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FERTILITY PRESERVATION—PAST, PRESENT AND FUTURE ENDEAVORS: "AN OUNCE OF PREVENTION IS WORTH A POUND OF CURE"—GNRH AGONISTS CO-TREATMENT SIGNIFICANTLY PRESERVES FERTILITY AND INCREASES PREGNANCY RATE IN ADDITION TO CYCLIC OVARIAN FUNCTION

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Background: The late effects of cancer treatment have gained a worldwide interest among hematologists, reproductive endocrinologists, oncologists, and all health care providers; the protection against iatrogenic infertility caused by chemotherapy assumes a high priority.

Methods: Recent metaanalyses of randomized, controlled trials (RCT's) concluded that GnRHa co-treatment along with chemotherapy significantly decreased premature ovarian failure (POF) rate. However, cyclic ovarian function is not equivalent to fertility (pregnancies). Therefore, we evaluated the PR after exposure to gonadotoxic chemotherapy+GnRHa vs. controls. We have administered a monthly depot intramuscular injection (IM) injection of GnRH-agonistic analogue to 300 young women exposed to gonadotoxic chemotherapy for malignant or non-malignant diseases, after informed consent for up to six months parallel to chemotherapy. These patients were compared to a control group of 200 patients of comparable age and treatment. The study was approved by the Institutional RB Ethics (Helsinki) Committee.

Results: Less than 13% developed POF in the GnRHa co-treatment group vs. 50% in controls (P<0.001). The remaining patients resumed cyclic ovarian function and 90 patients spontaneously conceived 180 times, and delivered 131 healthy neonates in the chemotherapy+GnRHa group. In the control group, only 55 pregnancies were reported in 31 patients (P=0.02). One patient, in the GnRHa group, spontaneously conceived three times and delivered three healthy neonates despite two stem cell transplantations (SCT), 11 years apart. GnRH-a co-treatment was beneficial not only against regular chemotherapy, but also in significantly decreasing the POF rate for lymphoma patients undergoing stem cell transplantation. Two recent prospective RCT (NEJM, 2015 and JAMA, 2016) and three international expert committees have concluded that GnRHa co-treatment in parallel to chemotherapy is beneficial in minimizing POF rate and increasing pregnancy rate in survivors and recommended its use. Moreover, GnRHa co-treatment along with cyclophosphamide pulse therapy is effective in lupus nephritis and other autoimmune diseases, necessitating treatment with alkylating agents. Recently, the ovarian stimulation for follicular aspiration/IVF and embryo/ova cryopreservation is successfully started anytime in the menstrual cycle, eliminating the previous experience of waiting for menstruation. The claim regarding equivocal efficiency of this method, raised by several publications, is challenged due to significant methodological errors in those studies. Future endeavors will examine the clinical use of sphingosine-1-phosphate and its analogs for fertility preservation, and the in vitro maturation of primordial follicles to mature fertilizable metaphase II oocytes ("artificial ovary").

Conclusions: GnRHa co-treatment in parallel to chemotherapy is beneficial in minimizing POF rate and increasing pregnancy rate in survivors. Therefore, it should be offered to every young woman before gonadotoxic chemotherapy in addition to cryopreservation of embryos, ova, and ovarian tissue.

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