Article

Anastrozole and Levonorgrestrel-Releasing Intrauterine Device in the Treatment of Endometriosis: A Randomized Clinical Trial.

Running title: Anastrozole and LNG-IUD in Endometriosis.

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Details of trial registration

Eudra CT System of the European Medicines Agency (London, 29-Sept-2008) Nº EudraCT: 2008-005744-17 (07/11/2008). Date of enrolment of first patient: 15/01/2009.

ABSTRACT: *Background:* Effectiveness of Anastrozole and levonorgestrel-releasing intrauterine device (LNG-IUD, Mirena®) in the treatment of endometriosis. *Methods:* Randomized clinical trial. Elegibility criteria: Endometriomas >3×4 cm, CA-125>35 U/mL and symptoms suggestive of endometriosis. Thirty-one women were randomized to anastrozole+Mirena®+Conservative Surgery(CS) (n=8), anastrozole+Mirena®+transvaginal ultrasound-guided puncture-aspiration(TUGPA) (n=7), Mirena®+CS (n=9), or Mirena®+TUGPA (n=7). Interventions: Anastrozole 1 mg/day and/or only Mirena® for 6 months. CS or TUGPA one month after starting medical treatment. *Results:* A significant improvement in symptoms during the treatment (difference of 43%, 95% CI 29.9-56.2) occurred, which was maintained at 1 and 2 years. It was more significant in patients treated with anastrozole. For CA-125, the most significant decrease was observed without anastrozole. After CS for endometriosis, a reduction of findings of endometriomas and long-term recurrences occurred, with or without anastrozole, although anastrozole seems to delay recurrences. At 4,2±1,7 years, 88% of the patients who underwent CS were asymptomatic, compared to only 21% if TUGPA was performed, with or without anastrozole (p=0.019). *Conclusion:* Dosing anastrozole for 6 months, starting one month before CS of endometriosis, reduces more significantly the painful symptoms and delays recurrences, but has no other significant advantages over the single insertion of LNG-IUD (Mirena®) during the same time.

Keywords: Aromatase inhibitors; Anastrozole; levonorgestrel-IUD; endometriosis; endometriomas; clinical trial

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Introduction

The therapeutic perspectives for endometriosis have been directed in the last years towards the use of a variety of new medications including immunomodulatory agents (i.e. local interleukin-2r [1]), selective estrogen and progesterone receptor modulators, GnRH antagonist, angiogenic inhibitors, or the third-generation aromatase inhibitors (AI) (i.e. Anastrozole and Letrozole), systemically and/or locally administered, and eventually without the need for surgery [2, 3-5]. Anastrozole inhibits aromatase and decreases the amount of estrogens in all tissues; thus, in positive aromatase endometriotic implants, it should prevent local estrogenic production and, therefore, endometriotic tissue proliferation [2, 6-8]. That estrogen suppression and subsequent response from the adenohypophysis could lead to an increase in gonadotropins with consequent ovarian stimulation and possible formation of dysfunctional cysts or eventual follicular rupture, ovulation, and pregnancy. Thus, in all studies in premenopausal women with endometriosis in which long-term AIs have been used, they have been associated with gonadotropin-releasing hormone (GnRH) analogues, to slow down gonadotropins and produce hypoestronism, or with progestins or oral contraceptive pills (OCP), which could also improve endometriosis and its symptoms. Our proposal was to associate Anastrozole administered orally for 6 months with a levonorgestrel-releasing intrauterine device (LNG-IUD), (Mirena®), during the same time period. Mirena® is a device that contains 52 mg of levonorgestrel (LNG) and releases it in situ 20 μg/24 hours. Thus, our therapeutic proposal was based on previous reports about both medications (Anastrozole [3, 4] and Mirena® [9]), with the later acting both as a contraceptive and atrophying the eutopic endometrium (by local effect of LNG) that would reduce or avoid the retrograde menstruation.

Study objective: We proposed a clinical trial (CT), whose main objective was to assess the efficacy of AI Anastrozole associated with LNG-IUD (Mirena®) (compared with Mirena® alone), in the treatment of moderate and severe endometriosis and its symptoms, along with laparoscopic or laparotomic conservative surgery (CS), or with transvaginal ultrasound-guided puncture-aspiration (TUGPA) of the endometriomas.

Material and methods

Study design. Randomized, comparative and controlled CT whose protocol (ENDOMET-IA-DIULNG08) was approved by the Ethics Committee of San Juan University Hospital (26-August-2008). It was registered in the Eudra CT System of the European Medicines Agency (London, 29-Sept-2008; Nº EudraCT: 2008-005744-17) (07/11/2008) and then authorized by the Spanish Agency for Medicines and Health Products (AEMPS) (10/11/2008).

Participants: Premenopausal women with endometriomas recruited at the Endometriosis and Reproductive Medicine Consultation of San Juan University Hospital. They had been advised for CS, did not currently desire pregnancy, and accepted the insertion of LNG-IUD (Mirena®) for 6 months and randomization to perform CS by laparoscopy or laparotomy, or only TUGDA of endometriomas, 1 month after the IUD insertion.

Inclusion criteria: Young women (< 41 y) with significant clinical symptoms (score of visual analogue scale (VAS) ≥ 4), elevated CA-125 (≥ 35 U/mL), and a transvaginal ultrasound (TVU) with suggestive findings of endometriomas (> 3×4 cm). These patients could have a previous diagnosis and treatment (medical and/or surgical) of endometriosis, but they should not have received medical treatment in the last 3 months.

Exclusion criteria: i) Pregnancy; ii) Infertility with current desire for pregnancy; iii) No previous sexual intercourse and/or non-acceptance of insertion of Mirena®; iv) Acute or recurrent pelvic inflammatory disease or genital tract infection; v) Uterine malformations and/or leiomyomas; vi) Any medical pathology that could contraindicate the treatment with Anastrozole or LNG-IUD.

Written informed consent was obtained from all patients before *randomization*. Participants were randomized by computer, determined at the Hospital Pharmacy after a telephone call from the Endometriosis Consultation. Between January 15, 2009 (date of inclusion of the first patient) and March 15, 2015, the eligibility criteria were analyzed in 52 patients who had ovarian cystic tumors

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suggestive of endometriomas, with indication to CS. After excluding 21 patients due to not meeting all the inclusion criteria, doubts in the ultrasound diagnosis, or because they declined to participate, the other 31 women were included, randomized, treated and followed up according to the following subgroups: (1) Anastrozole-Mirena-CS (n = 8); (2) Anastrozole-Mirena-TUGPA (n = 7); (3) no Anastrozole-Mirena-CS (n = 9); and (4) no Anastrozole-Mirena-TUGPA (n = 7).

Procedures. Medical treatments: (1) oral Anastrozole, 1 tablet of 1 mg daily for 6 months administered to patients in subgroups 1 and 2; (2) LNG-IUD (Mirena®) for all patients; (3) calcium carbonate and cholecalciferol (Ca + Vitamin D) to patients taking Anastrozole to avoid the damaging effects of AI on the bone. Surgical treatments: (1) laparoscopy (in 13 women, 76%) or laparotomy (in 4 women -in 2 was conversion-) with CS of endometriosis; or (2) TUGPA of endometriomas (in 14 women). All surgeries were performed or directed by the first author of the present study (PA).

Research plan: All patients will undergo a first analytical control, clinical exploration and TVU in the second half of the cycle, being randomized according to the subgroups previously exposed. Patients of subgroups 1 and 2 would start taking Anastrozole at the beginning of the next menstruation, placing the LNG-IUD (Mirena®) during it, as well as in the other subgroups. At the time, the surgical proposal to be practiced a month later was processed. Postoperative control follow-ups would be done at 3 and 6 months (time of withdrawal of Anastrozole and Mirena®); thereafter at 9, 12, 18, 24 months, and then annual follow-ups.

Assessments. All patients must have a detailed medical history about their antecedents and previous treatments, also including clinical exploration, TVU, hormonal and tumor marker analysis (CA-125, CA-19-9) and symptoms score using our VAS [maximum 10 points, including dysmenorrhea (0-3), deep dyspareunia (0-3), chronic pelvic pain (CPP, 0-3), and others (0-1)]. In all subsequent follow-ups, TVU, analysis and VAS score for symptoms were repeated.

We considered *recurrence* of the disease when an endometrioma was detected in any control, which persisted or grew in subsequent follow-ups, associated with an increase in VAS score and/or CA-125 level. In any case, the recurrences of small endometriomas (1.5-3 cm) and endometriomas greater than 3-4 cm are presented separately in the tables of results.

Outcomes. Primary endpoints: (1) reduction or disappearance of symptoms; (2) normalization of CA-125 values; (3) reduction or disappearance of endometriomas. Secondary endpoints: (1) decrease or disappearance of recurrences; (2) rate of reoperations; (3) subsequent pregnancy achievement; and (4) valuation of the clinical state in the last follow-up and the need for other treatments.

Safety and adverse events. In laparoscopic or laparotomic surgery, peritoneal fluid and biopsies or surgical specimens were collected for cytological and histopathological studies. In TUGPA, endometrioma fluids were also collected for cytological analysis. Side effects and adverse events were registered and considered in each patient follow-up.

Statistical analysis. Sample size: Based on previously published studies using AI [3,4,10,11] or LNG-IUD [9], we estimated a total sample size of 48 patients to study in a period of 3 years, which was prolonged another 3 years due to difficulties for recruitment. However, we decided to finish it in March 2015 due to its low rate, to the need to make a final report in September-2015 and also because the patients undergoing TUGPA were not showing good clinical results. Nevertheless, their follow-up continued to the final data collection in July-2017.

All data were entered into SPSS Statistics version 25.0 (IBM, Spain) to perform statistical analysis. Data are expressed as percentages, mean ± standard deviation (SD), median, minimum and maximum (min-max) values, and a 95% confidence interval (CI) (if applicable). The main dependent variables were the VAS score, the absence or presence of endometriomas in TVU, and the values of CA-125 and CA-19-9, as well as their evolution in later follow-ups. The main independent variables were Anastrozole+LNG-IUD or only LNG-IUD treatments, as well as CS or TUGPA of endometriomas. We applied descriptive statistical analysis for qualitative variables to determine frequencies and distribution using contingency tables and comparison of proportions. The chi-squared, Kruskal-Wallis, Mann-Whitney U and correlation tests were used to compare groups and parameters in the different follow-ups. For quantitative or numerical variables, we applied nonparametric tests for paired data to compare the values before and at 3, 6, and 9 months, and 1 and 2 years, and the last follow-up after treatment, calculating the Wilcoxon signed rank test, the signs

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test, the McNemar test (for dichotomous variants), and the marginal homogeneity test, noting in tables and graphs only the significant results. Likewise, nonparametric tests were applied to compare Anastrozole and non-Anastrozole groups. To determine the recurrence and reoperation rates, we calculated the percentage accumulated every 3 months up to 2 years, and then every year up to 6 years, pointing at the corresponding figures the patients at risk in each period, subtracting recurrences and loss to follow-up. All p values reported are 2-tailed, and $p<0.05$ was considered significant.

Results

Participants recruited and included in the study. The eligibility criteria were analyzed in 52 patients (see Fig. 1). After excluding 21 patients, 31 women were included in the CT and randomized in the 4 subgroups mentioned above. All patients had a LNG-IUD (Mirena®) for 6 months, and 15 of them also received Anastrozole for the same period. The latter were followed for 4.67 ± 1.63 years (95%CI: 3.76-5.57), and the first ones for 3.78 ± 1.77 years (95%CI: 2.84-4.72), without significant differences.

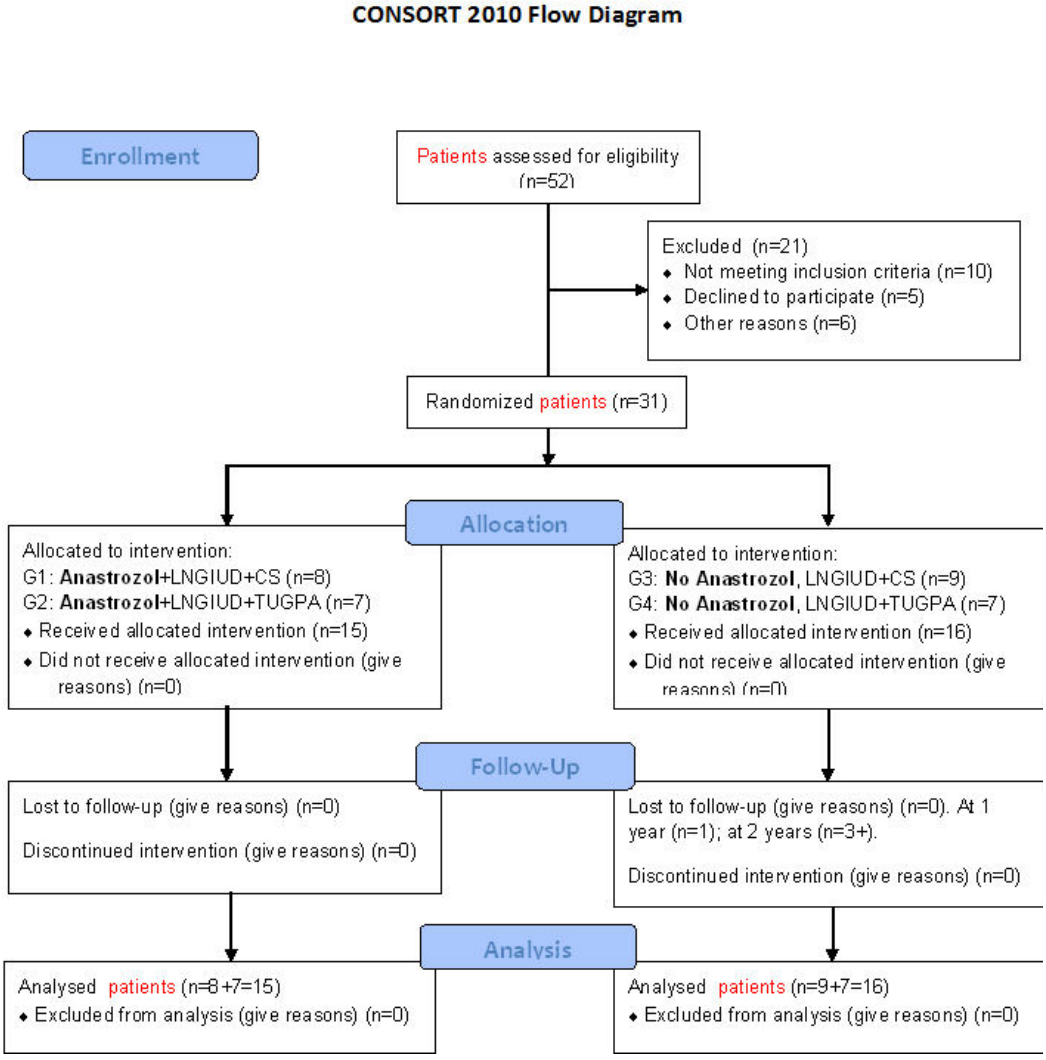

Figure 1. Trial profile.

Baseline characteristics. Table 1 shows the characteristics, antecedents, symptoms, laboratory tests, and ultrasound and operative findings of the four groups of patients. No significant differences were observed.

Table 1. Baseline characteristics of the patients included in the clinical trial.

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Characteristics	G1. Anastrozol+LNGIUD +CS (n=8)	G2. Anastrozol+LNGIUD +TUGPA (n=7)	G3. LNGIUD+CS (n=9)	G4. LNGIUD+TUGPA (n=7)
Age (y)	30.7±7.3 (21-40)	31.0±5.6 (24-40)	33.6±4.0 (26-40)	30.4±8.2 (20-40)
Parity≥1	3 (37.5%)	1 (14.3%)	5 (55.5%)	0 -
Infertility	0 -	1 (14.3%)	1 (11.1%)	1 (14.3%)
Antecedents:				
a.Endometriosis, MST	1 (12.5%)	1 (14.3%)	2 (22.2%)	2 (28.6%)
b.Endometriosis+myomas	1 (12.5%)	1 (14.3%)	0 -	0 -
c.Endometriosis-OCP	0 -	1 (14.3%)	0 -	2 (28.6%)
Symptoms: VAS/10	5.6±1.6 (3-8)	6.1±2.0 (4-9)	5.6±2.2 (3-9)	4.7±2.1 (3-8)
- Dysmenorrhea/3	2.1±0.2 (2-2.5)	2.1±0.6 (1.5-3)	1.7±0.6 (0.5-2)	1.8±0.9 (0.5-2.5)
- Dyspareunia/3	(7) 1.1±0.9 (0.5-3)	1.6±1.1 (0-3)	1.4±1.0 (0-3)	(4) 0.9±1.0 (0-2)
- CPP/3	1.7±0.9 (0-2.5)	1.4±0.8 (0.5-2.5)	1.7±1.0 (0-3)	1.8±1.5 (0-3)
Trasvaginal US/ovaries:				
a.endometriomas, RO	2 (25%)	0 -	4 (44.4%)	0 -
b.endometriomas LO	2 (25%)	3 (42.8%)	2 (22.2%)	5 (71.4%)
c.bilateral/kissing ovaries/rvs.	4 (50%)	4 (57.1%)	3 (33.3%)	2 (28.6%)
Analysis:				
- CA-125	80.5±57.8 (36-190)	90.4±37.6 (37-150)	56.3±12.9 (36-70.4)	87±42 (53-168)
- CA-19-9	44.9±63.5 (9.5-198)	(6)58.9±71 (2-191)	(8)38±19.4 (11-66)	(6)36.6±37 (11-111)
Diagnosis:				
a.endometrioma, RO	1 (12.5%)	0 -	3 (33.3%)	0 -
b.endometrioma, LO	1 (12.5%)	3 (42.8%)	2 (22.2%)	4 (57.1%)
c.pelvic endometriomas	6 (75%)	4 (57.1%)	3 (33.3%)	3 (42.8%)
d.recurrent endomet/rvs	0 -	0 -	1 (11.1%)	0 -
Surgery:				
a.TUGPA	0 -	7 (100)	0 -	7 (100)
b.laparoscopy, CS	7 (87.5%)	0 -	6 (66.7%)	0 -
c.laparotomy, CS	1 (12.5%)	0 -	3 (33.3%)	0 -
Findings in CS:				
a.endometriomas	4 (50%)	-	5 (55.5%)	-
b.Severe pelvic endomet+end-omas	3 (37.5%)	-	4 (44.4%)	-
c.endometriomas+myoma	1 (12.5%)	-	0 -	-
Histopathology:				
a.cytology compatible with endometriosis	-	7 (100)	-	7 (100)
b.endometriosis (cystic)	8 (100) (1 + Myo)	0 -	7 (77.7%)	0 -
c.atypical endometriosis	0 -	0 -	2 (22.2%)	0 -

Data are n (%), mean ± standard deviation [SD], and (min-max) values. TUGPA, transvaginal ultrasound-guided puncture-aspiration; CS, conservative surgery; MST, previous medical and

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surgical treatment; OCP, oral contraceptive pill; VAS, visual analogic scale; CPP, chronic pelvic pain; RO, right ovary; LO, left ovary; endomet, endometriosis; rvs, recto-vaginal septum.

Primary outcomes. Table 2 shows the evolution of the primary efficacy variables, up to 2 years, in the four groups. In the Anastrozole groups, especially in CS, the VAS values (mainly dysmenorrhea) were significantly reduced and kept low. Similar results were observed in the levels of tumor markers and the recurrence of endometriomas, but differences were not significant if TUGPA was performed. The reduction of VAS (dysmenorrhea and dyspareunia), CA-125, and endometriomas was equally significant in patients treated with LNG-IUD + CS without Anastrozole. CA-125 level also decreased significantly in the LNG-IUD + TUGPA –No Anastrozole group.

Table 2. Evolution of the primary efficacy variables in the four randomised groups of the clinical trial.

Group	Variable	Before Treatment (N), m±SD or n(%)	3 months (DT) (N), m±SD or n(%)	6 months (DT) (N), m±SD or n(%)	9 months (3m AT) (N), m±SD or n(%)	1 year (6m AT) (N), m±SD or n(%)	2 years (1,5y AT) (N), m±SD or n(%)
(1) Anastrozol+LNG-IUD							
+ CS:	*VAS/10*	(8) 5.6±1.6	(8) 2.4±1.2^{a1b2d2}	(8) 2.4±2.1^{a1d1}	(8) 2.3±1.3^{a1b2d2}	(8) 2.6±1.6^{a1b2d1}	(8) 2.4±1.6^{a1d1}
	-dysmenorrhea	2.1±0.2	1.1±0.7^{a1b1d1}	0.6±0.8^{a1b1d2}	1±0.5^{a2b2d2}	1.2±0.9^{a1b1d1}	1.1±0.7^{a1b1d1}
	-dyspareunia	(7) 1.1±0.9	(7) 0.4±0.5	(7) 0.6±1.1	(7) 0.4±0.6^{a1b1d1}	(7) 0.9±1.8	(7) 0.4±0.7
	-CPP	1.8±0.9	0.6±0.5^{a1b1d1}	0.6±0.4^{a1b1d1}	0.7±0.5^{a1b1d1}	0.8±0.5^{a1b1d1}	1.2±1.6
	TV ultras/ovaries:						
	-normal or dysfunctional	-	7(87.5)	5(62.5)	6(75)	7(87.5)	5(62.5)
	-simple cyst or small endomet	-	1(12.5)	3(37.5)	2(25)	1(12.5)	2(25)
	- endometriomas (rvs)	8(100)	0-^{a2b2d2}	0-^{a2b2d2}	0-^{a2b2d2}	0-^{a2b2d2}	1(12.5)^{a1b1d1}
	Tumor markers:						
	-CA-125	(8) 80.5±57.8	(7) 19.5±10.9^{a1d1}	(8)11.3±3.6^{a1b2d1}	(7) 24.2±26.2	(7)19.7±10.5^{a1b1d1}	(8)19.5±10.5^{a1b2d1}
	-CA-19-9	(8) 44.9±63.5	(7) 10.9±8.6^{a1}	(6) 6±3.1^{a1b1}	(6) 17.2±22.1^{a1}	(6) 12.7±13.8^{b1}	(7) 18.7±26.8
(2) Anastrozole+LNG-IUD							
+ TUGPA:	*VAS/10*:	(7) 6.1±2	(7) 3.1±3.1^{a1d1}	(7) 3.6±2.1^{a1b1d1}	(7) 4.9±2.5^{a1d1}	(5) 3.6±1.1	(4) 3.1±1
	-dysmenorrhea	2.1±0.6	0.5±0.9^{a1b1d1}	0.6±0.6^{a1b1d1}	1.4±0.4^{a1d1}	1.5±0.8	1.4±1
	-dyspareunia	1.6±1.1	0.9±1	1.1±1.1	1±1	0.5±0.4	0.4±0.2
	-CPP	1.4±0.8	0.8±0.9	1.4±1.1	1.5±1	1.1±0.7	0.8±0.5
	TV ultras/ovaries:					2 op (28.6)	3 op (42.9)

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	-normal or dysfunctional	-	1(14.3)	0-	0-	0-	0-
	-simple cyst or small endomet	-	3(42.9)	1(14.3)	1(14.3)	0-	3 (75)(42.9)
	-endometriomas (rvs)	7(100)	3(42.9)	6(85.7)	6(85.7)	5(100)(71.4)	1(25)(14.3)
	Tumor markers:						
	-CA-125	(7) 90.4±37.6	(7) 69.8±105.7	(7) 74±70.9	(6) 63.9±31.1	(5) 71.1±71.6	(4) 50.6±36.1
	-CA-19-9	(6) 58.9±71	(7) 21.3±16.5	(6) 64.9±100.8	(5) 29.8±22.2	(4) 46±56.3	(4) 17.5±11.8
(3) LNG-IUD, No Anastrozol							
+ CS:	*VAS/10:*	(9) 5.6±2.2	(9) 2.9±2^{a1d1}	(9) 3.1±1.8^{a1d1}	(9) 3.5±1.9^{a1b1d1}	(8) 4±2^{a1b1d1}	(6) 2.8±1.1
	-dysmenorrhea	1.7±0.6	0.8±0.7^{a1b1d1}	0.8±0.7^{a1b2d1}	1.4±0.9	1.5±1	(5) 1.3±1
	-dyspareunia	1.4±1	(8) 0.8±1	(8) 0.7±0.5^{a1b1d1}	(8) 0.7±0.7^{a1b1d1}	(7) 0.9±0.7^{a1d1}	(5) 0.4±0.5
	-CPP	1.7±1	0.8±0.9	1±0.7	0.8±0.8	1±1	(5) 0.4±0.5
	TV ultras/ovaries:						
	-normal or dysfunctional	-	8(88.9)	8(88.9)	5(55.6)	5(62.5)	3(50)
	-simple cyst or small endomet	-	0-	1(11.1)	1(11.1)	2(25)	2(33.3)
	-endometriomas (rvs)	9(100)	1(11.1)	0-	2(22.2)	1(12.5)	1(16.7)
	Tumor markers:						
	-CA-125	(9) 56.3±12.9	(8) 11.4±7.9 ^{a1b2}	(9)12.4±8.9^{a2b2d2}	(9) 16±9.1^{a2b2d2}	(8)16.7±10.8^{a1b2d2}	(6) 21.2±19^{a1b1d1}
	-CA-19-9	(8) 38±19.4	(6) 10.2±4^{a1}	(8) 14.8±11.3^{a1d1}	(8) 11.9±6.5^{a1b1d1}	(7) 12.1±6.8^{a1b1d1}	(6) 25.5±22.2
(4) LNG-IUD, No Anastrozol							
+ TUGPA:	*VAS/10:*	(7) 4.6±2.2	(7) 3.4±1.8	(7) 3±1.3	(7) 3.2±1.5	(6) 3.6±1.6	(2) 4.3±2.5
	-dysmenorrhea	1.6±0.7	1.4±0.9	1.1±0.9	1.4±0.6	1.3±0.5	(1) 1
	-dyspareunia	(4) 0.9±1	(6) 0.3±0.4	(6) 0.3±0.4	(5) 0.2±0.4	(4) 0.5±1	(1) 2
	-CPP	1.6±1.1	1.1±0.9	1.1±0.9^{a1d1}	0.9±0.7	1.1±0.9 (1 op, 14,3%)	(1) 2 (3 op, 42.9%)
	TV ultras/ovaries:						
	-normal or dysfunctional	-	1(14.3)	0-	0-	1(16.7)(14.3)	1(50)(14.3)

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-simple cyst or small endomet	-	2(28.6)	0-	0-	1(16.7)(14.3)	0-
- endometriomas (rvs)	7(100)	4(57.1)	7(100)	7(100)	4(66.7)(57.1)	1(50)(14.3)
Tumor markers:						
-CA-125	(7) 87±42	(7)26.9±18.1^{a1b1d1}	(7)26.6±21.9^{a1b1d1}	(7)42.2±37.8^{a1b1d1}	(6) 43.2±24.2^{a1d1}	(2) 51.7±3.4
-CA-19-9	(6) 36.6±37.4	(5) 15.1±14.3	(6) 12.3±13^{a1}	(5) 21.2±22.3	(5) 18.5±13.2	(2) 18.9±13.7

Data are n (%), mean ± standard deviation [SD]. Nonparametric tests (for two related samples) between values before treatment and at 3, 6, and 9 months, and 1 and 2 years. Test of ranges with Wilcoxon signs: a1 = p <0.05, a2 = p <0.01; a3 = p <0.001. Signs test: b1 = p <0.05, b2 = p <0.01, b3 = p <0.001. McNemar test (for dichotomous variants): c1 = p <0.05, c2 = p <0.01; c3 = p <0.001. Marginal homogeneity test: d1 = p <0.05, d2 = p <0.01, d3 = p <0.001. Only significant results are indicated. DT, during treatment; AT, after treatment; CS, conservative surgery; TUGPA, transvaginal ultrasound-guided puncture-aspiration; VAS, visual analogic scale; CPP, chronic pelvic pain; TV, transvaginal ultrasound; end, endometriomas; rvs, rectovaginal septum; op, operated.

A more detailed assessment of this evolution is represented in Fig. 2 (and in Fig. 3), according to the patients who took or not Anastrozole (in follow-up results, the re-operated cases were excluded). Fig. 2A shows that the percentage of reduction or improvement of the VAS score is more significant at 3 and 6 months, with or without Anastrozole, maintaining similar values during the follow-up period. On average, there was a significant improvement of symptoms during (difference 44%, 95%CI: 27.7-60.4) and after treatment at 6 months (43%, 95%CI: 29.9-56.2), which is maintained at follow-ups of 1 year (31%, 95%CI: 17.6-44.4) and 2 years (43.7%, 95%CI: 27.7-59.6). This improvement was more significant in those patients who had taken Anastrozole (at 3 months: 57%, 95%CI: 40.3-73.4; at 6 months: 51%, 95%CI: 33.3-68.7; at 1 year: 44.5%, 95%CI: 28-61; and at 2 years: 51.3%, 95%CI: 31.6-71). There are, however, no significant differences between Anastrozole and non-Anastrozole, except for at the 1-year follow-up (Mann-Whitney U test, p = 0.048). Fig. 3ABCD represents the evolution of the symptoms scaled over 10 (absolute value of the VAS), as well as the evolution of dysmenorrhea, dyspareunia, and CPP scaled over 3. The most significant improvements were for dysmenorrhea and CPP during the taking of Anastrozole.

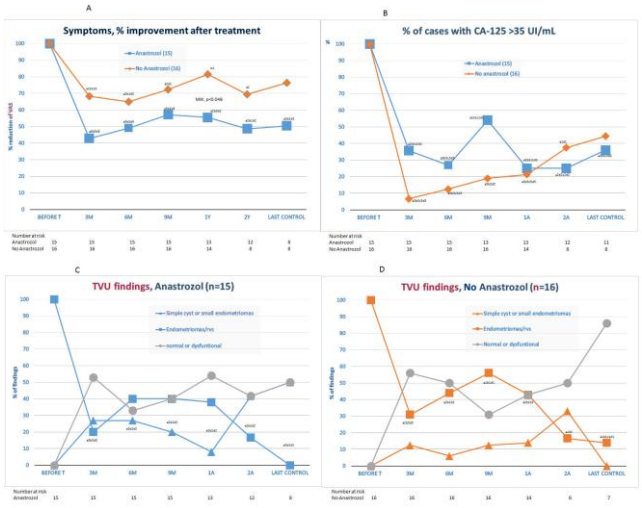

Figure 2. Evolution of the variables of primary efficacy: A, VAS, % improvement by treatment. B, % of cases with CA-125 >35 UI/mL. C, Ultrasound finding (TVU) in the CT under anastrozole (15 patients). D, Ultrasound finding (TVU) in the CT, no anastrozole (16 patients). Normal or dysfunctional= findings of normal ovaries or with dysfunctional cyst (luteal).

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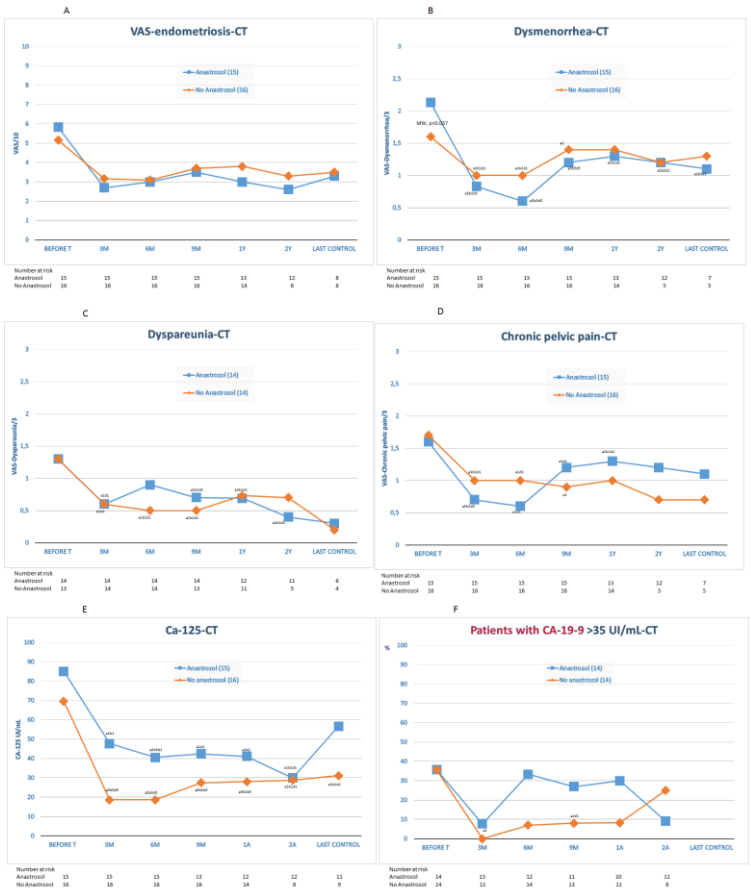

Figure 3. Evolution of the variables of primary efficacy: A, VAS. B, Dysmenorrhea. C, Dyspareunia. D, Chronic pelvic pain. E, CA-125 values in UI/mL. F, % of cases with CA-19-9 >35 UI/mL.

Regarding levels of CA-125 (Fig. 2B), we observed a significant reduction, similar to that of the VAS score, but only in those patients who did not take Anastrozole, in both the absolute values (fig 3E) and the percentage of cases with high level of this marker (>35 U/mL), at least up to 1 year. In these patients, the decrease of CA-125 values was 64% (95%CI: 40.8-87.3) at 3 months and 73.8% (95%CI: 64.2-83.4) at 6 months versus 49.6% (95%CI: 19.6-79.7) and 53.8% (95%CI: 25.7-81.6), respectively, in patients treated with Anastrozole + Mirena®. Likewise, the percentage of patients with elevated CA-19-9 was also reduced during treatment, especially in patients without taking Anastrozole (Fig. 3F).

The sonographic findings showed a similar behaviour (Fig. 2CD), with an increase of recurrent endometriomas until 9 months to 1 year that decreased when some patients were re-operated, but no significant differences were observed between Anastrozole and non-Anastrozole.

Secondary outcomes. Fig. 4 shows the recurrence and reoperation rates observed during a 6-year follow-up period. Although the recurrence rate was similar at 2 years with or without Anastrozole (50%), the use of this AI delayed their appearance; however, differences were not statistically significant. In groups 1 and 3, both with Mirena® + CS, there were few recurrences, with simple cysts or small endometriomas. However, in patients treated with Mirena® + TUGPA (groups 2 and 4), the endometriomas increased (together with reoperations) when the LNG-IUD was removed (see table 2). Lines of the cumulative percentage of reoperations were also similar with or without Anastrozole.

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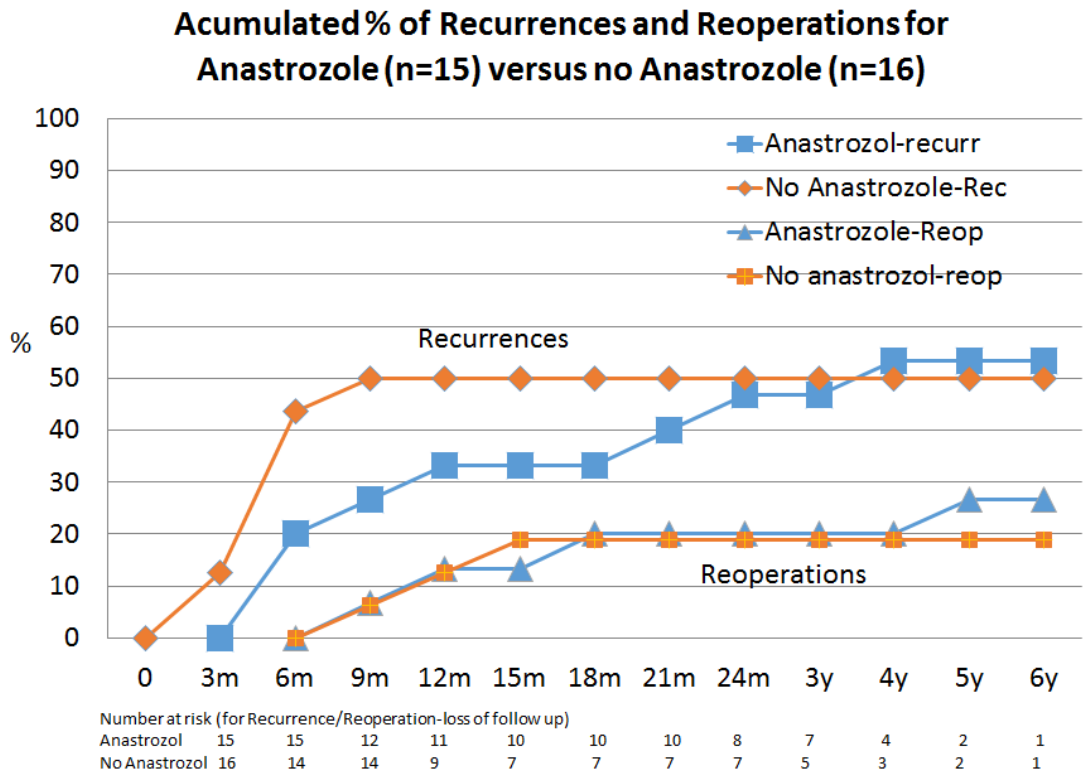

Figure 4. Accumulated % of recurrences and reoperations for anastrozole versus no anastrozole.

Fertility and clinical status of patients in the last control are shown in Table 3. Ten percent of them got pregnant and a 13% remained infertile. At 4.2 ± 1.7 years of follow-up (95%CI: 3.57-4.85; median 4 years, range 1-7 years), 25% of cases were reoperated, 13% showed persistent endometriosis (although these women evolved well taking pill or other medications –oral naproxen-), and 61.3% were asymptomatic without taking any medication. The more interesting finding is that 88% of the patients in which CS was performed, with or without Anastrozole, were asymptomatic after 3 to 5 years without medication or reoperation, compared with only 21% if TUGPA was performed, with or without Anastrozole. Differences were significant between groups 1 and 2 ($p = 0.004$) and between groups 3 and 4 ($p = 0.027$), being equally significant ($p = 0.019$) in the four groups.

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Table 3. Fertility and clinical status in last follow-up control of the patients included in the clinical trial.

Variable	Gr. 1. A+LNGIUD +CS [n=8]	Gr. 2. A+LNGIUD+ TUGPA [n=7]	Gr. 3. LNGIUD+CS [n=9]	Gr. 4. LNGIUD+ TUGPA [n=7]	Total CT [N=31]
Years until last control	4.4±1.8	5±1,5	3,4±1,3	4,2±1,3	4,2±1,7
Infertility	1 (12.5)	2 (28,6)	1 (11,1)	0-	4 (12,9)
Pregnancies/deliveries	0-	1 (14,3)[x]	1 (11,1)	1 (14,3)	3 (9,7)
Clinical status in last control:					
1. Reoperated:					
-new CS	0	4 (57.1)*	0	3 (42.8)	7 (22.6)
-Hyst+Adnexectomy	0-	0-	1 (11.1)	0-	1 (3.2)
2. Persist, well, taking OCP	1 (12.5)	2 (28.6)	0-	2 (28.6)	4 (12.9)
3. Well without medication	7 (87.5)*	1 (14.3)	8 (88.9)**	2 (28.6)	19 (61.3)***

Data are n (%) and mean ± SD. x, 1 case reoperation and then pregnancy. Statistical study, H of Kruskal-Wallis: * between gr1 and gr2, p =0 .004, ** between gr3 and gr4, p = 0.027. *** Chi-square Pearson among the 4 groups, p=0.019. A, anastrozole; CT, clinical trial; CS, conservative surgery; Hyst, hysterectomy.

Post-hoc or sensitivity analyses. No pathology related to the treatments was observed throughout the CT follow-up period.

Discussion

Our results show that oral administration of 1 mg/day Anastrozole for 6 months, beginning before CS intervention of endometriosis, reduces or improves significantly the symptoms associated with the disease (especially dysmenorrhea and CPP) during and after treatment, but has no other significant advantages over the single insertion of LNG-IUD (Mirena®), prior to CS, during that same time period. Values of CA-125 and CA-19-9 were more clearly normalized in those patients who did not take Anastrozole, and the recurrence and reoperation rates were similar at 2 years with or without Anastrozole. These, however, were adversely influenced by the performance of TUGPA. These findings clarify what was previously reported about the use of Anastrozole in the treatment of endometriosis, since they suggest that the clinical benefits reported after 6 months (pain relief, see Table S1) are partly due to the associated medications and that there are no other additional benefits about the endometriosis itself and its clinical evolution [3,4,10-13].

Strengths and weaknesses of the study. A possible limitation of this research is the low number of cases included in the CT because of the low recruitment rate and the poor preliminary results observed in the interim in patients treated with TUGPA. We trusted that these patients would evolve as well as those who were treated with CS, because of the additional use of Anastrozole and Mirena®, but it was not the case. However, the statistical tests are significant and, therefore, this is a valid CT although we could also consider this research as a pilot study that shows the poor results obtained performing TUGPA in endometriosis and which do not improve with the previous insertion of LNG-IUD (Mirena®) and/or oral Anastrozole for 6 months. Moreover, though Anastrozole offers a transient improvement of pain, it does not influence long-term evolution and recurrence or fertility in endometriosis. However, a possible bias in this study could be the use of vitamin D (VD) in women taking Anastrozole, although the data on VD and endometriosis are controversial [14,15].

The main strength of the study would be the strict randomization of cases of young women with endometriomas and elevated CA-125, for both patients taking or not Anastrozole and inclusion in CS or TUGPA during the medical treatment.

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Discussion of the findings in relation to other studies. Initial studies and CTs had described the AIs as promising therapeutic agents for treatment of endometriosis [2,4] since they could suppress the local estrogen produced by aromatase-positive implants and subsequent proliferative effect, as well as blocking the action on COX-2 and prostaglandin E2, the latter being responsible for inflammation [7,16]. However, in most of these studies the use of AIs (Anastrozole or Letrozole) was associated with OCP or GnRH analogues, so its beneficial effects could correspond to these other medications or their association, rather than to the AIs themselves. Other case reports, series and prospective CTs using mainly Letrozole associated with noretindrone acetate (NETA) or OCP, compared to the use of the OCP or NETA alone [12,13], have been published after 2008 (see Table S1). Results do not show significant clinical advantages, but more cost and side effects related to the administration of Letrozole. Anastrozole was used only in 3 patients [17] with improvement of CPP and minimal side effects. Systematic reviews [18,19] seem to conclude that AI may have a place in endometriosis treatment, but there is no clear evidence of improvement in endometriosis-associated infertility [20]; and the Committee Opinion No. 663 on Aromatase Inhibitors in gynaecologic practice [21] points that AI are a promising therapeutic option that may be useful for the management of endometriosis-associated pain in a combined therapy with progestins. In any case, when we proposed this prospective study to assess the efficacy of Anastrozole in endometriosis, we decided to associate it with the intrauterine insertion of an IUD containing LNG (for contraception and for a continued release of progestin). Previously Vercellini et al. [22] had published a pilot study using LNG-IUD versus expectant management after CS for symptomatic endometriosis with significant reduction of dysmenorrhea and risk of recurrence. Subsequently, other studies [9,23-30] have also shown that LNG-IUD is an effective and well accepted treatment to reduce dyspareunia and dysmenorrhea and increase quality of life in women with suspected endometriosis.

The results of our prospective CT show a greater improvement of the painful symptoms and a certain time delay in the occurrence of recurrence in patients taking Anastrozole (with Calcium + VD simultaneously), although there were no clear significant differences with the group of no Anastrozole or other positive efficacy data in the administration of Anastrozole associated with Mirena® (versus only Mirena®). The tumor marker levels were normalized more clearly in the patients who did not take Anastrozole and the rates of recurrence and reoperations were similar. Clearly, the worst result in short and long term was the performance of TUGPA (instead of CS), independently of the use of Anastrozole and Mirena®.

Conclusions

Anastrozole for 6 months, beginning before CS of endometriosis, although it improves more significantly the painful symptoms, has no other significant advantages over the single insertion of LNG-IUD (Mirena®) during that same time period. LNG-IUD (Mirena®) associated with CS also reduces significantly dysmenorrhea and dyspareunia, normalizes more effectively the values of CA-125, and also seems to decrease the rate of recurrences and long-term reoperations. However, the medical treatment associated with TUGPA is not very effective.

Future research directions should be focused on the observation of subsequent fertility, as well as to the long-term recurrences in a greater number of cases operated with CS after previous insertion of Mirena®, which could be maintained for 6-12 months, and even indefinitely, if patients do not want to get pregnant.

Supplementary Materials: Table S1. Clinical publications on the use of Aromatase Inhibitors in women with endometriosis. CPP, chronic pelvic pain; VAS, visual analogue scale; OCP, oral contraceptive pill.

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Author Contributions: P. Acién was the principal investigator in the FIS project and clinical trial, designed the study, made the review, tables and figures, and wrote the manuscript. I.Velasco participated in the FIS project and clinical trial as well as in the revision of the cases with endometriosis and reviewed the manuscript. M.Acién participated in the FIS project and clinical trial as well as in the revision of the cases with endometriosis, helped with the bibliographic search and reviewed the manuscript. PA had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest: We declare no competing interests.

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Ethical approval: All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki. And the protocol was approved by the Ethics Committee of San Juan University Hospital (26/08/2008). It was registered in the Eudra CT System of the European Medicines Agency (London, 29-Sept-2008; Nº EudraCT: 2008-005744-17) (07/11/2008) and then authorized by the Spanish Agency for Medicines and Health Products (AEMPS) (10/11/2008).

Informed consent: Written informed consent was obtained from all individual participants included in the study

Details of trial registration Eudra CT System of the European Medicines Agency (London, 29/09/2008) Nº EudraCT: 2008-005744-17 (07/11/2008). Date of enrolment of first patient: 15/01/2009.

References

1. Acién, P.; Velasco, I.; Acién, M.; Quereda, F. Treatment of endometriosis with transvaginal ultrasound-guided drainage and recombinant interleukin-2 left in the cysts: a third clinical trial. *Gynecol Obstet Invest 2010,* **69**, 203-211.
2. Bulun, S.E., Zeitoun, K.M., Takayama, K., Sasano, H. Molecular basis for treating endometriosis with aromatase inhibitors. *Hum Reprod Update* **2000**, *6*, 413-418.
3. Soysal S, Soysal M.E., Ozer, S., Gul, N., Gezgin, T. The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. *Hum Reprod* **2004**, *19*, 160-167.
4. Amsterdam, L.L., Gentry, W., Jobanputra, S., Wolf, M., Rubin, S.D., Bulun, S.E. Anastrazole and oral contraceptives: a novel treatment for endometriosis. *Fertil Steril* **2005**, *84*, 300-304.
5. Hefler, L.A., Grimm, C., van Trotsenburg, M., Nagele, F. Role of the vaginally administered aromatase inhibitor anastrozole in women with rectovaginal endometriosis: a pilot study. *Fertil Steril* **2005**, *84*, 1033-1036.
6. Acién, P., Velasco, I., Gutiérrez, M., Martínez-Beltrán, M. Aromatase expression in endometriotic tissues and its relationship to clinical and analytical findings. *Fertil Steril* **2007**, *88*, 32-38.
7. Tariverdian, N., Theoharides, T.C., Siedentopf, F., Gutiérrez, G., Jeschke, U., Rabinovich, G.A., Blois, S.M., Arck, P.C. Neuroendocrine-immune disequilibrium and endometriosis: an interdisciplinary approach. *Semin Immunopathol* **2007**, *29*, 193-210.
8. Velasco, I., Acién, P., Campos, A., Acién, M.I., Ruiz-Maciá, E. Interleukin-6 and other soluble factors in peritoneal fluid and endometriomas and their relation to pain and aromatase expression. *J Reprod Immunol* **2010**, *84*, 199-205.
9. Petta, C.A., Ferriani, R.A., Abrao, M.S., Hassan, D., Rosa e Silva, J.C., Podgaec, S., Bahamondes, L. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. *Hum Reprod* **2005**, *20*, 1993-1998.
10. Ailawadi, R.K., Jobanputra, S., Kataria, M., Gurates, B., Bulun, S.E. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. *Fertil Steril* **2004**, *81*, 290-296.
11. Remorgida, V., Abbamonte, L.H., Ragni, N., Fulcheri, E., Ferrero, S. Letrozole and desogestrel-only contraceptive pill for the treatment of stage IV endometriosis. *Aust N Z J Obstet Gynaecol* **2007**, *47*, 222-225.
12. Ferrero, S., Camerini, G., Ragni, N., Venturini, P.L., Biscaldi, E., Seracchioli, R., Remorgida, V. Letrozole and norethisterone acetate in colorectal endometriosis. *Eur J Obstet Gynecol Reprod Biol* **2010**, *150*, 199-202.

13. Ferrero, S., Remorgida, V., Venturini, P.L., Leone Roberti Maggiore, U. Norethisterone acetate versus norethisterone acetate combined with letrozole for the treatment of ovarian endometriotic cysts: a patient preference study. *Eur J Obstet Gynecol Reprod Biol* **2014**, *174*, 117-122.
14. Somigliana, E., Panina-Bordignon, P., Murone, S., Di Lucia, P., Vercellini, P., Vigano, P. Vitamin D reserve is higher in women with endometriosis. *Hum Reprod* **2007**, *22*, 2273-2278.
15. Miyashita, M., Koga, K., Izumi, G., Sue, F., Makabe, T., Taguchi, A., Nagai, M., Urata, Y., Takamura, M., Harada, M., Hirata, T., Hirota, Y., Wada-Hiraike, O., Fujii, T., Osuga, Y. Effects of 1,25-Dihydroxy Vitamin D3 on Endometriosis. *J Clin Endocrinol Metab* **2016**, *101*, 2371-2379.
16. Attar, E., Bulun, S.E. Aromatase inhibitors: the next generation of therapeutics for endometriosis?. *Fertil Steril* **2006**, *85*, 1307-1318.
17. Verma, A., Konje, J.C. Successful treatment of refractory endometriosis-related chronic pelvic pain with aromatase inhibitors in premenopausal patients. *Eur J Obstet Gynecol Reprod Biol* **2009**, *143*, 112-115.
18. Nothnick, W.B. The emerging use of aromatase inhibitors for endometriosis treatment. *Reprod Biol Endocrinol* **2011**, *9*, 87. doi: 10.1186/1477-7827-9-87.
19. Pavone, M.E., Bulun, S.E. Aromatase inhibitors for the treatment of endometriosis: A review. *Fertil Steril* **2012**, *98*, 1370-1379.
20. Abu Hashim, H. Aromatase inhibitors for endometriosis-associated infertility; do we have sufficient evidence?. *Int J Fertil Steril* **2016**, *10*, 270-277.
21. Committee Opinion No. 663. Aromatase inhibitors in gynecologic practice. *Obstet Gynecol* **2016**, *127*, e170-174.
22. Vercellini, P., Frontino, G., De Giorgi, O., Aimi, G., Zaina, B., Crosignani, P.G. () Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. *Fertil Steril* **2003**, *80*, 305-309.
23. Gomes, M.K., Ferriani, R.A., Rosa e Silva, J.C., Japur de Sá Rosa e Silva, A.C., Vieira, C.S., Cândido dos Reis, F.J. The levonorgestrel-releasing intrauterine system and endometriosis staging. *Fertil Steril* **2007**, *87*, 1231-1234.
24. Wong, A.Y., Tang, L.C., Chin, R.K. Levonorgestrel-releasing intrauterine system (Mirena) and Depot medroxyprogesterone acetate (Depoprovera) as long-term maintenance therapy for patients with moderate and severe endometriosis: a randomized controlled trial. *Aust N Z J Obstet Gynaecol* **2010**, *50*, 273-279.
25. Tanmahasamut, P., Rattanachaiyanont, M., Angsuwathana, S., Techatraisak, K., Indhavivadhana, S., Leerasiri, P. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-related pain: a randomized controlled trial. *Obstet Gynecol* **2012**, *119*, 519-526.
26. Cho, S., Jung, J.A., Lee, Y., Kim, H.Y., Seo, S.K., Choi, Y.S., Lee, J.S., Lee, B.S. Postoperative levonorgestrel-releasing intrauterine system versus oral contraceptives after gonadotropin-releasing hormone agonist treatment for preventing endometrioma recurrence. *Acta Obstet Gynecol Scand* **2014**, *93*, 38-44.
27. Kim, M.L., Cho, Y.J., Kim, M.K., Jung, Y.W., Yun, B.S., Seong, S.J. The efficacy of long-term maintenance therapy with a levonorgestrel-releasing intrauterine system for prevention of ovarian endometrioma recurrence. *Int J Gynaecol Obstet* **2016**, *134*, 256-259.
28. Chen, Y.J., Hsu, T.F., Huang, B.S., Tsai, H.W., Chang, Y.H., Wang, P.H. Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence: a randomized controlled study. *Am J Obstet Gynecol* **2017**, *216*, 582.e1-582.e9.
29. Kim, M.K., Chon, S.J., Lee, J.H., Yun, B.H., Cho, S., Choi, Y.S., Lee, B.S., Seo, S.K. Postoperative Levonorgestrel-Releasing Intrauterine System Insertion After Gonadotropin-Releasing Hormone Agonist Treatment for Preventing Endometriotic Cyst Recurrence: A Prospective Observational Study. *Reprod Sci* **2018**, *25*, 39-43.
30. Yucel, N., Baskent, E., Karamustafaoglu Balci, B., Goynumer, G. The levonorgestrel-releasing intrauterine system is associated with a reduction in dysmenorrhea and dyspareunia, a decrease in CA 125 levels, and an increase in quality of life in women with suspected endometriosis. *Aust N Z J Obstet Gynaecol* **2018**, *58*, 560-563. doi: 10.1111/ajo.12773.

Figure 1. Trial profile.

Figure 2. Evolution of the variables of primary efficacy: A, VAS, % improvement by treatment. B, % of cases with CA-125 >35 UI/mL. C, Ultrasound finding (TVU) in the CT under anastrozole (15 patients). D, Ultrasound

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finding (TVU) in the CT, no anastrozole (16 patients). Normal or dysfunctional= findings of normal ovaries or with dysfunctional cyst (luteal).

Figure 3. Evolution of the variables of primary efficacy: A, VAS. B, Dysmenorrhea. C, Dyspareunia. D, Chronic pelvic pain. E, CA-125 values in UI/mL. F, % of cases with CA-19-9 >35 UI/mL.

Figure 4. Accumulated % of recurrences and reoperations for anastrozole versus no anastrozole.