

## Comments on the letter “Fertility preservation and GnRHa for chemotherapy: debate”

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Thank you very much for the critical comments. Any critical comment on the use of GnRH analogs (GnRHa) to protect fertility during chemotherapy is of great value in further discussions of the controversial data and the controversial attitudes of endocrinologists and oocologists.

We fully agree with the authors of the letter that several studies support the efficacy of GnRHa to protect the ovaries, which we have also demonstrated in a review summarizing nine studies on the use of GnRHa [1]. We also agree with the authors that the efficacy of other fertility preserving techniques such as cryopreservation and transplantation of ovarian tissue need further evaluation and that their safety has still not absolutely been proven, as stated in our recent review about cryopreservation of ovarian tissue [2]. Finally, we are fully aware that GnRHa provide several additional advantages during chemotherapy such as reducing the risk of thrombocytopenia-associated menorrhagia.

However, we do not agree that GnRHa, in combination with cryopreservation of ovarian tissue and follicular aspiration, should be offered to all patients. We rather think

that the current status of scientific data needs critical reflection and consequently, the patients need to be counseled carefully about the pros and cons of all available technical options, resulting in highly individualized fertility preservation approaches.

We would like to comment on the letter in detail:

First, as stated in recent reviews, previous studies did support the efficacy of GnRHa to protect the ovaries [1, 3]. However, the scientific quality of these studies was limited as none of the studies was randomized.

Four recently published randomized studies have provided the following data: The study by Badaway et al. [4] involving 78 breast cancer patients, co-treated with GnRHa or untreated, revealed regular menstruations in 90 and 33%, respectively. The study by Ismail-Khan et al. [5], involving 49 breast cancer patients, revealed regular menstruations in 88 and 84%, respectively and the study by Gerber et al. [6] involving 60 breast cancer patients revealed regular menstruations in 93 and 97%, respectively. Behringer et al. [7] analyzed Hodgkin's lymphoma patients. Eleven patients were treated with escalated BEACOPP, receiving GnRHa, and 12 controls with oral contraceptives. They found a difference neither in the rate of amenorrhea nor in the concentration of anti-Mullerian hormone.

As only one of these four studies did demonstrate a GnRHa induced protective effect on the ovaries, it is not justified to argue that all patients should receive GnRHa. The only scientifically acceptable conclusions are, first, that the available data are still controversial, second, that further studies are needed, and third, that patients can be offered GnRHa but need to be informed about the controversial data.

Second, we agree with the authors that the safety and efficacy of cryopreservation of ovarian tissue need further evaluation. We also support their attitude that

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cryopreservation of ovarian tissue should therefore be combined with other techniques such as ovarian stimulation and cryopreservation of fertilized and unfertilized oocytes which can be combined safely and efficiently, as demonstrated in a recent pilot study [8].

Third, ovarian stimulation and cryopreservation of fertilized and unfertilized oocytes still remains the only technique that has been proven to be safe and efficient and should therefore be considered in all patients. New stimulation protocols allow ovarian stimulation in all patients within 2 weeks irrespective of their menstrual phase [9] and can even be used for breast cancer patients by using aromatase inhibitors which reduce estrogen levels [10]. Data of large registries, i.e. of the network FertiPROTEKT (<http://www.fertiprotekt.eu>), have revealed representative data in >200 patients on the age dependant number of collected oocytes and their fertilization rate following ovarian stimulation before chemotherapy. These data allow, for the first time, profound and reliable counseling of patients.

In summary, we believe that the efficacy of GnRHa in ovarian protection during chemotherapy has still not been proven. However, they can be offered to patients after careful counseling. We also think that additional techniques such as cryopreservation of ovarian tissue and ovarian stimulation should always be considered as additional procedures to increase the chance for a future pregnancy.

**Conflict of interest statement** None.

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