

Fertility preservation and GnRHa for chemotherapy: debate

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Dear editor

I have read with interest the review by Rodriguez-Wallberg and Oktay.¹ Although I agree with most of the written opinions for fertility preservation, an important point needs to be raised for the sake of complete and thorough information regarding such a crucial matter.

The authors claim that “Experimental data from prepubertal and adult mouse models treated with cyclophosphamide do not support the notion that a prepubertal stage would be protective for the primordial follicles”, citing their own abstract² which is not indexed in PubMed and cannot be evaluated. More importantly, they failed to mention several other peer review references^{3–6} concluding just the opposite, that gonadotropin-releasing hormone (GnRH) agonists are effective in minimizing chemotherapy induced gonadotoxicity in rodents and in humans: “This study has showed a dose-dependent protective effect of GnRH analog (GnRHa) on ovarian reserve against ovarian toxic chemotherapy, thus demonstrating an important role of GnRH analogs in fertility preservation.”³ Furthermore, several recent meta-analyses of randomized controlled trials^{7–10} also concluded that the pooled analysis of randomized studies shows that the temporary ovarian suppression induced by GnRHa significantly reduces the risk of chemotherapy-induced POF (premature ovarian failure) in young cancer patients.⁷ Nine prospective randomized studies were included in the most recent meta-analysis⁷ with 225 events of POF occurring in 765 analyzed patients. The pooled odds ratio (OR) estimate indicates a highly significant reduction in the risk of POF (OR = 0.43; 95% confidence interval [CI]: 0.22–0.84; $P=0.013$) in patients receiving GnRHa, without any evidence of publication bias. The Cochrane database analyses also concluded that:

The use of GnRH agonists should be considered in women of reproductive age receiving chemotherapy. Intramuscular or subcutaneous GnRH analogs seem to be effective in protecting ovaries during chemotherapy and should be given before or during treatment [...]¹⁰

Furthermore, opposite to the authors’ opinion and declaration regarding fertility,¹ several publications have found that the GnRH agonist co-treatment was also effective in increasing pregnancy rate in addition to decreasing premature ovarian failure.^{5,6,11,12} As we have recently summarized the case for and against GnRH agonist for fertility preservation, “An ounce of prevention is worth a pound of cure”.⁶ Since not all the

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methods are 100% successful, these young women deserve to be informed of all the possible modalities to minimize gonadal damage and preserve ovarian function and future fertility.⁶ It is recommended that GnRHa co-treatment is offered in addition to, and not instead of in vitro fertilization and cryopreservation of embryos, ova, and ovarian tissue, for fertility preservation. Furthermore, combining the various modalities for a specific patient may increase the odds of preservation of future fertility. There is no contraindication to ovarian biopsy for cryopreservation combined with GnRHa administration and follicular aspiration, as recently published.⁶ In cases where the chemotherapy has caused POF, as is frequently the case in total body irradiation and bone marrow transplantation, the patient has cryopreserved ova, embryos, or primordial follicles to fall back upon. However, in cases where conventional chemotherapy regimens such as those commonly used for young lymphoma patients are applied, GnRHa co-treatment may preserve ovarian function and prevent POF without necessitating the use of cryopreserved ova, embryos or ovarian tissue. Patients should be informed on uncertainties regarding the potential role of GnRHa and the association with adverse events like hot flushes, bone and muscle pains, mood changes, vaginal dryness, etc. Nevertheless, only a few of our 281 GnRHa co-treated patients wanted the estrogen/progestin add back therapy for minimizing side effects.⁶ Similarly, in a recent study¹³ there were no significant differences in the side effects between the GnRHa and control groups, except for the vaginal bleeding which was significantly lower in the GnRHa group.

Disclosure

The author has no conflicts of interest in this communication.

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Authors' reply

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Dear editor

We appreciate the recent comments on our article "Fertility preservation during cancer treatment: clinical guidelines"¹ by Dr Blumenfeld. As we point out in our article, in females the vast majority of clinical studies investigating gonadal protection by gonadotropin-releasing hormone analogs (GnRHa) during chemotherapy have been small, retrospective, and uncontrolled, and they have almost exclusively used resumption of menstruation as a surrogate marker for fertility. Recent clinical data indicate that fertility is reduced after a chemotherapeutic treatment, even if menstrual cycles are resumed,² and studies investigating fertility are lacking and require long-term follow-up.

The development of sensitive biochemical ovarian markers of ovarian reserve has permitted, in recent years, the investigation of the subsequent benefit of GnRHa during chemotherapy, and some randomized clinical trials have been published. Those studies have not demonstrated any benefits after GnRHa co-treatment with regard to serum concentrations of inhibin B and/or anti-Müllerian hormone, which are considered as gold standard markers of ovarian reserve today.^{3–5} A higher pregnancy rate after GnRHa use in those studies has not been demonstrated either.^{3–5}

The results of our recent experiments in mice, published in the summer supplement of *Human Reproduction* last year,⁶ do not support the fact that the mouse ovaries might be less susceptible to chemotherapeutic-induced follicle damage just

because of the fact of being at a pre-pubertal stage, but that was the only variable investigated in that experiment, and the doses of cyclophosphamide administered in the pre-pubertal group were equivalent to those administered in the adult mice group.

As data from clinical and experimental studies are still conflicting, and given the fact that our guidelines are intended as clinical recommendations, they should be in line with international guidance for fertility preservation, such as that provided by the American Society of Clinical Oncology (ASCO).^{7,8} At the time of publication of our manuscript, neither the ASCO nor other large scientific groups had recommended the use of GnRHa for fertility protection during cancer treatment. The provision of information on recognized effective methods for fertility preservation to patients should be encouraged.

Disclosure

The authors have no conflicts of interest in this communication.

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