Comment on GnRH analogue cotreatment with chemotherapy for preservation of ovarian function

To the Editor:

With great interest we have read the systematic review and meta-analysis by Bedaiwy et al. (1). The outcomes of the meta-analysis suggest a potential benefit of GnRH analogues as a cotreatment with chemotherapy in preserving future fertility, with higher rates of spontaneous resumption of menstruation and ovulation.

Six randomized controlled trials (RCTs) met the inclusion criteria. One of the largest studies was published in 2009 (2). After publication, this study was criticized for significant methodologic weaknesses, invalidating any conclusion based on it (3). Additional criticisms were that the study group consisted of very young women compared with European and American women with breast cancer, had an unlikely low resumption of menstruation (namely, only 33% of the control subjects), and had a short follow-up time (maximum 8 months after the last dose of chemotherapy) (4). Based on these criticisms, we doubt the wisdom of including this controversial study.

We performed a new meta-analysis excluding this controversial study (2) (Fig. 1). According to this new meta-analysis, the incidence of premature ovarian failure is not significantly different anymore (odds ratio [OR] 2.25, 95% confidence interval [CI] 0.65–7.78) compared with the original meta-analysis in which a potential benefit of GnRH analogs was suggested (OR 3.46; 95% CI 1.13–10.57). The I^2 test in the original meta-analysis was 66%, and in our new meta-analysis the I^2 test was 51%, showing a high amount of heterogeneity in the original meta-analysis. An I^2 value of 50% and higher is defined as moderate, above 75% as high (5).

The published review furthermore included a follow-up of only 6 months from the ZORO trial (6) and refrained from reporting the 24 months' follow-up that was also reported from this trial. This way, the original meta-analysis turned out to be more in favor of intervention with GnRH analogues: The results after a follow-up of 24 months in this study did not show a difference in resumption of menses between the GnRH agonists and the control group. With a follow-up of only 6 months, the OR in the new meta-analysis would be 2.33 (95% CI 0.80–6.77). Including the follow-up of 24 months in the new meta-analysis (Fig. 1) results in an OR of 2.25 (95% CI 0.65–7.78).

Although the authors acknowledge the high risk of bias because of missing data of noncompliant patients in four out of six studies included, in three of the six studies included there were also other forms of bias: significantly different baseline FSH levels and significantly different periods of follow-up between GnRH analogue and control groups. By including studies with questionable data, the authors introduced a high risk of potentially invalid conclusions. Finally, there was financial support provided by a pharmaceutical company.

Taking all these arguments together, we think that there is not enough evidence yet to consider cotreatment with GnRH analogues in premenopausal women receiving chemotherapy. Results of large high-quality trials have to be awaited before making strong conclusions.

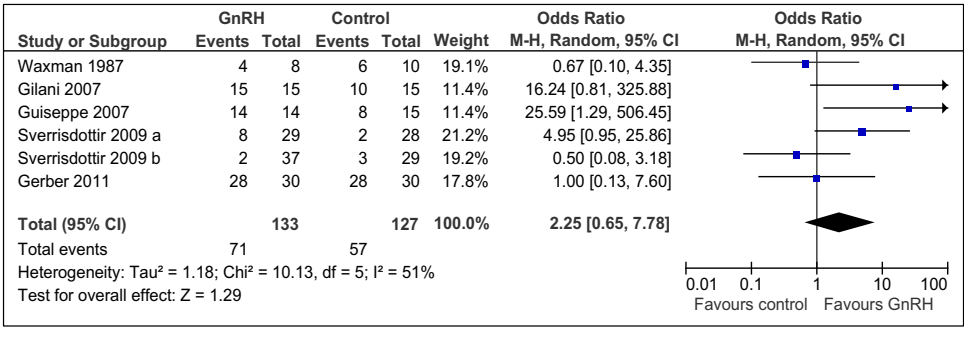
Eva Balkenende
Taghride Dahhan, M.D.
Fulco van der Veen, M.D, Ph.D.
Mariëtte Goddijn, M.D, Ph.D.
Center for Reproductive Medicine, Academic Medical Center Amsterdam, University of Amsterdam, Amsterdam, the Netherlands

June 21, 2011

doi:10.1016/j.fertnstert.2011.07.1112

FIGURE 1

Follow-up of 24 months in the new meta-analysis.



Letter to the editor. Fertil Steril 2011.

REFERENCES

1. Bedaiwy MA, Abou-Setta AM, Desai N, Hurd W, Starks D, El-Nashar SA, et al. Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: a systematic review and meta-analysis. Fertil Steril 2011;95:906–14.
2. Badawy A, Elnashar A, El-Ashry M, Shahat M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. Fertil Steril 2009;91:694–7.
3. Oktay K, Sonmezer M. Questioning GnRH analogs for gonadal protection in cancer patients. Fertil Steril 2009;92:e32.
4. Peccatori F, Demeestere I. GnRH analogue for chemotherapy-induced ovarian damage: too early to say? Fertil Steril 2009;92:e33.
5. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60.
6. Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol 2011;29:2334–41.