Abstract Details

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A new strategy to assess safety of controlled ovarian stimulation protocols for oocyte vitrification as a fertility preservation technique in breast cancer patients.

Biography

MªJosé Soriano completed her bachelor's degree in Biotechnology at Polytechnic University of Valencia (2014). Then, she specialized in Reproductive Medicine through the master's degree in Biotechnology of Human Assisted Reproduction at University of Valencia (2014-2016). MªJosé is currently completing her PhD studies with Dr. César Díaz-García at IVI Foundation-IIS La Fe. She has been awarded with a Predoctoral Health Research Training Contract (2018-2021). She has over 5 years' experience in andrology, embryology, IVF laboratory techniques and female preservation.

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Study question:

Could controlled ovarian stimulation (COS) protocols affect the proliferative and metastatic potential of breast cancer (BC) cells?

Summary answer:
Ovarian stimulation with Letrozole for oocyte vitrification might be safely used as a fertility preservation (FP) technique in hormone-dependent breast cancer women.

What is known already:
BC is the most common malignancy in women at reproductive age. Treatment with high-dose chemotherapy in female patients may impose deleterious effects on the ovary. COS protocols to obtain oocytes for vitrification are frequently used within FP patients but associate a rise in supra-physiological estradiol (E2) levels. This effect could increase the proliferation of tumour cells, being probably detrimental for BC women. Nevertheless, standard COS has been recently adapted by using aromatase inhibitors such as Letrozole, leading a maximum E2 peak similar to that found in a natural cycle. Unfortunately, there is still little evidence regarding safety of such approaches.

Study design, size, duration:
Experimental in vivo study. Forty 5-week old Nude-nu female mice were allocated to the following experimental groups: BC (n=10), BC and FSH stimulation (BC-FSH, n=10), BC and Letrozole stimulation (BC-LTZ, n=10), Control FSH stimulation (CT-FSH, n=5) and Control Letrozole stimulation (CT-LTZ, n=5). BC was induced in the three first groups while controls received a saline solution injection. Animals were maintained for 5 months and then sacrificed to collect tissue and blood samples for further analysis.

Participants/materials, setting, methods:
One million of human MCF-7 BC cells, previously transfected with the mCherry fluorescent protein, were injected into the left renal capsule of BC, BC-FSH and BC-LTZ mice. Two days after xenograft, COS was induced by 10IU FSH or 1mg/ml Letrozole + 10IU FSH, followed by ovarian triggering with 10IU hCG at 48h. Cell proliferation was biweekly monitored by a non-invasive in vivo imagen system (IVIS) to record fluorescence signal and also assessed by Ki-67 immunostaining.

Main results and the role of chance:
When tumour growth was assessed by means of total radiant efficiency signal ([p/s]/[μW/cm^2), BC and BC-LTZ mice presented a statistically significant lower expression when compared to BC-FSH group ($6.1x10^{10}$±$2.0x10^{10}$, $9.6x10^{10}$±$3.2x10^{10}$ and $1.6x10^{11}$±$4.5x10^{10}$; $p<0.01$ and $p<0.05$, respectively), five months after xenograft. Metastasis was not detected in the BC and BC-LTZ groups, nevertheless, metastatic lesions were observed in BC-FSH mice. The in vivo monitoring results by IVIS were concordant with the histological assessment of tumour lesions after sacrifice. Tumour size was slightly lower in BC group than in BC-LTZ (0.3±0.2 cm^2 vs 0.5±0.2 cm^2). However, lesions in BC-FSH group were considerably increased (1.2±0.3 cm^2, $p<0.01$). Cell proliferation, by Ki-67 immunostaining, was also performed in kidney samples to validate these data. Similar proliferation levels were found in the BC and BC-LTZ groups (10.3±0.9% and 11.5±0.6%). However, BC-FSH revealed a significant increase in tumour cell proliferation (28.8±1.6%, $p<0.01$). Lastly, mean serum E2 levels of BC and both Letrozole stimulated groups were comparable (BC: 186.9±56.0 pg/ml, BC-LTZ: 193.9±78.2 pg/ml and CT-LTZ: 119.8±50.7 pg/ml) whereas FSH-treated animals registered significantly higher E2 concentrations (BC-FSH: 431.2±56.2 pg/ml and CT-FSH: 330.9±57.0 pg/ml, $p<0.05$). All these results confirmed that COS with Letrozole did not induce the tumour development.

Limitations, reasons for caution:
This is the first experimental study evaluating the effect of COS protocols over a human BC tumour cell line using a non-invasive in vivo system to monitor cell growth. Although the promising results, further experiments with primary human tumour cells would be required to validate the current data.

Wider implications of the findings:
This study provides evidence on the safety of COS with Letrozole for BC patients. These results could be essential in reassuring current indications for FP techniques and counselling to patients and health-care professionals. Thus, patients with BC could safely underwent the gold standard FP technique, oocyte vitrification.

Keywords:
Fertility preservation
breast cancer
controlled ovarian stimulation
Letrozole