Impact of Herbal Therapy in Women with Endometrial Hyperplasia in Private Clinic.

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ABSTRACT:

Introduction: Endometrial hyperplasia in pre-menopausal women causes great morbidity in increasing vaginal bleeding (duration of menstrual cycle or amount of bleeding), in addition to its association with abnormal ovulation. So the treatment should address both of these issues. One of the treatment options is herbal medicine. **Aims of this study:** To assess the effect of the dietary supplement (AMS[®]FibroMed) in women complaining from endometrial hyperplasia.

Patients and Methods: This interventional study was conducted in Al-Amal center for infertility treatment in Baghdad for a period of 3 months; from February 2014 to March 2017, on eighty female patients who were complaining from abnormal vaginal bleeding and were diagnosed to have endometrial hyperplasia. Oral consent was obtained from all the participants, and all patients were put on AMS[®]FibroMed with a dose of 2 capsules daily.

Results: Endometrial thickness significantly decreased by $3.52 \pm 2.83 \text{ mm} (34.20\% \pm 26.63\%)$ compared to also statistically significant but less change in days of bleeding $2.17 \pm 1.71 \text{ days} (25.28\% \pm 19.55\%)$, with a mean difference of $8.62\% \pm 16.88\%$, and endometrial thickness had significantly reduced more than bleeding.

Conclusion: AMS[®]FibroMed was effective in reducing endometrial thickness and duration of bleeding, and can be used as fertility preserving therapy in endometrial hyperplasia.

I. INTRODUCTION

Traditional medicine is "the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, used in the maintenance of health and in the prevention, diagnosis, improvement or treatment of physical and mental illness"⁽¹⁾.Endometrial hyperplasia occurs when the *endometrium*, the lining of the *uterus*, becomes too thick⁽⁷⁾. It is not cancer, but in some cases, it can lead to cancer of the uterus⁽⁸⁾.Endometrial hyperplasia most often is caused by excess estrogen without progesterone⁽⁹⁾. If ovulation does not occur, progesterone is not made, and the lining is not shed ⁽¹⁰⁾. Endometrial hyperplasia usually occurs after menopause, when ovulation stops and progesterone is no longer made⁽¹³⁾. It also can occur during perimenopause, when ovulation may not occur regularly⁽¹⁴⁾. Endometrial hyperplasia is classified as simple or complex.

Endometrial thickness is a commonly measured parameter on routine gynaecological ultrasound and MR imaging $^{(22)}$. Normal values for endometrial thickness range from 2 to 16 millimeters, depending on the stage of the menstrual cycle $^{(25)}$.

AMS[®] FibroMedformula is an advanced formula for healthy uterus from AMS[®] (America Medic and Science). It is an all-natural product, with herbal ingredients that minimize the chances of side-effects when compared with other alternative chemical drugs, used in the treatment of uterine disorders. It also decreases estrogen levels, promotes hormonal balance, increases energy, helps with painful cramps and it can improve emotional feelings. It improves uterine disorder.

AMS[®] FibroMed formula contains the following ingredients per daily serving of 2 capsules: Motherwort 20mg, Goldenseal Root 25mg, Chaste Berry extract 40mg, Licorice Root 100mg, Eleuthero root 200mg and a proprietary blend of Burdock Root, Red Clover and Echinacea.

Chasteberry: It has been used to ease menstrual problems, premenstrual syndrome (PMS), menopausal symptoms, some types of infertility, and acne⁽³⁴⁾ and to stimulate the production of breast milk⁽³³⁾.

Motherwort: Used for a variety of purposes, including prevention of <u>uterine infections</u> in women, regulation of menstrual cycle, treatment of painful menstrual periods⁽³⁵⁾, treatment of bleeding following drug-induced abortion⁽³⁶⁾ and treatment of polycystic ovarian syndrome⁽³⁷⁾.

Trifoliumpratense, the Red Clover, shows benefits in endometriosis and uterine fibroids due to its activity on estrogen receptors. It is used in hormonal replacement therapy ⁽³⁸⁾. It may have chemoprotective properties (protects healthy tissue from the toxic effects of Chemotherapy ⁽³⁹⁾). It has positive effects in reducing the

symptoms related to estrogen loss — such as <u>hot flashes</u>, insomnia, weight gain, bone fractures or osteoporosis, cardiovascular problems, and inflammation of the joints $^{(40)}$.

Burdock Root extract is known to have high <u>potassium concentration</u>. It has a vasodilator effect, by which it helps to prevent <u>atherosclerosis</u>, heart attacks, and stroke⁽⁴¹⁾.Italso regulates insulin and glucose levels and aids in the detoxification process in the liver⁽⁴²⁾.

Licorice root is believed to be helpful for hormonal disorders such as fatigue, mood swings, and hot flashes in menopausal women⁽⁴³⁾. It has antispasmodic, anti-inflammatory and a mild estrogenic activity which may improve PMS symptoms such as mood swings, breast tenderness, nausea and bloating, as well as menstrual cramps⁽⁴⁴⁾.

Eleuthero Root, also known as Siberian Ginseng, is a known remedy to relieve menstrual disorders and menopausal symptoms and it is used to stimulate the endocrine gland and also assimilate vitamins and minerals⁽⁴⁸⁾.

Goldenseal(Hydrastiscanadensis), is used for <u>urinary tract infections</u> (UTIs) ⁽⁴⁵⁾, <u>internal bleeding</u>, bleeding after <u>childbirth</u>, liver disorders, cancer, <u>chronicfatigue</u>. It helps to lower blood pressure and blood sugar levels and it improves irregular heartbeats. Goldenseal lowers cholesterol and low-densitylipoprotein levels (Bad Cholesterol). ⁽⁴⁶⁾.

Echinacea, known to be efficient in strengthening the immune system and fighting colds and it can also be used to fight fatigue⁽⁴⁷⁾.

On the other hand, uterine bleeding is another issue that is associated with endometrial hyperplasia ⁽⁴⁹⁾. A normal menstrual cycle is 21–35 days in duration, with bleeding lasting an average of 5 days and a total blood flow between 25 and 80 mL (soaking a pad/tampon every 2 hours or less) ⁽⁵⁰⁾.

Ultrasonography

The endometrial thickness should be measured in the sagittal plane or long axis or, with transvaginal U/S, as it is the best. ⁽²¹⁾ The measurement is of the thickest echogenic area from one basal endometrial interface across the endometrial canal to the other basal surface, care should be taken not to include the hypoechoic myometrium in this measurement⁽²³⁾. The transvaginal ultrasonography study performed to detect the endometrial thickness. Serial transvaginal ultrasound take to the patients at different time of menstrual cycle to evaluate the thickness of endometrium before and after the females take the drugs.

The normal endometrium changes in appearance as well as in thickness throughout the menstrual cycle $incloud^{(22)}$:

1-in the menstrual and early proliferative phase it is a thin, brightly echogenic stripe comprising of the basal layer; minimal fluid can be appreciated endovaginally within the endometrium in the menstrual phase.

2-in the late proliferative phase it develops a trilaminar appearance: outer echogenic basal layer, middle hypoechoic functional layer, and an inner echogenic stripe at the central interface.

3-in the secretory phase it is at its thickest and becomes uniformly echogenic, as the functional layer becomes oedematous and isoechoic to the basal layer ; there is through transmission and posterior acoustic enhancement noted.

The postmenopausal endometrium should be smooth and homogeneous ⁽²⁴⁾.

In premenopausal patients, there is significant variation at different stages of the menstrual cycle⁽²⁵⁾.

1- During menstruation: 2-4 mm

2- Early proliferative phase (day 6-14): 5-7 mm

3- Late proliferative / preovulatory phase: up to 11 mm

4- Secretory phase: 7-16 mm

5- Following dilatation and curettage or spontaneous abortion: <5 mm, if it is thicker consider <u>retained products</u> of conception.

II. AIM OF THE STUDY

To assess the effect of the herbal medicine (AMS[®] FibroMed) in women complaining from endometrial hyperplasia.

III. PATIENTS AND METHODS

This interventional study was conducted in Al-Amal center for infertility treatment in Baghdad for a period of 3 months; from February 2014 to March 2017, on eighty female patients who were complaining from abnormal vaginal bleeding and diagnosed to have endometrial hyperplasia. Oral consent was obtained from all the participants, and all patients were put on AMS[®] FibroMedtwo capsules daily. This protocol had been approved by the review board of AL-Amal center for infertility treatment.

Investigations:

All females enrolled in this study were examined generally and gynecologically. They had abnormal vaginal bleeding and diagnosed with endometrial hyperplasia by vaginal ultrasound by investigator. History and general examination included; Age, menarche, regulation menstrual cycle, days of bleeding and amount, body mass index, hair distribution, goiter, anemic, jaundice, surgical scars.Gynecological examination included; normality of outer genital organs, pelvic examination (PV) to exclude any mass, warm Cusco speculum was introduced to reveal any pathological lesion such as cervical polyps, infection, vaginal discharge, and erosions.

Inclusion criteria:

- 1. Abnormal vaginal bleeding with endometrial hyperplasia.
- 2. Normal basal hormonal study.
- 3. Age between 20- 50 years.

Exclusion criteria

Patients with hormonal disturbances, polycystic ovary and polycystic ovarian syndromes, patients with hypertension, diabetes mellitus and other endocrine disorders, obvious pathological lesions as fibroid, polyps or congenital anomaly of female genital tract.

Hormonal study

Serial hormonal tests were performed to the females by using Mini Vidas – France (Compact multipara-metric immune-analyzer) at day two of cycle this included FSH, LH, prolactin, and E2, at day 9-11 the hormones investigated were LH, and E2, and at day 21 only progesterone was done.

Statistical analysis:

Data tabulation, input and coding was done by the use of IBM[©] SPSS[©] (Statistical Package for the Social Sciences)Statistics Version 22, and figures were plotted using GraphPad Prism version 7.00, and Minitab[®] version 17.1.0.

Paired sample t-test and independent sample t-test were used to compare between numerical and normally distributed variables, and Wilcoxon Signed Ranks Test andMann-Whitney U were used to compare between numerical and abnormally distributed variables. Partial correlation models and binary logistic regression model were done to assess the effect of improvement in endometrial hyperplasia and reduction of days of menstruation on pregnancy. Correlation coefficient between -0.3 to -0.5 were considered to have weak negative correlation, and values between zero and 0.3 were considered to have no relationship. Comparison of the statistical significance of the difference between two the zero- order correlation and partial correlation was dose using one sample z-test.

IV. RESULTS

A total of 80 female patients presented with endometrial hyperplasia, their mean age was 39.66 ± 11.5 years, and their mean BMI was 29.34 ± 4.07 kg/m².

Endometrial thickness before AMS[®] FibroMed therapy was 10.006 ±1.92 mm, it decreased to 6.48 ±2.64 mm, with a mean difference of 3.52 ± 2.83 mm, and this decrement was statistically significant with a p-value of 0.018. Comparing days of bleeding (menstrual cycle days) after treatment reviled a statistically significant difference after treatment with a mean difference of 2.17 ±1.71 days, as before treatment it was 8.08 ±2.29 days and after treatment it became 5.91 ±2.34 days; (Table 1, figures 1 and 2).

In order to identify which decreased more, we calculated the percent change of endometrial thickness and days of menstruation; endometrial thickness decreased by $34.20\% \pm 26.63\%$ compared to less change in days of bleeding of 25.28% $\pm 19.55\%$, with a mean difference of 8.62% $\pm 16.88\%$, so endometrial thickness had significantly reduced more than bleeding; (Table 2, figure 3).

In order to identify the benefit of this therapy for conception, all variables (including age and BMI) was compared between pregnant group, and non-pregnant group. Age and BMI were significantly higher in non-pregnant group, with means of 42.94 ± 11.19 years and 31.0 ± 3.26 kg/m² in latter group compared to mean age of 33.57 ± 9.78 years and 26.25 ± 3.62 , with a statistically significant mean decrement of 9.37 years and 4.74 kg/m². Percent change of endometrial thickness in pregnant women was $34.20\% \pm 26.63\%$ compared to $25.58\% \pm 19.55\%$ with statistically significant decrement of 8.62%, also the same applies to percent change of days of menstruation, which was $40.11\% \pm 8.90\%$ before treatment and decreased by 22.36% to $17.75\% \pm 19.28$ after treatment. (Table 3, figure4)

Further analysis was done to investigate the effects of different variables on pregnancy, it was found that age and BMI had more effect on pregnancy than percent change of endometrial thickness or days of menstruation. It was noticed that age had a statistically significant but weak negative correlation with pregnancy

of -0.376, the same applies to BMI with a statistically significant but weaker negative correlation of -0.263, and higher odds for developing pregnancy by 1.133 times and 1.369 times for younger age and lower BMI, respectively.

Percent change of endometrial thickness also had statistically significant but with weaker positive correlation of 0.265 for developing pregnancy, also percent change of days of menstruation had a statistically significant and weaker correlation of 0.226 for developing pregnancy, and their odds for developing pregnancy was statistically not significant.

Table (5) showed that there was a statistically significant effect of age and BMI in controlling for the percent changes of endometrial thickness and days of bleeding after AMS[®] FibroMed therapy, also these percent change had a statistically significant effect in controlling for BMI effect on pregnancy, but age was an independent factor that had statistically significant influence on conception outcome.

Table (1): Comparison of endometrial thickness and menstruation days before and after	AMS®
Fibro Med therapy	

Variables	Before ther	ару	After therapy		Difference		P-value
	Mean	SD	Mean	SD	Mean	SD	
Endometrial	10.006	1.92	6.48	2.64	3.52	2.83	*0.018
thickness							
Days of	8.08	2.29	5.91	2.34	2.17	1.71	**0.000
menstrual cycle							
* paired sample t-test ** Wilcoxon Signed Ranks Test							



Figure (1): Boxplot of endometrial thickness before and after treatment



Figure (2): Boxplot of menstrual cycle duration before and after treatment

 Table (2): Comparison of endometrial thickness and menstruation days percent change after AMS[®]

 Fibro Med therapy

r ibi o wied therapy							
	Endometa thickness	metrial Days of menstrua ness cycle		nenstrual	Difference		P-value
	Mean	SD	Mean	SD	Mean	SD	*0.000
Percent	34.20	26.63	25.58	19.55	8.62	16.88	
change (%)							
* Wilcoxon Signed Ranks Test							







	Pregnancy			Difference	P-value		
	+ve		-ve				
	Mean	SD	Mean	SD	Mean		
Age	33.57	9.78	42.94	11.19	-9.37	*0.000	
BMI	26.25	3.62	31.0	3.26	-4.74	*0.000	
PC of endometrial thickness	34.20	26.63	25.58	19.55	8.62	**0.000	
PC of days of menstruation	40.11	8.90	17.75	19.28	22.36	**0.000	
* independent sample t-test ** Wilcoxon Signed Ranks Test							

Table (3) Comparison between variables according to pregnancy outcome



PC of MD : Perncent change of mentrual cycle days

Figure (4) distribution of variables according to pregnancy outcome

Table (4): partial correlation and multivariate binary logistic regression model between pregnancy and percent change of endometrial thickness and percent change of days of menstruation

mensu dation							
Pregnancy			Odd's ratio	**P-value			
	*r	P-value					
Age	-0.376 ^a	0.000	1.133	0.001			
BMI	-0.263 ^a	0.010	1.369	0.020			
PC of	0.265 ^b	0.012	0.956	0.073			
endometrial							
thickness							
PC of days of	0.226 ^b	0.023	0.941	0.152			
menstruation							
* partial correlation coefficient;							
a: in control by PC of endometrial thickness and PC of days of menstruation							
b:in control by Age and BMI							
** binary logistic regression							

Variable	Zero-order (Pearson) correlation	Partial correlation	Z test	P-value
Age	-0.389	-0.376	0.094	0.924
BMI	-0.560	-0.263	2.255	0.024
PC of endometrial thickness	0.543	0.265	2.09	0.036
PC of days of menstruation	0.549	0.226	2.40	0.016

Table (5): influence of age and BMI in controlling for percent change of endometrial thickness and percent change of days of menstruation effect on pregnancy and vice versa

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V. DISCUSSION

There are no FDA approved treatment for endometrial hyperplasia, but the treatment options include monitoring, progestin, or hysterectomy. ⁽²⁶⁾ Other options include Gonadotropin-releasing hormone (GnRH), aromatase inhibitors, ovulation induction, metformin, danazol, weight reduction might be enough in some patients (e.g. bariatric surgery), and hysteroscopic resection of endometrial hyperplasia. ⁽²⁷⁻³⁴⁾

Herbs might be used as supplements for some gynecology conditions, such as symptoms of menopause, PMS, cyclic mastalgia, dysmenorrheal, and infertility⁽³⁵⁾.

Herbs are natural compounds and presumed to be safe but it may have side effect which could be dangerous or even lethal, as it had been reported recently, whether as direct toxic effect, allergy, contaminants, or interactions with other medications or herbs, to increase safety and consistency, more research are needed to study the pharmacodynamics, stability, and bioavailability of herbs. ⁽³⁶⁾

Echinacea is considered an immune booster as it ability to increase WBC counts (basophil and mast cells), red clover has phytoestrogen which could be used to battle postmenopausal symptoms ⁽³⁷⁾

In the current study there was significant improvement after treatment with AMS[®] FibroMed in both endometrial thickness and in days of bleeding by 34.20 mm and 25.58 days, respectively, and this could be a promising fertility preserving treatment, as options such as progestin, danazol or hysterectomy will definitely have the women unable to conceive, with multiple side effects and morbidity.

In the current study some women got pregnant throughout the study period, and data analysis revealed that percent change of endometrial thickness and days of bleeding were statistically more in pregnant women compared to others, which indicated a favorable effect of therapy on endometrial epithelium, and age was correlate with pregnancy, which meant that younger women were more likely to get pregnant while they were on AMS[®] FibroMed, because it did not alter the hormonal level to cause a temporary infertility (like danazol), but rather it promoted pregnancy or at least didn't halter it.

Although there are no studies to label AMS[®] FibroMed composition to be teratogenic, or mutagenic, there are no studies to prove it as a safe drug during pregnancy, or around the duration of fertilization.⁽³⁷⁾Conclusions and recommendations:

VI. CONCLUSIONS

1. AMS[®] FibroMed was effective in reducing endometrial thickness and duration of bleeding.

2. AMS[®] FibroMed can be used as fertility preserving therapy in endometrial hyperplasia.

Recommendations:

1. Putting more effort in doing controlled randomized trial to assess AMS[®] FibroMed, or other herbal medications in treating gynecological diseases.

2. Examination for any teratogenic effects of herbal medication in order to take care when using it.

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