Fertility Preservation

Oncofertility, social egg freezing and the transgender experience

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Update on fertility preservation from the Barcelona International Society for Fertility Preservation–ESHRE–ASRM 2015 expert meeting: indications, results and future perspectives

Francisca Martinez, on behalf of the International Society for Fertility Preservation–ESHRE–ASRM Expert Working Group

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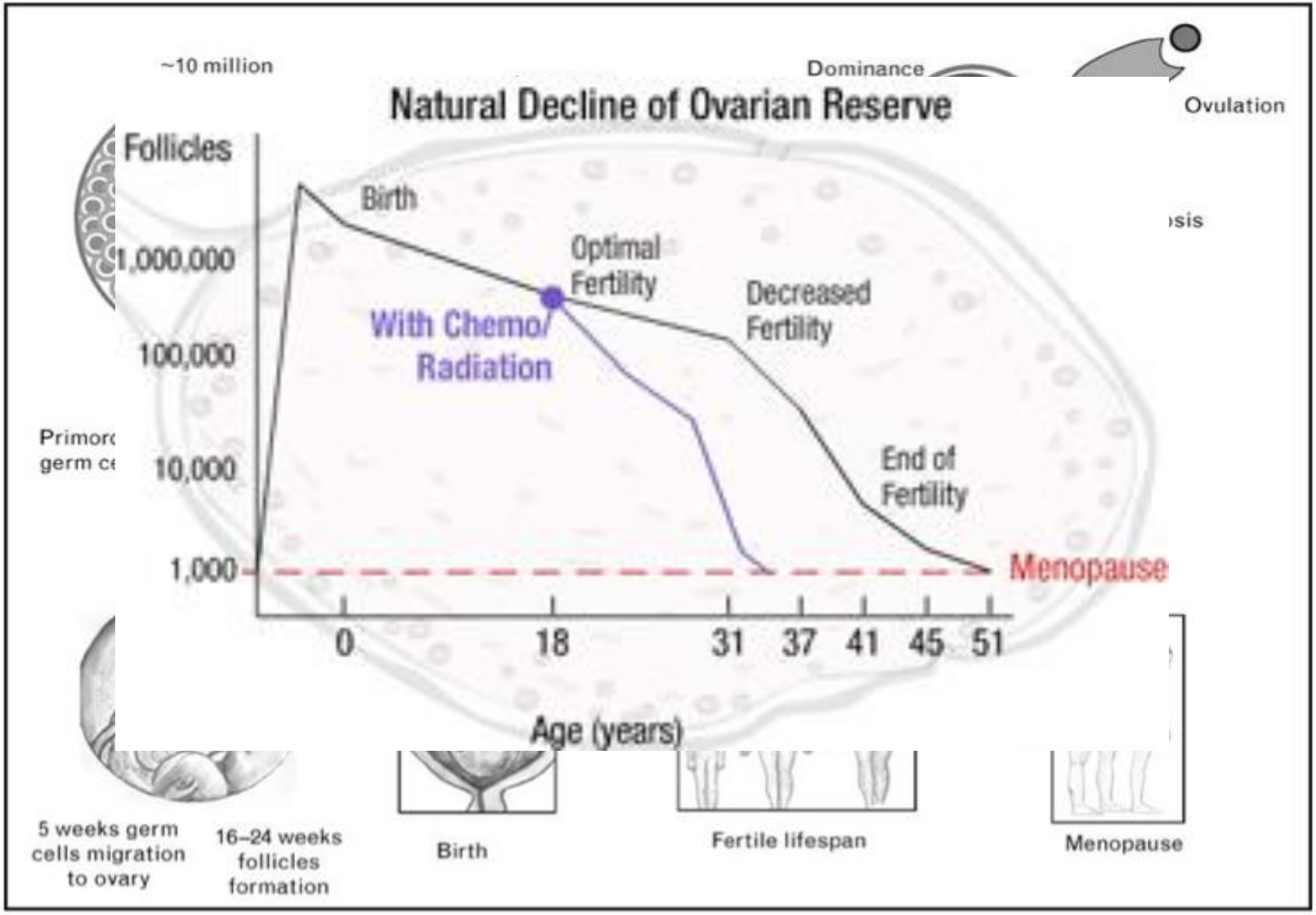
Fertility Preservation

- Oncofertility
  - Chemotherapy
  - Radiotherapy
- Fertility preservation
  - Female
  - Male
- Transgender fertility preservation
- Elective oocyte cryopreservation (social egg freezing

Oncofertility

- 10% of cancers occur in women under 45yo
  - 50% have gonadotoxic treatment
  - 83% survive
- Treatment, not disease itself → premature ovarian failure
  - Chemotherapy
  - Radiotherapy
- Loss of fertility
- Menopause related complications

Gonadotoxicity



Risk of gondal dysfunction

Sonmezer & Oktay 2004

High risk

- Cyclophosphamide
- Ifosfamide
- Chlormethine
- Busulfan
- Melphalan
- Procarbazine
- Chlorambucil

Medium risk

- Cisplatin
- Carboplatin
- Doxorubicin
- Dactinomycin

Low risk

- Vincristine
- Methotrexate
- Bleomycin
- Mercaptopurine
- Vinblastine

Cyclophosphamide will induce permanent amenorrhea in high doses dependent on age

5g at age 40

10g at age 30

20g at age 20

Koyama *et al*. 1977

Risks of radiotherapy

Impact depends on;

- –field of treatment
- –dose of radiation
- –fractionation

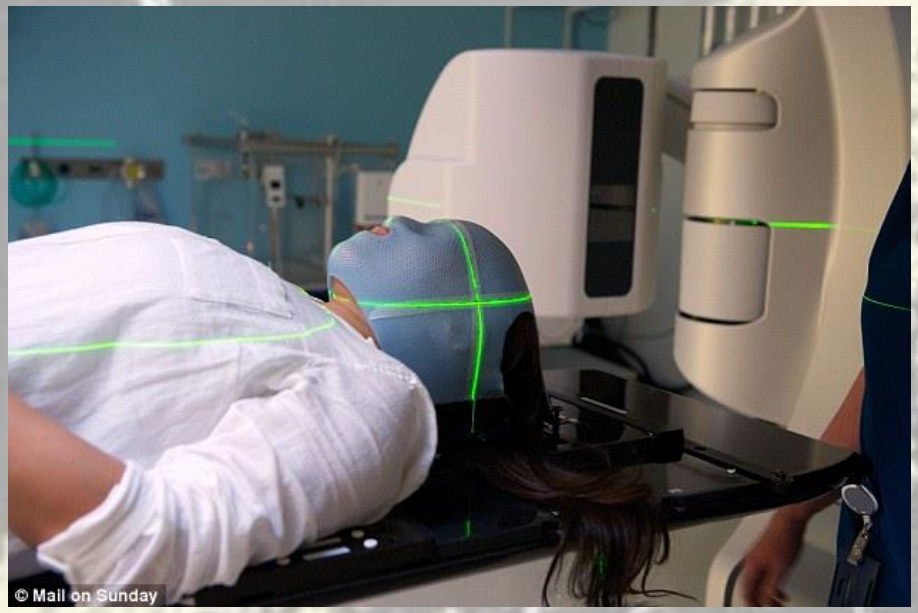
Risks of radiotherapy

- Estimated dose at which half oocytes depleted is 2Gy.
- At birth 20 Gy to ovaries will cause ovarian failure
- Women <30 15 Gy
- Women <40 14 Gy
- Women >40 6Gy (Hamish *et al.* 2005)

Risk of radiotherapy

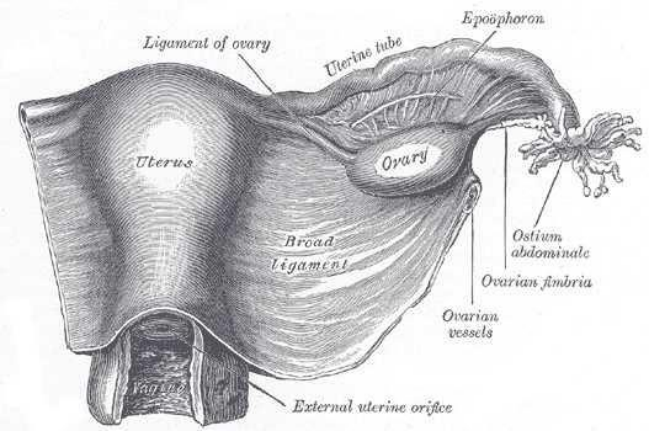
In addition;

- CNS irradiation may lead to hypogonadotrophic hypogonadism



Uterine effects of radiotherapy

- Decreased endometrial vascularisation
- Decreased endometrial thickness
- Myometrial fibrosis
- Poor uterine development post insult



Fertility Preservation for cancer

COSA–AYA guideline 2011

- Discuss fertility
- Impact of tx on reprod/hormonal fxn
- Options for protection/preservation
- Managing fertility preservation process
- Long term monitoring/follow-up

Options for fertility preservation

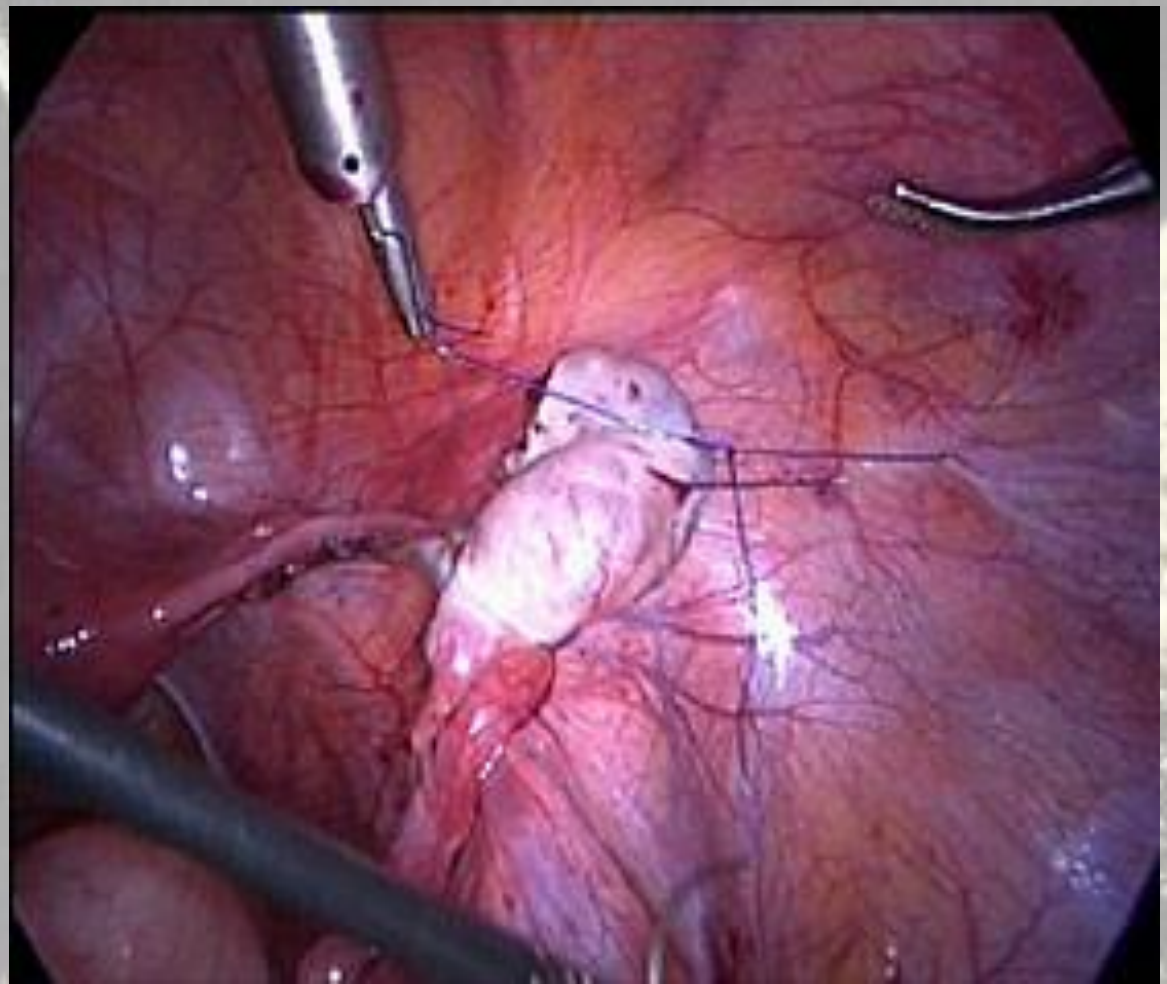
- Conservative
- Hormonal suppression
- Cryopreservation
  - Oocytes
  - Embryos
  - Ovarian tissue
- Surgical
  - Ovarian transposition
  - Uterine transplantation

Conservative

Low Risk <20% of women develop amenorrhea post-treatment	AC in women 30-39	Breast cancer
	CMF, CEF, or CAF x 6 cycles in women under 30	Breast cancer
	Non-alkylating chemotherapy: ABVD, CHOP, COP	Hodgkin lymphoma, NHL
	AC (anthracycline, cytarabine)	Acute myeloid leukemia (AML)
	Multi-agent therapies	ALL
Very Low/ No Risk Negligible effect on menses	MF (methotrexate, 5-FU)	Breast cancer
	Vincristine (used in multi-agent therapies)	Leukemia, Hodgkin lymphoma, NHL, neuroblastoma, rhabdomyosarcoma, Wilms' tumor, Kaposi's sarcoma
	Radioactive Iodine	Thyroid cancer
High Risk >80% of women develop amenorrhea post-treatment	Whole abdominal or pelvic radiation doses ≥ 6 Gy in adult women	Multiple cancers
	Whole abdominal or pelvic radiation doses ≥ 15 Gy in pre-pubertal girls ≥ 10 Gy in post-pubertal girls	Wilms' tumor, neuroblastoma, sarcoma, Hodgkin lymphoma
	TBI radiation doses	Bone marrow transplant/stem cell transplant (BMT/SCT)
	CMF, CEF, CAF x 6 cycles in women 40 +	Breast cancer
	Cyclophosphamide 5 g/m² in women 40+	Multiple cancers
	Cyclophosphamide 7.5 g/m² in girls < 20	Non-Hodgkin lymphoma (NHL), neuroblastoma, acute lymphoblastic leukemia (ALL), sarcoma

Surgical

- Transposition of ovaries – for radiotherapy

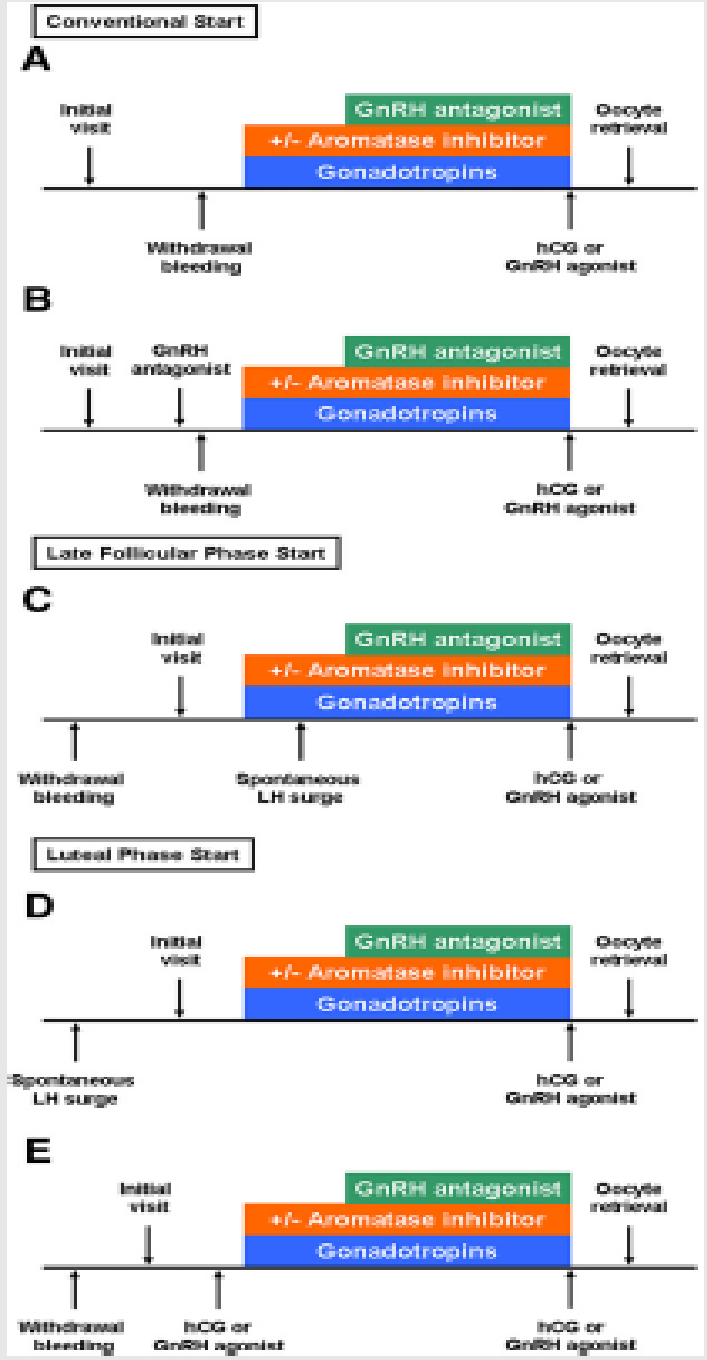


Medical

- Hormonal suppression
  - GnRH agonists
    - During chemotherapy – quiescent ovaries less susceptible
    - Recent RCT - POEMS
      - Protects against POF
      - Reduces risk of early menopause
      - Increased CPR
      - improved disease-free and overall survival in triple negative breast cancer
    - Risk of ↓BMD and ↑vasomotor symptoms

Embryo cryopreservation

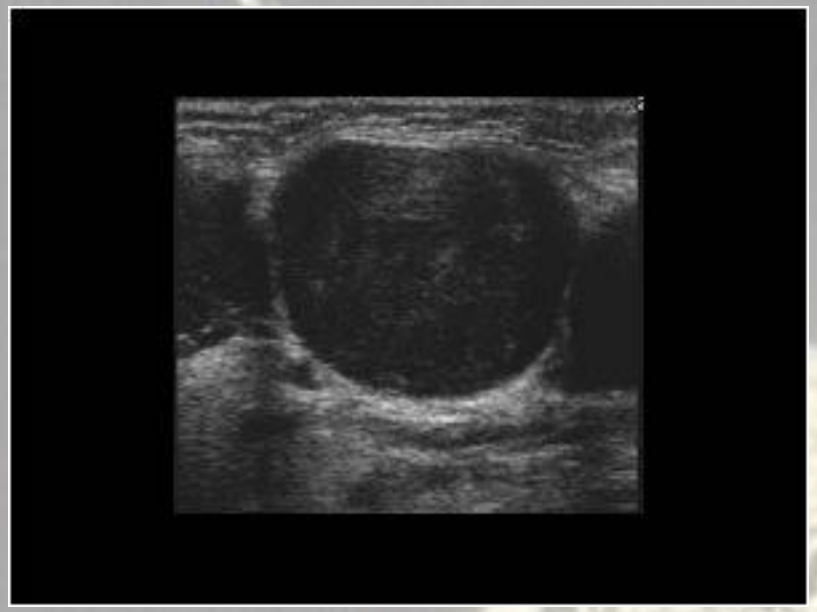
- Established, ideal treatment for couple
- ‘Standard’ COH + IVF
- “Rapid” IVF still requires
  - Time from the next menstrual cycle
  - Approx 2 weeks for hyperstimulation
- Shorter treatment options
  - Random start IVF
  - IVM

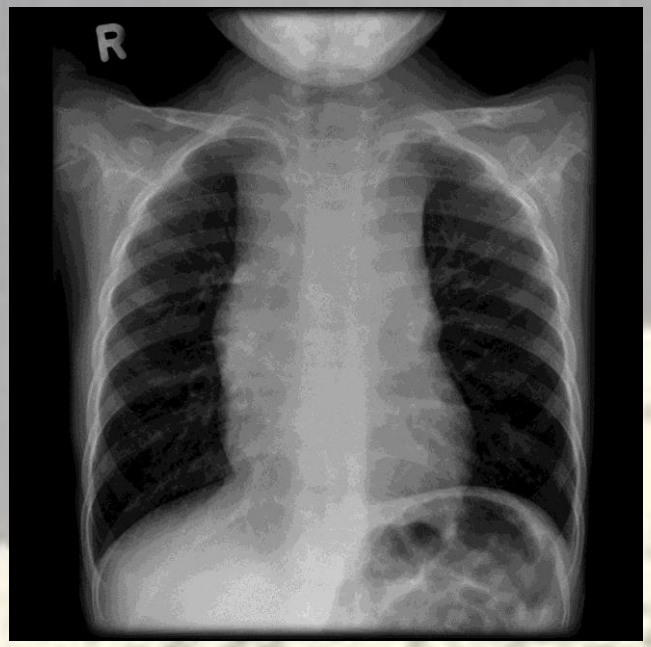


Conventional and random start antagonist IVF protocols for cancer patients undergoing fertility preservation. COS can be started with spontaneous menses (A) or with menses following luteolysis

Embryo cryopreservation

- Assess suitability





Oocyte cryopreservation

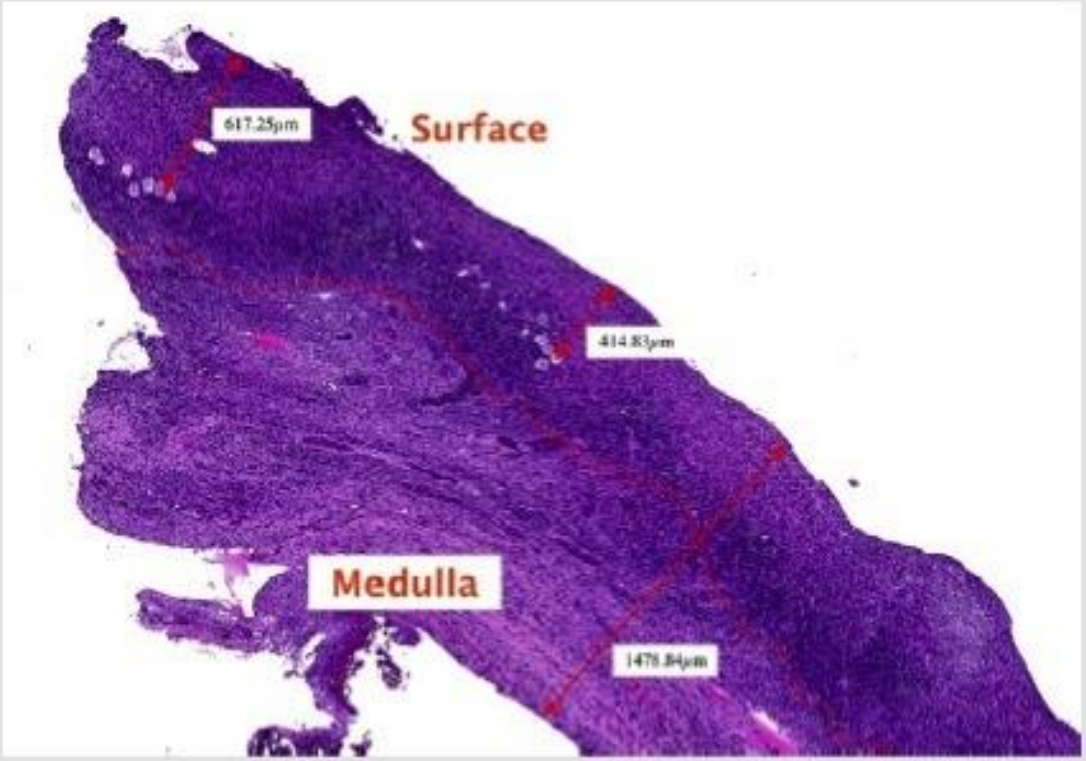
- For woman not in relationship
- Same assessment and stimulation protocols as for embryo
- Freeze mature oocyte
- Frozen = fresh
- Vitrification better than slow freeze
- Not possible in pre-pubertal
- ‘Insurance’ only for women <38

Peri-pubertal oocyte cryopreservation

- Possible (>13yo) but invasive
- Variable FSH-sensitivity of follicles
- ?Competence of oocytes of young girls
- ?Effect of high dose E2 on growth – data lacking
- In depth physical and psychosocial evaluation is ESSENTIAL

Ovarian tissue preservation

- Experimental

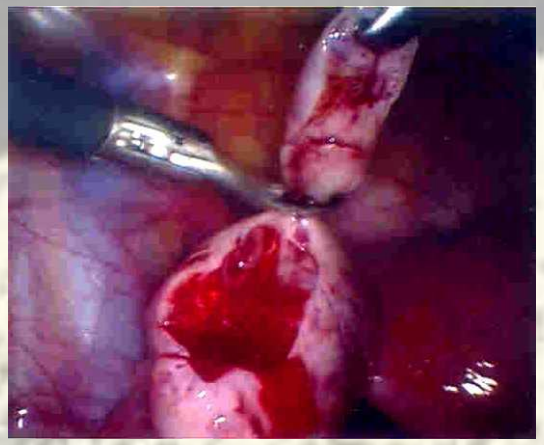


Ovarian cortical biopsy demonstrating the distance between the mesothelium and primordial follicles, ranging from 414 µm to 617 µm.

Donnez. Transplantation of ovarian tissue. Fertil Steril 2013.

Ovarian tissue preservation

- Advantages
  - Storage of large number of follicles
  - Rapid process – any time in cycle
  - Pre-pubertal possible



- Disadvantages
  - Transplantation – risk of ischemic injury
  - Reduction of ovarian reserve
  - Theoretical risk of re-introduction of cancer cells

Pre-pubertal ovarian tissue

- First live birth from tissue preserved from prepubertal girl
- Still experimental
- Oopherectomy required
  - Ex vivo IVM
  - Autotransplantation
- 3-5 year lifespan post transplantation

Risk of ovarian metastasis according to cancer type.

High risk	Moderate risk	Low risk
Leukemia	Breast cancer Stage IV Infiltrating lobular subtype	Breast cancer Stage I–II Infiltrating ductal subtype
Neuroblastoma	Colon cancer	Squamous cell carcinoma of the cervix
Burkitt lymphoma	Adenocarcinoma of the cervix	Hodgkin's lymphoma
	Non-Hodgkin lymphoma	Osteogenic carcinoma
	Ewing sarcoma	Nongenital rhabdomyosarcoma
		Wilms tumor

Note: Adapted from Sonmezer and Oktay (4) and modified according to the recent literature: Ewing sarcoma and NHL were recategorized from low to moderate risk.

Dolmans. Risk of transplanting malignant cells. Fertil Steril 2013.

Autotransplantation

- At least 2 years post ‘cure’
- Placement
  - Orthotopic
  - Heterotopic

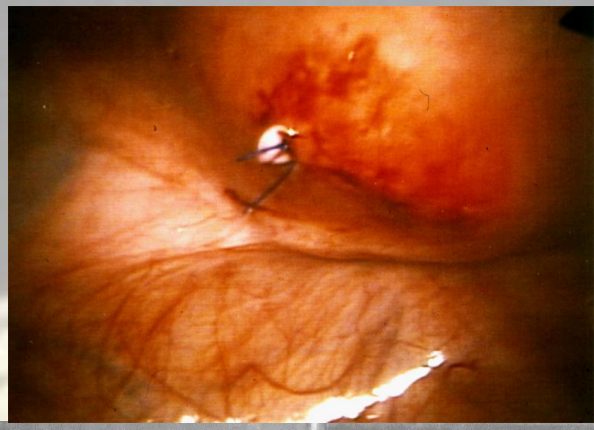


Table 4: Comparison of fertility preservation options for females

	Egg freezing	Embryo freezing	Ovarian tissue freezing
Invasiveness	Minimal	Minimal	Moderate
Time required	12-17 days	12-17 days	½ day
Partner required	no	yes	no
Survival rates after freezing	60%	80%	Reasonable
Expectation of success	Good if get enough eggs	Excellent if get enough embryos	Low currently

Sterility post cancer

- Options
  - Use of cryopreserved gametes/embryos
  - Donation
  - Surrogacy
  - Adoption
  - COUNSELLING!
  - Premature menopause management

What about boys?

- Often forgotten –
  - 50% never get offered fertility preservation
  - Majority desire fathering children, <25% cryopreserve.

- Fertility is a major concern for high percentages of male cancer survivors

Effects on male fertility

- Radiotherapy
  - Dose dependent (high risk - >6Gy, no risk <0.2Gy)
  - Central – hypo/hypo
- Chemotherapy
  - Alkylating agents
  - Combination protocols
- Surgery
  - Orchidectomy
  - RPLND

Fertility preservation options

- Post pubertal
  - Ejaculated semen sample
  - Electro-ejaculation
  - Surgical sperm retrieval(PESA/TESA)

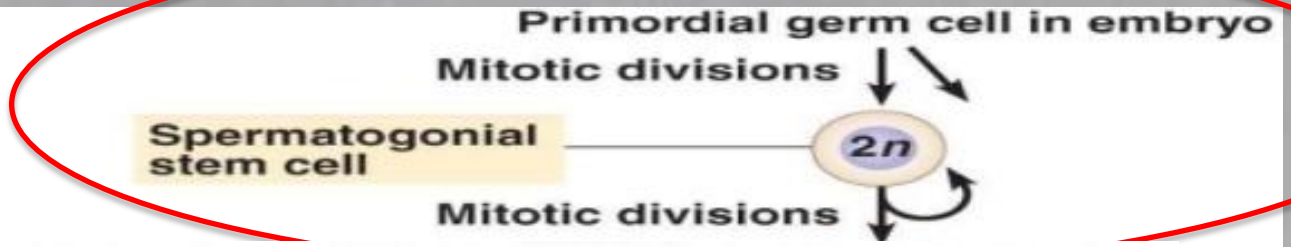
(note risk of disease induced azoospermia)

- Pre pubertal – ALL EXPERIMENTAL
  - Testicular tissue preservation
    - Spermatogonial stem cell culture
    - De novo testicular morphogenesis
    - Grafting (auto/xeno)
    - Organ culture
  - Somatic tissue – stem cell therapy

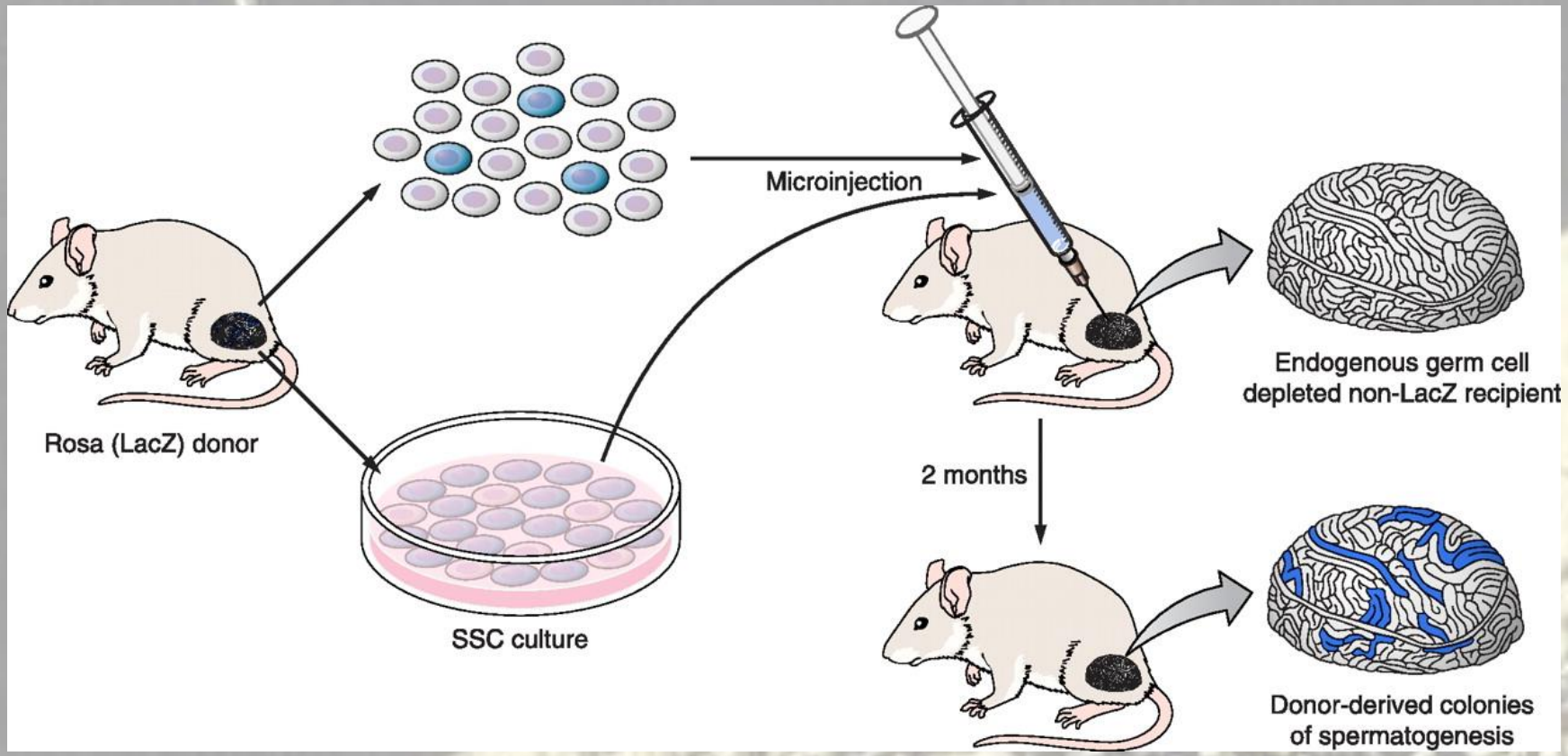
Future Fertility

- Reproductive medicine is only able to help approx 70% of couples within 5 years (Pinborg 2008)
- Donor gametes ONLY option
  - Men with NOA
  - Women with POI
  - Same sex couples/transsexual couples
- "Artificial Gametes" – gametes generated by manipulation of self progenitor or somatic cells (Hendriks 2015)

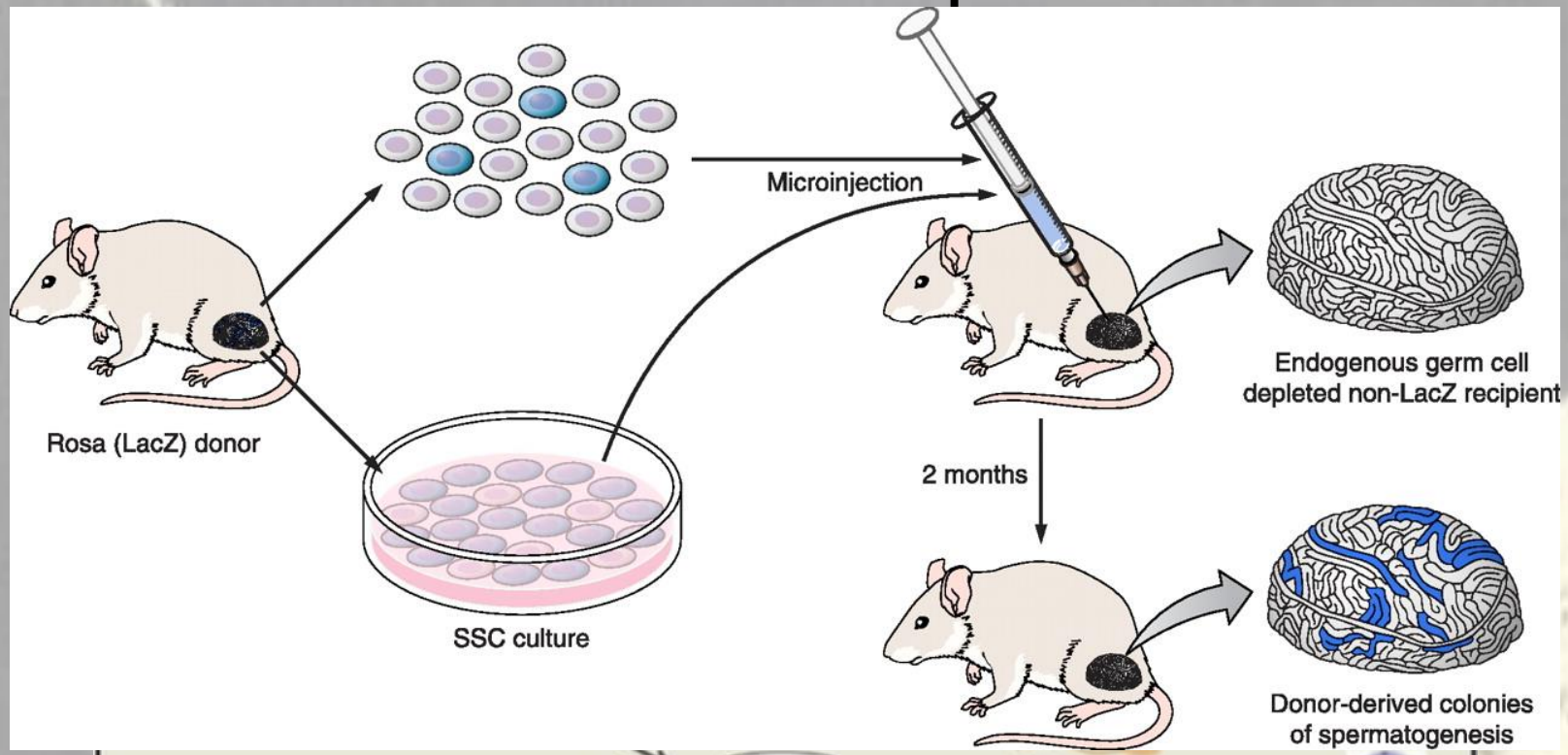
Spermatogonial stem cells

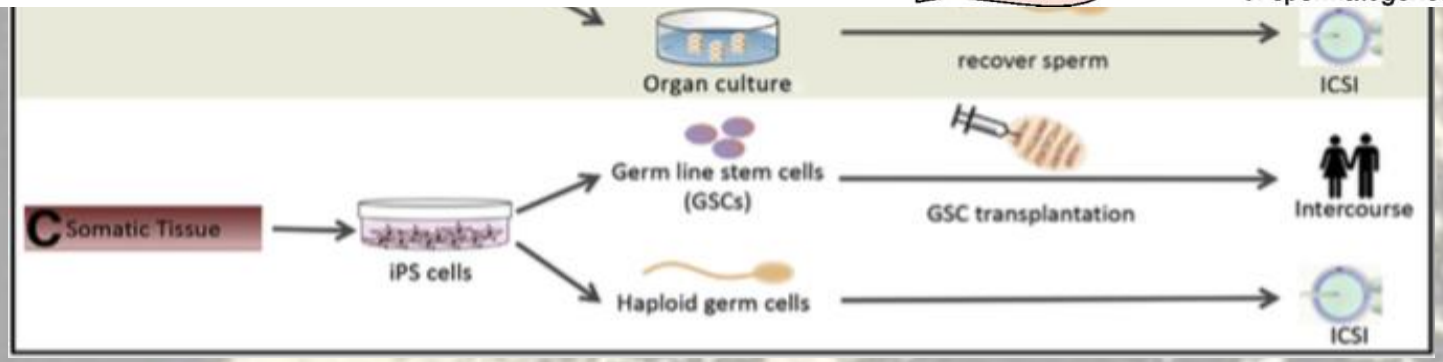


Spermatogonial stem cells



SSC therapies

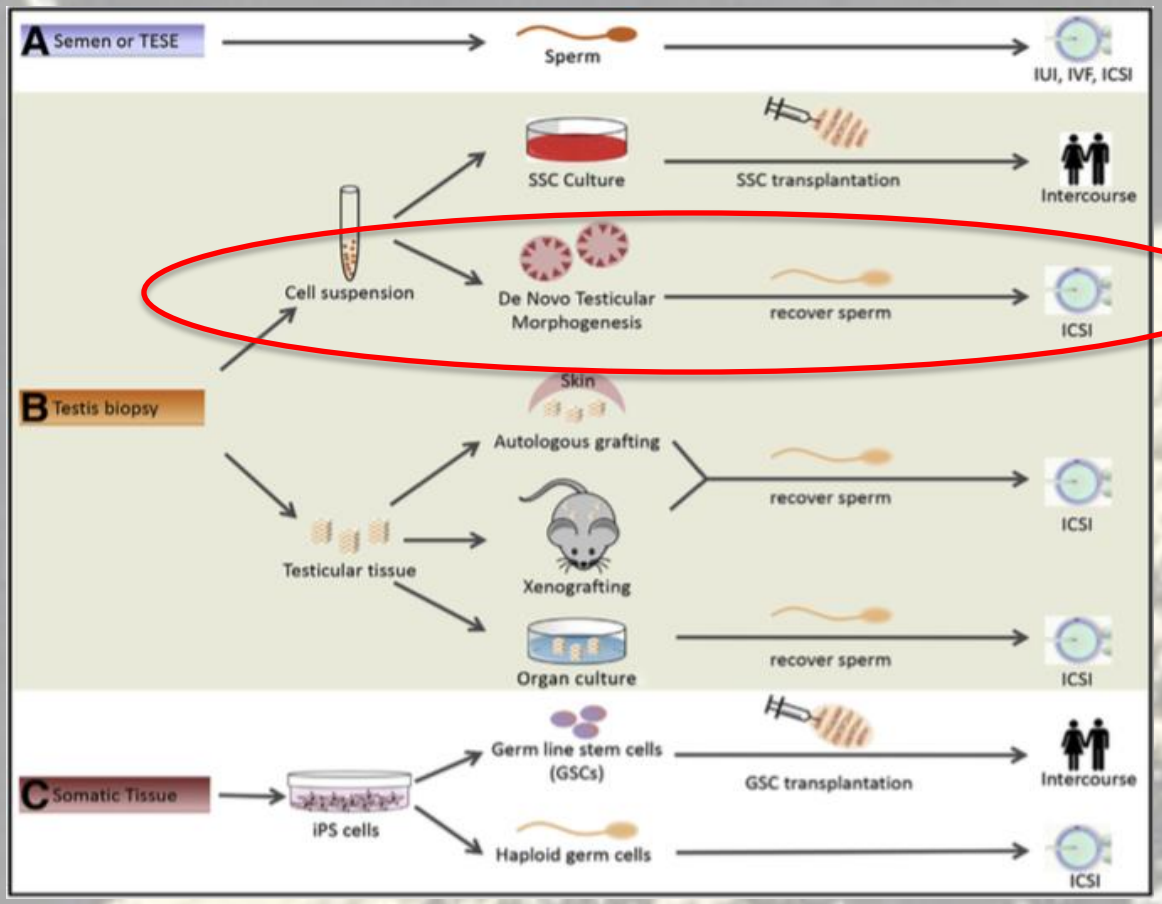




Gassei & Orwig Fertility and Sterility 2016

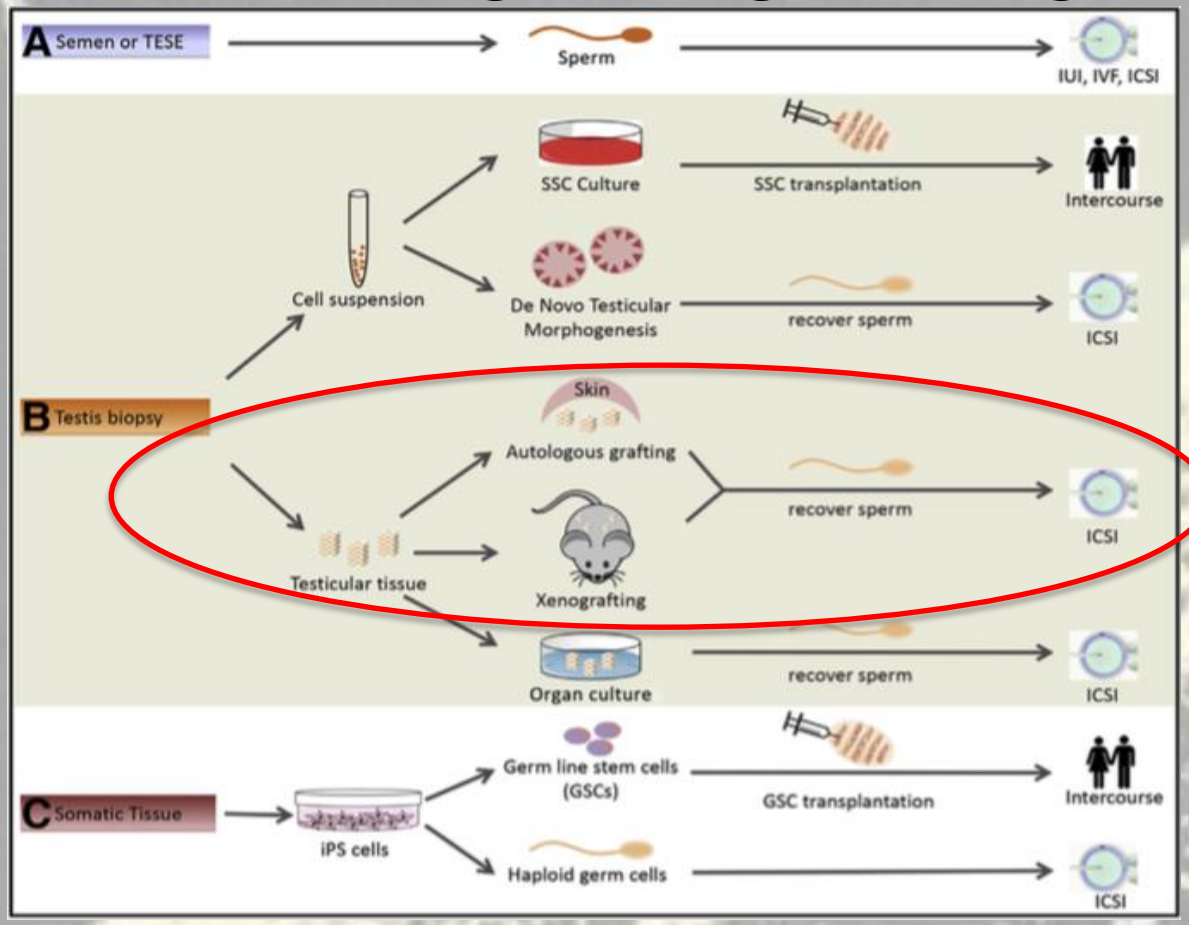
SSC – other methods

- Denovo testicular morphogenesis



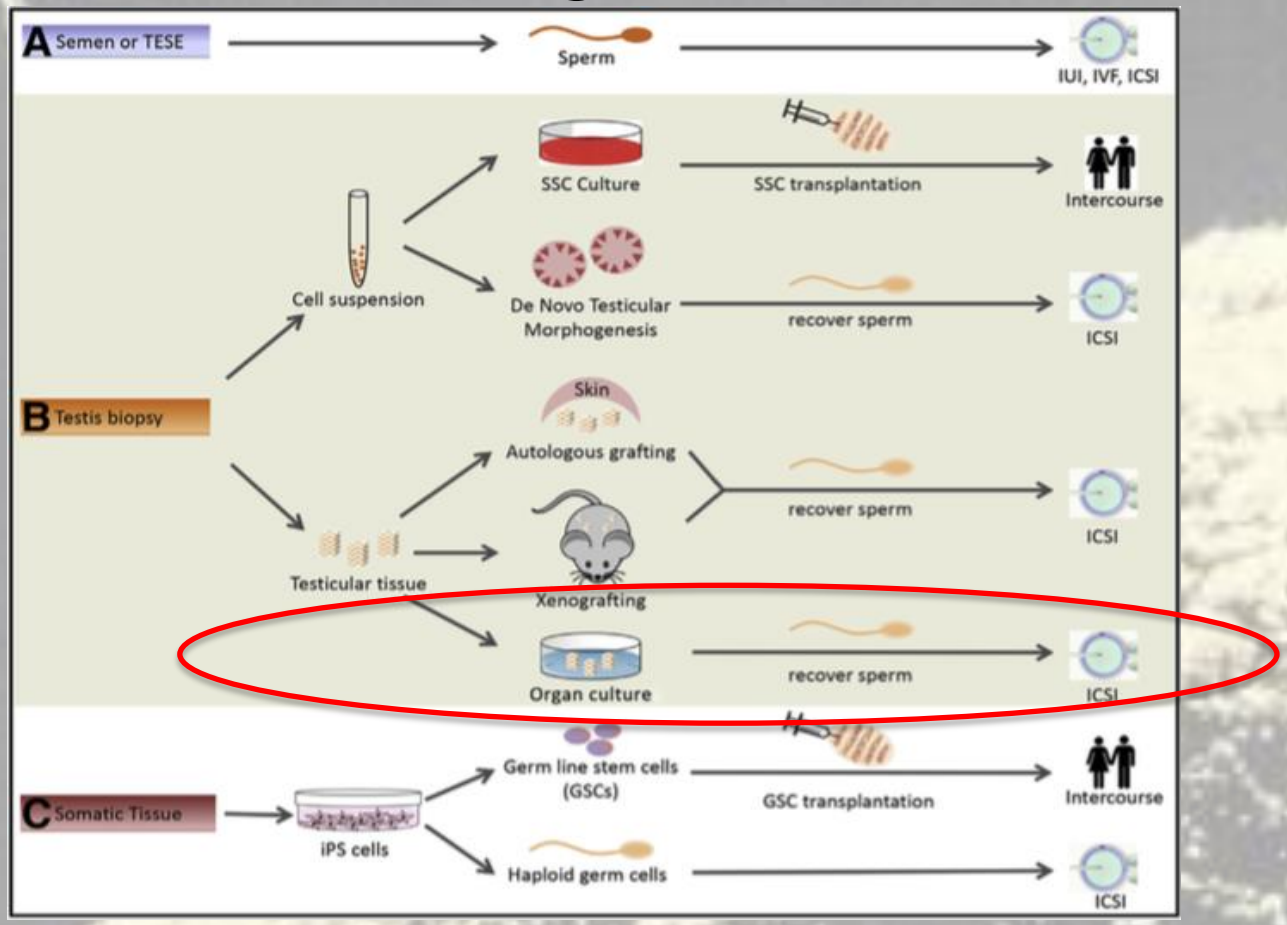
SSC – other methods

- Testicular tissue grafting/xenografting



SSC – other methods

- Testicular tissue organ culture



The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 685 • January 2017

Committee on Adolescent Health Care

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care in collaboration with committee members Nancy Sokkary, MD, and Veronica Gomez-Lobo, MD.

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Access to fertility services by transgender persons: an Ethics Committee opinion

Ethics Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Gender Diversity/Transgender

- Gender diversity service – CAMHS, PMH
- Assessment of gender dysphoria
- MDT
  - Psychiatry, psychology, endocrinology, fertility, speech therapy
- Must live as transgender for period of time before institution of therapy
- Stage 1 – puberty blockers (GnRHa)
- Stage 2 – cross hormone (E2, T)
- Stage 3 - surgery

Transgender fertility preservation

- Trangender female
  - Pre pubertal – testicular tissue (novel technology)
  - Post pubertal – semen sample OR testicular biopsy
  - Post cross hormone – cease and watch for return of spermatogenesis. Months
- Transgender male
  - Pre pubertal – ovarian tissue preservation
  - Post pubertal – oocyte cryopreservation
  - Post cross hormone – cease and watch for return of ovarian function (weeks). ? Long term effects.

Transgender fertility preservation

Journal of Adolescent Health 61 (2017) 40–44

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Original article

Low Fertility Preservation Utilization Among Transgender Youth

Leena Nahata, M.D. [a,b,*], Amy C. Tishelman, Ph.D. [c,d], Nicole M. Caltabellotta, B.A. [b], and Gwendolyn P. Quinn, Ph.D. [e,f]

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Elective Oocyte Cryopreservation

WIRED

No, Companies Shouldn't Pay Women to Freeze Their Eggs

SHARE TIME

MARY ANN MASON AND TOM EKMAN SCIENCE 04.11.17 09:00 AM

NO COMPANIES SHOULDN'T PAY

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Fertility problems
Opinion

It's not a perk when big employers offer egg-freezing – it's a bogus bribe

Suzanne Moore

Elective Oocyte Cryopreservation

- "Ideal" number to store
  - Maternal age
  - Maternal and paternal health
  - Goals of the individual (1 or more children)
- Assume frozen = fresh

Elective Oocyte Cryopreservation

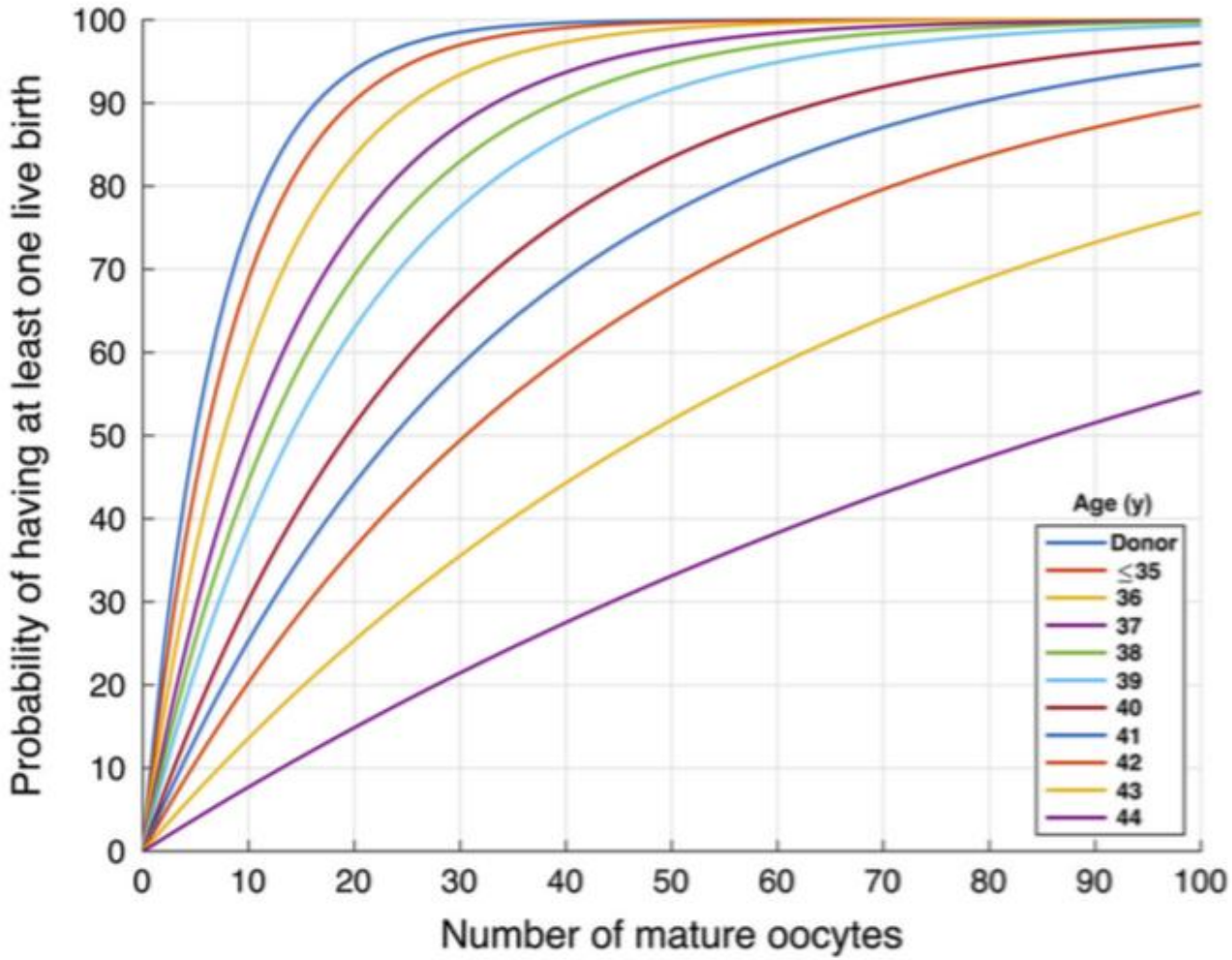

Figure 1 Live birth predictions by age and number of mature oocytes retrieved. Each curve shows the percent likelihood that a patient of a given age will have at least one live birth according to Equation 2, based on the number of mature oocytes retrieved and frozen.

Fertility preservation

Thank you