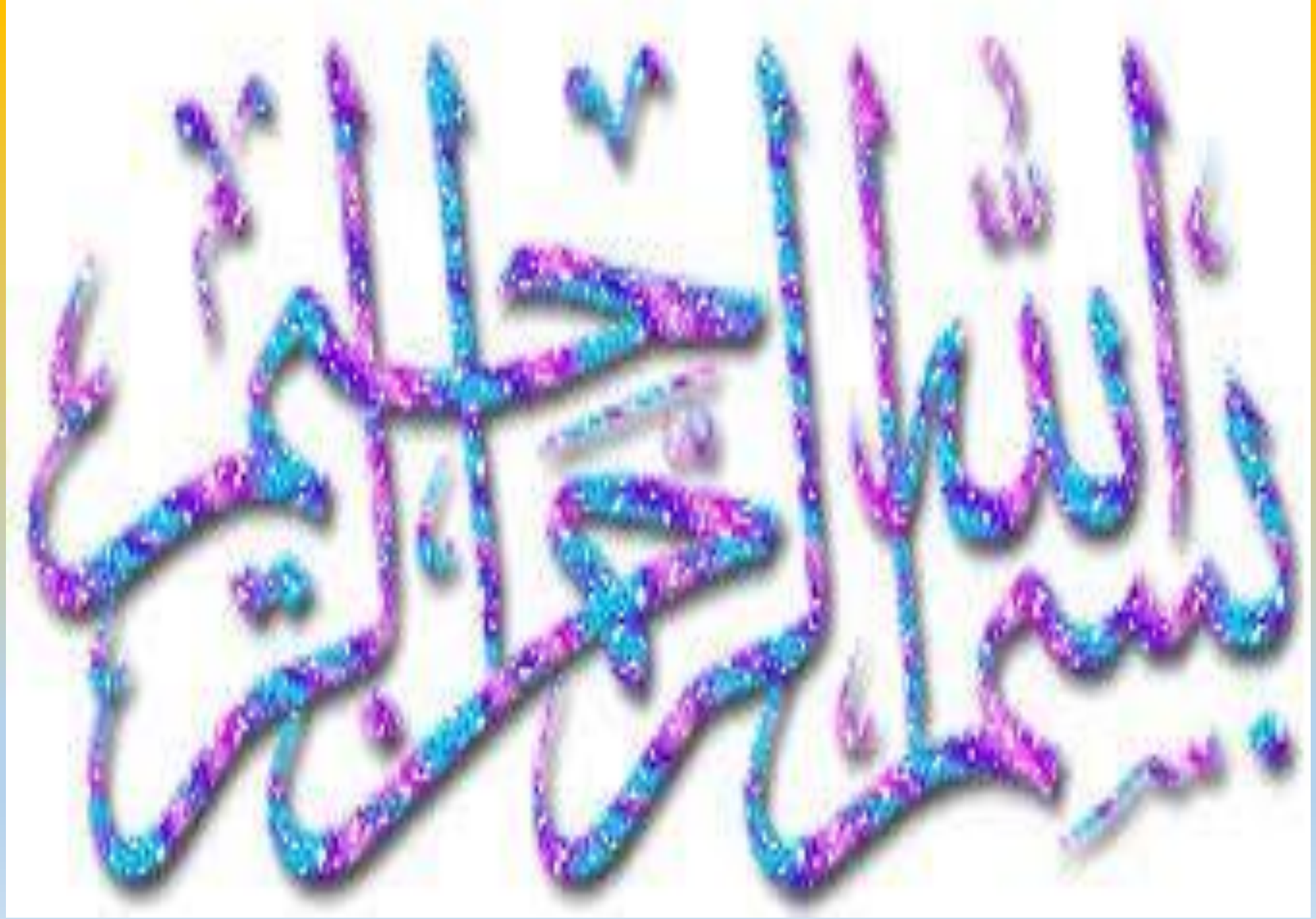
بسم الله الرحمن الرحيم

# FERTILITY PRESERVATION in Endometriosis

Kh . Shadjoo

**Advanced Laparoscopic Fellowship**

**ACEMIG**

AVICENNA Center for Endometriosis and Minimally Invasive Gynecology

1401.5.20

# Endometriosis

6-10% of reproductive age women

175 million people

Chronic pelvic pain and Infertility

30-50% in infertile women

quality of life reduced

# Endometriosis and infertility

- mechanical obstruction caused by pelvic adhesions
- local and systemic inflammatory state with increased concentration of cytokines in peritoneal fluid
- impaired embryo receptivity and implantation
- altered emberyogenesis
- decreased fertilization rate& decreased pregnancy rate

# The impact of endometriosis on ovarian reserve

- Diminished serum anti-Müllerian hormone (AMH)
- lower antral follicle counts (AFC)
- low ovarian reserve

# The impact of endometriosis on ovarian reserve

- lower response to controlled ovarian stimulation(COH)
- higher doses of gonadotropins used for stimulation
- ovarian response to hyper-stimulation for IVF treatments was halved
- (Somigliana et al., 2011)

# The impact of endometriosis on ovarian reserve

- women operated bilateral endometriomas entered menopause earlier (Coccia et al..,2011)
- low but consistent risk of post-surgical ovarian failure
- Serum AMH decreased significantly after surgery
- (Raffi et al., 2012; Somigliana et al.,2012)
- ovarian function test results were severely compromised in
- 10–15% of the operated gonads
- (Busacca et al., 2006; Benaglia et al.,2010)

# Endometriosis  surgery &ovarian reserve

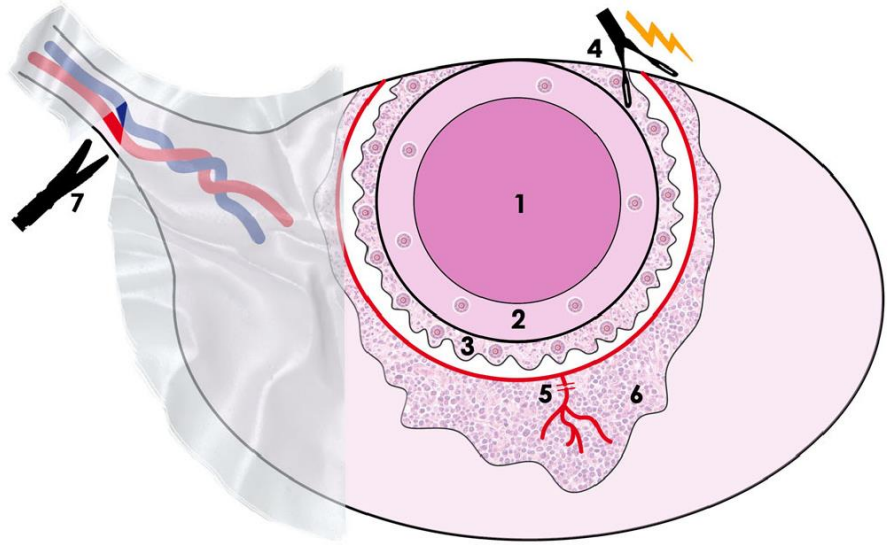


**Fig. 1** The causes of follicle loss during surgery for endometriosis involve injury to blood vessels and stroma and removal of healthy cortex. *1* Endometrioma. *2* Pseudocapsule of the endometrioma. *3* Healthy cortex containing significant number of follicles stripped with pseudocapsule. *4* Coagulation of vascular bed. *5* Blood vessels injuries. *6* Oedema/inflammation. *7* Adhesiolysis and subsequent injuries of the bloody vessels

human reproduction ORIGINAL ARTICLE ESHRE pages

# ESHRE guideline: management of women with endometriosis†

| | Grade of recommendation |
|---|---|
| In infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Hart, et al., 2008). | A |

ORIGINAL ARTICLES: ENDOMETRIOSIS

# The impact of laparoscopic cystectomy on ovarian reserve in patients with unilateral and bilateral endometriomas

Saeed Alborzi, M.D., Pegah Keramati, M.D., Masoomeh Younesi, M.D., Alamtaj Samsami, M.D., and Nasrin Dadras, M.D.

Department of Obstetrics and Gynecology, Infertility Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

**Objective:** To evaluate the effects of laparoscopic cystectomy on ovarian reserve in patients with endometriomas.
**Design:** Prospective study.
**Setting:** Private and university hospitals.
**Patient(s):** A total of 193 patients with endometriomas undergoing laparoscopic cyctectomy.
**Intervention(s):** Serum levels of antimüllerian hormone (AMH), FSH, and $E_2$, as well as antral follicle count (AFC) were measured preoperatively and 1 week, 3 and 9 months postoperatively for AMH, and 3 months for other values.
**Main Outcome Measure(s):** Ovarian reserve based on the comparison of AMH alterations. The secondary end points are changes in FSH, $E_2$, and AFC.
**Result(s):** Serum AMH level decreased significantly from the baseline (3.86 ± 3.58 ng/mL) to 1 week (1.66 ± 1.92 ng/mL), 3 months (2.06 ± 2.5 ng/mL), and 9 months (1.77 ± 1.76 ng/mL) postoperatively. Those patients with bilateral endometriomas had significantly lower levels of AMH, 1 week, 3 and 9 months after operation. Also, patients older than 38 years had lower postoperative AMH levels. The FSH levels increased significantly from baseline to 3 months postoperatively. The AFC level increased significantly from baseline to 3 months after operation.
**Conclusion(s):** The AMH level decreased and the FSH level increased after laparoscopic cystectomy for endometriomas, especially in older patients and those with bilateral cysts. (Fertil Steril® 2014;101:427–34. ©2014 by American Society for Reproductive Medicine.)
**Key Words:** Laparoscopic cystectomy, endometrioma, ovarian reserve

**Discuss:** You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/alborzis-laparoscopic-cystectomy-ovarian-reserve-endometrioma/

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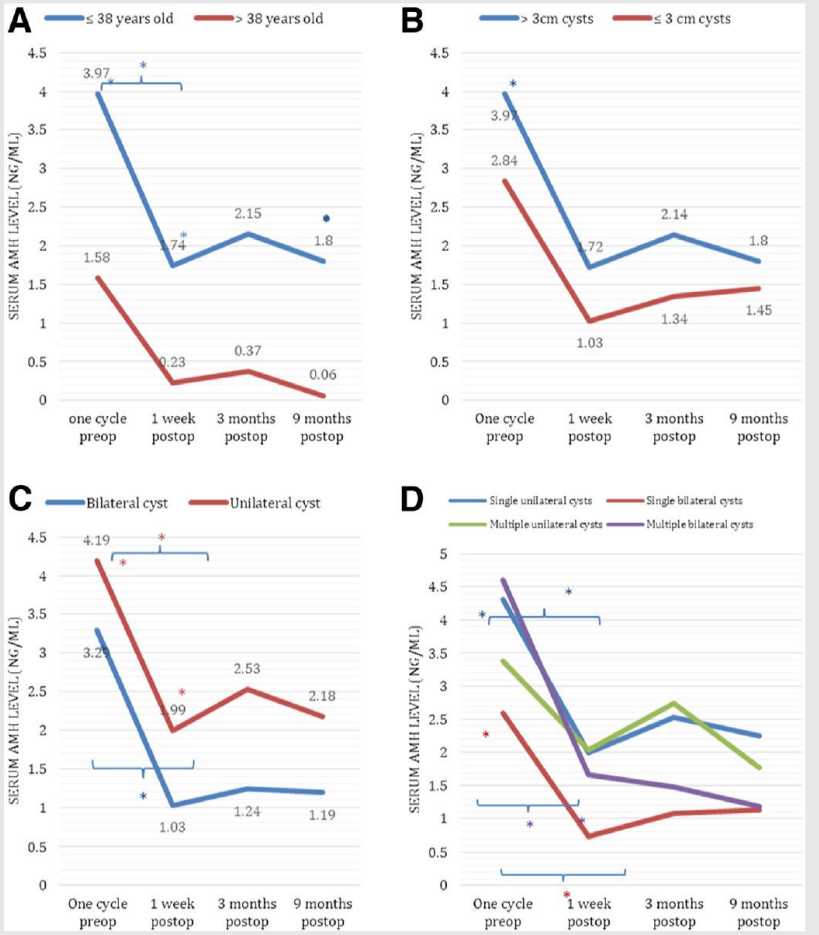



Changes in serum antimullerian hormone (AMH) levels in different age (A), size (B), bilatrality (C), and number (D) groups. Asterisks denote statistically significant changes; values are reported in the text. (D) One-way analysis of variance (ANOVA) with post hoc least significant difference (LSD) test was used to compare the groups. A significant decrease in AMH levels was observed at the third postoperative (postop) month in multiple bilateral endometriomas compared with single unilateral and multiple unilateral cysts. Preop = preoperative.

*Alborzi. Ovarian reserve after endometrioma excision. Fertil Steril 2014.*

# Parameters influencing reduced ovarian reserve by surgery

| | |
|---|---|
| I | Mono/bilateral endometriomas<br>Removal of bilateral endometriomas more harmful |
| II | Pre-surgical ovarian reserve<br>Low ovarian reserve and/ or advanced age results in more detrimental impact of surgery on ovarian reserve |
| III | Characteristic and follicle density of the endometrioma's wall<br>Fibroblastic type: younger patients, high number of follicles<br>Fibrocystic type: older patients have small number of follicles |
| IV | Capability of the surgeon<br>Ability of the surgeon to minimize removal of healthy tissue<br>Identifying endometriotic infiltration extent and lesion borders<br>Minimizing coagulation during the surgery |
| V | Disease recurrence<br>► Need for repeated surgical interventions |

## TREATMENT. Main objectives:

- Reduce pain
- Delay recurrence for as long as possible
- Preserve and improve fertility

Donnez J et al. Front Biosci 2012

## RISKS OF SURGICAL REMOVAL:

- Risk of postsurgical ovarian failure
- Experience of the laparoscopist
- Risk of disease recurrence
- Impaired ovarian vascularization
- Costs
- No improvement of reproductive outcomes


Tsoumpou I et al. Fertil Steril. 2009

# Reproductive capacity

- seriously affected by:
- Age
- Genetic syndromes
- Treatments(gonadal toxicity)

- Fertility preservation (FP) is a fundamental issue for individuals of:
- reproductive age (both male and female)
- prepubescent boys and girls whose future fertility may be compromised.

# INDICATIONS FOR FP

- Oncological indication
- Non-oncological Medical Indications

## TABLE 1

**Non-oncological conditions requiring fertility preservation.**

| Indication | Disease |
|---|---|
| Autoimmune diseases (6, 7) | Systemic lupus erythematosus (SLE)<br>Behcet's disease<br>Churg-Strauss syndrome (eosinophilic granulomatosis)<br>Steroid resistant glomerulonephritis<br>Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)<br>Inflammatory bowel diseases<br>Rheumatoid arthritis Pemphigus vulgaris |
| Hematopoietic stem cell transplantation (7, 8) | Autoimmune diseases unresponsive to immunosuppressive therapy<br>Haematological diseases (sickle cell anaemia, thalassaemia major, plastic anaemia) |
| Medical conditions causing POI (9) | Altered hypothalamic–pituitary–gonadal axis (10, 11)<br>Ovarian oophoritis<br>Benign ovarian tumours<br>Mosaic Turner's syndrome<br>Fragile X Mental Retardation 1 (12)<br>Galactosaemia (13)<br>Beta-thalassaemia<br>(14)<br>Endometriosis (15) |
| Male genetic disorders | Klinefelter's syndrome (6) |
| Testicular damage (16) | |
| Gender reassignment procedures (17) | |
| Severe body trauma requiring surgical intervention | |

*Note:* POI = premature ovarian insufficiency.

*Martinez. Update on fertility preservation. Fertil Steril 2017*

# Delayed Childbearing

- Female fertility decreases gradually
- significantly after age 32 years
- and faster after 37 years

- The term ‘AGE banking’
- (oocyte banking for anticipated gamete exhaustion) has been
- proposed for oocyte cryopreservation

# AVAILABLE PROCEDURES FOR FP

- embryo cryopreservation
- oocyte cryopreservation (slow freezing or vitrification)

- oocyte cryopreservation is increasingly preferred
- **Mature oocyte vitrification** is preferred in post- pubertal women
  - when gonadotoxic treatment can be delayed to allow
  - time for controlled ovarian stimulation (COS)
- **Harvesting of immature oocytes** would be an option for patients
  - unable to undergo COS such as prepubertal girls
  - Women with aggressive or hormone-sensitive cancers
- **IVM** improves outcomes in breast cancer patients undergoing
- COS for FP

# Ovarian tissue cryopreservation(OTC)

- experimental technique
- FP option in paediatric patients
- hormone-dependent diseases

## TABLE 2

**Clinical outcomes from fertility preservation techniques in women.**

| Author | FP technique | Women/Indication | Outcome |
|---|---|---|---|
| Dolmans et al., (18) | Embryo cryopreservation | 54/Cancer<br>33 returned/20 ET | 22% LBR per ET<br>nine pregnancies<br>Four deliveries |
| Oktay et al., (19) | Embryo cryopreservation | 33/Breast cancer<br>18 returned/55 ET | 45% LBR per ET<br>26 pregnancies<br>18 deliveries |
| Cobo et al., (20) | Oocyte vitrification | Ovum donation programme | 6.5% oocyte-to-baby rate.<br>CLBR increased with the number of oocytes used |
| Cobo et al., (21) | Oocyte vitrification | Delaying childbearing or non-oncological medical conditions | 50% LBR per patient in women ≤35 years old<br>22.9% LBR per patient in women >36 years old |
| Donnez et al., (22) | Ovarian tissue cryopreservation | | N = 111 cases, 32 conceived<br>29.0% LBR per patient |

*Note:* FP = fertility preservation; ET = embryo transfer; LBR = live birth rate; CLBR = cumulative live birth rate.

*Martinez. Update on fertility preservation. Fertil Steril 2017.*

# RESULTS OF ART AFTER FP

## Women

Among women undergoing oocyte vitrification

- Age
- Non-oncological medical conditions
- LBR per patient of 50% among women aged 35

- 22.9% among those aged >36 years after the transfer of embryos
- obtained from vitrified oocytes
- CLBR was higher and increased faster among younger women

# Ovarian tissue reimplantation

- Reimplantation of this tissue :
- the pelvic cavity (orthotopic)

- elsewhere (heterotopic)

- has the potential of restoring fertility and ovarian hormone secretion

# Cryopreservation of the whole ovary

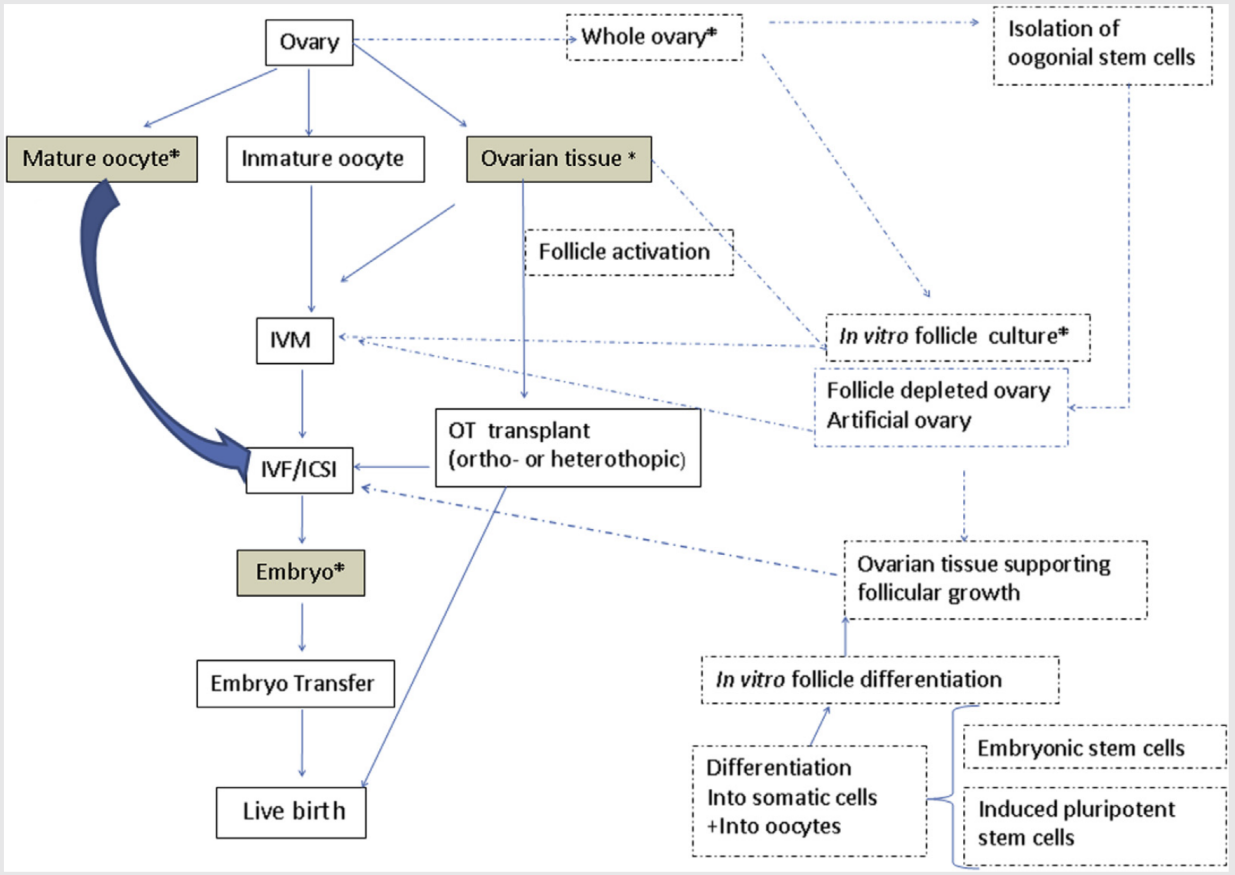
- more problematic
- increased size of their ovaries
- the difficulty of achieving adequate perfusion and penetration of the
- cryoprotectants agents through the whole organ

- the inherently different freezing and thawing optima for the
- different cell types in both the ovary and blood vessels

# RESULTS OF ART AFTER FP
# Women

- embryo cryopreservation has high pregnancy success rates
- Outcomes in cancer patients are scarce

- Success rates associated with oocyte vitrification are superior
- to slow freezing


Ovary
Whole ovary*
Isolation of oogonial stem cells
Mature oocyte*
Inmature oocyte
Ovarian tissue *
Follicle activation
IVM
In vitro follicle culture*
Follicle depleted ovary
Artificial ovary
OT transplant
(ortho- or heterothopic)
IVF/ICSI
Embryo*
Ovarian tissue supporting follicular growth
Embryo Transfer
In vitro follicle differentiation
Embryonic stem cells
Differentiation
Into somatic cells
+Into oocytes
Induced pluripotent stem cells
Live birth

- Artificial gametes
  - The use of primordial germ cells (PGC

- New fertoprotective agents
- anti-apoptotic properties
- reduce follicle loss in animal models
- prevent follicle activation

- Embryo and oocyte cryopreservation

- first-line FPmethods in postpubertal women

- Metaphase II oocyte cryopreservation
- (vitrification) is the preferred option
-

# cryopreserved ovarian tissue

- Cumulative evidence for restoration of ovarian function
- and spontaneous pregnancies after ART following orthotopic
- transplantation of cryopreserved ovarian tissue supports
- its future consideration as an open clinical
- application.

- Semen cryopreservation is the only established FP technique
- in men
- Testicular tissue cryopreservation should be recommended
- in pre- pubertal boys even though fertility restoration strategies
- by auto transplantation of cryopreserved testicular
- tissue have not yet been tested for safe clinical use in
- humans.

# 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

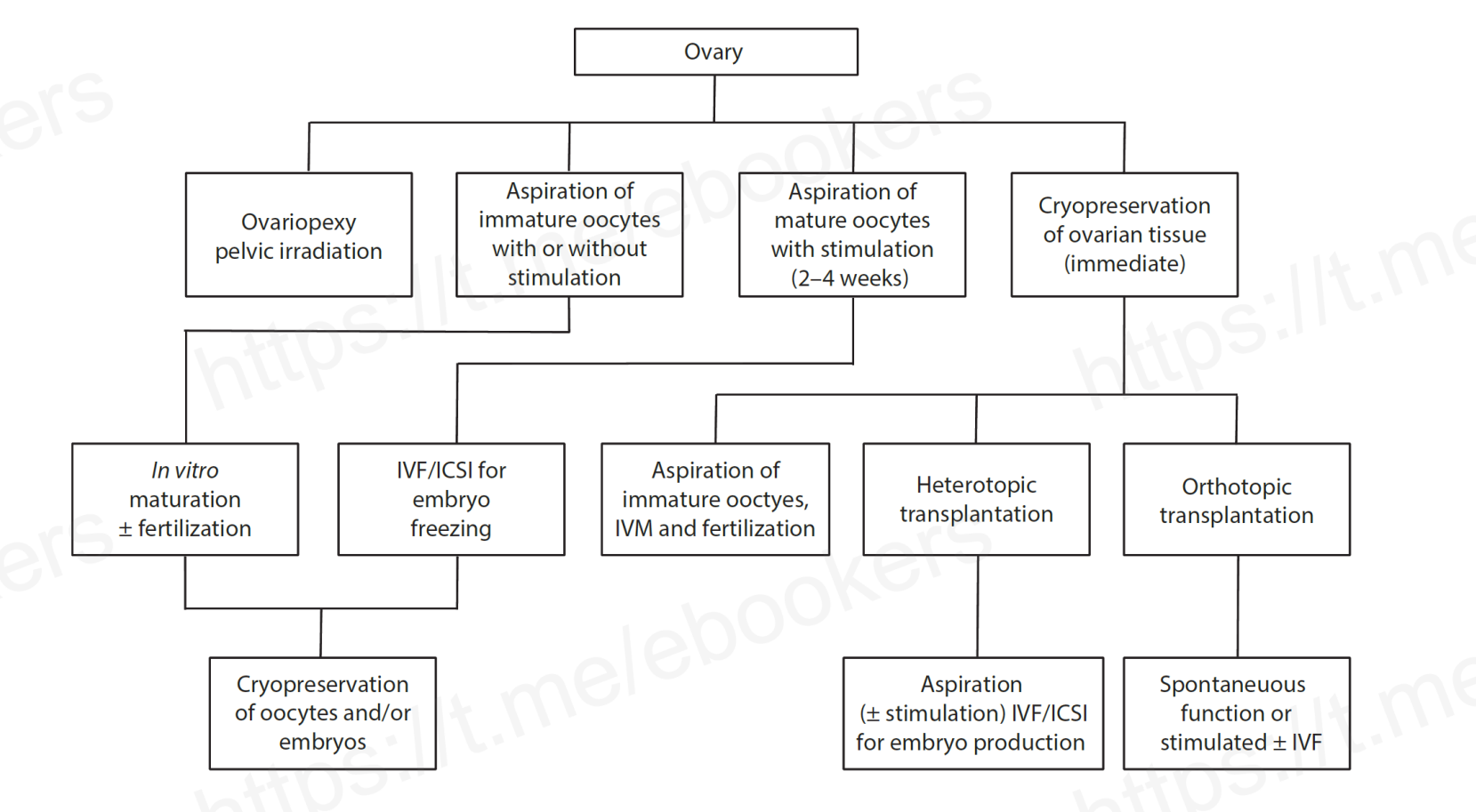
Hospital Universitario Dexeus, Gran Via Carlos III, 71-75, 08208, Barcelona, Spain

**Study Question:** What progress has been made in fertility preservation (FP) over the last decade?
**Summary Answer:** FP techniques have been widely adopted over the last decade and therefore the establishment of international registries on their short- and long-term outcomes is strongly recommended.
**What Is Known Already:** FP is a fundamental issue for both males and females whose future fertility may be compromised. Reproductive capacity may be seriously affected by age, different medical conditions and also by treatments, especially those with gonadal toxicity. There is general consensus on the need to provide counselling about currently available FP options to all individuals wishing to preserve their fertility.
**Study Design, Size, Duration:** An international meeting with representatives from expert scientific societies involved in FP was held in Barcelona, Spain, in June 2015.
**Participants/Materials, Setting, Methods:** Twenty international FP experts belonging to the American Society of Reproductive Medicine, ESHRE and the International Society of Fertility Preservation reviewed the literature up to June 2015 to be discussed at the meeting, and approved the final manuscript. At the time this manuscript was being written, new evidence considered relevant for the debated topics was published, and was consequently included.

**Box 1.** Indications for fertility preservation

| | |
|---|---|
| Gonadotoxic treatment of malignancy | i) Chemotherapy/radiotherapy<br>ii) Reproductive tract surgery |
| Genetic conditions | i) Turner syndrome<br>ii) Fragile X permutation<br>iii) X chromosome aberrations |
| Surgery for reproductive tract disease | i) Ovarian endometriosis<br>ii) Ovarian neoplasms<br>iii) Cervical/uterine neoplasia |
| Autoimmune conditions | i) Autoimmune oophoritis<br>ii) Treatment of connective tissue disease |
| Counteract effects of ovarian ageing | 'Social' fertility preservation |

# FERTILITY PRESERVATIONS STRATEGY



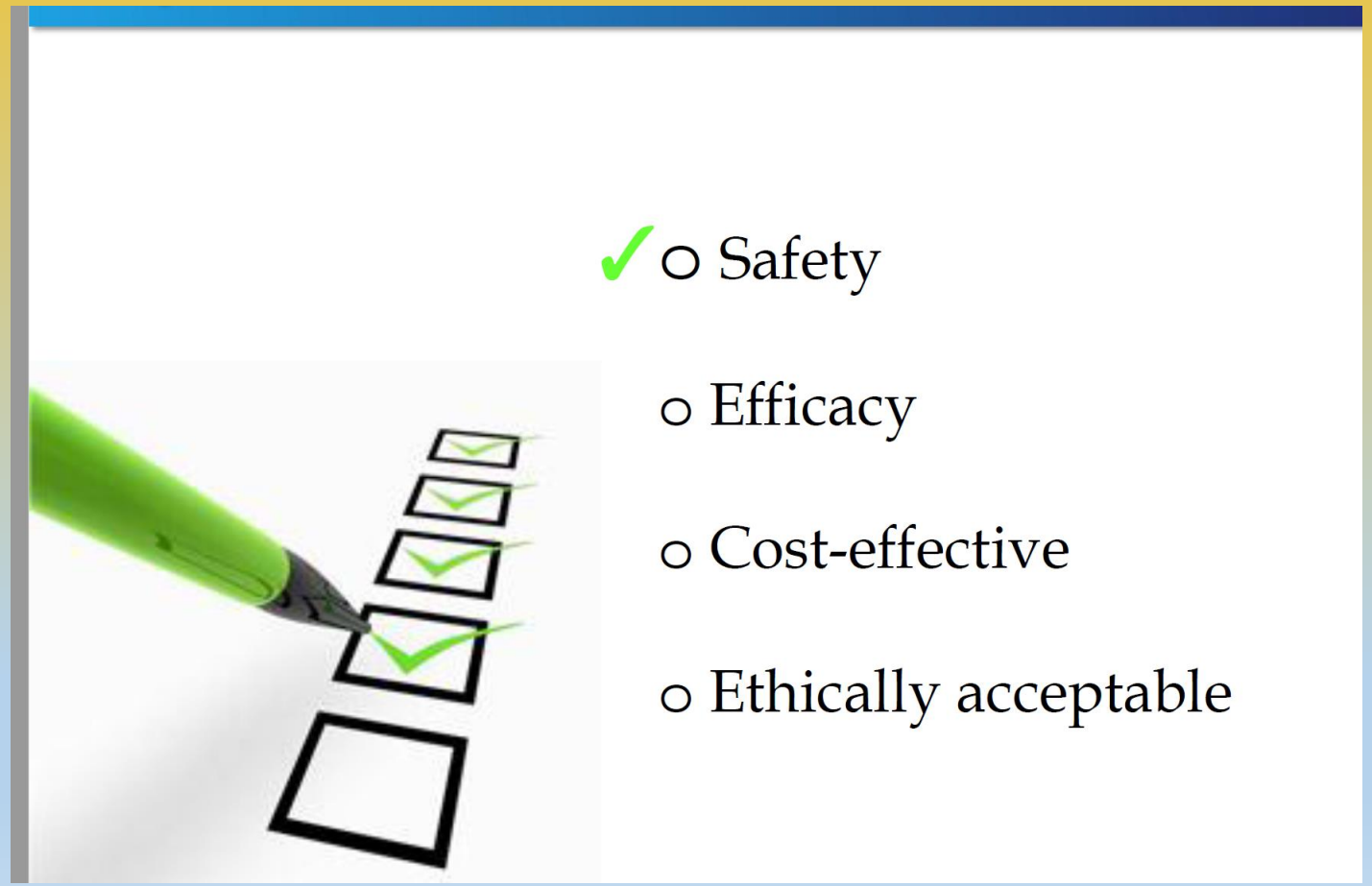
# Fertility preservation techniques (FPT)$_{endometriosis}$

- Personalized counseling should be offered to all patients with endometriosis
- Age
- extent of ovarian involvement
- Current ovarian reserve
- previous and impending surgeries for endometriosis
- current success rates with FPT
- possible risks associated with FPT

# Fertility preservation techniques (FPT)

- oocytes freezing
- embryos freezing
- ovarian tissue cryopreservation (OTCP)

# Oocytes freezing



# Oocytes freezing

## IVI) Safety for the patient

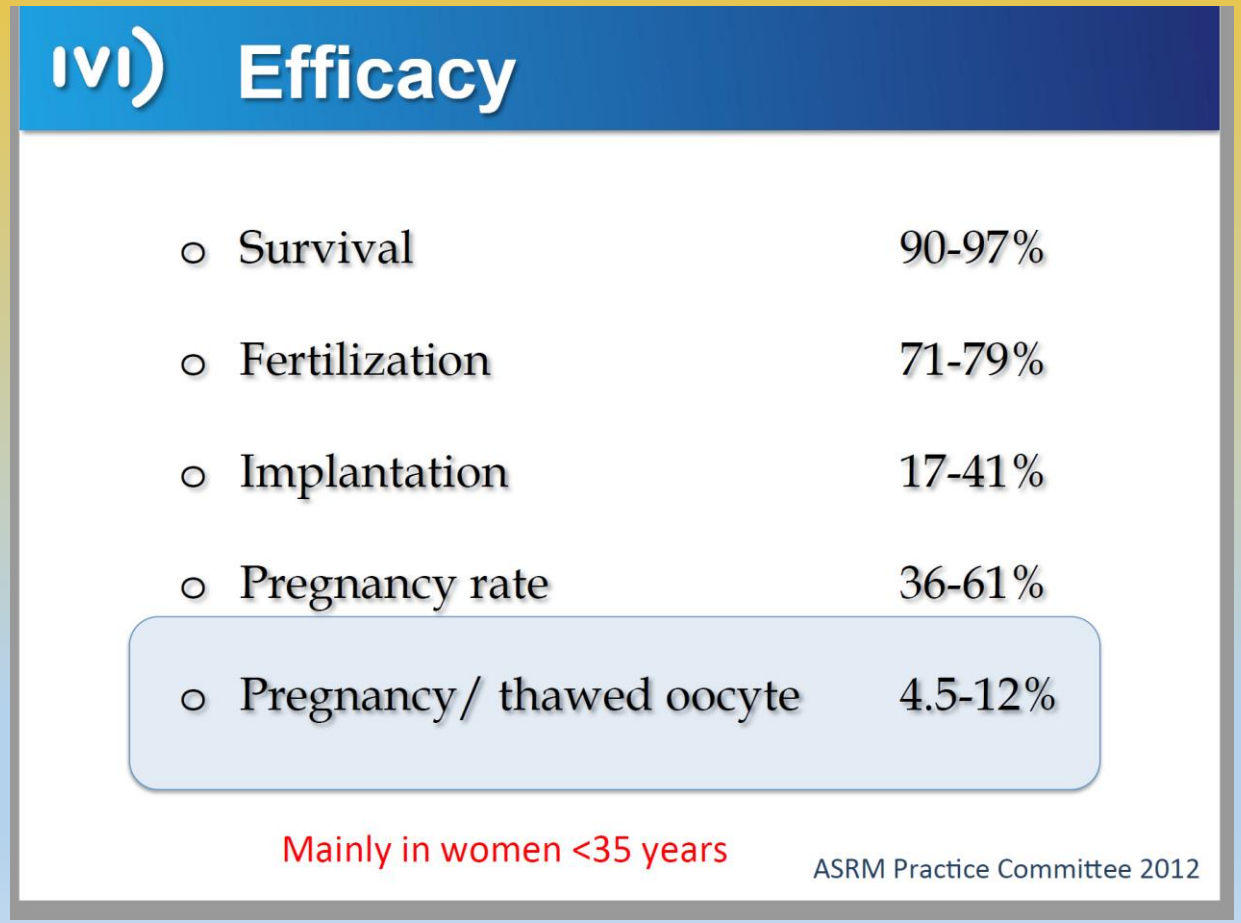
- Current protocols
  - rFSHr / Antag/ GnRHa

| Complications | 0.41% (17) |
|---|---|
| Intraabdominal bleeding | 0.34% (14) |
| Severe pain | 0.05% (2) |
| Ovarian torsion | 0.02% (1) |

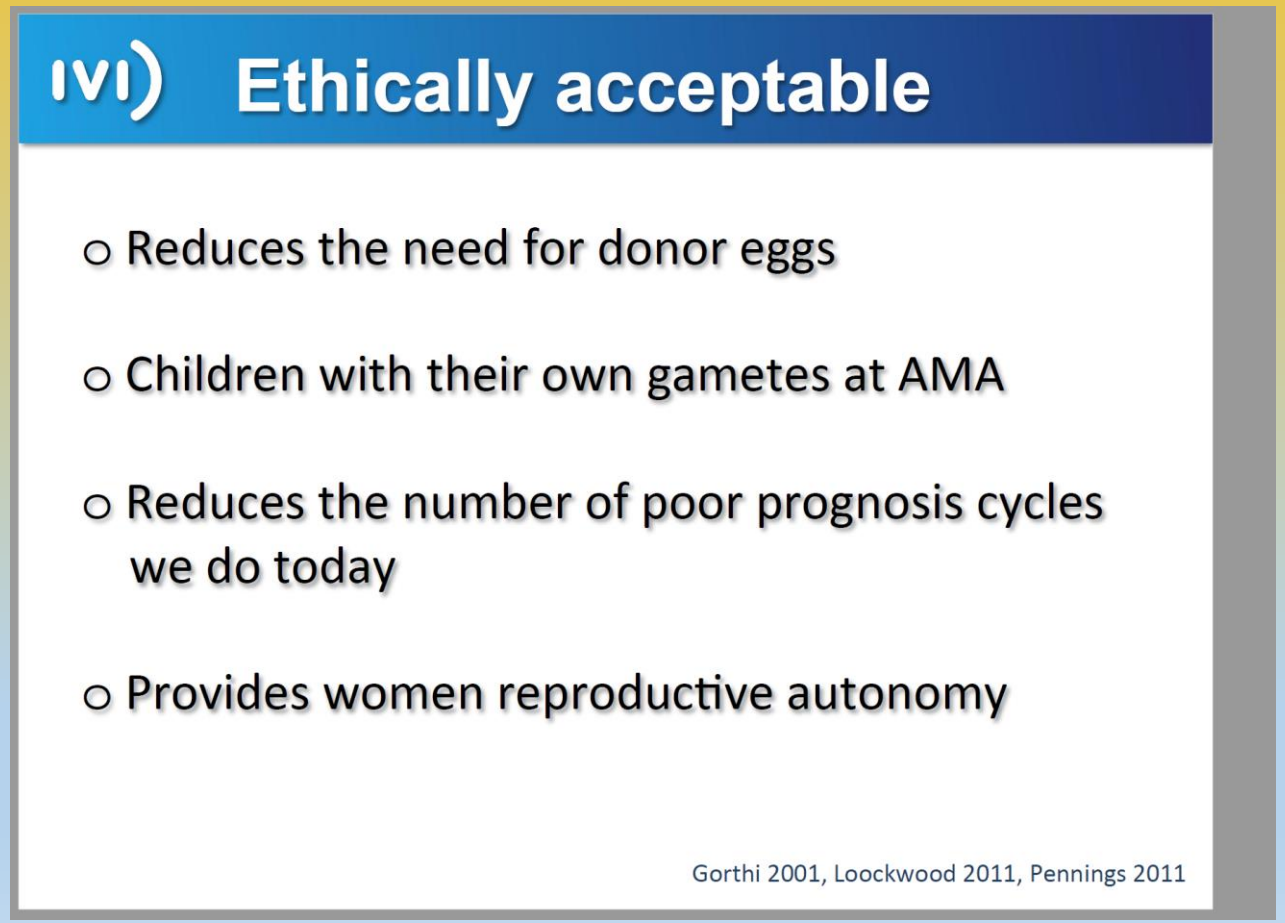
Bodri et al. 2008

- No risk of OHSS
  - No hCG
  - No embryo transfer

# Oocytes freezing



# Oocytes freezing



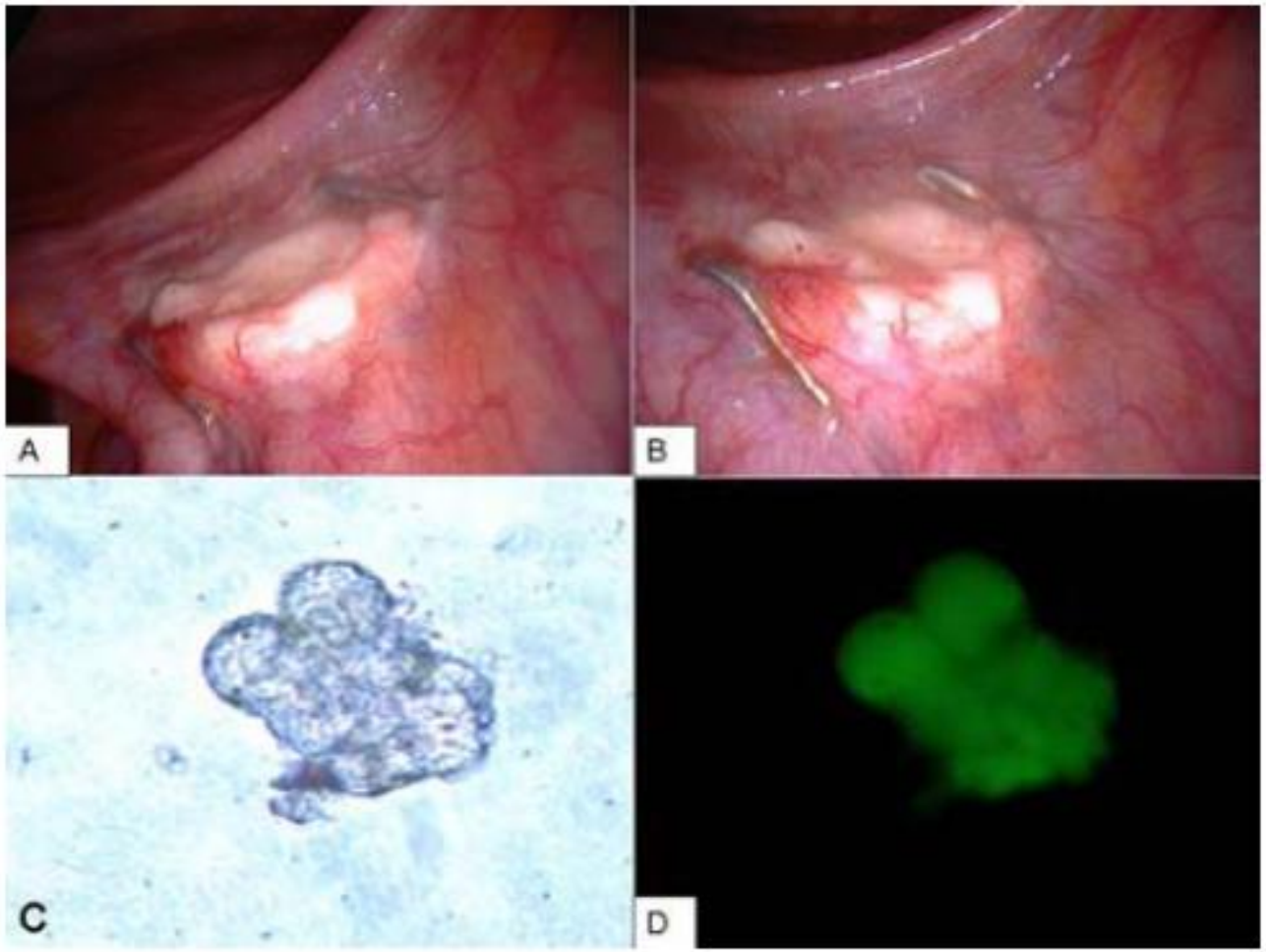



**Figure 3.** At second look laparoscopy, macroscopically viable-looking ovarian tissue of +/- 1cm in size was visible in the grafted area of the two patients and a biopsy was taken (A and B). In part of the biopsy from one patient, six viable follicles were detected after collagenase isolation and vital fluorescent staining (C and D).

Human Reproduction Vol.20, No.9 pp. 2556–2558, 2005
Advance Access publication May 19, 2005
doi:10.1093/humrep/dei109

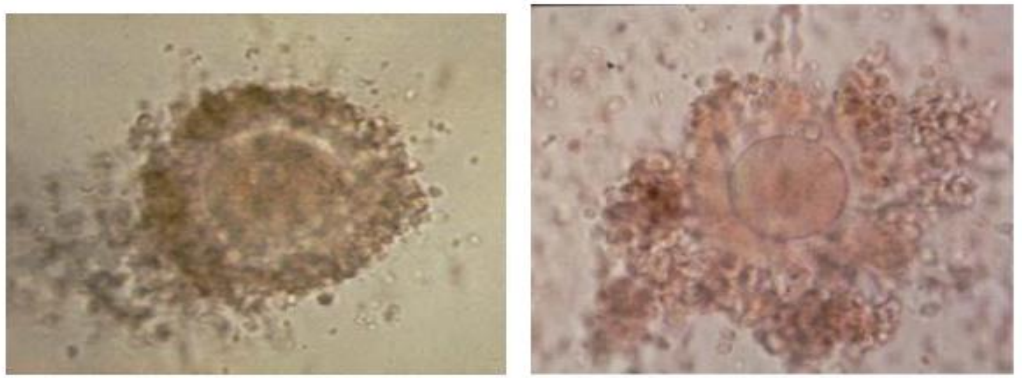
# In Vitro Maturation

# Birth of a healthy infant after *in vitro* oocyte maturation and ICSI in a woman with diminished ovarian response: Case report

**Barbro Fridén[1,3], Julius Hreinsson[2] and Outi Hovatta[2]**

[1]Department of Obstetrics and Gynaecology, Varberg Hospital, Varberg, Sweden and [2]IVF Unit, Department of Clinical Science, Division of Obstetrics and Gynaecology, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

[3]To whom correspondence should be addressed at: Department Obstetrics and Gynecology, Varberg Hospital, 448 13 Varberg, Sweden. E-mail: barbro.friden@lthalland.se



Immature Oocyte Immediately after retrieval

Mature Oocyte After 36 hours of Retrieval

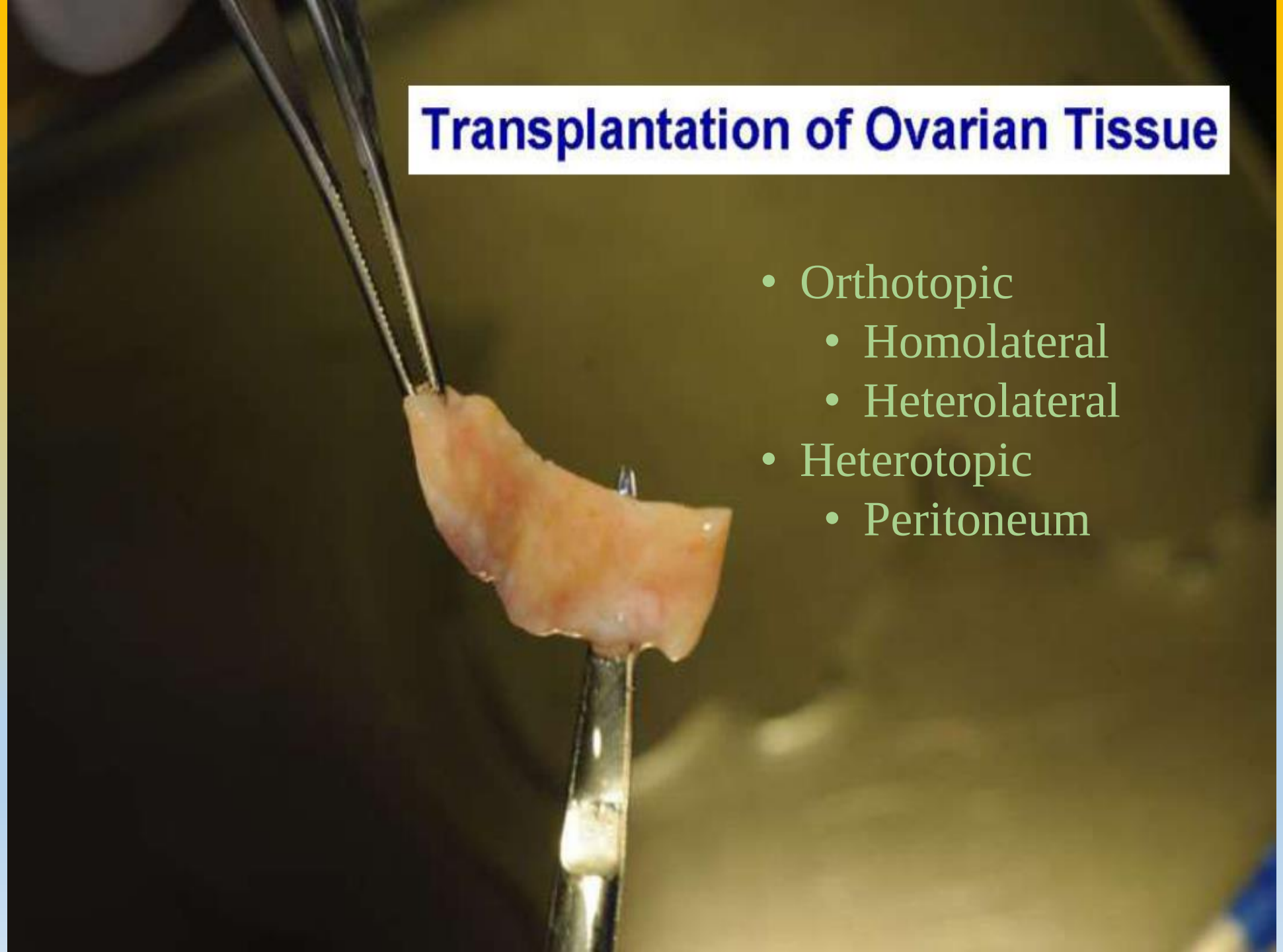
A B C D

During COC sliding, it is possible to observe clearly whether or not the oocyte cytoplasm contains a germinal vesicle

# Ovarian cortex tissue preservation(octp)

- Medical contraindication for ovarian hyperstimulation

- Prepubertal  patients


Transplantation of Ovarian Tissue
• Orthotopic
• Homolateral
• Heterolateral
• Heterotopic
• Peritoneum

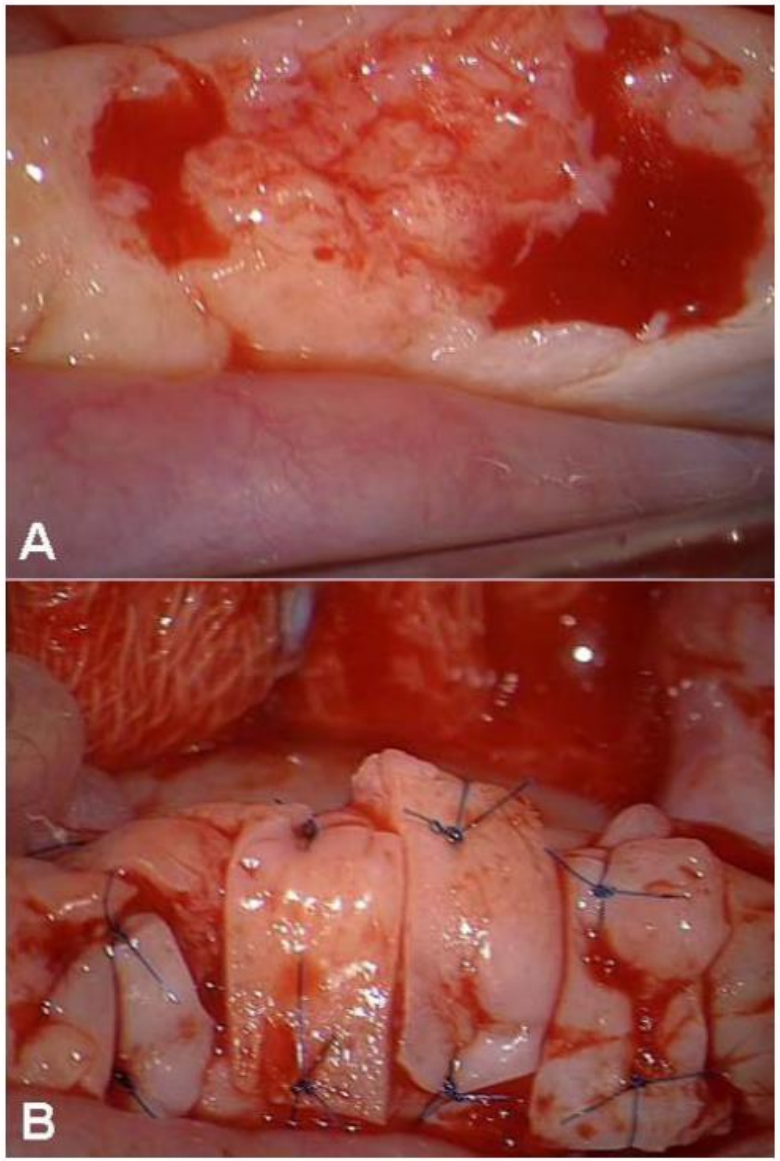
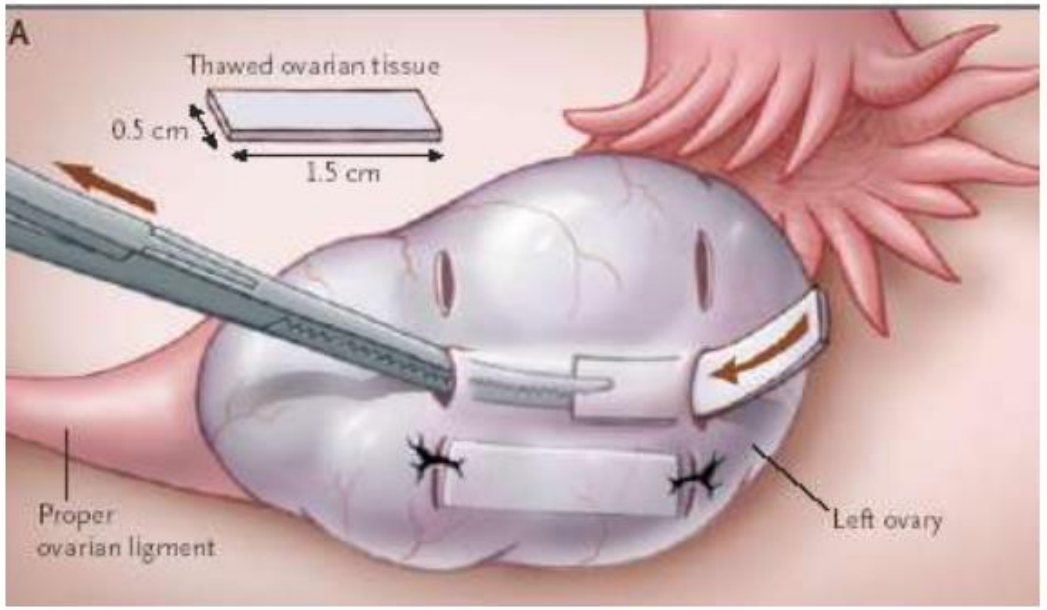



**Figure 5**. In the other eight cases, ovarian tissue was reimplanted onto the remaining ovary after removal of the native cortex (A). In most cases, large strips of ovarian tissue were attached to the decorticated medulla with stitches (B). Reproduced with permission from (17).




The NEW ENGLAND JOURNAL of MEDICINE

Meirow, Dor *et al*
***2005***

***Thanks for your attention***