PROJECT 1

DoS: Giorgia Mangili

Title: **OPTIMIZING THE OPPORTUNITY FOR FEMALE FERTILITY PRESERVATION IN YOUNG PATIENTS WITH CANCER**

Curriculum: Experimental and Clinical Medicine

Residency Program: Obstetrics and Gynecology

Link to OSR/UniSR personal page: https://research.hsr.it/en/divisions/experimental-oncology/gynecologic-oncology.html

Project description (*Number of characters, including spaces*: 2.000 - 3.000):

Over the past 20 years, advances in oncological therapies led to improved cancer survival rates. This remarkable result entails an increasing number of women facing infertility because of treatment gonadotoxicity. Currently, there is still a lack of studies on fertility preservation techniques in female cancer patients.

Postpubertal patients have the option for oocyte cryopreservation (OC) if chemotherapy can be delayed for 2 weeks. It requires controlled ovarian hyperstimulation (COH) with gonadotropins and oocyte retrieval by aspiration.

Ovarian tissue cryopreservation (OTC) is the only option available to prepubertal girls and adult women who cannot delay therapy or undergo COH. Ovarian tissue is harvested without prior stimulation and transplanted back after cancer remission. There are no data on the opportunity to perform OTC after chemotherapy, for patients not eligible at diagnosis.

Today, estimating the likelihood of conception with these techniques is challenging, since follow-up data is limited. Many questions in the field of oncofertility remain unanswered, particularly on the mechanisms of chemotherapy-induced ovarian damage, thus limiting the availability of ovarian protection strategies. There is still an open debate in the literature about the supposed protective effect of GnRH analogs on ovarian reserve.

This project's aims will be:

Pre-clinical activities:

- (year 1-2) To investigate the mechanisms by which doxorubicin and cyclophosphamide, chemotherapeutics commonly used in young patients, cause follicle loss in a murine model, and the effects of GnRH co-administration. Data from a platform of high-resolution mice ultrasound imaging with enhanced contrast agents (CEUS) will be analyzed, to assess and characterize ovarian vascularization and number/size of follicles before and after chemotherapy with or without GnRH concurrent administration. Immunohistochemical analyses will be performed on murine ovarian specimens to support imaging findings.
- (year 2-3) To perform histological and immunohistochemical analyses on frozen-thawed ovarian tissue of cancer patients undergoing OTC before and after chemotherapy, to evaluate markers of vascularization, apoptosis and fibrosis.

Clinical activities:

(year 1-2)

- To evaluate fertility outcomes and oncological safety of patients diagnosed with breast cancer, sarcoma and hematological malignancies undergoing OC and OTC; specific analyses will be carried out on the subset of BRCA1-2 mutated breast cancer patients to better define their responsiveness to ovarian stimulation;
- To evaluate outcomes and safety of OTC after 1 or 2 courses of chemotherapy;

(year 2-3)

- To define safety of COH in breast cancer patients before treatment (chemotherapy or surgery) by clinical and instrumental evaluation, assessing variations of tumor ultrasound features and biological parameters, and measuring systemic hormonal levels before and after OC;
- To evaluate feasibility of COH in patients aged ≤ 20 years.

Skills to be acquired by the student:

During the 3-year training program the student will acquire clinical skills in cancer patients' fertility evaluation, counselling and management, and translational research skills in histopathological analyses on murine and human ovarian specimens, immunohistochemistry staining and data analysis. The student will be engaged in presentation of results and drafting of scientific papers.

References (max. 3)

1. Venturini M, Bergamini A, Perani L, et al. Contrast-enhanced ultrasound for ovary assessment in a murine model: preliminary findings on the protective role of a gonadotropin-releasing hormone analogue from chemotherapy-induced ovarian damage. Eur Radiol Exp. 2018;2(1):44.

2. Kimler B, Briley S, Johnson B, et al. Radiation-induced ovarian follicle loss occurs without overt stromal changes. Reproduction (2018), 155(6), 553-562.

3. Fisch B, Abir R. Female fertility preservation: past, present and future. Reproduction. 2018 Jul;156(1):F11-F27.