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Report on Repeated Mifepristone Treatment for Uterine Fibroids or Endometriosis

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Abstract

Background: No information is available on how repeated administration of mifepristone could affect women's health.

Methods: A total of 101 and 36 subjects who participated in up to 2 and 3 mifepristone trials to treat endometriosis or uterine fibroids, respectively, carried out at the "Eusebio Hernandez" Hospital, Havana, Cuba.

Results: Subjects who repeated mifepristone to treat fibroids did so for 7.3 ± 2.5 months, minimum and maximum of 6 and 15 months, respectively. The average rest interval was 9.7 ± 6.2 months, minimum and maximum of 3 and 30 months, respectively. In subjects repeating mifepristone for endometriosis, the average was 18 ± 2.0, with a minimum and maximum of 12 and 24 months, respectively. The average rest interval was 8.3 ± 5.3 months, 95% CI = 7.6 - 8.9, minimum and maximum of 3 and 30 months, respectively. No change in women's health was detected months after termination of final mifepristone treatment.

Conclusions: Repeating low doses mifepristone treatment up to 3 - 4 times for 3, 6 or 9 months duration with variable rest intervals between sessions, did not seem to involve any risk to health. More studies to confirm the long-term safety of repeated low dosage mifepristone are mandatory.

Keywords: Mifepristone; Fibroid; Endometriosis; Antiprogestins; Repeated use

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Introduction

The antiprogestin mifepristone (RU 486) has proved itself to be very effective in treating uterine fibroids and endometriosis, although regarding this latter condition there is less published scientific evidence available [1-21]. The therapeutic effect of this medication can be observed whilst being administered and during a variable post-treatment phase in both maladies. Mifepristone comes close to having the perfect profile to treat ailments such as uterine fibroids and endometriosis in need of medicaments possessing as it does: a) high efficacy, b) absence or minimum side effects, c) chance of being used repeatedly over long periods, and d) relatively low cost.

The focus of this paper is determining adverse effects of repeated administration of mifepristone. The common side effects that one would expect to see when mifepristone treatment is administered are hot flushes, a slight raise in liver transaminases, an increase of the endometrial thickness and some histological changes in the endometrium [1-21].

The antiprogestins could induce a hormonal climate of estrogenic predominance which at times leads to endometrial thickening; something that could lead to think about the existence of simple hyperplasias that might turn into premalignant lesions. Fortunately, today it is known that endometrial thickenings greater than 8 mm and apparent in percentages ranging between 20 and 35% have histological changes as defined by Mutter et al and Horn et al, and most recently by Fiscella et al which have come to be called PAECs, (progesterone associated endometrial changes) which in principle lack pathological significance since they are simply cystic dilatations of the endometrial glands and changes in the structure and morphology of the endometrial stroma [22-24].

We need to know how the repetition of several treatments with mifepristone could influence women's health. That is why it was decided to write down this report to identify how safe the use of mifepristone was in women who repeated treatment sessions of 3, 6 or 9 months duration with variable rest periods in between.

Table 1. Characteristics of the Studies, Duration of Mifepristone Treatment, Doses Administered and Number of Subjects Included in Each Clinical Study of Endometriosis

Study	Characteristics of the study and duration of the treatment	Dosage mifepristone administered					Total
		Placebo	2.5 mg	5 mg	10 mg	25 mg	
1	6 months treatment + 6 months follow-up (randomized)			13	---	13	26
2	6 months treatment (no follow-up) (randomized)	90	90	90	90	---	360
Total	---	90	90	103	90	13	386

Material and Methods

This is not a literature review or a meta-analysis of the studies we have carried out on the use of mifepristone to treat endometriosis or uterine fibroids. This is a report based on those subjects who repeated mifepristone treatment at least twice either for endometriosis or uterine fibroids. All of those studies have been published before with the exception of the second trial on endometriosis which is in data processing and analysis prior to publication. The rest are listed in the bibliography section. The clinical trial program using mifepristone to treat endometriosis consists of 2 clinical studies,

Table 2. Characteristics of the Studies, Duration of Mifepristone Treatment, Doses Administered and Number of Subjects Included in Each Clinical Study of Fibroids

Study	Characteristics of the study, duration of treatment	Dosage mifepristone administered				Total
		Placebo	2.5 mg	5 mg	10 mg	
1	3 months treatment (randomized)	---	---	50	50	100
2	3 months treatment + 6 months follow-up (randomized)	---	---	48	52	100
3	6 months treatment + 12 months follow-up (randomized)	---	---	88	88	176
4	9 months treatment + 18 months follow-up (randomized)	---	---	35	35	70
5	3 months treatment + 9 months follow-up	---	110	110	---	220
6	3 months treatment (no follow-up) (randomized)	60	---	60	---	120
7	3 months treatment (pre-surgery) (randomized)	---	71	75	---	146
Total	---	60	181	466	225	932

one already published [25] and another which began in November 2010 with the last subject terminating treatment with mifepristone at the end of may 2013 (Table 1). The clinical trial program using mifepristone to treat uterine fibroids consists of 7 completed studies (Table 2), initiated in January 2007 and concluded on the 30th of August 2012. Both for endometriosis or uterine fibroids, all those trials were carried out at "Eusebio Hernandez" Gynecology and Obstetrics Teaching Hospital, Havana, Cuba. Institutional Review Board approvals for all those studies were obtained. Also, all subjects gave their written informed consent to participate in each of the studies mentioned in this paper.

All trials on uterine fibroids were carried out by the same research team and all of them with identical methodology, varying only the treatment periods. The same applies for endometriosis studies, 1 already published and the other in processing an analysing data prior to publication.

Criteria to select subjects on which this article is based were: 1) having participated in at least two of our research program studies using mifepristone to treat uterine fibroids or endometriosis bearing in mind: a) the duration of the treatment period, b) the rest period between treatment periods, c) the dosage administered, 2) performance of endometrial biopsies pre- and post-treatment, blood analyses to determine hepatic transaminases: aspartate-amino-transferrase (ASAT) and aspartate-alanino-transferrase (ALAT), ultrasound examination to measure endometrial thickness at the end of treatment. When a subject presented a raise in the hepatic transaminases these were repeated till normal values were obtained.

We included in the report women who refused a final endometrial biopsy because all other information was available and because they not refused all final endometrial biopsies but at least one of them.

The final results of the variables were analyzed at the beginning and end of each mifepristone treatment period. None of the subjects who participated in the studies suffered either endometriosis or fibroids simultaneously.

Regarding the rest period between treatments with mifepristone, mainly for subjects with endometriosis who experience a rapid return of symptoms, we felt that a minimum 3-months period free of treatment, based in our clinical experience, was sufficient to be "cleaned" of mifepristone effects.

Besides the data collection concerning health or illness record, when included in each study all subjects were summoned for an in-depth interview regarding their general state of health and anything else of relevance in order to check out any relationship with previous mifepristone treatment. They were also questioned about any post- or intra-treatment pregnancies.

The information is presented by way of percentages, means, standard deviations, 95% confidence intervals for means (CI) and maximum (Max) and minimum (Min) values per case. Normal approximation for proportions was used to compare variables between the endometriosis and fibroid groups. A $P < 0.005$ was considered significant.

Results

A total of 386 and 932 subjects had been included in the clinical trials on the use of mifepristone to treat endometriosis or uterine fibroids, respectively. Split into fibroid and endometriosis pathology Table 3 shows the results obtained of all variables studied in those women who underwent two or more mifepristone treatments.

All subjects requesting repetition of mifepristone treatment for endometriosis were accepted, which is to say that there was 0% rejection. Of the subjects who attended the fibroid program consultancy to repeat the mifepristone treatment, 5/932 (0.5%) were not readmitted because 3 of them had adenomyosis, 1 because the fibroid had grown a lot by the end of the follow-up period and 1 because in the previous study the fibroid did not modify with mifepristone treatment; these last 2 subjects were recommended to undergo surgery to cure the condition once and for all.

Four of the women who repeated treatment for endometriosis presented transaminases values of 51, 56 and 59 IU for ASAT and 1 case with 59 IU for ALAT, respectively. The raised ASAT and ALAT scores never coincided in the same subject. Among of the subjects who repeated mifepristone treatment for fibroids in 2 of them hepatic transaminases were higher than normal: 1 with 49 IU (ASAT) and 1 with 51 IU (ALAT). In all cases, reference scores were 46 and 49 UI for ASAT and ALAT, respectively.

No subject reported hot flushes once mifepristone treatment had finished and more than 95% menstruated normally between 28 and 35 days after terminating treatment; the remaining subjects menstruated between 46 and 61 days after coming off mifepristone in both endometriosis and fibroids groups.

The results of the initial endometrial biopsies previous to the first treatment of the 101 subjects who later repeated treatment for endometriosis were as follows: 33/101 (32.7%) presented proliferative endometrium, 47/101 (46.5%) secretory endometrium, 7/101 (6.9%) were not suitable for diagnosis and 14/101 (13.9%) were not indicated as it was not required by protocol. The results of the initial endometrial biopsies previous to the first treatment of the 36 subjects who later repeated mifepristone treatment for uterine myomas were as follows: 9/36 (25.0%) and 9/36 (25.0%) were secretory and proliferative endometrium, respectively. In 18/36 (50.0%) initial endometrial biopsy was not indicated as it was not required by protocol.

For women who repeated treatment either for endometriosis or uterine fibroids in the endometrial biopsies carried out before beginning the second, third or fourth mifepristone treatment there was no diagnosis of PAEC in the cases where

Table 3. Variables in Those Women Who Underwent Two or More Mifepristone Treatments

Results	Endometriosis N = 386	Fibroids N = 932	P
Subjects repeating treatments	101/386 (26.2%)	36/932 (3.9%)	< 0.001
With 2 treatments cycles	62/101 (61.4%)	34/36 (94.4%)	< 0.001
With 3 treatments cycles	32/101 (31.7%)	2/36 (5.6%)	< 0.001
With 4 treatments cycles	7/101 (6.9%)	0/36 (0.0%)	0.053
Mean treatment period (months)	18 ± 2.0; 95% CI = 17.4 - 22; Min = 12; Max = 24	7.3 ± 2.5; 95% CI = 6.5 - 8.2; Min = 6; Max = 15	
Mean "rest" interval (months)	8.3 ± 5.3; 95% CI = 7.6 – 9; Min =3; Max = 30	9.7 ± 6.2; 95% CI = 7.6 - 11.9; Min = 3; Max = 30	
Median of mifepristone dose	5 mg	5 mg	-----
Liver transaminases raised	4/101 (4.0%)	2/36 (5.6%)	0.344
Hot flushes (%)	18/101 (17.8%)	8/36 (22.2%)	0.282
Endometrial thickness > 8 mm	26/101 (25.7%)	8/36 (22.2%)	0.337
Pregnancies	8/101 (7.9%)	0/36 (0.0%)	0.041
Live born baby	8	----	----
Women who refused final endometrial biopsies	18/101 (17.8%)	8/36 (22.2%)	0.282
Final biopsies performed over the total number of possible final endometrial biopsies	197/248 (79.4%)	29/74 (39.2%)	< 0.001
PAEC	19/197 (9.6%)	9/35 (25.7%)	0.004

PAEC had been diagnosed in the final endometrial biopsy of the previous treatment nor in those where there was no diagnosis of PAEC. Neither in the subjects treated for endometriosis nor those treated for uterine myomas was endometrial hyperplasia diagnosed once mifepristone treatment had been terminated. Three months or more after termination of mifepristone treatment either for endometriosis or fibroids no histological sign of the medication was to be found in any subject.

As we write this paper, 16/386 (4.1%) pregnancies have been reported out of all the subjects on the mifepristone program for the treatment of endometriosis; in 15 cases healthy newborn babies were born and 1 subject miscarried when 12 weeks pregnant. Of all subjects treated with mifepristone for uterine fibroids 8/932 (0.9%) became pregnant, 8 of them ended up giving birth to healthy newborn babies, 4 of them were diagnosed infertile due to fibroids: 1 who became pregnant involuntarily decided to terminate the pregnancy early.

In total, in the subgroup participating in the mifepristone program for uterine fibroids there were 3/932 (0.8%) subjects who received chemical treatment whilst taking mifepristone: 1 was a personal decision and 2 because of excessive bleeding; and during the study program follow-up periods we know that 23/932 (2.5%) received chemical treatment.

In no subject in either endometriosis or uterine fibroids subgroup did we detect any illness, alteration, physical or psychic disorder that might be related to mifepristone in the period encompassed between initiation and termination of treatment. All changes or alterations in health apparent in these subjects during this time are similar or comparable to

those in the general population, with the exception of the positive changes or alterations in health such as intentional pregnancies which generally occurred after treatment in both subgroups.

Discussion

This report has two important flaws: 1) Major adverse effects of a medication are usually rare, and might not be captured by the low numbers of subjects that were in this description, 2) Also, as the goal was to show that repeated administration of mifepristone was safe for the women who did so, then we did not a comparison against a single course of mifepristone, thus there was no control group.

Despite not being the main analytical aim of this report, we are very struck by the fact that subjects treated for endometriosis have a significantly higher treatment repetition rate than those treated for fibroids, 101/386 (26.2%) versus 36/932 (3.9%), $P < 0.001$. We believe this is due to various factors: 1) almost all the studies of mifepristone used to treat uterine fibroids had long or relatively long post-treatment follow-up periods therefore reducing the possibility of repeating treatment, 2) greater efficacy of the mifepristone treatment for endometriosis, 3) greater post-treatment period free of mifepristone symptoms in the uterine fibroid groups (average of 6 to 9 months) than in the endometriosis groups, 4) some subjects in the uterine fibroid groups decided to opt for surgery after treatment thus sorting out their problem once and for all and consequently did not repeat treatment, and 5) some reached menopause.

The fact that 26.2% of the subjects treated with mifepristone for endometriosis repeat treatment between 2 and 4 times with an average rest period of only 8.3 ± 5.3 months speaks well of strong subject adherence to treatment doubtlessly due to its effectiveness. This interval would probably be smaller were it not obligatory to forego treatment for a minimum of 3 months at the end of each study before starting another or repeating the same one.

None of the 105/137 (76.6%) subjects undergoing initial pre-treatment endometrial biopsy in any of the treatment cycles for either of the two conditions was histologically diagnosed with PAEC. After termination of mifepristone treatment no histological sign of the medication was to be found in any subject; this is very important since, despite the PAECs being considered non-pathological, they disappear when mifepristone is discontinued. When menstruation starts, the PAEC-bearing endometrium is eliminated. This report has the deficiency that, in total, 26/137 (19.0%) women refused to have performed the final endometrial biopsy at the end of a treatment cycle. Perhaps, the incidence of PAEC would have been somewhat higher than the reported here if those women had had done such examination.

This ties in, moreover, with what happens to the surgical specimens in the study carried out by Bagaria et al [1], obtaining as it does an extremely high percentage of hyperplasias 12/19 (63.1%) at the end of treatment with 10 mg mifepristone which disappear completely when some time after termination of treatment these subjects undergo surgery and a histological sample is taken. In other words, the PAECs disappear in our study and in the Bagaria et al study the simple or without atypical complex hyperplasias when mifepristone treatment is discontinued [11]. He almost certainly obtains this high percentage of hyperplasias due to not applying the diagnostic criteria agreed upon by the panel of experts who met in North America in 2008 and led to the publications of Horn et al [22] and Mutter et al [23].

It is striking that PAECs in the post-treatment biopsies from the uterine fibroid subgroup were significantly higher to that from the endometriosis subgroup: 9/35 (25.7%) versus 19/197 (9.6%), respectively, $P = 0.004$. We can find no logical explanation for this result as there should not be any difference in the endometrial response to the action of mifepristone dependent on whether the subject suffers from uterine fibroids or endometriosis. In fact, for example, the increases in endometrial thickness in our previous studies into both conditions [4-9, 25] and in both subgroups in the present study are similar. Anyway, given that the PAECs are considered to be "physiological" modifications of the endometrium, the only point of importance to be noted in this section is the non-existence of any case of endometrial hyperplasia or of any other pathology either in the post-treatment biopsies or, of course, in the pre-treatment biopsies regardless of whether it was the second, third or fourth treatment.

The pre-treatment endometrial thicknesses had normal scores in both conditions, however, whether they had been elevated or not in the previous cycle. The transaminases which were slightly elevated in both subgroups, in minimal percentages and clinically irrelevant, showed normal scores in all pre-treatment analytical determinations whether they had been elevated or not in the previous cycle. On the other hand, these elevations were so insignificant it may have been due to a laboratory imprecision. The hot flush rates presented by these subjects in both treatment groups dropped to zero at the end.

The number of subjects to undergo surgery during the follow-up phase may be somewhat superior since the follow-up rate in this period is, logically, quite high and we do not know whether those who abandoned the follow-up at some point and could not be contacted by the research team did so because they felt well or because they decided to have an operation or by any other reason.

One of the main differences between the two subgroups in this study is the different mean age, since the subjects in the endometriosis group is approximately 12 years younger than the fibroid subgroup whose average age is closer to the menopause and this may be reflected in the hormonal profile despite being of little clinical significance. Nevertheless,

from a safety point of view with respect to the use of mifepristone we believe it to be irrelevant whether the subjects suffer from endometriosis or fibroids because the differences in this respect are minimal.

Given that there was no sign of any untoward impact or repercussion in the overall state of health of these subjects and that, despite the increase in endometrial thickness, there were no histological pathologies and the transaminase elevations were clinically irrelevant we could conclude that: 1) repeating up to 3 - 4 low-dose mifepristone treatments of 3, 6 or 9 months duration with variable rest intervals in between did not seem to carry any health risk, 2) it would be advisable to carry out even longer studies to confirm the long-term safety of the continued or repeated use of low dose mifepristone.

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