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How to preserve fertility in young women exposed to chemotherapy? The role of GnRH-a and sphingosine-1-phosphate in addition to cryopreservation of embrya, oocytes, or ovaries

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Decreased secretion of the pituitary gonadotropins, by decreasing gonadal function, may possibly protect against the sterilizing effects of chemotherapy. Although previous suggestions have been made claiming that primordial germ cells fare better than germ cells that are part of an active cell cycle, this hypothesis has not been seriously tested clinically, until recently. The only prospective randomized study performed by now, have found that GnRH-a protected the ovary against cyclophosphamide-induced damage in Rhesus monkeys by significantly decreasing the number of follicles lost during the chemotherapeutic insult. A long-term follow-up of 240 children, 15 years of age or younger, treated for Hodgkin lymphoma [HL] showed azoospermia in 83% of the boys, whereas only 13% of the girls suffered POF. Since ovarian function was preserved in most long-term survivors who were treated prepubertally for lymphoma, but only in about half of similarly treated adult patients, it was clinically logical and therefore tempting to create a temporary prepubertal milieu in women in the reproductive age before and during the chemotherapeutic insult. We have administered a monthly depot IM injection of GnRH-agonistic analogue to more than 250 young patients exposed to gonadotoxic chemotherapy for malignant or non-malignant diseases, after informed consent, starting before chemotherapy for up to six months, in parallel and until the end of chemotherapeutic treatment . Less than 7% developed irreversible hypergonadotropic amenorrhea. The remaining patients (>93%) resumed cyclic ovarian function, and 51 patients spontaneously conceived 71 times, and were delivered of 62 healthy neonates. These patients were compared to a control group of over 130 patients of comparable age (15-40), who were similarly treated with chemotherapy but without the GnRH-a adjuvant. Neither the age, nor the diagnoses, ratio between HD or non-Hodgkin lymphoma differed between the two groups. Similar doses of radiotherapy exposure and ratios of patients treated by radiotherapy in addition to chemotherapy were experienced by the two groups. Moreover, the cumulative doses of each chemotherapeutic agent and the mean or median radiotherapy exposure did not differ between the groups. Our and others' results support the effectiveness of GnRH-a administration also to patients receiving cyclophosphamide pulses for SLE and other autoimmune diseases. Recently we have experienced the first worldwide reported case of spontaneous successful deliveries of THREE healthy neonates after TWO repeated BMT's, concurrently treated with GnRH-a during the gonadotoxic chemotherapy. How can we possibly explain the beneficial effect of the GnRH-a for minimizing the gonadotoxic effect of chemotherapy, in particular that of alkylating agents?

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