Medical treatment for uterine fibroids: Does current evidence mandate a change in clinical guidelines?

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Abstract

Current medical practice has seen, in the last two decades, a change of paradigm due to the appearance and growth of evidence based medicine. Although there have been numerous, and many times justified, critiques regarding this type of medical practice, currently, evidence based medicine has become the norm, not the exception, at a global level. The uterine fibroid represents the most frequent benign tumor in women of child reproductive age, its prevalence being estimated between 20 and 40%. As such, it represents a pathology which is often seen in all gynecology services worldwide. The principal treatment for these tumors is represented by hysterectomy, these procedure also being most frequently for uterine fibroids. Also, uterine fibroids are the most frequent indication for hysterectomy. An American study from 2012 showed that uterine fibroids have an annual incidence estimated at 0.92% in the United States of America and that 94% of women diagnosed will have at least one diagnostic or therapeutic procedure in the year following the diagnostic. Using these data, the authors of the study estimate that the annual direct and indirect costs in the USA are between 5.89 and 34.37 billion dollars, using the 2010 value of the dollar. An important part of these costs is represented by the absence from the workplace (7.8 billion dollars). As such, the economic impact of uterine fibroids is actually higher than the cost for managing breast, colon or ovarian cancer, reaching around half the costs for treating diabetes mellitus. Although uterine fibroids present such a high prevalence, possible complications and a steep cost, there were only a handful of studies which allowed an evaluation of the efficacy of different treatments. Recommendations with a clear scientific value have been hard to formulate due to this problem. Donnez et al., cited in an editorial from the prestigious "New England Journal of Medicine", written by Stewart, present two randomized clinical trials which were done to gain a better grasp on the drugs used in the treatment of uterine fibroids. The editorialist concludes that the studies finally present strong evidence for the treatment of uterine fibroids, representing a step forward in the medical therapy of these tumors.

Keywords: *Uterine Fibroids, SPRM, leuprolide acetate, safety profile, ulipristal acetate*

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The uterine fibroid represents the most frequent benign tumour in women of child reproductive age, its prevalence being estimated between 20 and 40%[4,5]. As such, it represents a pathology which is often seen in all gynecology services worldwide. The principal treatment for these tumors is represented by hysterectomy. Also, uterine fibroids are the most frequent indication for hysterectomy[4,7,8].

An American study from 2012[6] showed that uterine fibroids have an annual incidence estimated at 0.92% in the United States of America and that 94% of the women diagnosed will have at least one diagnostic or therapeutic procedure in the year following the diagnostic. Using these data, the authors of the study estimated that the annual direct and indirect costs in the USA are between 5.89 and 34.37 billion dollars, using the 2010 value of the dollar. An important part of these costs is represented by the absence from the workplace (7.8 billion dollars). As such, the economic impact of uterine fibroids is actually higher than the cost for managing breast, colon or ovarian cancer, reaching around half the costs for treating diabetes mellitus[6].

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only a handful of studies which allow an evaluation of the efficacy of different treatments. Recommendations with a clear scientific value have been hard to formulate due to this problem[9].

Certainly, the two studies published by Donnez et al.[2,3] this year will solve a part of this problem, as both evaluate the efficacy of ulipristal acetate (UPA) as a medical treatment for uterine fibroids.

Over the course of time estrogens have been considered the key players in the etiopathogenesis of these tumors[10], but several recent studies have shed light on the essential role of progesterone in this process. Also, a couple of smaller randomized studies have shown that selective modulators of progesterone receptors (SPRMs) reduce the volume of uterine fibroids and can control the bleeding caused by these tumors[11-13].

This class of SPRMs which includes UPA as well as, also known as RU 486, are not yet in clinical use due to the controversies regarding the use of mifepriston for medically induced abortion[14].

One of the aforementioned clinical trials compared UPA with placebo in a randomized, controlled, double-blind, phase III study, in which 6 countries and 38 medical centers participated, out of which 6 were located in Romania.

The main objectives were the demonstration of the superior efficacy of 5 or 10 mg of UPA + iron daily in comparison with placebo + iron daily. The primary end-points for the trial were represented by the reduction of excessive uterine bleeding and the reduction of the total volume of uterine fibroids before the surgical intervention. The secondary end-points were the amelioration of symptoms caused by the tumor (e.g. quality of life and pain), the evaluation of the capacity of UPA to reduce the uterine volume and the capacity of UPA + iron, as compared to placebo + iron, to correct the anemia caused by uterine fibroids.

A number of 242 women with ages between 18 and 50 years were randomized to receive 5 mg UPA + 80 mg iron, 10 mg UPA + 80 mg iron or placebo + 80 mg iron, in a ratio of 2:2:1, for 13 weeks. For inclusion in the study, the patients had to have symptomatic uterine fibroids eligible for surgery at the end of the study, but not bigger than a 16 weel pregnacy, with at least one fibromatous nodule with a diameter of over 3 cm, but less than 10 cm, according to ultrasound measurements, presented with anemia caused by uterine fibroids, anemia defined as a value of hemoglobin of less than 10.2 g/dl and a Pictorial Blood-loss Assessment Chart (PBAC) score during menstrual bleeding higher than 100 in the first 8 days of menstruation[15-18].

In the six months following the end of treatment, 109 out of 242 patients sustained surgical were operated, whilst the other patients had regular check-ins at weeks 17, 26 and 38. Regarding the results, if we come back to the primary end-points of the study, we must admit they surpassed our expectations: menstrual bleeding was controlled with a PBAC score <75 for 91% of the patients who received 5 mg UPA and for 92% of the patients who received 10 mg UPA, in comparison with 19% for those who received placebo ($p<0.001$ for all comparisons). After 7 days of treatment, the bleeding was controlled for 75.9% of the patients who received 5 mg UPA and for 92.7% of the patients who received 10 mg UPA. Also, 50% of the patients in the first and 70% of the patients in the second group became amenorrheic at the end of the first menstrual cycle, in comparison to the patients in the placebo group who presented menorrhagia during multiple successive cycles ($p<0.05$ for all comparisons) (Figure1). After the last administration of the study drug, menstruation became normal after a mean period of 30 days.

Anemia presented a better prognosis as well in the two groups of patients treated with UPA, both the level of hemoglobin and the hematocrit being higher as compared to those of the patients treated with placebo (all comparisons were statistically significant).

Regarding the reduction of the fibroid volume, this was clinically bigger in both groups of patients treated with UPA as compared to the placebo group (all comparison were statistically significant): a statically significant higher number of UPA treated patients presented a reduction of at least 25%, as well as a reduction of the total uterine volume of at least 25% at the end of the treatment period. This reduction was higher for the women who received 5mg of UPA. The fibroid volume was evaluated both in each center and by a centralized group of investigators who analyzed the MRI images.

In comparison with placebo, both UPA doses led to a reduction in pain, especially moderate and severe pain, this reduction being comparable with the post-surgical pain reduction obtained using narcotic or non-narcotic analgesics. Pain was measured used the McGill questionnaire[19].

There were no significant differences in adverse events in the three groups of patients, with headaches and breast discomfort being the most frequent adverse events reported by the women who received UPA. However the difference was not statically significant in comparison with the placebo group.

The second randomized clinical trial[3] compared the two doses of UPA (5 mg and 10 mg of UPA orally administered) and a GnRH agonist, leuprolide acetate which

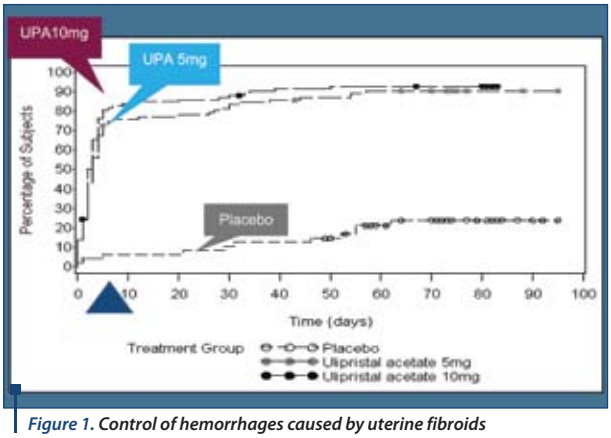

Figure 1. Control of hemorrhages caused by uterine fibroids

was administered intramuscularly at a dose of 3.75mg monthly. The purpose of the study was to demonstrate the non-inferiority of UPA in comparison with leuprolide acetate in the control of bleeding caused by the uterine fibroids as well as the evaluation of the sagety profile of the adverse events. This comparison was done because GnRH agonists are still considered the best medical therapy for uterine fibroids[20,21].

The study was a randomized, double-blind, controlled, phase III study, in which 307 patients received 5 mg UPA daily and a saline of physiological serum, 10 mg UPA daily and a saline of physiological serum or 3.75 mg leuprolide acetate monthly with the purpose of evaluating the efficacy and the safety profile of UPA in comparison with leuprolide acetate for the pre-operative treatment of symptomatic uterine fibroids[3]. The criteria used for inclusion and exclusion from the study were similar to those from the previously discussed study[2], with the exception of hemoglobin level which no longer constituted a participation criteria. The magnitude of metrorrhagies was measured using the PBAC score.

The results showed that after 13 weeks 90% of the patients who received 5 mg UPA, 98% of the patients who received 10 mg UPA and 89% of the patients who received leuprolide acetate achieved a PBAC score <75 in the previous month, thus demonstrating the non-inferiority of UPA in controlling the bleeding, with the 10 mg dose actually being superior to leuprolide acetate ($p=0.03$)(3). Both doses of UPA led to a faster control of hemorrhage ($p<0.001$). Amenorrhea appeared faster for the patients who received UPA, after a mean duration of 7 days for the women who received 5 mg UPA, 5 days for the women who received 10 mg UPA and 21 days for the women who received leuprolide acetate ($p<0.001$). All the treatment groups presented similar improvements of the pain caused by the uterine fibroids, of the quality of life and of the hemoglobin level. Menstruation reappeared after a mean period of 31-34 days in the first two groups, compared to 43 days in the last group[3].

All the three treatment groups presented a volume reduction for the biggest 3 uterine fibroids, with a mean reduction at 13 weeks of 36% in the first group, 42% in the second group and 53% in the third, differences that did not reach statistical significance. The uterine volume was diminished significantly more (47%) in the patients who received leuprolide acetate, in comparison with the other two groups (20% and 22%).

At the end of the treatment period, 157 out of the 307 patients underwent surgery. For the patients who were not operated, similar benefits were seen from the point of view of hemorrhagic control, pain and quality of life improvement in the three groups.

For the patients who did not underwent surgery and were assigned to receive UPA, a better sustained mean uterine fibroid reduction was observed at 6 months after the end of treatment, in comparison with the patients who did not underwent surgery and received leuprolide acetate (44.8% vs. 54.8% vs 16.6%, $p<0.005$). The authors assumed that this effect would have been produced by the apoptosis of leiomyoma cells which would have been induced by UPA[3,22-27].

Dosing of plasmatic estradiol for all the patients receiving UPA has shown similar values with those in medium follicular phase, as opposed to the patients treated with leuprolide acetate who presented low values of estradiol, similar to those from post-menopause. As such, hot-flashes were more common in this group (41.6%) as compared to the other two groups which were treated with UPA (11.3% and 9.7%)[3].

A similarity between the two studies discussed in this article[2,3] is represented by the laboratory results: there were no significant differences in the levels of glucose, corticotrophin, prolactin, hepatic biomarkers or cholesterol between the patients treated with UPA and those who received placebo[2], on one hand, and no differences between the levels of corticotrophin, thyrotropin, prolactin or glucose between the patients treated with UPA and those treated with leuprolide acetate, on the other hand. The only exception was a marker of bone depletion which was significantly more reduced in the groups treated with UPA, suggesting a higher bone resorption in the group treated with leuprolide acetate[3].

The investigation of the safety profile of UPA also included its effects on the endometrium. The investigation was performed through endometrial biopsies done using Pipelle de Cornier, with the biopsies being executed before therapy, at the end of treatment (3 months) and after 6 months of follow-up without receiving any treatment for the patients who did not undergo hysterectomy of endometrial ablation. The biopsies were evaluated by 3 independent blinded investigators, experts in gynecological pathology, at a central level and were based on a rating scale which used the common descriptors for endometrial histology. These new and benign histological modifications which were induced by UPA treatment are described as "endometrial changes associated with the modulators of progesterone receptors" (PAEC) and should not be confounded with endometrial hyperplasia[28].

The incidence of PEAC was similar in both groups treated with UPA (60%) and it regressed spontaneously after treatment ending[2,3].

Finally, after analyzing the data of these two studies, we could conclude that: UPA rapidly stops excessive bleeding (in one week), it normalizes menstrual bleeding for 90-98% of the patients (PBAC<75) and induces amenorrhea for 75% of the patients[3]; UPA reduces the volume of the three biggest uterine fibroids (35% for UPA 5mg and 42% for UPA 10 mg) and the reduction in volume for all uterine fibroids seems to be maintained for up to 6 months after ending treatment[3]; patient's quality of life is also improved to levels comparable to those of healthy women[3]; for the majority of patients, menstruation and ovulation reappear in one month after the end of treatment[2,3]; UPA, in comparison with leuprolide acetate, seems to control bleeding more rapidly and in a consequent manner (7 vs. 30 days); UPA also maintains the reductions in uterine fibroid volume for up to 6 months (-44.8 % and -54.8 % for UPA 5 mg and 10 mg, as compared to -16.5%

for leuprolide acetate)[3] and presents a superior safety profile because estradiol levels are maintained at middle follicular phase levels[3].

However, what could be the limitations of these studies? Among them, we mention: the short treatment period; the low number of black patients who present a higher prevalence of uterine fibroids with a younger age at which tumors appear and who also have more severe form[1,29]; the patients included in the study had a lower body mass index (BMI) and the uterine volume was also smaller than that of women included in previous studies[1,30]; ovulation was not evaluated systematically, which may have caused some metrorrhagies to be caused by other factors except uterine fibroids[1].

Apart from these limitation, we still have to answer our first question: Do these studies have the external validity required to impose this treatment in usual clinical practice? Considering the study design, the answer is most likely yes. Taking into account the costs associated with uterine fibroids, except for the American study already discussed[6], we can also use the information from an European study which could be easier applied to the Romanian medical system. According to this study, the number of women hospitalized for uterine fibroids in 2005 was: 64.299 (1,53/1000 women) in Germany, 37.787 (1,17/1000 women) in France and 18.274 (0,71/1000 women) in UK. The annual cost of the interventions was 212.313.090 Euros in Germany, 73.278.270 Euros in France (excluding the salary of surgeons and anesthetists from the private system) and 52.674.672 Euros in UK. The percent of surgical interventions for uterine fibroids, including hysterectomies, was 84.9% in Germany, 59.7% in France and 64.1% in UK[31].

If we consider this high number of hysterectomies in light of the 2011 cohort study published by Musallam et al. in Lancet shows that, in a group of 227425 patients with major non-cardiac surgery, 69229 presented pre-operative anemia and the mortality and morbidity was significantly higher in the group with pre-operative anemia[32], then we can assume that these two recent studies of UPA will represent a landmark for the treatment of uterine fibroids. ■

Conflicts of interest

The author (Lucian Puscasiu) has received publication and speaking fees as well as travel expenses and fees in connection with a launch symposium in March 2012 in Barcelona from the company Gedeon-Richter.

Also the author (L.P.) has received investigators fees from the company ICON during the PEARL I study.

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