CEOG Clinical and Experimental Obstetrics & Gynecology

Efficiency of GnRH analogues in treating large functional ovarian cysts

S. Zervoudis[1], G. Iatrakis[2], E. Tomara[3], A. Bothou[3], P. Peitsidis[2], G. Mastorakos[4]

[1] Rea Hospital Breast Dept, Technological Educational Institute of Athens, Athens
[2] Department of Obstetrics & Gynecology, Technological Educational Institute of Athens, Athens
[3] University of Athens, Midwifery Department, Technological Educational Institute of Athens, Athens
[4] University of Athens, Clinical Endocrinology, Aretaieio Hospital, Athens (Greece)

Summary

Aim: The aim of this study was to determine the potential therapeutic benefit of a single administration of a GnRH analogue in premenopausal women presenting large functional ovarian cysts (FOCs) (diameter > five cm). *Materials and Methods:* Fifty-one patients (median age 37.4 years) diagnosed with ovarian cysts, presumed benign based on transvaginal and/or transabdominal ultrasound, were divided in three study groups. Patients of group A received no medication whereas patients of groups B and C were treated with a single administration of a GnRH analogue and combined oral contraceptives, respectively. Patients were re-examined after a three-month period. Three of the 51 patients were lost in follow-up or stopped the treatment. *Results:* Complete resolution of the ovarian cysts was observed in eight (50%), 14 (70%), and eight (67%) patients of groups A, B, and C, respectively. No side effects were observed in either of the three groups. The positive therapeutic effect in group B did not reach statistical significance compared with the two other groups ($p > 0.05$). *Conclusion:* A new option of treating large FOCS through a single-dose of a GnRH analogue is proposed and should be carefully considered. Further research is needed in order to evaluate GnRH analogues as an alternative treatment.

Key words: Functional ovarian cysts; GnRH analogues; Benign ovarian tumors.

Introduction

Functional ovarian cysts (FOCs) are common and may occur in women of all ages, mainly in those of reproductive age [1]. Usually, FOCs are either follicular cysts or corpus luteum cysts that develop during the physiologic procedure of ovulation [2]. Most of them are incidentally found during bimanual gynecological (pelvic) examination and/or ultrasound. In general, they remain asymptomatic until their resolution [3]. If a FOC is found during pelvic examination, further evaluation with transvaginal and/or transabdominal ultrasound is required [4].

In order to evaluate a patient with a FOC, the anatomic position, the size and the morphology of the mass, age, and the reproductive status of the patient should be considered [5]. The prevalence of FOCs varies from almost 8% to 18% depending on the criteria of the studies and the pre- or postmenopausal status [6]. Prevalence, in premenopausal women reaches 8% while in postmenopausal women it is about 14% (with annual incidence of 8%). Fifty percent of these FOCs will persist for at least one year [7, 8]. The age of the patient has a strong impact on the differential diagnosis [9].

In addition, according to ultrasound and clinical features, the clinicians can exclude urgent conditions and malignancy [3]. Color Doppler can be used as complementary mean of evaluation in order to report the blood flow in the ovarian mass [10, 11]. Other markers of malignancy result from magnetic resonance imaging and laboratory tests such as CA 125, HE4, TATI, and CA72.4 [5, 12]. However, the conclusive diagnosis of the type of the ovarian mass will be given through surgical exploration and histopathologic evaluation. Depending on the type of the adnexal mass, as well as on the clinical and the laboratory findings, the clinicians will determine the therapeutic and follow-up strategies.

In case of FOCs, the therapeutic use of combined oral contraceptives (COCs) is considered a "classic" approach [10]. Based on recently published data, the COCs by inhibiting pituitary gonadotropins suppress follicular growth and ovulation, reduce the risk of cyst occurrence, and eventually prevent the formation of new ones [2]. Unfortunately, there are no other therapeutic agents that block the pituitary-ovarian axis and are extensively studied and tested in humans. In this study, the authors investigated an alternative hormonal approach that could be efficacious in large FOCs and compared it to the use of COCs that is the use of GnRH analogues.

Materials and Methods

Fifty-nine premenopausal female patients, who participated in this clinical study, were consecutively diagnosed during a three-

Revised manuscript accepted for publication January 19, 2015

year period (2011-2013) in Rea Maternity Hospital (Athens, Greece) with one ovarian cyst sizing more than five-cm in diameter. This diagnosis came up incidentally during pelvic examination. All participants underwent transvaginal ultrasound (including color Doppler ultrasound) and suspicious findings were discovered in eight patients. Serum CA 125 and HE4 were measured in all participants. The latter tumor marker was measured considering that, commonly, it is not increased in benign conditions as conversely happens with the CA 125 marker. In the 51 patients considered malignancy-free after the ultrasound examination, the levels of these markers remained within normalcy, as expected. Women lost to follow-up and those with suspicious findings in ultrasonography were excluded from the study. None of the 51 patients included in the study was suffering from a severe disease including breast or endometrial cancer and none was pregnant or breastfeeding. Written informed consent was signed from all participants.

The selected dose of the GnRH agonists was a single dose of 11.25 mg of triptorelin while the treatment with COCs contained 30 mcg of ethinyl estradiol and 3 mg of drospirenone. The 51 consecutively selected patients separated in three groups with similar characteristics. Participants randomly assigned to receive their medication during the first appointment after clinical examination. Group A, consisted of 16 patients and received no medication for these FOCs. In groups B and C, 22 and 13 patients were included, respectively. Patients of group B were treated with a single dose of a GnRH analogue while patients of group C received a treatment with COCs. Two patients of group B decided not to adhere to the suggested treatment and one patient in group C was lost to follow-up. Thus, the final number of patients included in this study was 48 (with a median age of 37.4 years). A new appointment was arranged after three months for a transvaginal ultrasound test, which was performed by the same gynecologist with the same ultrasound imaging machine.

Results

After the second visit, complete resolution of the FOCs was observed in eight patients of group A (50%), in 14 patients (70%) of group B, and in eight patients of group C (67%) (Figures 1, 2). Treatment with the GnRH analogue in group B was well-tolerated. The number of patients with resolved FOCs in this group, did not show statistically significant difference as compared with the patients of the two other groups studied ($p > 0.05$). The size of the FOCs of the patients of all groups studied that did not resolve remained unchanged while none of the patients studied presented new FOCs during the study duration.

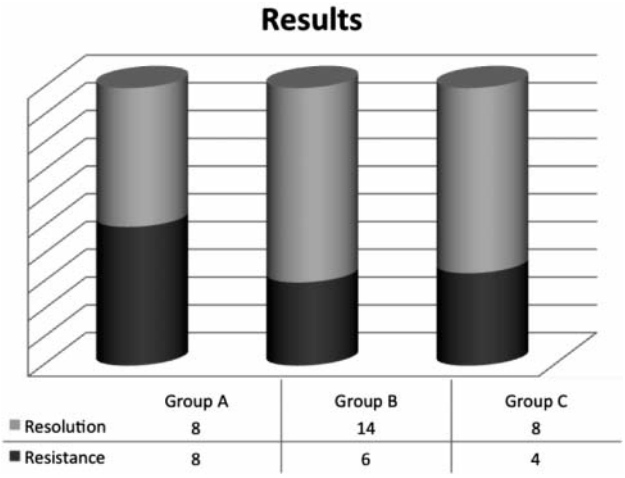

Figure 1. — Results for each study group expressed as percentages.

Discussion

As it is aforementioned, the efficiency of GnRH analogue alone as treatment of FOCs in otherwise healthy women has not been studied before. They were used once in a randomized blind clinical trial for the treatment of bovine ovarian cysts [13]. Also, there were used in some other studies, as co-treatment with tamoxifen in women with breast cancer who had developed ovarian cysts [14-16]. The ovarian cyst formation is a relatively common side effect of tamoxifen either in premenopausal or postmenopausal women with breast cancer. In the women of a prospective controlled study, the cure rate of the ovarian cyst was 97% [14].

Figure 2. — Results for each study group, expressed as percentages.

For the general population, the use of COCs reduces the risk of development cyst of FOCs, due to the resulting suppression of follicular growth and ovulation [17]. However, the current low-dose COCs are at disadvantage because they cannot succeed the suppression of all follicular activity [18, 19] while high-dose COCs seem to protect against cyst development [20] with probable more side effects.

Considering the effects of COCs, it was hypothesized that they may decrease the size and hasten the resolution of the existing cysts. Both of these hypotheses were demolished after a Cochrane review, which included the results of eight randomized trials with a total number of 686 women treated by any type of COCs [21]. The conclusion appeared to be the same for all cysts, either for those that were bearing upon ovulation induction or those that occurred spontaneously. Consequently, the actual predominant recommendation is that COCs are not to be used for this purpose [18, 21].

Conclusion

Given the aforementioned results, GnRH analogues could be a new alternative therapeutic proposal. Although GnRH analogues are used successfully in different gynecologic conditions [22], it is the first time that a single administration of a GnRH analogue is used successfully in women with FOCs. Further studies with increased number of patients could alter the future recommendations and confirm this new therapeutic indication.

References

[1] Helm C.W.: ''Ovarian cysts''. *Medscape*, 2014. Available at: http://emedicine.medscape.com/article/255865-overview
[2] Horlen C.: ''Ovarian cysts: a review''. *US. Pharm.*, 2010, *35*, 1.
[3] American College of Obstetricians and Gynecologists: ''ACOG Practice Bulletin No. 83: Management of adnexal masses''. *Obstet. Gynecol.*, 2007, *110*, 201.
[4] Le T., Giede C., Salem S., Lefebvre G., Rosen B., Bentley J., *et al.*: ''Initial evaluation and referral guidelines for management of pelvic/ovarian masses''. *J. Obstet. Gynaecol. Can.*, 2009, *31*, 668.
[5] Muto G.M.: ''Approach to the patient with an adnexal mass''. UptoDate, 2013. Available at: http://www.uptodate.com/contents/approach-to-the-patient-with-an-adnexal-mass
[6] Ross E.K., Kebria M.: ''Incidental ovarian cysts: when to reassure, when to reassess, when to refer''. *Cleve. Clin. J. Med.*, 2013, *80*, 503.
[7] Borgfeldt C., Andolf E.: ''Transvaginal sonographic ovarian findings in a random sample of women 25–40 years old''. *Ultrasound Obstet. Gynecol.*, 1999, *13*, 345.
[8] Greenlee R.T., Kessel B., Williams C.R., Riley T.L., Ragard L.R., Hartge P., *et al.*: ''Prevalence, incidence, and natural history of simple ovarian cysts among women >55 years old in a large cancer screening trial''. *Am. J. Obstet. Gynecol.*, 2010, *202*, 373.
[9] Hoffman S.M.: ''Differential diagnosis of the adnexal mass''. *UptoDate*, 2014. Available at: http://www.uptodate.com/contents/differential-diagnosis-of-the-adnexal-mass
[10] Muto M.G.: ''Management of an adnexal mass''. *UptoDate*, 2014. Available at: http://www.uptodate.com/contents/management-of-an-adnexal-mass?source=search_result&search=management+of+adnexal+mass&selectedTitle=1~122
[11] American College of Obstetricians and Gynecologists: ''The role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer. Committee Opinion No. 477''. *Obstet. Gynecol.*, 2011, *117*, 742.
[12] Wiwanitkit V.: ''CA-125 and risk of malignancy index for screening for malignancy in fertile aged females with ovarian cyst, which is more cost effectiveness?'' *Indian J. Med. Paediatr. Oncol.*, 2013, *34*, 72.
[13] Dinsmore R.P., White M.E., Guard C.L., Jasko D.J., Perdrizet J.A., Powers P.M., Smith M.C.: ''A randomized double blind clinical trial of two GnRH analogues for the treatment of cystic ovaries in dairy cows''. *Cornell. Vet.*, 1987, *77*, 235.
[14] Kourounis G., Zervoudis S., Michail G., Fotopoulos A.: ''Tamoxifen induced ovarian cysts in postmenopausal breast cancer patients treated with GnRH agonists: a prospective controlled study''. *Obstetrica si Ginecologia*, 2005, *LIII*, 79.
[15] Shulman A., Cohen I., Altaras M.M., Maymon R., Ben-Nun I., Tepper R., Beyth Y.: ''Ovarian cyst formation in two pre-menopausal patients treated with tamoxifen for breast cancer''. *Hum. Reprod.*, 1994, *9*, 1427.
[16] Shusan A., Peretz T., Mor Yosef S.: ''Therapeutic approach to ovarian cysts in tamoxifen-treated women with breast cancer''. *Int. J. Gynecol. Obstet.*, 1996, *52*, 249.
[17] Thomin A., Daraï E., Chabbert-Buffet N.: ''Medical treatments of presumed benign ovarian tumors''. *J. Gynecol. Obstet. Biol. Reprod. (Paris)*, 2013, *42*, 774.
[18] American College of Obstetricians and Gynecologists: ''ACOG Practice Bulletin No. 110. Noncontraceptives uses of hormonal contraceptives''. *Obstet. Gynecol.*, 2010, *115*, 206.
[19] Holt V., Cushing-Haugen K.L, Daling J.R.: ''Oral contraceptives, tubal sterilization, and functional ovarian cyst risk''. *Obstet. Gynecol.*, 2003, *102*, 252.
[20] Brun J.L., Le Touzé O., Leng J.J.: ''Traitement medical et chirurgical des kystes de l' ovaire fonctionnels''. J. *Gynecol. Biol. Reprod.*, 2001, *30*, 4S41.
[21] Grimes D.A., Jones L.B., Lopez L.M., Schulz K.F.: ''Oral contraceptives for functional ovarian cysts''. *Cochrane Database Syst. Rev.*, 2014, *4*, CD006134.
[22] Zervoudis S., Iatrakis G., Navrozoglou I.: ''Reproduction after breast cancer''. *Best Pract. Res. Clin. Obstet. Gynaecol.*, 2010, *24*, 81.

Address reprint requests to:
S. ZERVOUDIS, M.D., Ph.D.
Rea Hospital
Suggrou Avenue 383
Palaio Faliro, 17564 (Greece)
e-mail: szervoud@otenet.gr