
In the Name of God

Fertility Preservation in Female Cancer Patients;

Experience of ROYAN Institute

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ROYAN Institute
2023

Oncofertility

- Approximately 10% of female cancer cases occur under the age of 45 years.
- other medical conditions requiring treatment that may threaten ovarian function and subsequent fertility.

American Cancer Society. Cancer facts and figures 2012

- Oncofertility is a new transversal concept that describes an integrated network focused on medical methods to spare or preserve reproductive function in patients diagnosed with cancer.
- The term was coined in 2006 in the USA, although the history of oncofertility dates back to 1971, with the signature of the National Cancer Act.

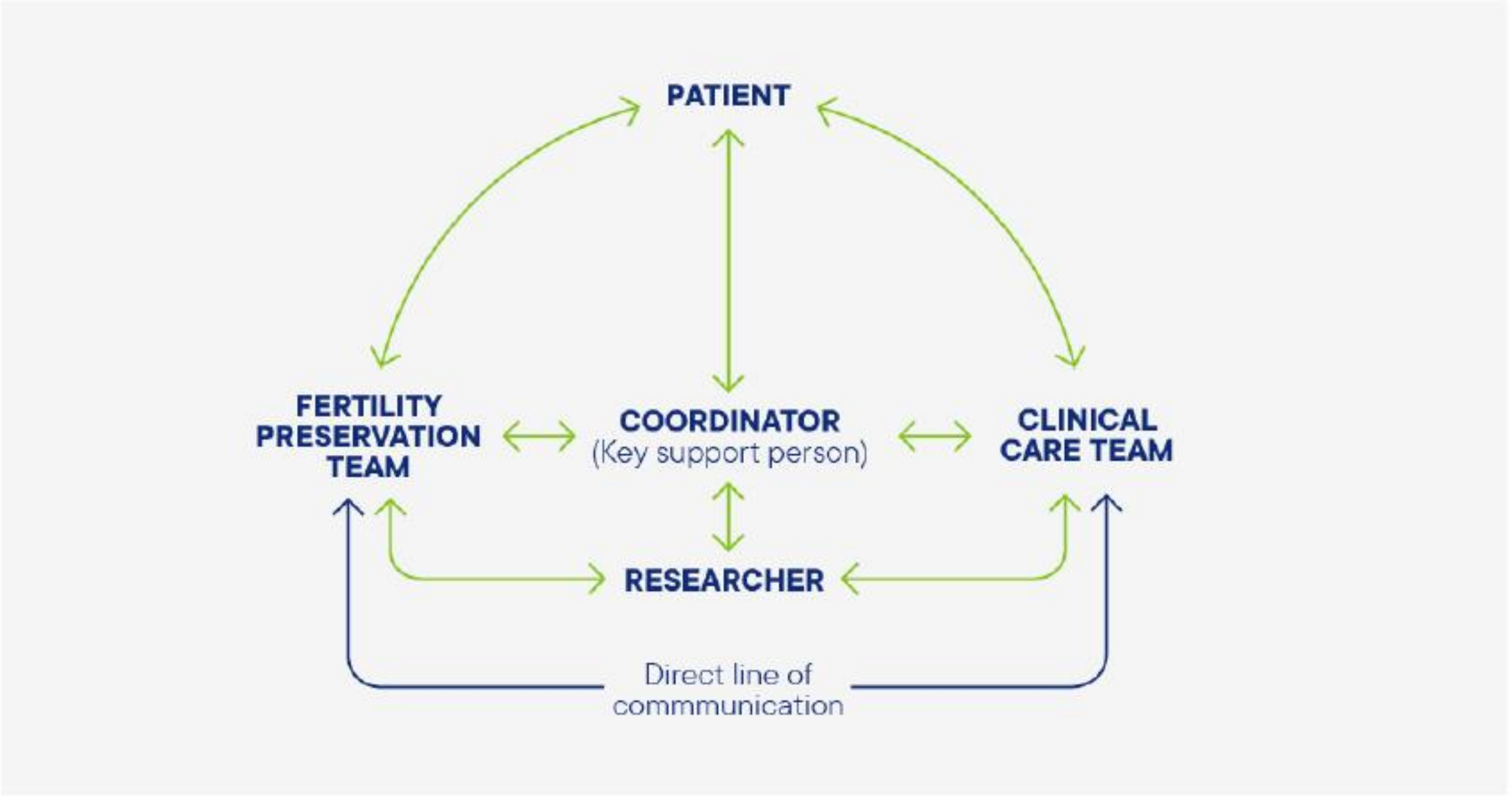
Melan K, Amant F, Veronique-Baudin J, Joachim C, Janky E. Fertility preservation healthcare circuit and networks in cancer patients worldwide: what are the issues? BMC cancer. 2018;18(1):192.

- ASCO Recommendations on Fertility Preservation in Cancer Patients state as follows:
- “As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists”

The Members of multidisciplinary oncofertility preservation Team

- Reproductive endocrinologist, and urologist
- Oncologist, Hematologist
- sexologist
- Advanced laparoscopic surgeon
- High risk pregnancy specialist
- Radiologist
- Anesthesiologist
- Embryologist
- Pathologist
- Oncofertility nurse
- Ethic specialist, and forensic specialist
- Psychologist
- Genetic counselor
- Cardiologist
- ……..

Figure 2 The multidisciplinary team and the role of the "coordinator"



Fertility Preservation Methods

- **Standard methods:**
  - Embryo cryopreservation;
  - Oocyte cryopreservation.
- **Experimental methods:**
  - Ovarian transposition;
  - Ovarian suppression with GnRH analogous;
  - Ovarian tissue cryopreservation;
  - In Vitro Maturation.

Fertility Preservation Methods in Pre-pubertal Girls

- Ovarian tissue cryopreservation
- Ovarian transposition
- In Vitro Maturation.

Oocyte and/or Embryo Cryopreservation

Adult established fertility preservation method.

Age		Maximum: 45 years (Belgium)
Time interval before cancer treatment	> 2 weeks	
No history of chemotherapy	Minimum: 6 months	

Ovarian Stimulation and Freezing of Oocytes

- **The decisive factor in ovarian stimulation is:**
  - Maximization of the oocyte yield;
  - Minimization of the complication rate;
  - Cancer treatment started immediately.

von Wolff M, Germeyer A, Liebenthron J, Korell M, Nawroth F. Practical recommendations for fertility preservation in women by the Ferti PROTEKT network. Part II: fertility preservation techniques. Archives of gynecology and obstetrics. 2018;297:257-67.

Ovarian Stimulation and Freezing of Oocytes

- It should be noted that fertilized oocytes can only be transferred to the woman after the consent of both partners, so preserving some oocytes in an unfertilized state should be considered, even in the case of a stable partnership.

von Wolff M, Germeyer A, Liebenthron J, Korell M, Nawroth F. Practical recommendations for fertility preservation in women by the Ferti PROTEKT network. Part II: fertility preservation techniques. Archives of gynecology and obstetrics. 2018;297:257-67.

Ovarian Stimulation

- **Standard protocol for stimulation:** antagonist protocol
- **Ovulation induction** using GnRH agonists (triptorelin0.2 mg s.c.) ↓OHSS
- **Random start stimulation:**
  - Stimulation initiated at any time during the menstrual cycle;
  - A second stimulation is started around 5 days later;
  - Time required for double stimulation is 30 days.

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Reducing the Estradiol Concentration in Estrogen-Sensitive Tumors

- To reduce the increasing estrogen concentrations during ovarian stimulation, the addition of aromatase inhibitors, e.g., letrozole 5 mg (2.5 mg BID) is recommended.

von Wolff M, Germeyer A, Liebenthron J, Korell M, Nawroth F. Practical recommendations for fertility preservation in women by the Ferti PROTEKT network. Part II: fertility preservation techniques. Archives of gynecology and obstetrics. 2018;297:257-67.

The Effectiveness of Oocyte Vitrification

- Oocyte survival rate: 92%
- Fertilization rate: 77%
- Pregnancy rate: 36%

	Patients with Cryopreservation (n)	Patients with at least one embryo transfer (n(%))	Patients with at least one tissue transplantation (n(%))	Patients who used cryopreserved sperm (n(%))
Oocytes	2097	129/2097 **(6.1%)**		
Ovarian Tissue	3845		114/3845 **2.9%)**	
Sperm	11,798			974/11798 **(8.3%)**

Utilization Rates of oocytes, ovarian tissue and sperm after cryopreservation as a fertility preservation measure. *Fertility preservation in oncological and non-oncological diseases*
Eds. M. von Wolff & F. Nawroth, Springer 1st edition. 2020

von Wolff M, Germeyer A, Liebenthron J, Korell M, Nawroth F. Practical recommendations for fertility preservation in women by the Ferti PROTEKT network. Part II: fertility preservation techniques. Archives of gynecology and obstetrics. 2018;297:257-67.

Ovarian Transposition (Oophoropexy)

- The effects of radiotherapy on ovarian function are considerable.
- A dose of 2 Gy to the ovaries reduces the follicular density by half when targeted radiotherapy is performed in the pelvic area.
- Ovarian transposition can be offered when pelvic irradiation is performed as cancer treatment.

Pelvic radiotherapy is often performed in Hodgkin's and non-Hodgkin's lymphoma, rectal cancer, Ewing's sarcoma of the pelvis, and cervical Cancer
Fertprotekt2018

von Wolff M, Germeyer A, Liebenthron J, Korell M, Nawroth F. Practical recommendations for fertility preservation in women by the Ferti PROTEKT network. Part II: fertility preservation techniques. Archives of gynecology and obstetrics. 2018;297:257-67.

Ovarian Transposition (Oophoropexy)

- Procedure is relatively simple to perform.
- Ovary is transposed via laparoscopy or mini-laparotomy toward the pelvic walls laterally or behind the uterus medially.
- Utero-ovarian ligament(s) and peritoneum adjacent to the infundibulopelvic ligament(s) are incised mobilization of the ovary so as to allow movement outside the radiation field.

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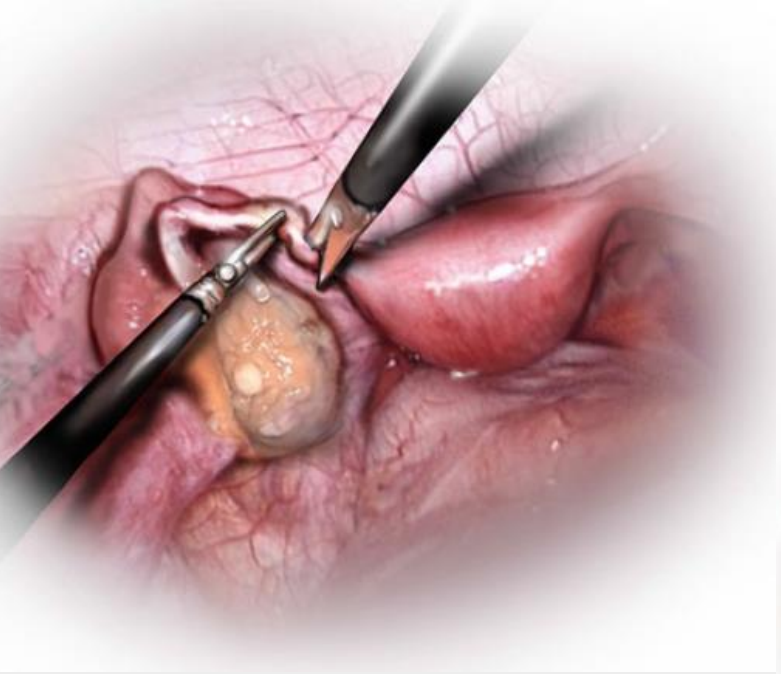
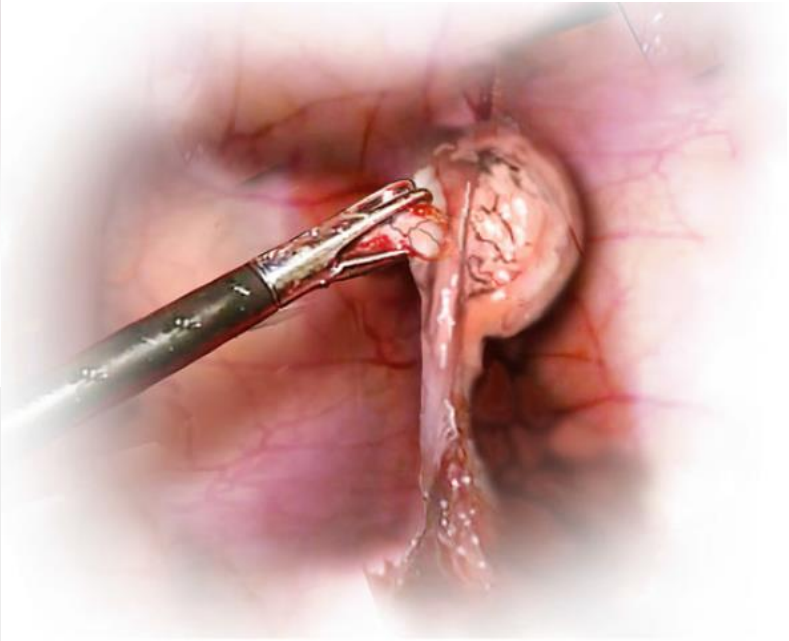


Common locations for ovarian transposition:
- intra-abdominal paracolic gutters
- anterior to psoas muscles
- lower paracolic gutters



Ovarian Suppression with GnRH-analogous

- **Hypothesis:** Inactivation of ovarian activity lead to a reduced sensitivity to cytotoxic effects.
- **Efficacy:**
  - Meta-analyses showed a significantly lower rate of POI.
  - A significant influence on later pregnancy chance not been proven.

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Ovarian Tissue Cryopreservation and Transplantation

Age	Maximum: 35 years (38 years for women with a high ovarian reserve)
Time interval before cancer treatment	< 2 weeks
POF Risk	> 50%
No High Risk of Ovarian Metastasis	Leukaemia Neuroblastoma Burkitt lymphoma Ovarian carcinoma

Ovarian Tissue Cryopreservation and Transplantation

- Does not require ovarian stimulation;
- Can be performed immediately;
- Only method available in children;
- Restore global ovarian function;
- Further investigation is needed.

von Wolff M, Germeyer A, Liebenthron J, Korell M, Nawroth F. Practical recommendations for fertility preservation in women by the Ferti PROTEKT network. Part II: fertility preservation techniques. Archives of gynecology and obstetrics. 2018;297:257-67.

Transplantation of Ovarian Tissue

Autotransplantation involves :

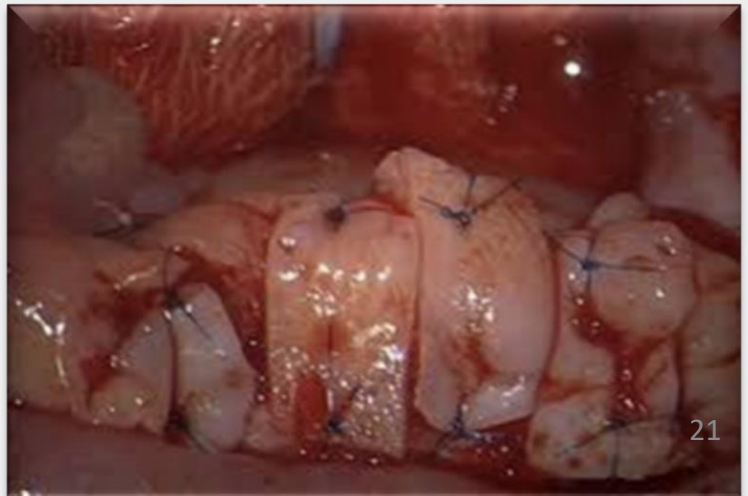
Orthotopic transplantation

Heterotopic transplantation

The ovarian tissue is mainly transplanted orthotopically, i.e., into the pelvic wall lateral to the ovaries, into or onto the ovary.

The amount of ovarian tissue to be transplanted usually corresponds to approximately 15–25% of an entire ovary.
Van der Ven H, 2016

During the transplantation, the patency of the tubes should be checked and, if necessary, a hysteroscopy should also be considered. Michael von Wolff 2018

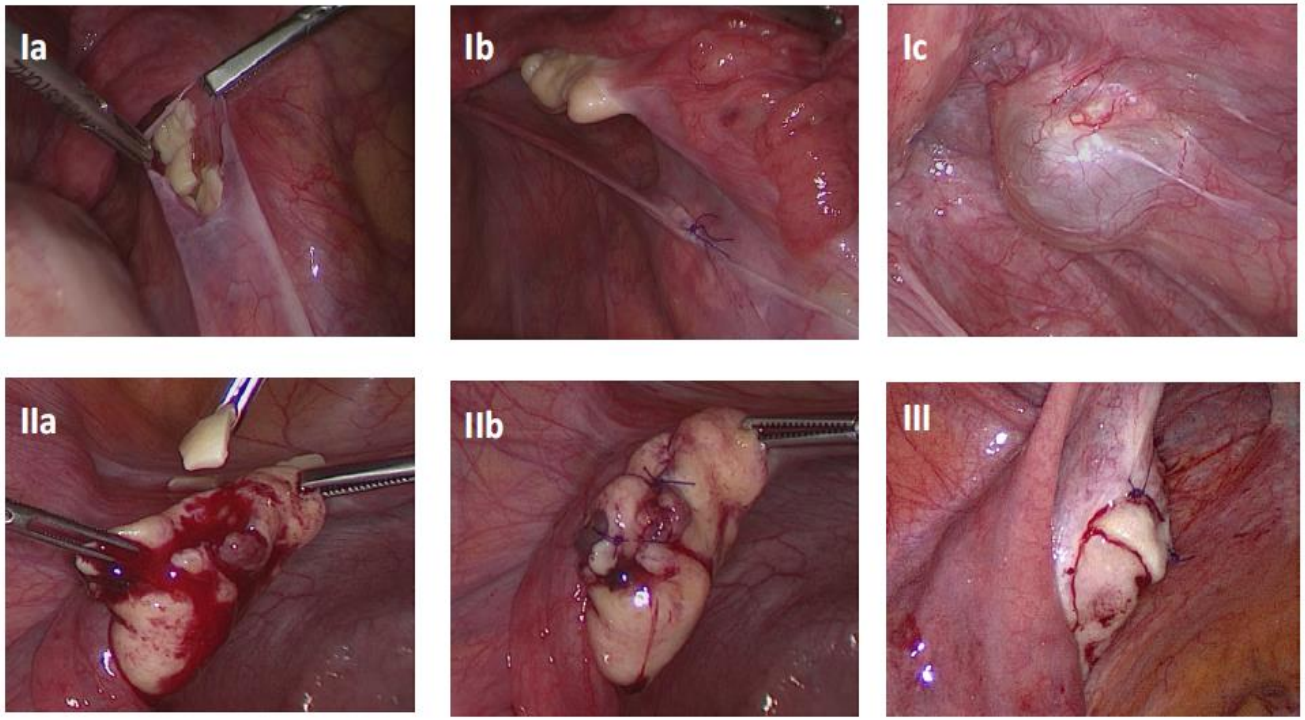


Orthotopic transplantation

1. into the pelvic wall lateral to the ovaries
2. into the ovary
3. onto the ovary

Advantages :

the possibility of natural conception as the ovarian tissue is in close proximity to the fallopian tube, and a favorable environment for follicular development



A transplant onto the ovary best imitates the physiological anatomy, but requires the greatest laparoscopic-microsurgical expertise and the duration of surgery (1–2 h) is the longest. A transplant into the pelvic wall is then least physiological localization, but surgically the easiest to perform and the operation only takes about ½–1 h.

Royan institute

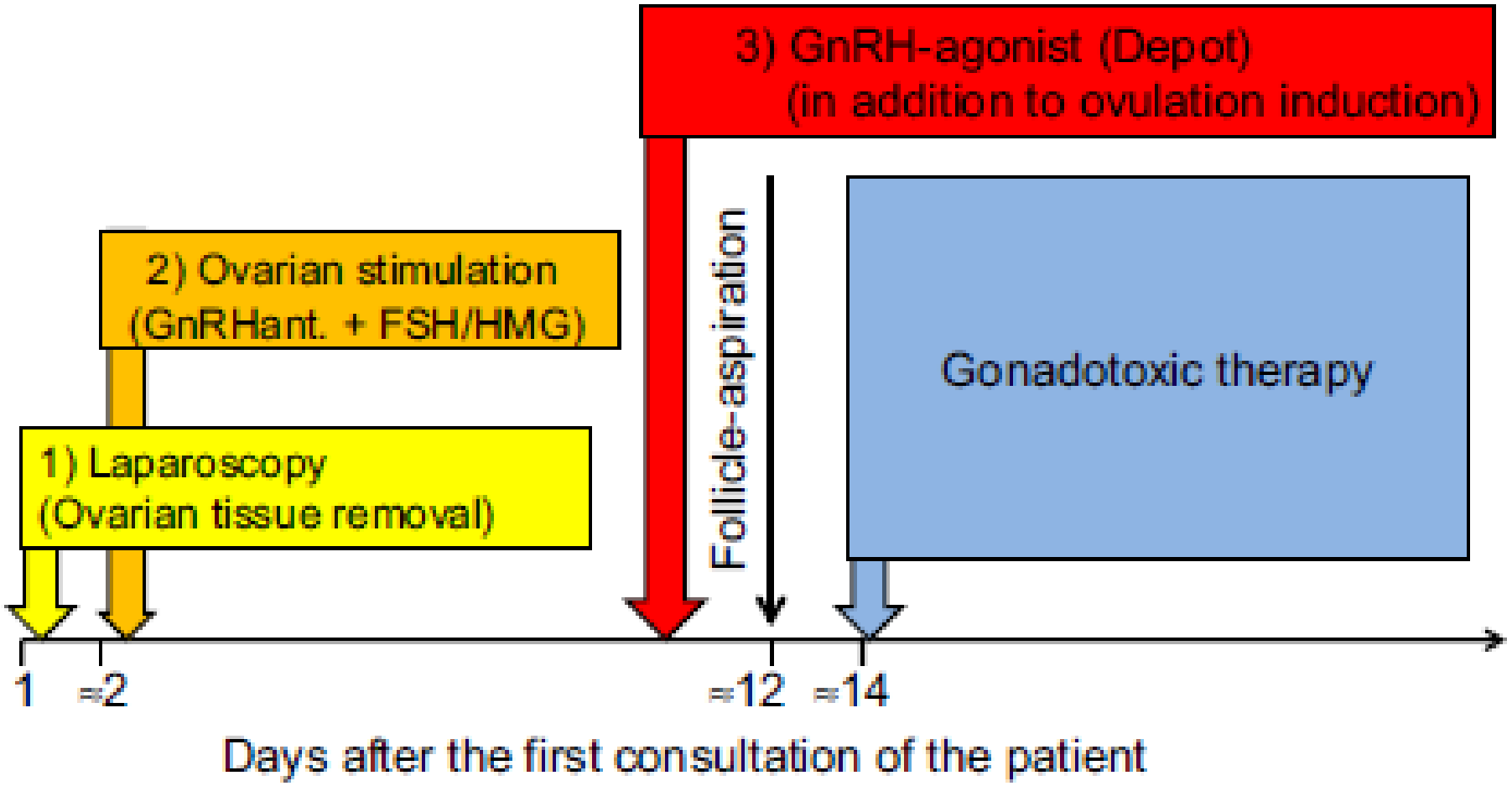


Fig. 2 Combination of the three main techniques to preserve fertility before gonadotoxic therapy

Conservative Gynecologic Surgery

- Centered on doing less radical surgery, to spare fertility.
- Radical trachelectomy restricted to stage IA2 to IB cervical cancer.
- Other gynecologic malignancies, less radical surgery, of sparing the reproductive organs.
- Ovarian cystectomy for early-stage ovarian cancer.

Peccatori FA, Azim HA, Orecchia R, Hoekstra H, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology. 2013;24:vi160-vi70.

In Vitro Maturation

- IVM is experimental method for fertility preservation
- For IVM, the chances of success with a fresh transfer are relatively high in some centers;
- Only be performed in women with a very high AFC and only if the 2 weeks required for stimulation not available.

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Fertility Preservation Experience in ROYAN Institute

History

- Despite the decades-long history of FP in cancer patients in the world, this field is about a decade old in Iran, where ROYAN Institute is the most important active institution in the field.
- The start of clinical activity: 2014
- The formation of specialized taskforce: 2017

The Members of Taskforce

- The clinical team
- The research team

Taskforce Activities

- The taskforce uses the world's latest, cutting-edge fertility preservation methods, including the oophoropexy, and the freezing of embryos, eggs, sperm, and ovarian, to preserve fertility in adult women and men, and immature girls.
- It also pursues the mission of conducting relevant research projects aiming to improve the current treatment methods.

The Members of Clinical Team

- Reproductive endocrinologist, and urologist
- Oncologist, Hematologist
- Advanced laparoscopic surgeon
- High risk pregnancy specialist
- Radiologist
- Anesthesiologist
- Embryologist
- Pathologist
- Oncofertility nurse
- Ethic specialist, and forensic specialist
- Psychologist
- Genetic counselor
- cardiologist

The Members of Research Team

- Reproductive endocrinologist, and urologist
- Oncologist, Hematologist
- Research embryologist
- Genetic specialist
- Stem cell & developmental biologist
- Epidemiologist
- Ethic specialist
- Research coordinator

New Oncology Patient

Admission

Visit by an Infertility Specialist

Determination of Fertility Preservation Indication

Determination of Fertility Preservation Option

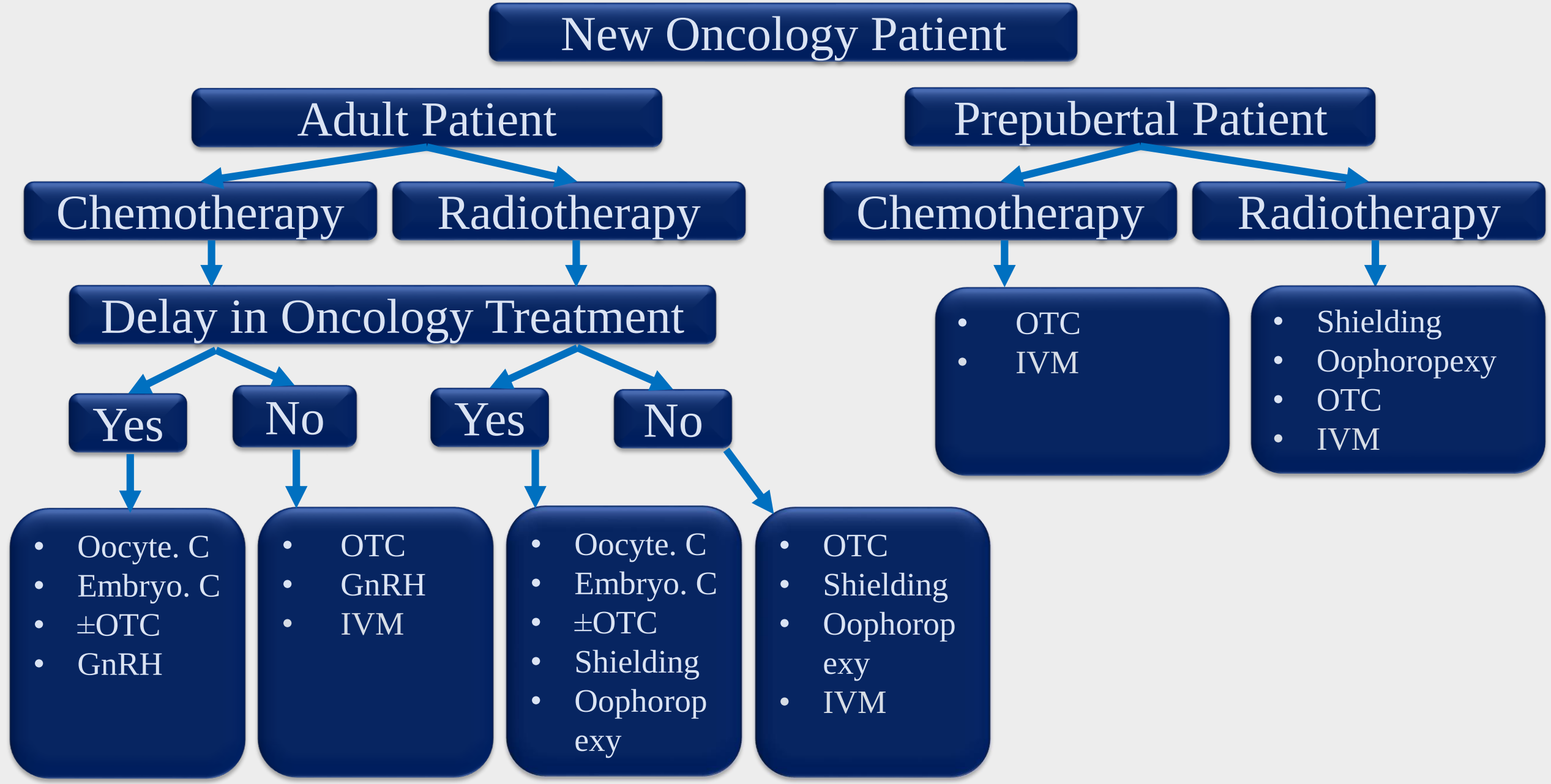
Referrals & Consultations

Refer to

- Lab
- Doppler Ultrasound (Abdominal & Pelvic)
- Forensic Medicine
- Ovarian Bank

Consultation

- Oncologist
- Anesthesiologist
- Psychologist
- Others


New Oncology Patient
Adult Patient
Prepubertal Patient
Chemotherapy
Radiotherapy
Chemotherapy
Radiotherapy
Delay in Oncology Treatment
• OTC
• IVM
• Shielding
• Oophoropexy
• OTC
• IVM
Yes
No
Yes
No
• Oocyte. C
• Embryo. C
• ±OTC
• GnRH
• OTC
• GnRH
• IVM
• Oocyte. C
• Embryo. C
• ±OTC
• Shielding
• Oophoropexy
• OTC
• Shielding
• Oophoropexy
• IVM

The total number of patients referred to Royan Institute (1394 to 1402/03/31)	417 patients
Age	11-45 years
Age <18 years	14 patients
Marital status	About 50% single and 50% married
Patients separation according to the cancer type	Breast cancer: 45% Lymphoma: 20% Other types of cancer: 35% (Including ovarian tumors, endometrial cancer, Ewing's sarcoma, osteosarcoma, gastrointestinal cancers, brain tumors, and thyroid cancer.

Oocyte Cryopreservation	167 patients
Embryo Cryopreservation	89 patients
Oocyte & Embryo Cryopreservation	40 patients
Ovarian Tissue Cryopreservation	13 patients
Oocyte & OTC Cryopreservation	1 patient
Ovarian tissue Transplantation	2 patients
Ovarian Transposition	4 patients

OTC & OTT in ROYAN Institute

- Almost 100 OTC and two transplantations have been performed for cancer patients in ROYAN Institute since 2010.
- The first transplantation case was a 23-year-old patient, whose ovarian tissue was preserved at the age of 19 years because of bowel cancer. The outcome was the restoration of ovarian endocrine function by orthotopic transplantation.
- The second transplantation was performed in 2019 on a 41-year-old patient, who underwent bilateral oophorectomy and hysterectomy due to uterine adenocarcinoma at the age of 37. However, this orthotopic transplantation was not successful.

We are pleased to inform you that your manuscript entitled **"Case Report: Auto-transplantation of Vitrified Human Ovarian Tissue"** has been accepted for publication in **Cell Journal (Yakhteh)**. In the future, a galley proof of your manuscript in Cell J format will be sent to you. Thank you for considering our journal for publishing your research. We are look forward to receiving your future manuscript.

Sincerely Yours;
Ahmad Hosseini, (Ph.D.)
Editor-in-Chief of Cell J
Telefax:+982122510895

Research Projects

Activation of intracellular signaling pathways in In vitro culture of cryopreserved human ovarian tissue. Dr. B Ebrahimi et al, 2017.

Effect of Silibinin on fertility preservation in breast cancer mice model under chemotherapy with cyclophosphamide. Dr. P Afsharian et al, 2017.

Evaluation of lycopene effect on in vitro culture of immature mouse testis following vitrification. Dr. B Ebrahimi et al, 2018.

Investigation of genomic variations in circulating tumor cells of ovarian cancer. Dr. M Totonchi et al, 2018.

Reconstruction of isolated ovarian cells activity in secondary POF women after seeded on the decellularization matrix of normal ovary following xeno-transplantation to Nude mouse. Dr. R Fathi et al, 2019.

Comparison of ovarian stimulation response in patients with breast cancer and oocyte donors undergoing GnRH antagonist controlled ovarian stimulation at Royan Institute: A retrospective study. Dr. F Ghaffari et al, 2019.

Evaluation of the relationship between Vitamin D levels with oocyte quality in breast cancer patients compared with control group undergoing GnRH antagonist therapy. Dr. F Ghaffari et al, 2019.

Improving human ovarian tissue cryopreservation technique using trehalose. Dr. M Rezazadeh et al, 2019.

Comparison of the outcome of ovarian stimulation cycles with random start in the mid- to late- follicular phase with cases of ovarian stimulation in luteal phase after oocyte maturation trigger using GnRH-agonist in cancer patients referred to the ROYAN Institute 2014-2020. Dr. F Ghaffari et al, 2020.

Ovarian reserve and response to stimulation among oncofertility patients undergoing random start fertility preservation compared to standard ovarian stimulation in non-cancer patients in ROYAN Institute 2014-2021. Dr. F Ghaffari et al, 2021.

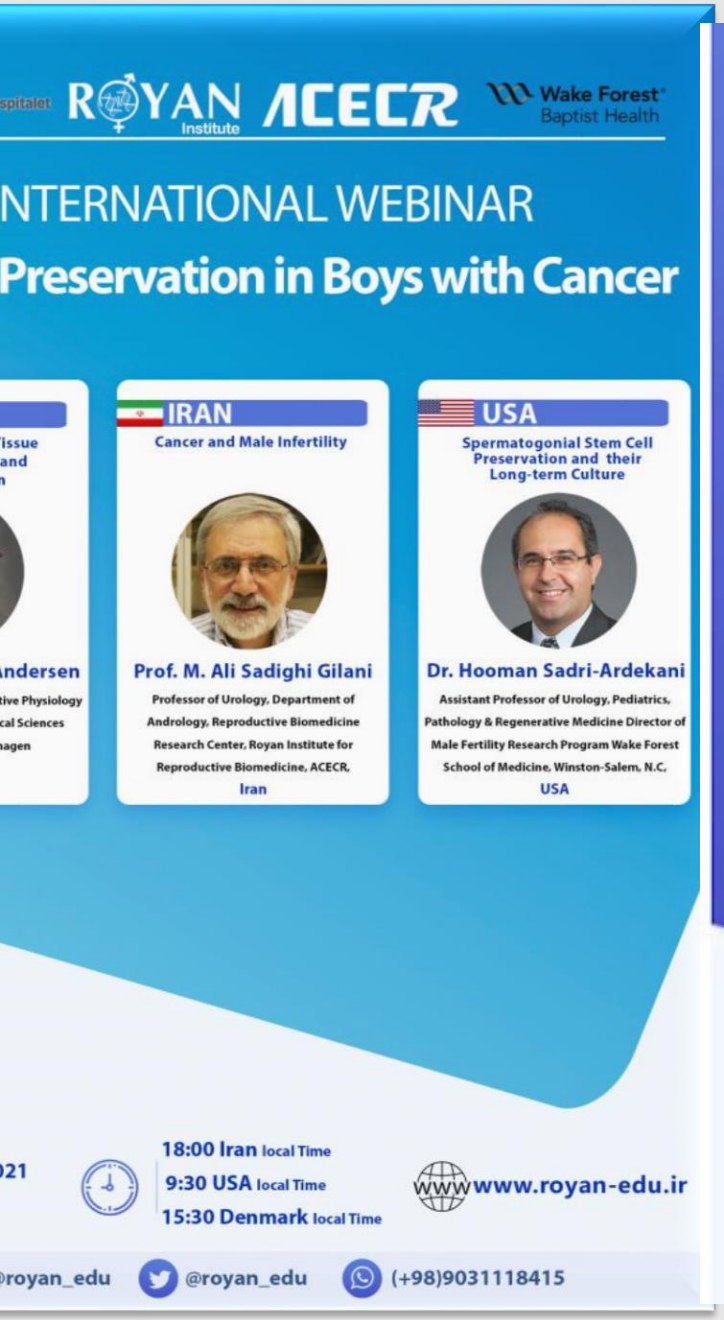
Controlled ovarian stimulation in cancer patients under 18 years old referred to Royan Institute 2014-2021. Dr. F Ghaffari et al, 2021.

Isolation and differentiation of VSELs derived from onco-treated patients' ovary into oocyte-like cells in-vitro. Dr. S Tavana et al, 2021.

Effect of carob (Ceratonia siliqua) extract on fertility preservation in breast cancer mice model under therapy with Cyclophosphamide. Dr. P Afsharian et al, 2022.

The relationship between of different hormone receptors and ovarian response in breast cancer patients referred to fertility preservation before chemotherapy. Dr. F Ghaffari et al, 2022.

Scientific Educational Courses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Prof. M. Ali Sadighi Gilani
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USA
Spermatogonial Stem Cell Preservation and their Long-term Culture
Dr. Hooman Sadri-Ardekani
Assistant Professor of Urology, Pediatrics, Pathology & Regenerative Medicine Director of Male Fertility Research Program Wake Forest School of Medicine, Winston-Salem, N.C, USA
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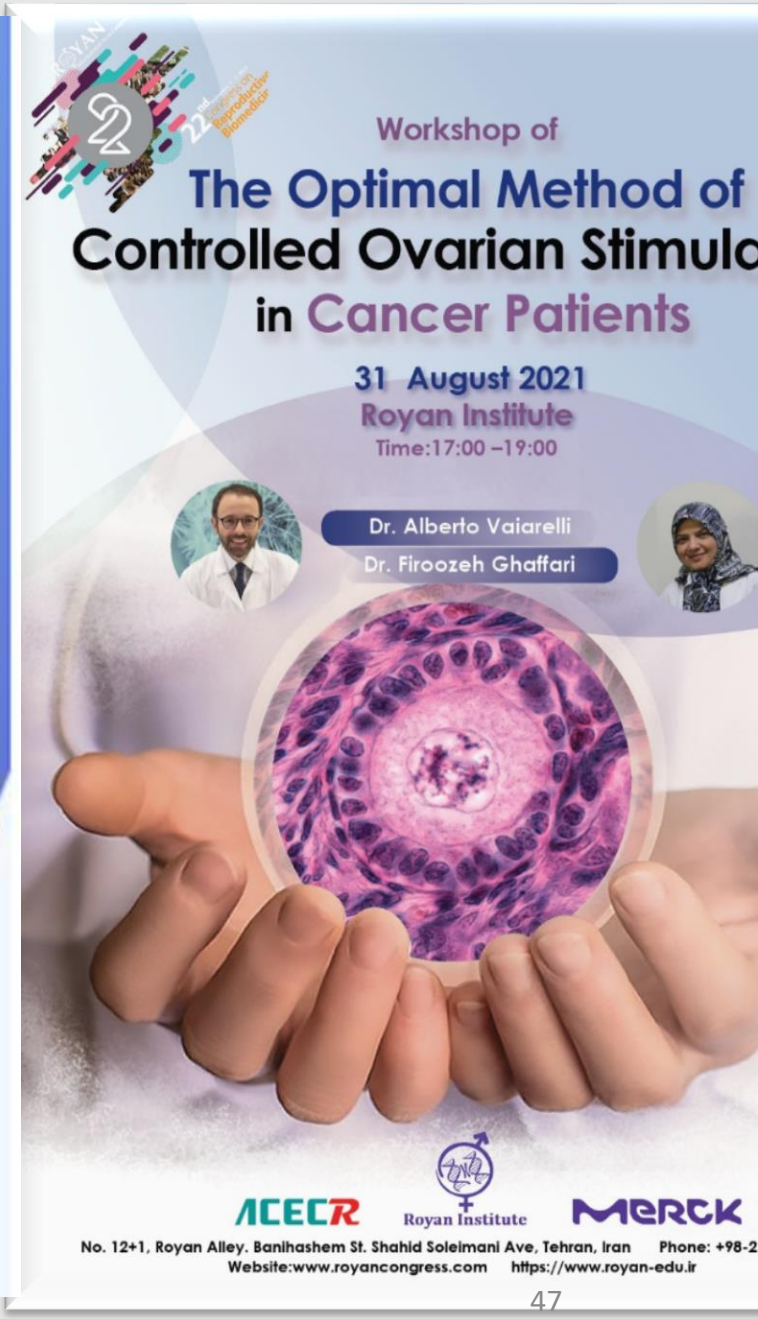
Workshop of
The Optimal Method of
Controlled Ovarian Stimula
in Cancer Patients
31 August 2021
Royan Institute
Time:17:00 –19:00
Dr. Alberto Vaiarelli
Dr. Firoozeh Ghaffari
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اهداف وبینار
• بحث پیرامون سرطان پستان از دیدگاه اپیدمیولوژی
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• بحث پیرامون نقش مشاوره ژنتیک برای بیماران مبتلا به سرطان پستان
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