Arch Gynecol Obstet (2010) 282:717–718
DOI 10.1007/s00404-010-1486-1

LETTER TO THE EDITOR

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

**Michael von Wolff · Juliane Raddatz · Michael K. Bohlmann · Petra Stute · Thomas Strowitzki · Markus Nitzschke**

Received: 12 April 2010 / Accepted: 13 April 2010 / Published online: 29 April 2010


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 ocologists.

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

M. von Wolff (✉) · P. Stute · M. Nitzschke
Department of Gynecological Endocrinology and Reproductive Medicine, Woman's University Hospital of Bern, Effingerstrasse 102, 3010 Bern, Switzerland
e-mail: Michael.vonWolff@insel.ch

J. Raddatz · T. Strowitzki
Department of Gynecological Endocrinology and Reproductive Medicine, Woman's University Hospital of Heidelberg, Heidelberg, Germany

M. K. Bohlmann
Department of Obstetrics and Gynecology, University Hospital of Schleswig–Holstein, Campus Luebeck, Luebeck, Germany

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.

## References


1. Blumenfeld Z, von Wolff M (2008) GnRH-analogues and oral contraceptives for fertility preservation in women during chemotherapy. Hum Reprod Update 14:543–552
2. von Wolff M, Donnez J, Hovatta O, Keros V, Maltaris T, Montag M, Salle B, Sonmezer M, Andersen CY (2009) Cryopreservation and autotransplantation of human ovarian tissue prior to cytotoxic therapy—a technique in its infancy but already successful in fertility preservation. Eur J Cancer 45:1547–1553
3. Beck-Fruchter R, Weiss A, Shalev E (2008) GnRH agonist therapy as ovarian protectants in female patients undergoing chemotherapy: a review of the clinical data. Hum Reprod Update 14:553–561
4. Badawy A, Elnashar A, El-Ashry M, Shahat M (2009) Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. Fertil Steril 9:694–697
5. Ismail-Khan R, Minton S, Cox C et al (2008) Preservation of ovarian function in young women treated with neoadjuvant chemotherapy for breast cancer: a randomized trial using GnRH agonist (triptoreline) during chemotherapy. J Clin Oncol 26(Suppl 1):12s Abstract 524
6. Gerber B, Dieterich M (2010) Ovarielle Protektion unter Chemotherapie durch GnRH-Agonisten. Gynäkologische Endokrinologie 1:41–46
7. Behringer K, Wildt L, Mueller H, Mattle V, Ganitis P, van den Hoonaard B, Ott HW, Hofer S, Pluetschow A, Diehl V, Engert A, Borchmann P, on behalf of the German Hodgkin Study Group (2010) No protection of the ovarian follicle pool with the use of GnRH-analogues or oral contraceptives in young women treated with escalated BEACOPP for advanced-stage Hodgkin lymphoma. Final results of a phase II trial from the German Hodgkin Study Group. Ann Oncol. doi:10.1093/annonc/mdq066
8. von Wolff M, Zeeb C, Lawrenz B, Germeyer A., Neunhoeffer E, Strowitzki T (2009) Cryopreservation of ovarian tissue and cryopreservation of oocytes can be efficiently combined and performed within 2 weeks before chemotherapy. Hum Reprod 24(1) Abstract Book P-392
9. von Wolff M, Thaler CJ, Frambach T, Zeeb C, Lawrenz B, Popovici RM, Strowitzki T (2009) Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. Fertil Steril 92:1360–1365
10. Azim AA, Costantini-Ferrando M, Lostritto K, Oktay K (2007) Relative potencies of anastrozole and letrozole to suppress estradiol in breast cancer patients undergoing ovarian stimulation before in vitro fertilization. J Clin Endocrinol Metab 92:2197–2200