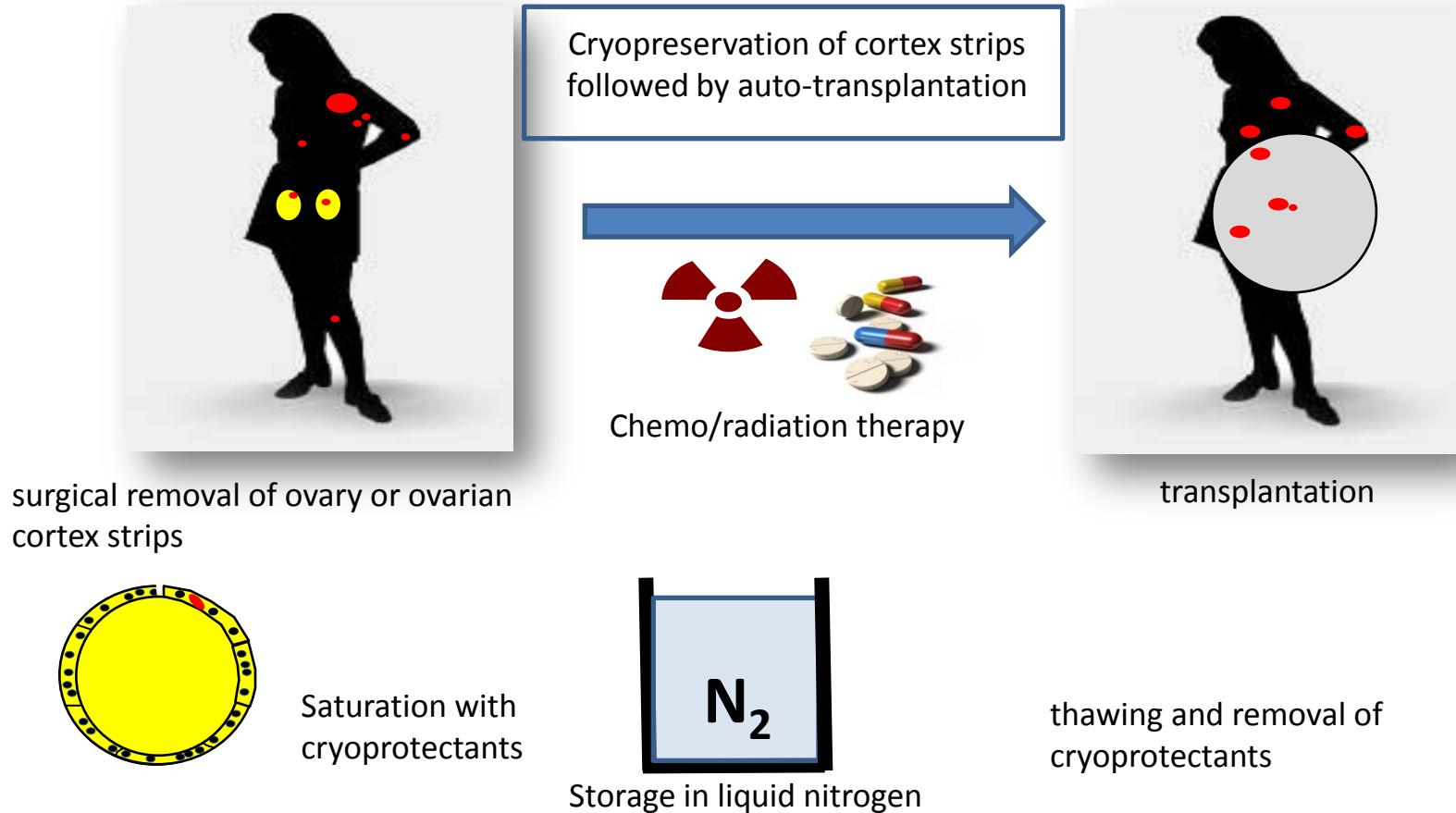
LBR after OTC and Transplantation



Donnez and Dolmans, 2017 NEJM

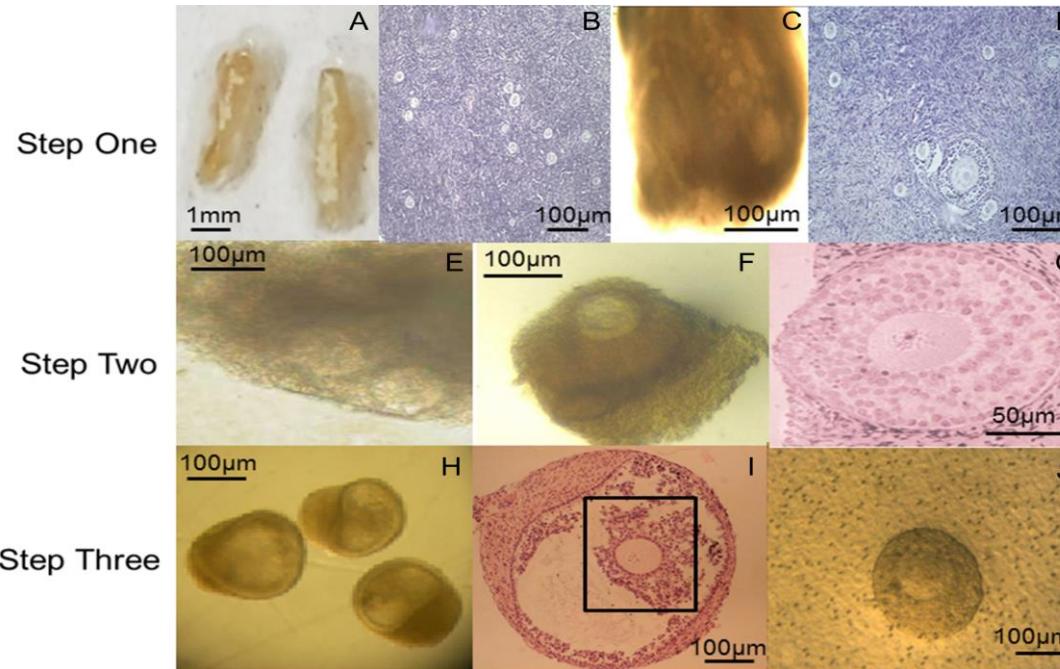
Risks

Reintroduction of cancer



Risks

In-vitro maturation

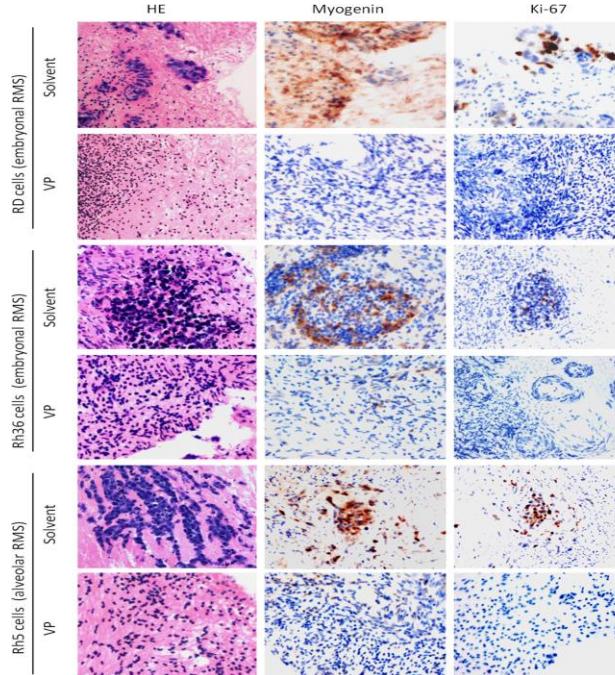


MHR: Basic science of reproductive medicine, Volume 24, Issue 3, 30 January 2018, Pages 135–142, <https://doi.org/10.1093/molehr/gay002>

The content of this slide may be subject to copyright: please see the slide notes for details.

OXFORD
UNIVERSITY PRESS

Purging



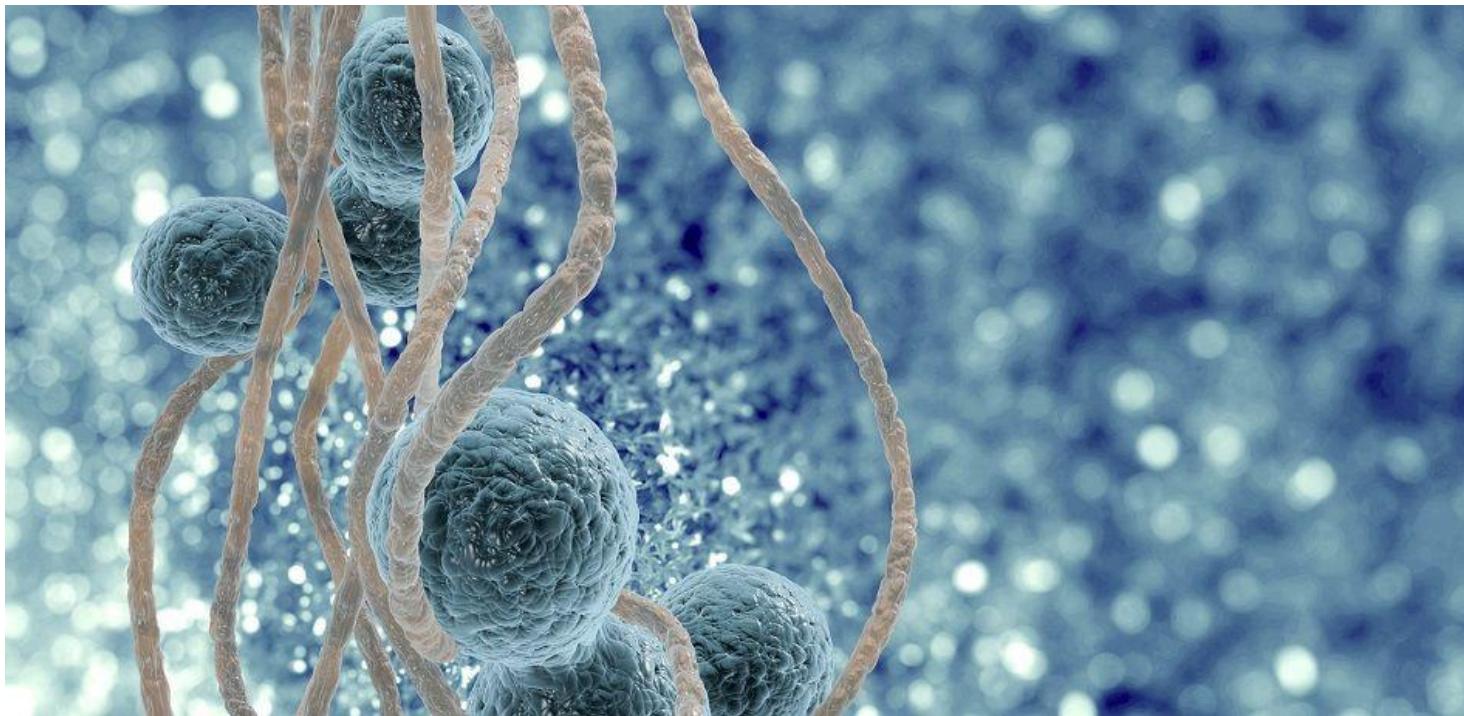
Human Reproduction, Volume 34, Issue 3, 28 December 2018, Pages 506–518, <https://doi.org/10.1093/humrep/dey384>

The content of this slide may be subject to copyright: please see the slide notes for details.

OXFORD
UNIVERSITY PRESS

Risks

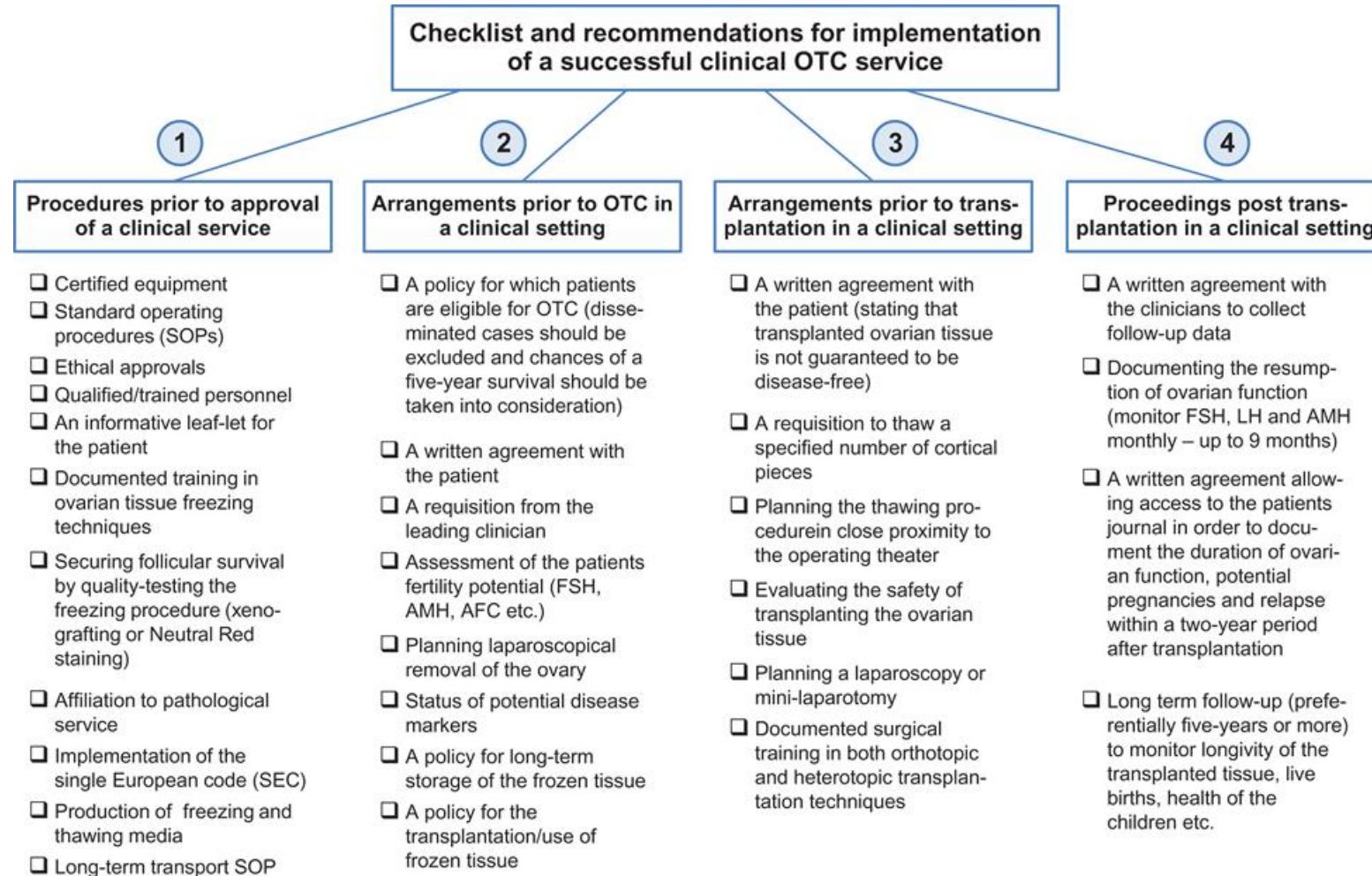
Artificial ovary



- Risk of reimplantation of cancer
- Experimental status
- Xenotransplantation
- Success rates
- Incapacity of will (young children)
- Additional risk of surgical complications
- Life expectancy

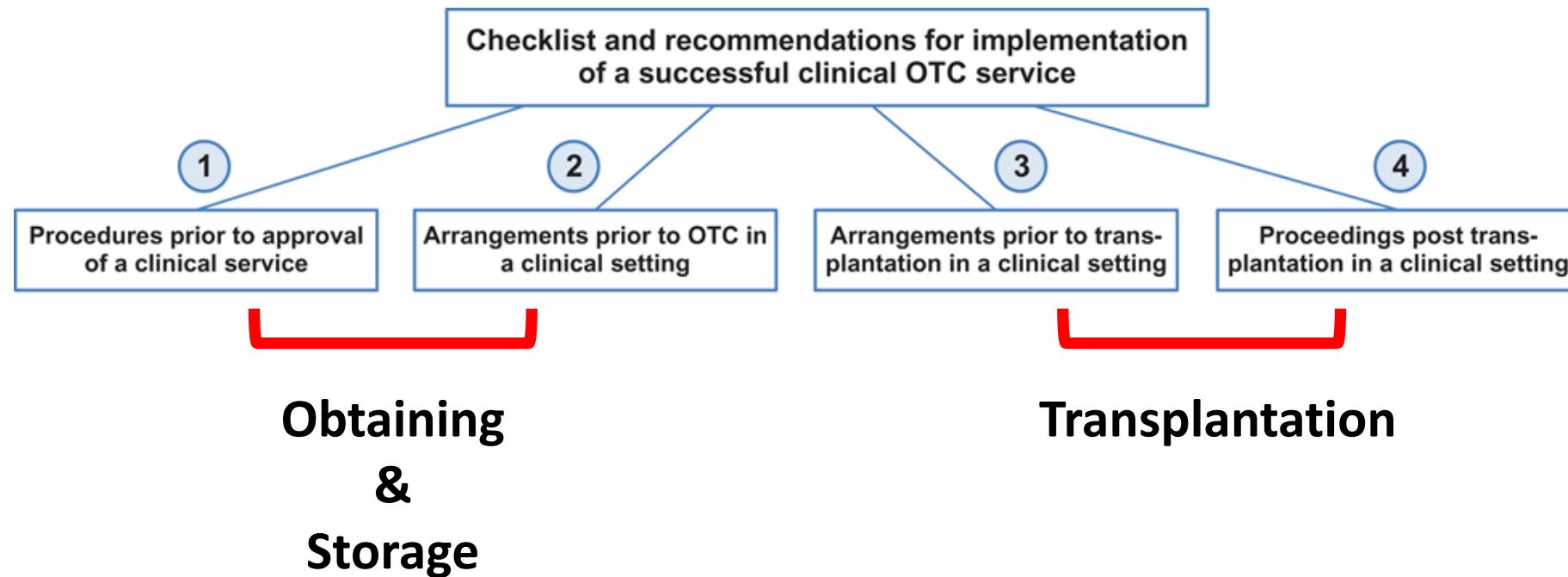
Quality

Quality assurance and control



Andersen CY, 2018

Quality assurance and control



Andersen CY, 2018

Take home messages

Ovarian tissue banking

- Rapid increase application OTC

- Rapid increase application OTC
- High pregnancy rates

- Rapid increase application OTC
- High pregnancy rates
- Lot of research on risk reduction

- Rapid increase application OTC
- High pregnancy rates
- Lot of research on risk reduction
- Expectation: common technique and good FP option
- .

- Rapid increase application OTC
- High pregnancy rates
- Lot of research on risk reduction
- Expectation: common technique and good FP option
- Quality assurance and control deserves attention
- .

Acknowledgements

Members SIG Fertility Preservation NVOG
Louwé, Van den Berg, Benneheijs

Belgian colleagues:
Dolmans, Demeestere

