

Ovarian cortical biopsy for fertility preservation

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Financial Disclosure

- I have no financial relationships to disclose

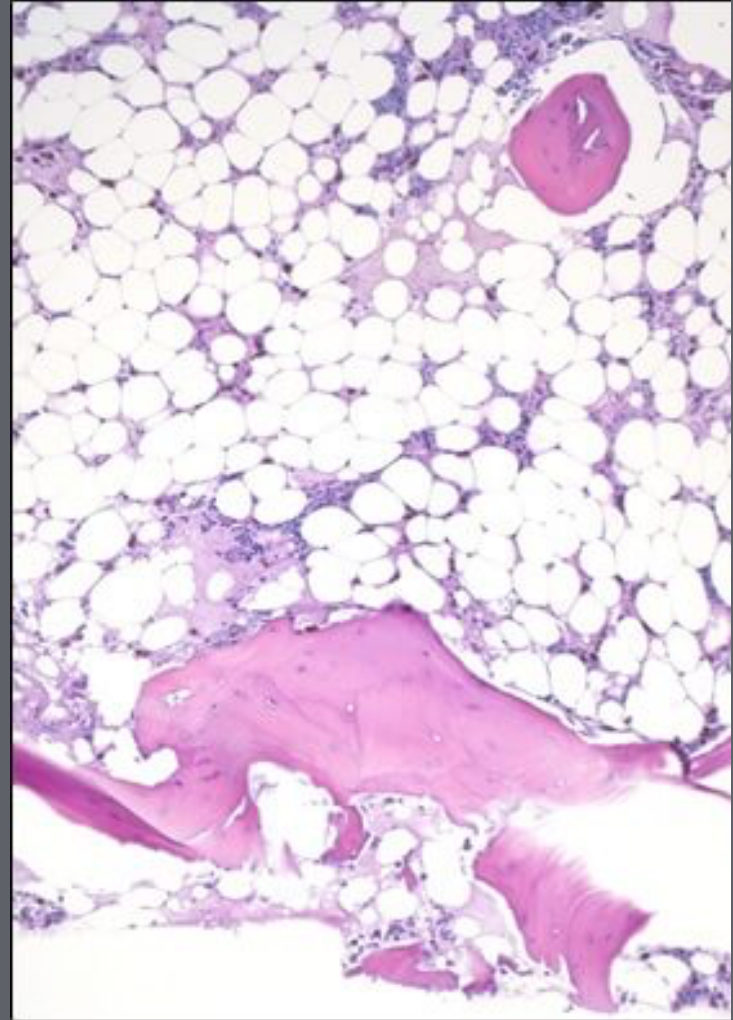
Objectives

- Review current state and indications for pediatric and AYA ovarian tissue cryopreservation
- Outline surgical techniques and freezing process for cortical biopsies
- Compare cortical biopsy vs oophorectomy for FP in pediatric and AYA patients
- Demonstrate reimplantation using minimally invasive techniques

Case Presentation

Fertility
preservation
consult:

6 year old
female with
aplastic anemia
pending HSCT



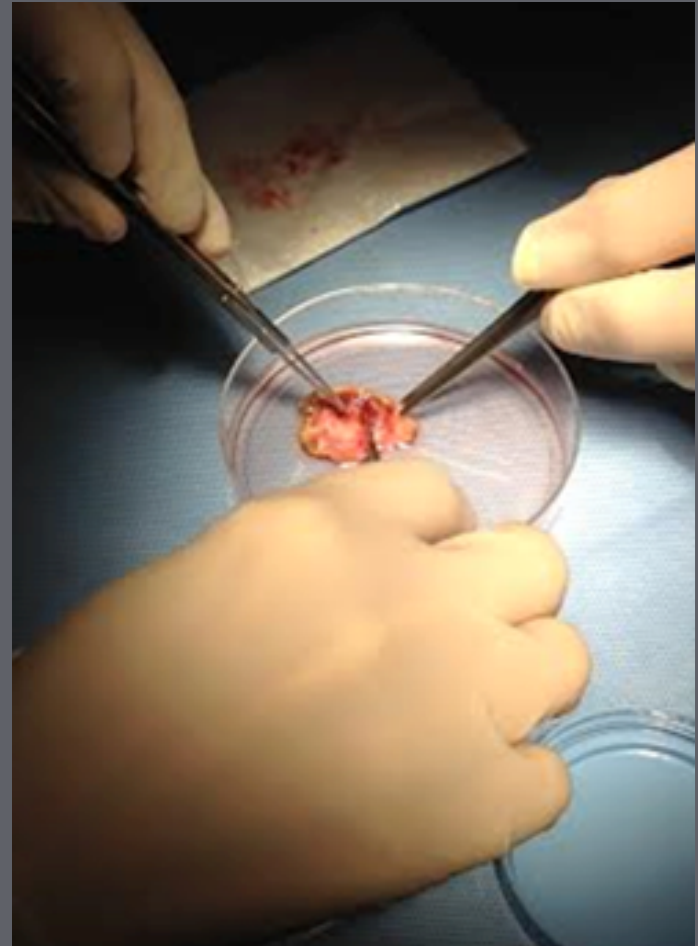
Childhood cancers

- In 2018, >15,000 children in the United States <19yo were diagnosed
- Survival is improving!
 - 1970s- 5-year survival rate of ~ 60%
 - 2010s- > 80% survive > 5 years after diagnosis
 - 400k survivors in the US today
- Late effects
 - Infertility

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA: A Cancer Journal for Clinicians* 2018; 68(1):7-30

Pediatric OTC

- Efficient method to preserve thousands of follicles
 - Malignant / non malignant indications
 - Concern for reintroduction of cells
- Prepubertal
 - IVF and ovarian stimulation may not be possible
 - Concomitant surgical procedure
- Pubertal
 - IVF and ovarian stimulation may not be desirable, affordable or expedient



COMING SOON!

ASRM to lift “experimental” designation of OTC

ASRM PAGES

Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Access to OTC in pediatric/AYA pts

- Adolescents may feel uncomfortable discussing:
 - Infertility
 - Early menopause
 - Sexual function
- In children, it may be many years before these conversations would need to take place
 - Children may have limited understanding regarding reproduction and sexual function
- Ethical considerations (prognosis, posthumous)

Selection for OTC

EDINBURGH CRITERIA?

Age younger than 35 years

A realistic chance of surviving for five years

A high risk of premature ovarian insufficiency (>50%)

No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis; Mild, non-gonadotoxic chemotherapy acceptable if younger than 15 years

Informed consent (from parents and, where possible, patient)

Negative serology results for human immunodeficiency virus, syphilis, hepatitis B

Not pregnant and no existing children

Wallace WH, Smith AG, Kelsey TW, et al. Fertility preservation for girls and young women with cancer: population-based validation of criteria for ovarian tissue cryopreservation. *Lancet Oncol.* 2014 Sep;15(10):1129-36

Unanswered questions

- *Cortical biopsy vs oophorectomy?*
 - *How much tissue is needed to achieve a successful live birth?*
- What is the best surgical method to procure and reimplant the tissue?
- What is the best system and location to deliver the tissue?
- What is the best method of cryopreservation (slow freeze or vitrification)?

Current state of OTC

- First livebirth in 2004
- Now > 150 livebirths worldwide from orthotopic tissue reimplantation
- Only offered in the United States under IRB approved registries



Donnez J, Dolmans MM, Demylle D, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. *Lancet*. 2004;364: 1405–1410.

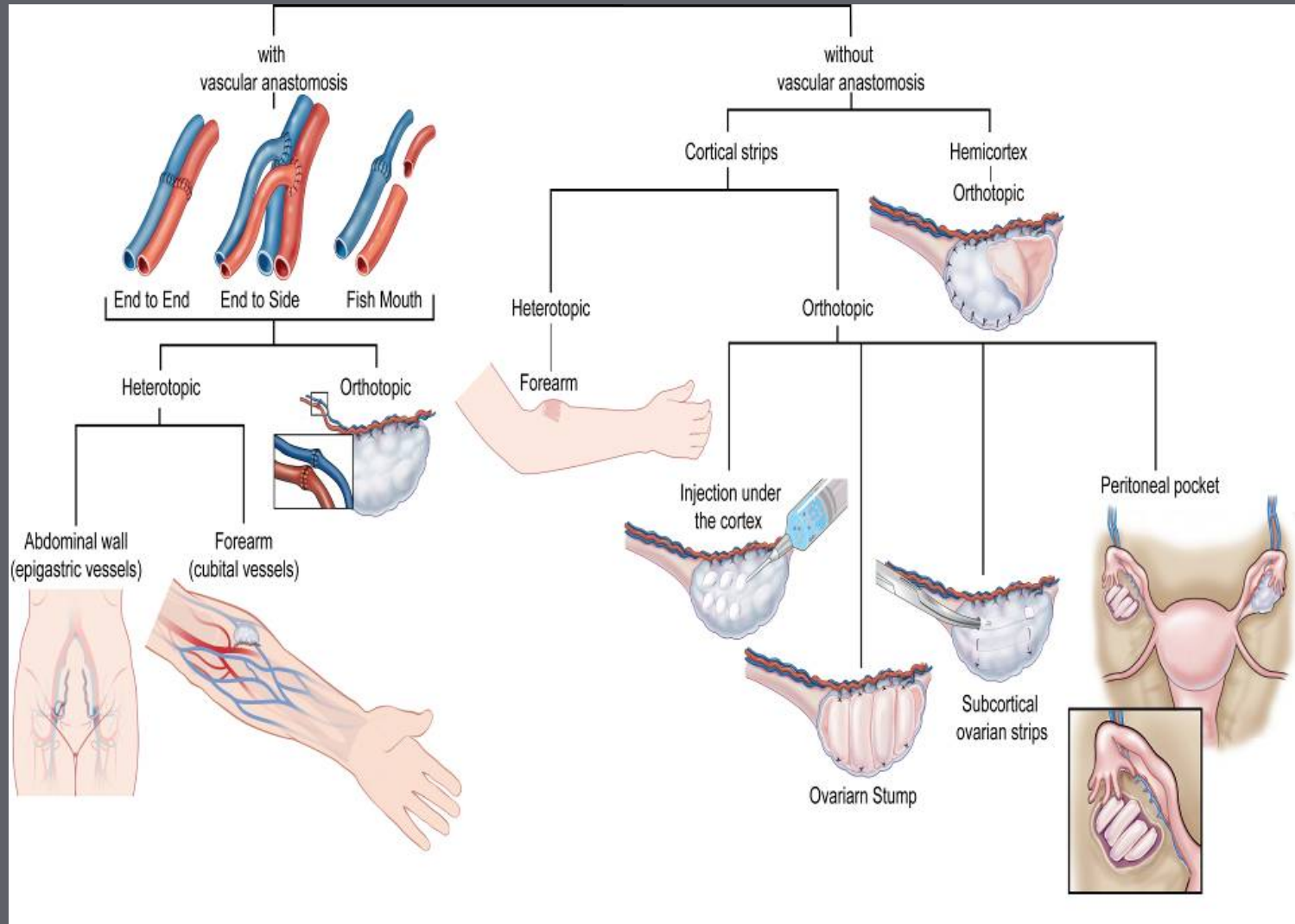
Current state of OTC

- Birth outcomes
 - Almost half become pregnant and 1/3 achieve LB
 - Most success is from adult women
- 2009 systematic review
 - 1000 pts (0.4-20.4 years)
 - 18 transplanted with autologous tissue <21yo - 10 LB
- First live birth from prepubertal child (14yo) in 2015- now 9yo



- Meiorow D, et al. Fertility and sterility. 2016;106(2):467-474.
- Van der Ven H, et al.. Human reproduction. 2016;31(9):2031-2041
- Corkum KS et al, Journal of Pediatric Surgery. 2019
- Demeestere I, et al Human reproduction. 2015;30(9):2107-2109.

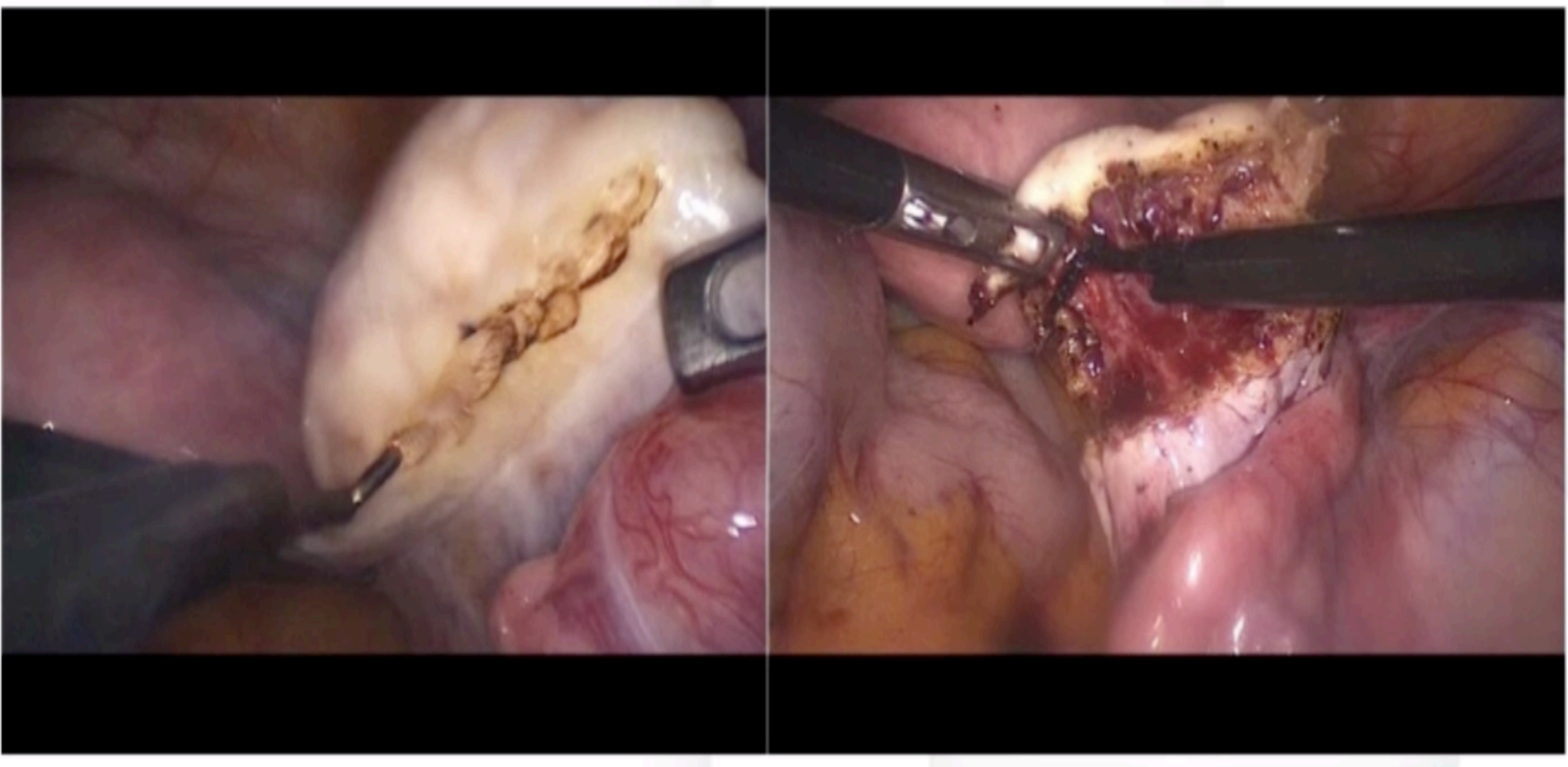
Current state of OTC



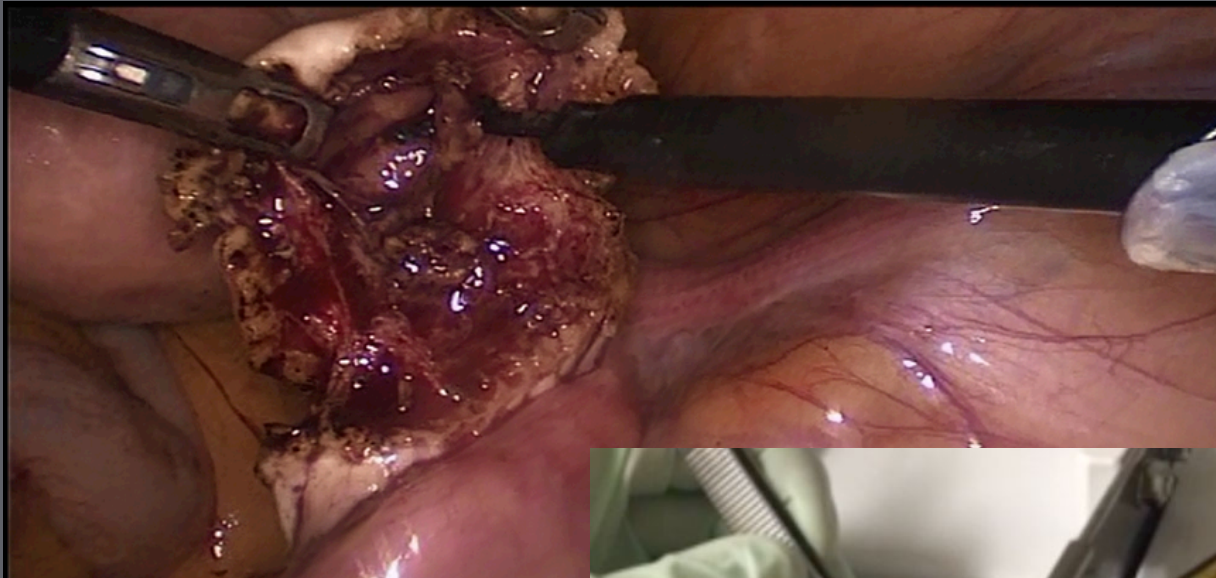
Limitations of OTC

- Only 2 livebirths yet reported from tissue frozen in prepubertal girls
- No livebirths from heterotopic reimplantation
 - 2 livebirths from peritoneal implantation
- Currently not indicated for induction of puberty or long term endocrine restoration
 - Graft longevity MAX up to 7 years

Ovarian cortical biopsy technique



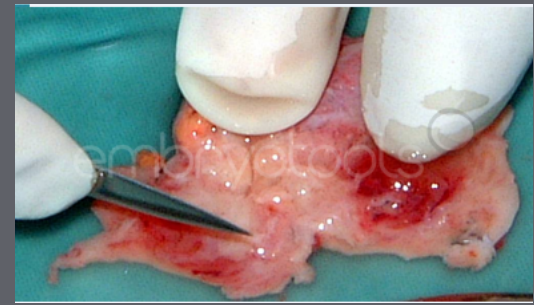
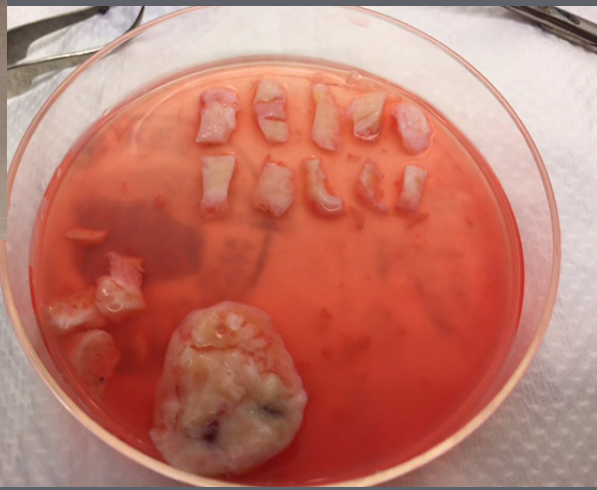
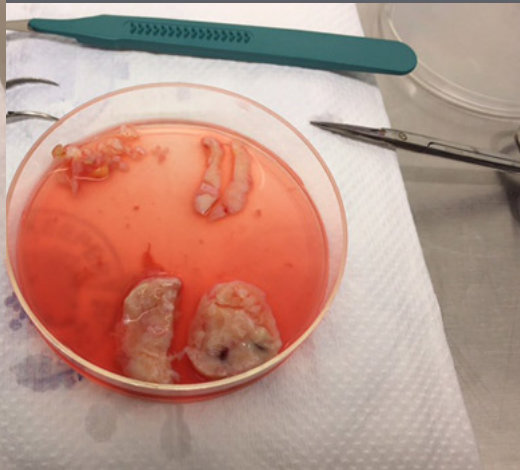
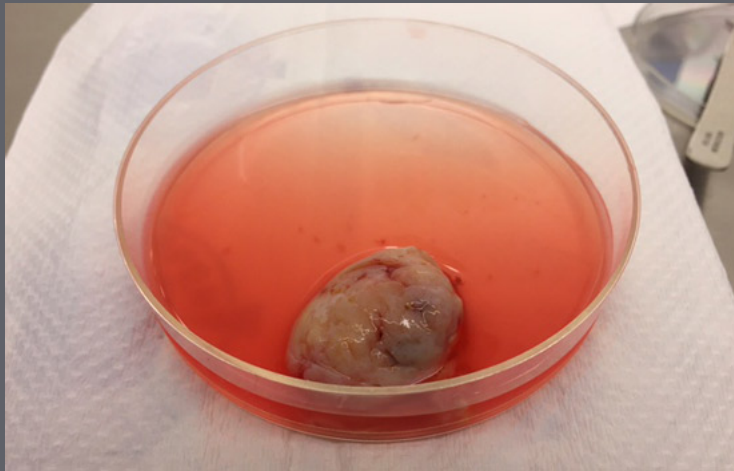
Ovarian cortical biopsy technique



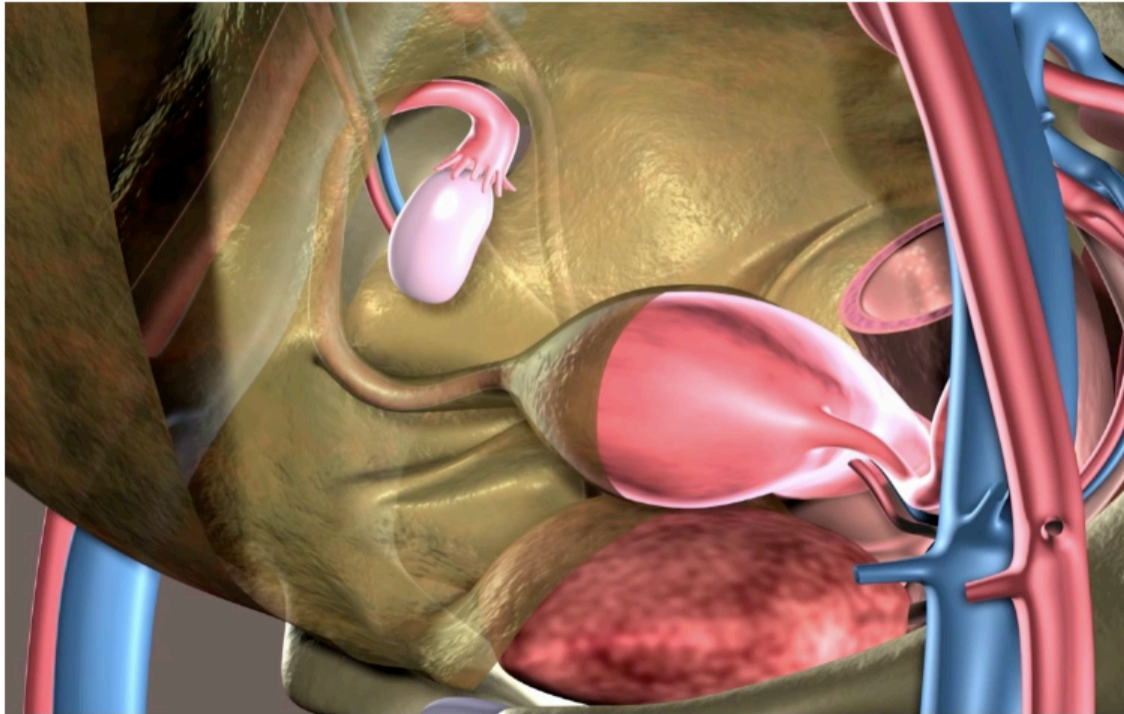
Why cortical biopsy vs oophorectomy?

- Ease of tissue dissection and preparation
- More anatomic site for reimplantation
- Paucity of data on efficacy in prepubertal girls
- Leaves more native ovary if residual function is achieved
- Less potential for ureteric injury

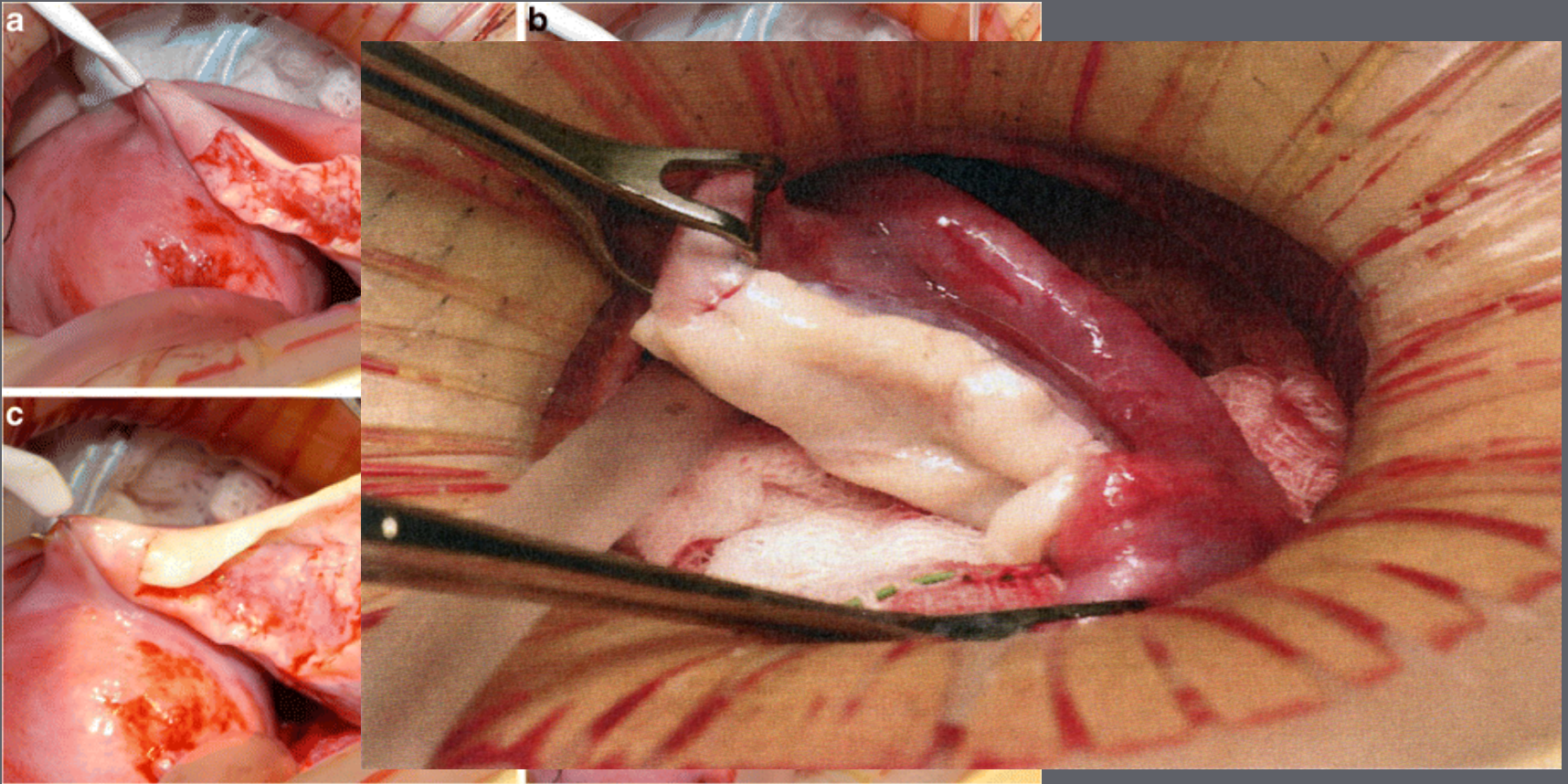
Ease of preparation



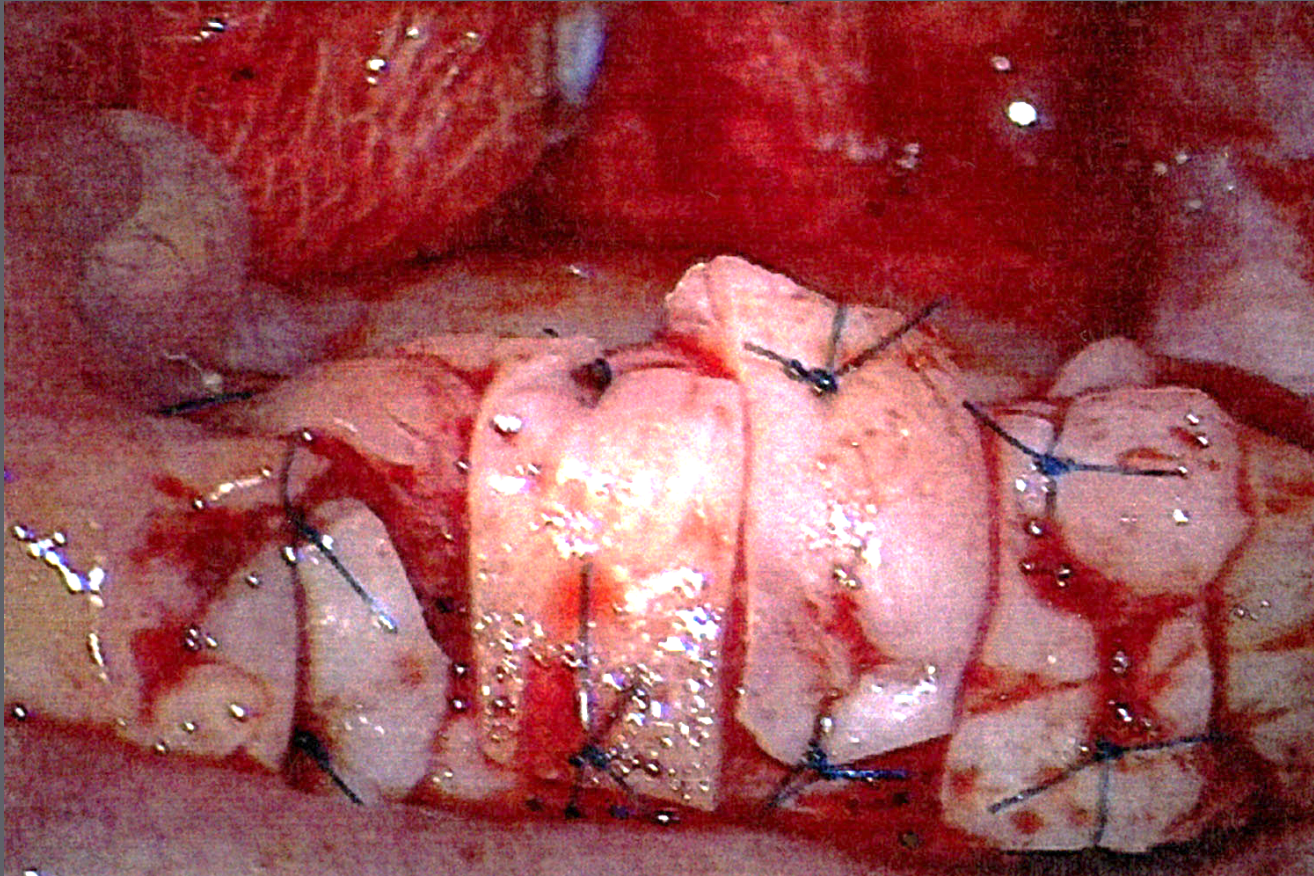
Ovarian Re-implantation: Ovarian Medulla Present



Tissue spread within peritoneal pockets?

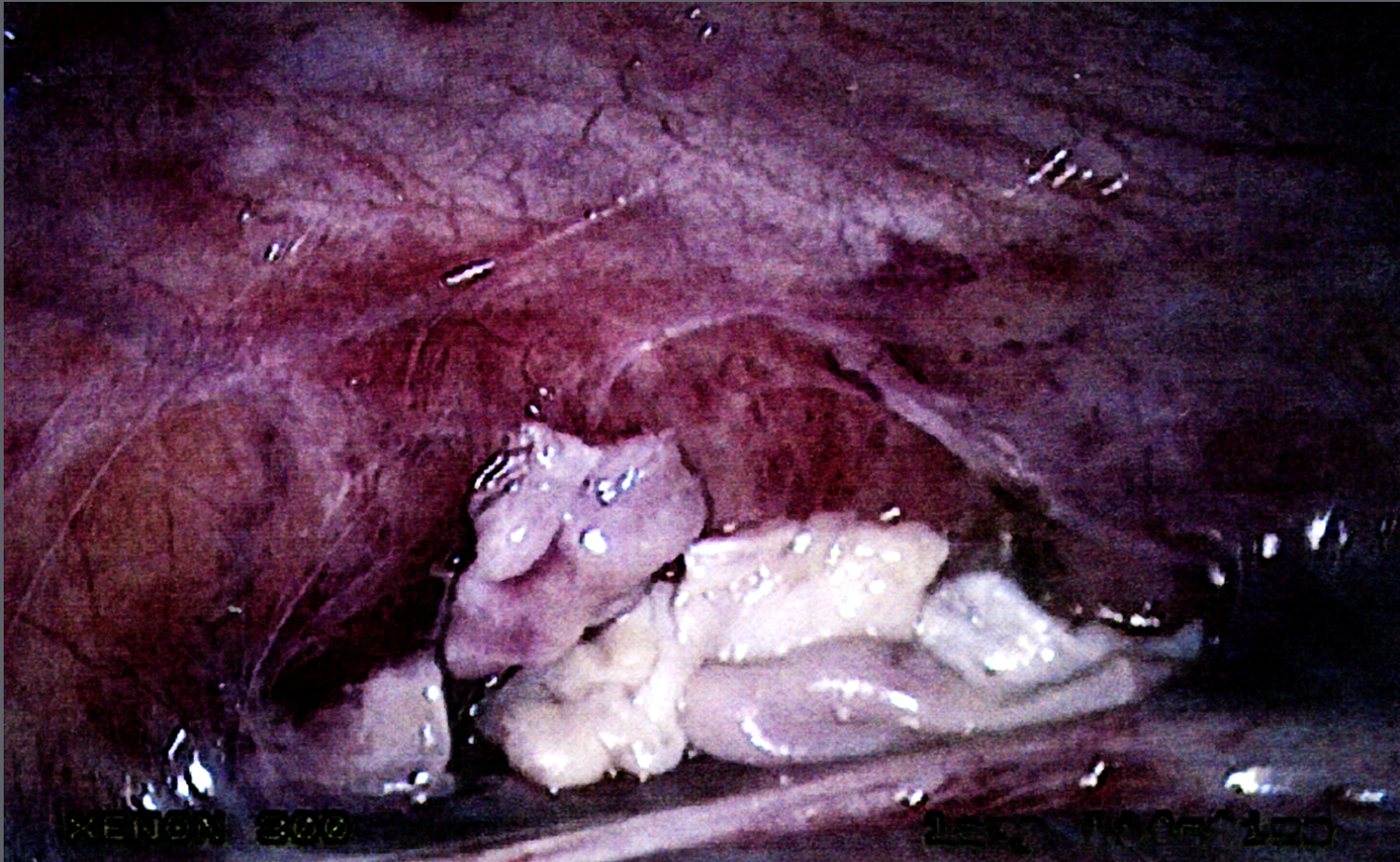


Tissue spread within peritoneal pockets?



Courtesy of Dr. Donnez

Peritoneal window

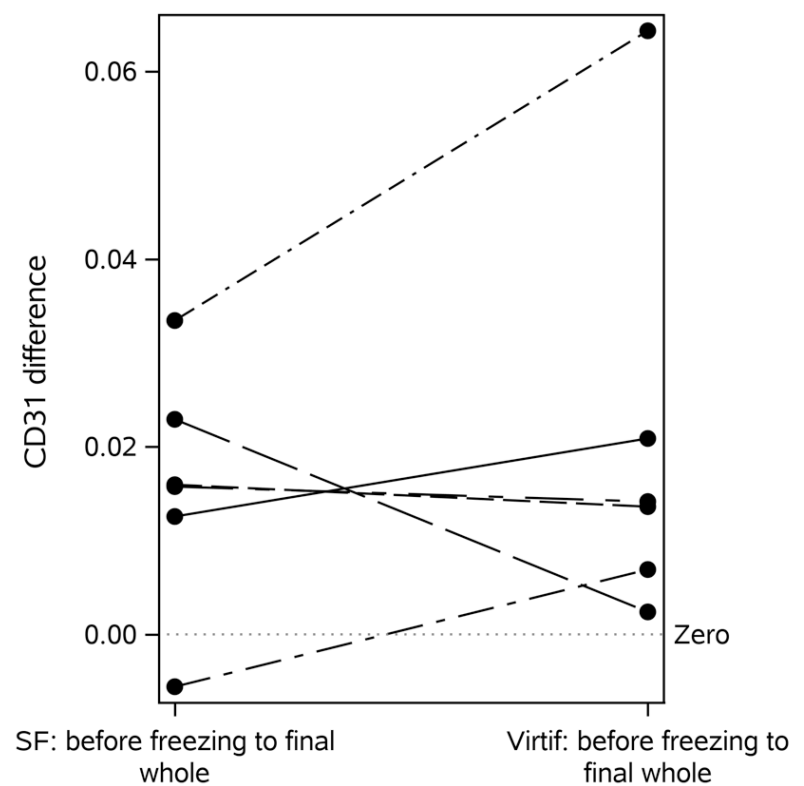
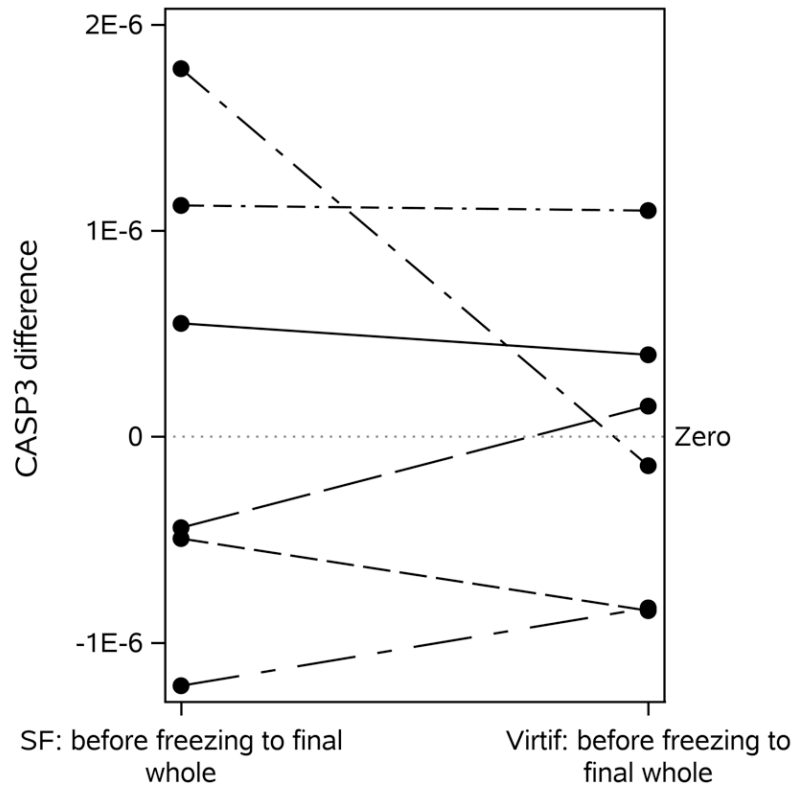


Sheep model for OTC

- 6 ewes underwent 18 procedures
 - Recovery / freezing of ovarian cortex
 - Thawing / orthotopic regrafting of cortex
 - Retrieval of transplanted tissue
- IHC staining with CCASP3 and CD31 apoptosis markers at each stage
- ***We were unable to retrieve tissue for sufficient analysis from peritoneal pockets due to spread***

Davis & Flyckt et al., 2019 (in preparation)

Sheep model for OTC



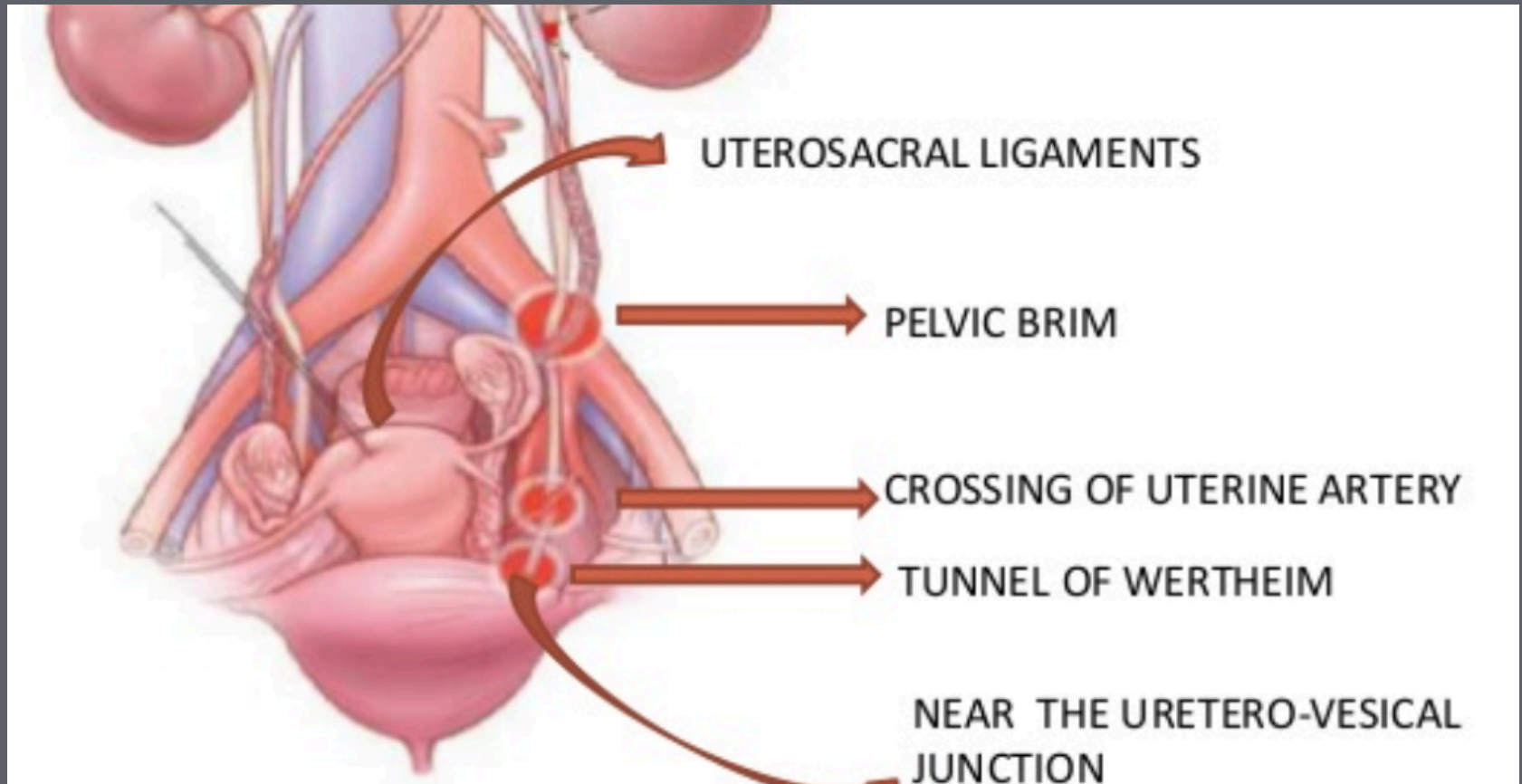
Davis & Flyckt et al., 2019 (in prepration)

Residual ovarian function after HSCT

- Allogeneic: 14-25% recovery of ovarian function
 - Young, no total body irradiation
- Autologous: A study of 17 women who underwent autologous SCT showed that five (29%) recovered their ovarian function and that the recovery rate for women younger than 25 years was 79%

Schimmer AD, Quatermain M, Imrie K, Ali V, McCrae J, Stewart AK, et al. Ovarian function after autologous bone marrow transplantation. *J Clin Oncol*. 1998;16:2359–2363

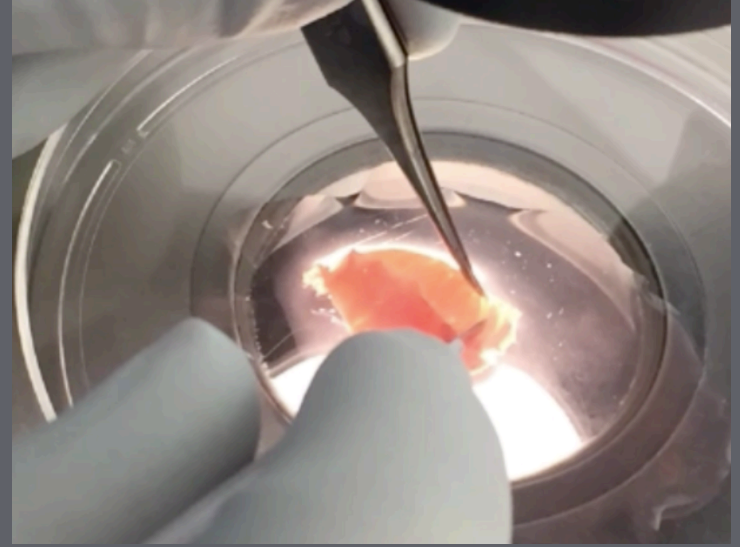
Ureteric injury at pelvic brim



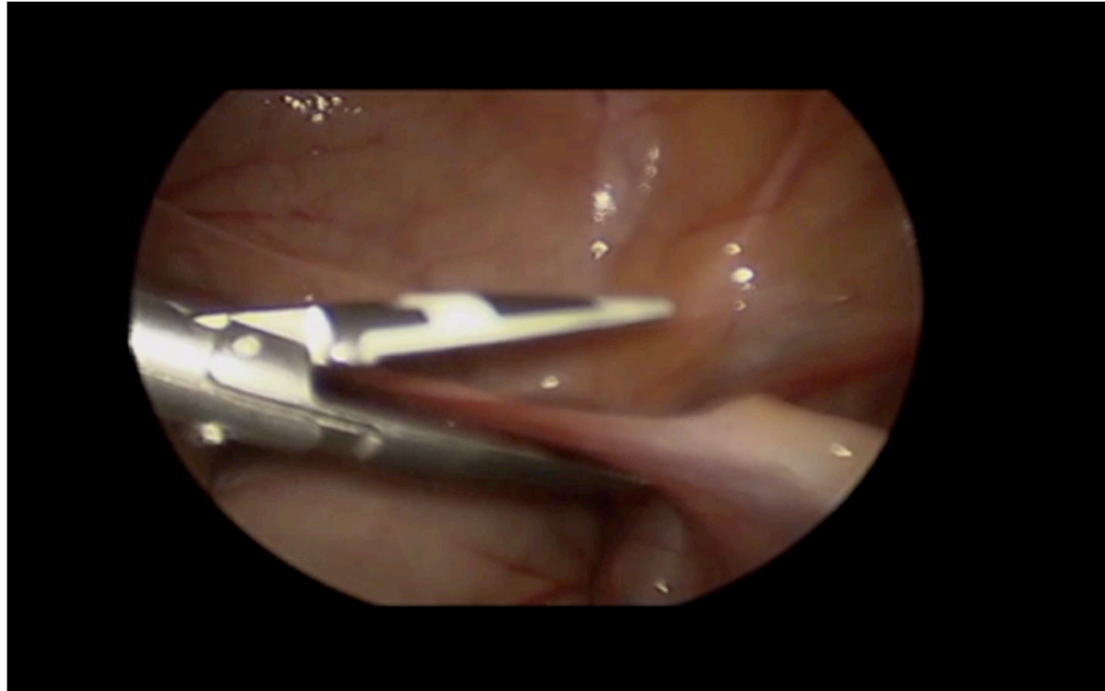
Case Presentation

Fertility
preservation
surgery in 6yo:

- Combined
with port
placement



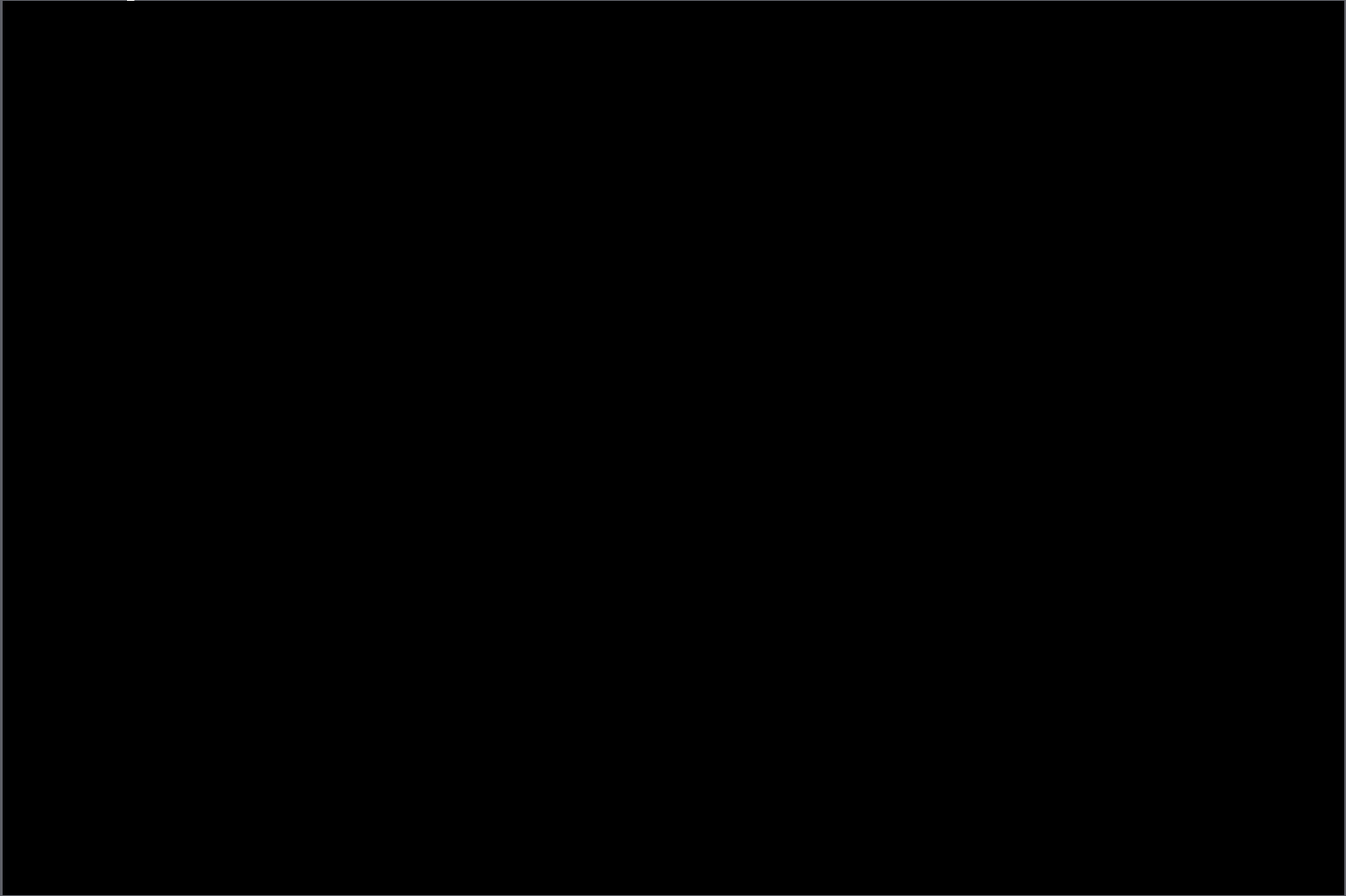
Case Presentation



 Cleveland Clinic

OTC 9

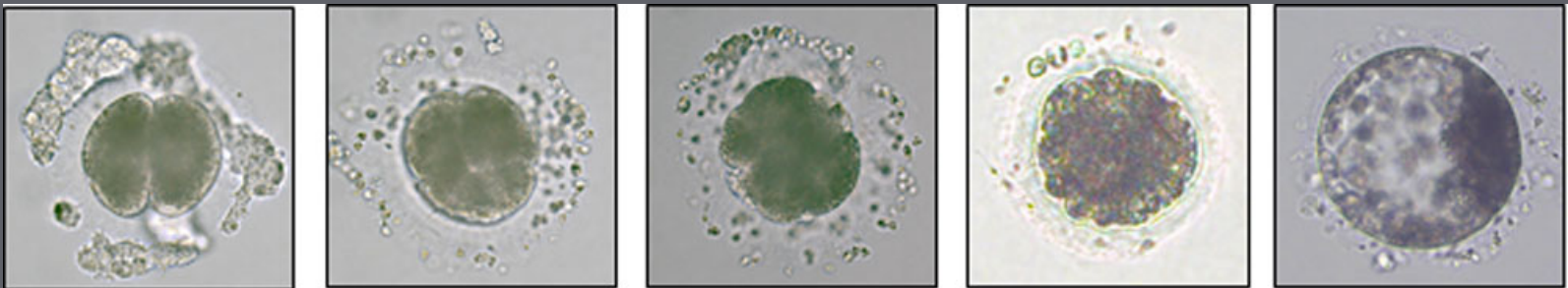
Reimplantation





Optional slide: In vitro maturation of immature oocytes

- Experimental, live birth rates are still low
- Could be used with or without frozen ovarian tissue
- 2014- first live birth from a patient who underwent oophorectomy for ovarian cancer using IVM from frozen ovarian tissue
 - Proof of concept
 - Reduce risk of malignant contamination with autotransplantation



Discussion

- In reality, I do typically take ovary in young girls (SIZE)
- Potential for IVM from ovarian tissue? If so, need more tissue...
- Other factors
 - Prior chemotherapy and planned chemotherapy- how likely is POI?
 - How sick is the patient- if I have to get in and out or if platelets are low, oophorectomy is easier and faster
 - Surgeon comfort/skill
 - History of prior ovarian surgery
 - Is ovarian transposition or other surgeries planned that will alter pelvic anatomy
 - Guided discussion with family and child if possible