

## EVALUATION OF CLINICAL EFFICACY AND SAFETY OF OVOUTOLINE FORTE TABLET AN HERBAL FORMULATION IN DYSFUNCTIONAL UTERINE BLEEDING (DUB)

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### ABSTRACT

**Background:** To evaluate the clinical efficacy and safety effect of Ovoutoline Forte tablet a marketed herbal formulation of Emami Limited, in Dysfunctional Uterine Bleeding (DUB).

**Methods:** 57 women patients' age range between 20 to 40 years, suffering from Dysfunctional Uterine Bleeding symptoms like mid cycle bleeding, late cycle bleeding and irregular periods.

**Results:** 100%, 96.49% and 94.74% improvement was observed in patients with DUB symptoms like mid cycle bleeding, late cycle bleeding and irregular periods after ZOFT medication respectively. Upper Abdomen USG was normal in all the 57 patients, no uterine fibroids was reported.

**Conclusion:** Dysfunctional Uterine Bleeding symptoms like mid cycle bleeding, late cycle bleeding and irregular periods were taken care off.

**Key Words:** Ovoutoline forte tablet, Dysfunctional uterine bleeding, Mid cycle bleeding, Late cycle bleeding and irregular periods.

### BACKGROUND

Dysfunctional uterine bleeding (DUB) is defined as excessively heavy, prolonged or frequent bleeding of uterine origin that is not due to pregnancy or any recognizable pelvic or systemic disease. It is, therefore, a diagnosis of exclusion. The mechanisms for the abnormal bleeding and the site from which it arises are largely unknown. Menstruation is a very complex process involving oestrogen and progesterone and their receptors, endometrial vasculature, endometrial vasoactive substances, processes of tissue breakdown and remodeling, and endometrial repair and regeneration.

Dysfunctional uterine bleeding is the diagnosis in 40–60% of women with excessive menstrual bleeding which is defined as greater than 80 mL blood loss (normal menstrual loss <80 mL). Heavy menstrual bleeding may affect a woman's health both medically and socially, causing problems such as iron deficiency anemia and social phobia respectively. Dysfunctional uterine bleeding is the commonest cause of iron deficiency in the developed world and of chronic illness in the developing world.<sup>1</sup>

There are two types of DUB: ovulatory and an ovulatory. Ovulatory DUB accounts for about 80% of cases. In ovulatory DUB the menstruation is regular, preceded by ovulation and heavy but of normal duration. It is most common in women in their 30s. An ovulatory DUB is more likely to occur at the beginning and end of the reproductive years. The menstrual cycle is irregular and the bleeding is heavy and may be prolonged.

Medical management is the treatment of choice for DUB, with surgical intervention being reserved for the small proportion of women with medical treatment failures. However, studies have shown that the response to conventional hormone replacement therapy (HRT) is poor/only partial.<sup>2,3</sup> In addition, withdrawal bleeding and other side effects such as oedema, bloating, premenstrual irritability, lower abdominal cramps, dysmenorrhoea and breast heaviness occur in 10% of women receiving HRT,<sup>4</sup> thus limiting compliance with this form of treatment.

In Ayurveda *Rakta yoni Asradgdhara* (DUB) the increase *rakta* and *pitta* leads excess flow of the *pitta* through the genital tract. The blood flow does not stop even in the pregnancy. The pregnancy does not continue because of the excess blood flow.<sup>5</sup> DUB is also one of the factors responsible for infertility in females.

In recent times many natural plant derived phytoestrogens have been used to treat various gynaecological disorders. Containing several plant extracts of Lodhra (*Symplocos racemosa*) extract - 150 mg, Ashoka (*Saraca indica*) extract - 100 mg, Shatavari (*Asparagus racemosus*) extract - 100 mg, Yashtimadhu (*Glycyrrhiza glabra*) extract - 50 mg, Tagar (*Valeriana wallichi*) extract - 50 mg, Guduchi (*Tinospora cordifolia*) extract - 25 mg, Sweet jiraka (*Cuminum cyminum*) 25 mg, Sunthi (*Zingiber officinale*) extract - 25 mg with multiple (relevant) pharmacological properties.

Ovoutoline Forte tablet is one such (non-hormonal) herbal formulation, which has been

advocated in the treatment of menstrual disorders. The purpose of the present study, therefore, was to evaluate the effectiveness of Ovoutoline Forte tablet in relieving the symptoms of DUB.

## METHODS

**Sample Size:** 57 patients completed study (Total Enrolled: 60 i.e. 3 patient dropout during study)

**Trial period:** 3 months for each patient

**Design of the study:** Open Observational Trial.

**Drug & dosage:** Ovoutoline Forte tablet twice a day after food with a glass of Luke warm water (approx. 250 ml.) maintaining 12 hours gap in between, for 3 months (90 days).

**Follow - Up:** The follow-up was carried out after 30 days of treatment.

**Duration of the study:** 90 days drug therapy with a follow up for 30 days without drug.

**Study period:** 12 months.

**Study Site:** Mahavir Hospital, Latti Plot, Opp. District Library, Near C. J. Hospital, Surendranagar - 363001, Gujarat, India.

**Subject Inclusion Criteria:** Enrollment: Patients found eligible were judged by the inclusion & exclusion criteria. Patients were formally informed about the study.

**Informed consent:** A written informed consent was obtained from all the patients, indicating purpose and nature of clinical trial-herbal formulation. The procedures to be carried out and the potential risks and benefits were explained to the study patients in detail in non-technical terms. They were assured that they can withdraw from the study at any time without explaining their action

**Medication and treatment:** The patients were treated with Ovoutoline Forte, 1 tablet, twice daily and the treatment period was 3 months. The medicine was kept in secured storage in the office of the principle investigator and was allotted to the patients following a random number table.

**Criteria for Exclusion:** Patients who develop secondary complication of Colitis, intestinal obstruction etc. Any other serious illness e.g. Hepatic/ renal failure. Patient with diagnosed other than arthritis like Gallbladder stone, Hepatomegaly. Patient receiving any other method of treatment.

**Parameters for evaluation:** Clinical efficiency parameters: all patients enrolled into the study were subjected to through history taking and clinical examination and also questionnaire as part of the screening procedure and was re-evaluated at the end of the study (clinical research form). Apart from clinical examination and questionnaire, the selected investigation was done, before and after medication.

Each subject visited at least 5 clinic visits during the study.

**Safety information:** Any serious adverse event is not expected but the clinical research form has the provision for recording any serious adverse event if it happens and the principle investigator of the trial would report the sponsor same on urgent basis.

**Concomitant medication:** Subject were advised not to use any concomitant medication unless absolutely necessary. If any concomitant medication was used, its record was maintained in a separate section of the clinical research form.

**Confidentiality:** All procedure in the study was carried out maintaining strict confidentiality. Patient identity, medical condition and trail data will not be disclosed to or discussed with any third party. Criteria regarding DUB symptoms were mid cycle bleeding, late cycle bleeding and irregular periods.

**Routine Examination and Assessment:** The full details of history and physical examination of the patients was recorded as per the Performa (Forms I & II):

- 1) Clinical assessment was done and recorded on '0' day (before ZOFT medication), 30<sup>th</sup> day, 60<sup>th</sup> day, 90<sup>th</sup> day and 120<sup>th</sup> day. Regularity or irregularity of menstrual cycle along with DUB symptoms like mid cycle bleeding, late cycle bleeding and irregular periods. Grading score of symptoms was done as per its severity observed in an individual patient (like occasionally = 0, mild = 2, moderate = 4, sever = 6). All this parameters were observed during the period of ZOFT medication (Figure No. 1-3).
- 2) Upper Abdomen USG and uterine fibroid study was performed on 0<sup>th</sup> and 90<sup>th</sup> day.

## RESULTS

**Primary Outcome Measure:** Improvements were observed in clinical symptoms of ZOFT medicated 57 women patients age range between 20 to 40 years old. A significant improvement was observed in clinical symptoms like mid cycle bleeding, late cycle bleeding and irregular periods after ZOFT medication. % improvement was observed for different clinical symptoms, during the study (Table No. 1 and Figure 4 - 6).

- 1) Mid cycle bleeding were observed in all the patients on '0' day but after ZOFT medication 3.51% (30<sup>th</sup> day), 36.84% (60<sup>th</sup> day), 96.49% (90<sup>th</sup> day) and 100% (120<sup>th</sup> day) improvement was observed in all the 57 patients.
- 2) Late cycle bleeding was improved from 30<sup>th</sup> day by 15.79%, 59.65% (60<sup>th</sup> day), 92.98% (90<sup>th</sup> day) and 96.49% at the end of study.

- 3) Irregularity of periods was also a concern for DUB. Irregular period days were improved from 30<sup>th</sup> day by 12.28%, 59.65% (60<sup>th</sup> day), 92.98% (90<sup>th</sup> day) and 94.74% (120<sup>th</sup> day).

Upper Abdomen USG was normal in all the 57 patients, no uterine fibroids were reported.

#### **Statistical Analysis for Primary Outcome**

**Measure:** Clinical assessment was done (symptoms score Occasionally = 0 Score, Mild = 2 Score; Moderate = 4 Score and Sever = 6; as per the Clinical trial format) and recorded on the zero day (i.e. one day before administering the trial drug), 30<sup>th</sup> day, 60<sup>th</sup>, 90<sup>th</sup> and 120<sup>th</sup> day final day of the follow-up.

As the score of DUB symptoms were reduced towards the end of the trial 90<sup>th</sup> day with medication and other 30 days without medication (i.e. a total of 120 days), it revealed a significant activity of the Ovoutoline Forte tablet formulation, as shown in Table No. 2 and Figure 7 - 9. Results were reported by mean  $\pm$  S.E.M., the test of significance was statistically analyzed by using one way ANOVA test, followed by Dunnett's multiple comparison test ( $p < 0.01$ ). Statistical analysis was done by using software Graph pad Prism Demo version 3.

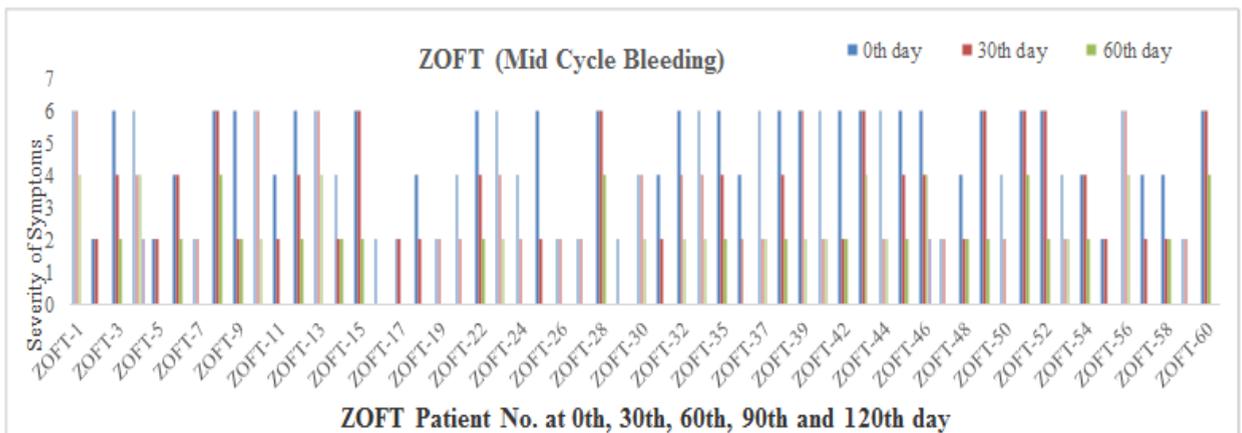
**Table 1: % Improvement for Mid Cycle Bleeding, Late Cycle Bleeding and Irregular Periods.**

Day / Treatment	Mid Cycle Bleeding			Late Cycle Bleeding			Irregular Periods		
	Symptoms Present in Patient	Symptoms Absent in Patient	% Imp.	Symptoms Present in Patient	Symptoms Absent in Patient	% Imp.	Symptoms Present in Patient	Symptoms Absent in Patient	% Imp.
0th day	57	0	0.00	57	0	0.00	57	0	0.00
30th day	55	2	3.51	48	9	15.79	50	7	12.28
60th day	36	21	36.84	23	34	59.65	23	34	59.65
90th day	2	55	96.49	4	53	92.98	4	53	92.98
120th day	0	57	100	2	55	96.49	3	54	94.74

**Table No. 2: Treatment of PCOS Symptoms, Ovaryl tablet.**

Day	Mid Cycle Bleeding	Late Cycle Bleeding	Irregular Periods
0 <sup>th</sup>	4.6316 ± 0.2133	3.6491 ± 0.2010	3.9298 ± 0.1937
30 <sup>th</sup>	3.3333 ± 0.2312**	2.4561 ± 0.2402**	2.5965 ± 0.2180**
60 <sup>th</sup>	1.6140 ± 0.1092**	1.0877 ± 0.1943**	0.9825 ± 0.1814**
90 <sup>th</sup>	0.0702 ± 0.0492**	0.1404 ± 0.0683**	0.1404 ± 0.0683**
120 <sup>th</sup>	0.0000 ± 0.0000**	0.0702 ± 0.0492**	0.1053 ± 0.0597**

All values are in mean ± S.E.M., \* p<0.01 = significant vs. Control (0<sup>th</sup> day untreated patients); \*\* p<0.01 = more significant vs. Control (0<sup>th</sup> day untreated patients); ns = Non-Significant, n = 57



**Figure 1: Mid Cycle bleeding symptom at 0<sup>th</sup> day, 30<sup>th</sup> day, 60<sup>th</sup>, 90<sup>th</sup> and 120<sup>th</sup> day**

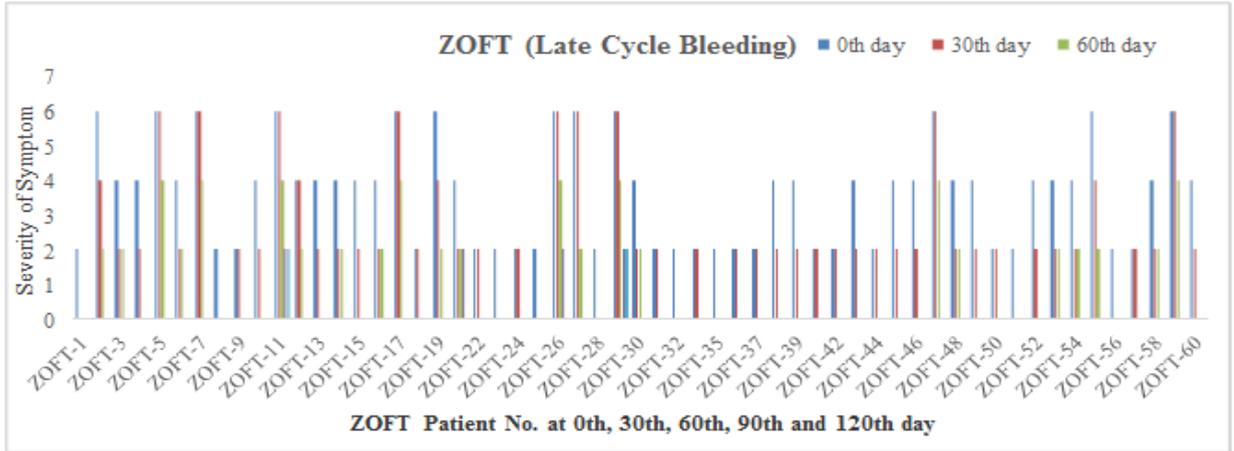


Figure 2: Late Cycle Bleeding symptom at 0<sup>th</sup> day, 30<sup>th</sup> day, 60<sup>th</sup>, 90<sup>th</sup> and 120<sup>th</sup> day

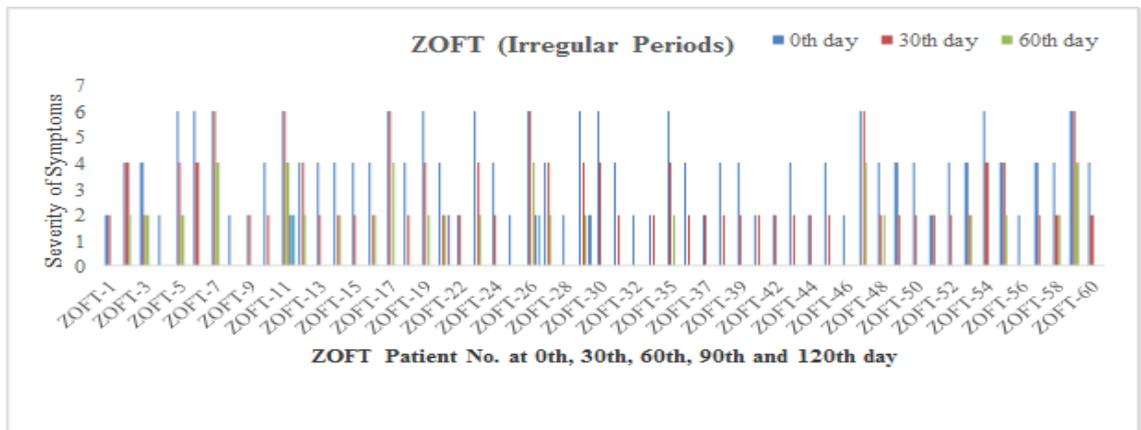


Figure 3: Irregular Periods symptom at 0<sup>th</sup> day, 30<sup>th</sup> day, 60<sup>th</sup>, 90<sup>th</sup> and 120<sup>th</sup> day

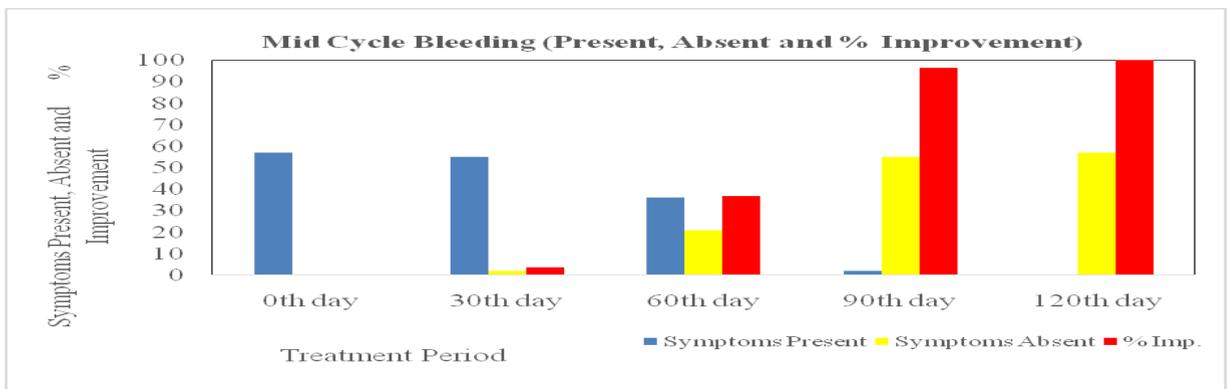


Figure No. 4: Mid Cycle Bleeding at 0<sup>th</sup>, 30<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup> and 120<sup>th</sup> day

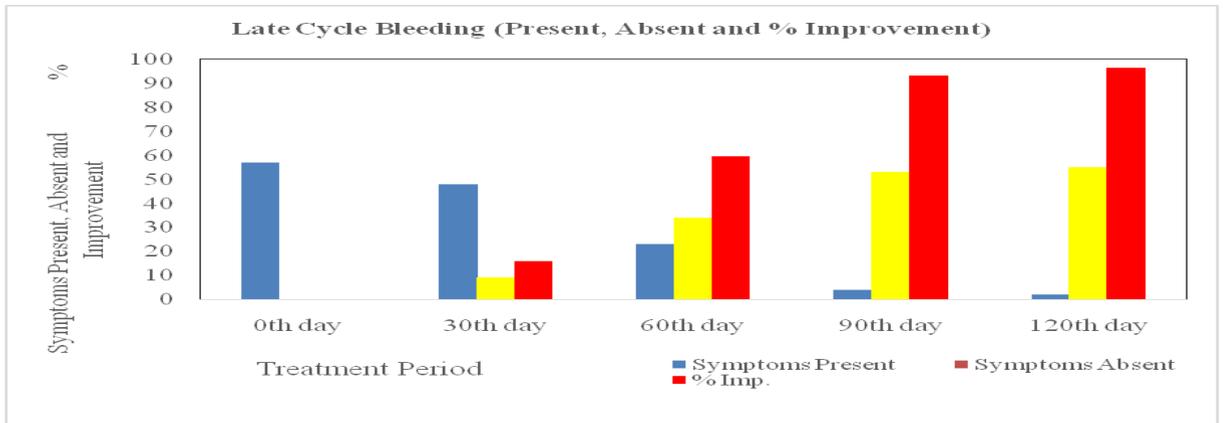


Figure No. 5: Late Cycle Bleeding at 0<sup>th</sup>, 30<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup> and 120<sup>th</sup> day

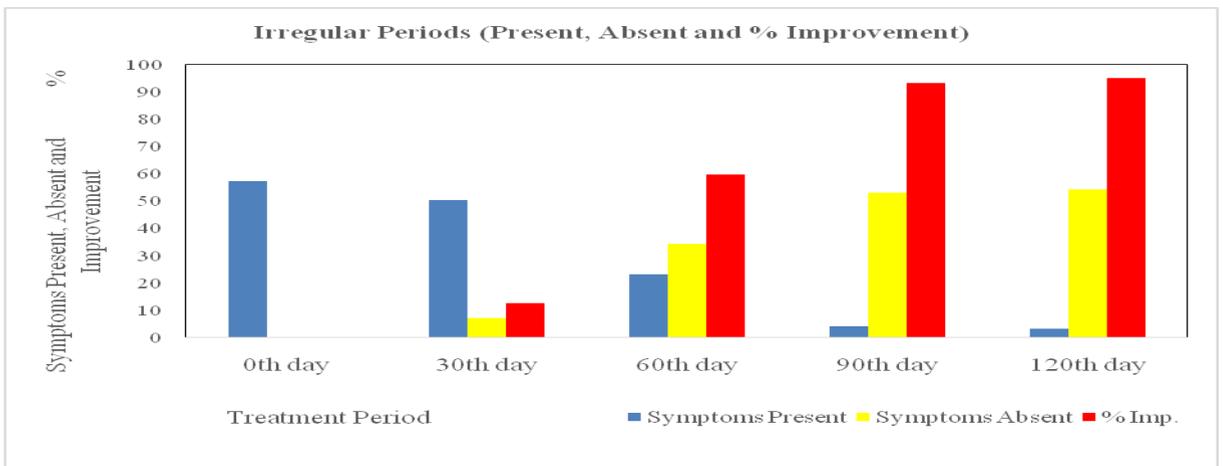


Figure No. 6: Irregular Periods at 0<sup>th</sup>, 30<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup> and 120<sup>th</sup> day

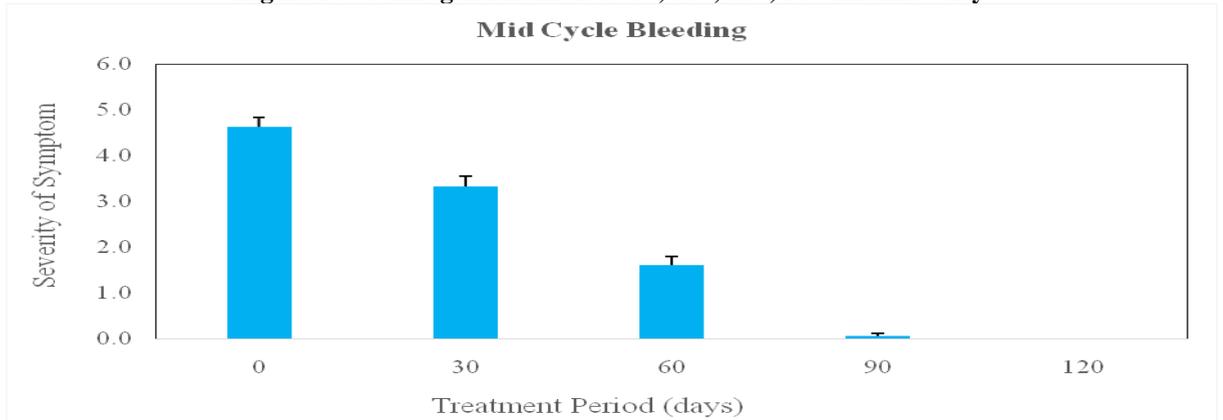
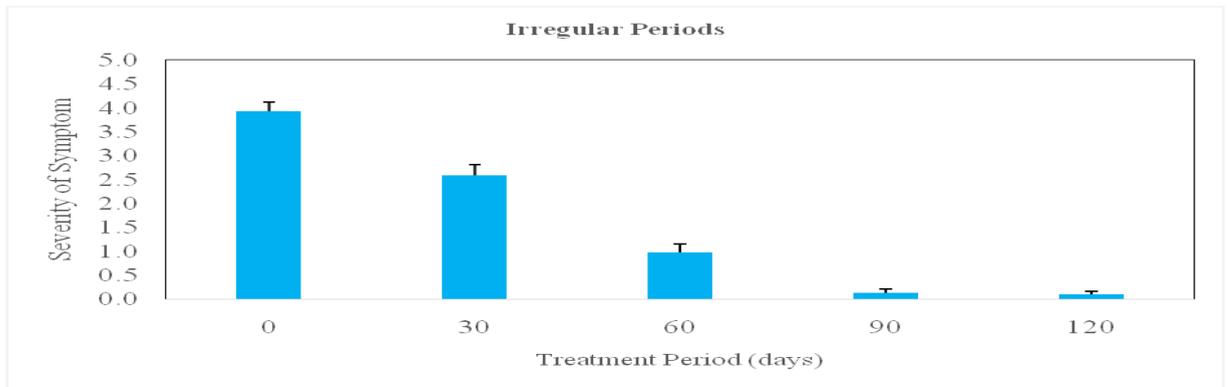


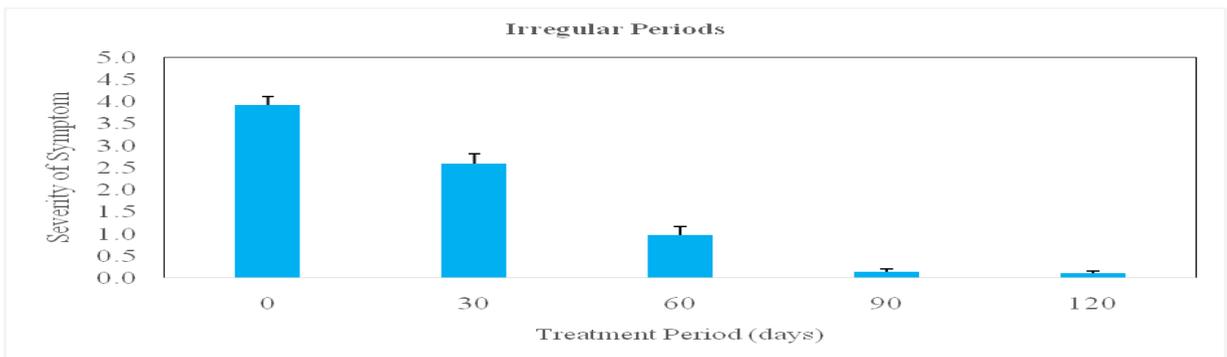
Figure No. 7: Graph of Mid Cycle Bleeding, Severity of Symptoms versus treatment period for Ovoutoline Forte tablet.

All values are in mean ± S.E.M., \* p<0.01 = significant vs. Control (0<sup>th</sup> day untreated patients); \*\* p<0.01 = more significant vs. Control (0<sup>th</sup> day untreated patients); ns = Non Significant, n = 57



**Figure No. 8: Graph of Late Cycle Bleeding, Severity of Symptoms versus treatment period for Ovoutoline Forte tablet.**

All values are in mean ± S.E.M., \* p<0.01 = significant vs. Control (0<sup>th</sup> day untreated patients); \*\* p<0.01 = more significant vs. Control (0<sup>th</sup> day untreated patients); ns = Non Significant, n = 57



**Figure No. 9: Graph of Irregular Periods, Severity of Symptoms versus treatment period for Ovoutoline Forte tablet.**

All values are in mean ± S.E.M., \* p<0.01 = significant vs. Control (0<sup>th</sup> day untreated patients); \*\* p<0.01 = more significant vs. Control (0<sup>th</sup> day untreated patients); ns = Non Significant, n = 57

**DISCUSSION**

As per the study design, total 60 patients were incorporated out of which 57 continued till the end of study. Patients were selected as per inclusion criteria and who doesn't fall in any one of the exclusion criteria. All necessary laboratory investigations were completed before starting the treatment with Ovoutoline Forte tablet. The patients selected had complaint of inadequate clinical symptoms like mid cycle bleeding, late cycle bleeding and irregular periods.

**0<sup>th</sup> Day Visit:** All the patients were given the samples of test medicine, Ovoutoline Forte tablet. Patients were informed about the dose, effect of the drug and were advised to have follow up as per schedule, up to four months and if any harmful or unwanted or unexplained effect was noted and the drug should be stopped immediately and to inform as soon as possible. A complete general and upper abdominal

USG examination of each patient was carried out in detail, to note any change in further visits.

**30<sup>th</sup> Day Visit:** After 30 days they were further called for the consultation. Each patient was examined in detail for their clinical symptoms like mid cycle bleeding, late cycle bleeding and irregular periods. No any significant harmful effect noted with the use of the product. The responses regarding the improvement in symptoms for patient were satisfactory at least. ZOFT-20, patient did not report for the study (patient lost) and pregnancy was reported positive in ZOFT-33.

**60<sup>th</sup> Day Visit:** At the end of 60<sup>th</sup> day they were further called for the consultation. Each subject was examined in detail for their clinical symptoms like mid cycle bleeding, late cycle bleeding and irregular periods symptoms were showing signs of improvement. Pregnancy was reported positive in ZOFT-40.

**90<sup>th</sup> Day Visit:** At the end of 90<sup>th</sup> day they were further called for the consultation. Each subject was examined in detail for their clinical and upper abdominal USG examination. Mid cycle bleeding, late cycle bleeding and irregular period symptoms were showing signs of improvement. Normal upper abdominal USG with no uterine fibroids. Patients were told for last follow up after 30 days, the duration between 91<sup>st</sup> days to 120<sup>th</sup> day was observation period, for clinical symptoms without ovaryl tablet.

**120<sup>th</sup> Day Visit:** In that last visit they were examined as previously done, the difference in pre and post treatment parameters. The observations reported and the benefits noted from this product in DUB women are discussed in detail.

Generally in clinical practice, the basic complaint almost by all the patients was mid cycle bleeding, late cycle bleeding and irregular periods symptoms were significantly reduced.

Ovoutoline Forte tablet is a polyherbal formulation containing Lodhra (*Symplocos racemosa*) extract, Ashoka (*Saraca indica*) extract, Shatavari (*Asparagus racemosus*) extract, Yashtimadhu (*Glycyrrhiza glabra*) extract, Tagar (*Valeriana wallichii*) extract, Guduchi (*Tinospora cordifolia*) extract, Sweet jiraka (*Cuminum cyminum*), Sunthi (*Zingiber officinale*) extract, along with excipients.

Lodhra bark is astringent, refrigerant, anti-inflammatory, febrifuge, haemostatic and stomachic. It is useful in leucorrhoea and gonorrhoea.<sup>6</sup>

One of the uses of the Ashoka bark is in the treatment of menstrual disorders associated with excessive bleeding, congestion, and pain. Preparation of the Ashoka bark is used in leucorrhoea, uterine fibroids, benefits the endometrium and uterine muscles and this makes it effective as a uterine tonic for irregular menstrual cycles.<sup>7</sup>

*Asparagus racemosus* cleanses, nourishes, and strengthens the female reproductive organs and so, it is traditionally used for pre-menstrual syndrome, amenorrhoea, dysmenorrhoea, menopause and pelvic inflammatory disease like endometriosis.<sup>8</sup> Shatavari is considered as the most potent female health tonic. It also supports deeper tissue and builds blood, helping in treating infertility, prevents miscarriage and acts as a post-partum tonic as it increases lactation, regularizes the uterus and balances hormones, probably due to phyto-estrogens. Shatavari is also suggested for its soothing agent upon systemic dryness which is part of the natural aging process.<sup>9</sup>

Liquorice roots are useful in sexual debility, epilepsy, fever, coughs, skin diseases, swellings, acidity, leucorrhoea, bleeding, vitiated conditions of vata and dosha.<sup>10</sup>

*Valeriana wallichii* has considerable reputation for its traditional use in inflammatory conditions, leucorrhoea, uterine fibroids<sup>11</sup>, pain.<sup>12</sup>

*Tinospora cordifolia* is commonly known as, "Amrita" or "Guduchi" is an important drug of Indian System of Medicine and used in medicines since times immemorial. The drug is well known as Indian Bitter and prescribed in fever, diabetes, jaundice, urinary problems, skin disease, leprosy<sup>13</sup>, leucorrhoea.<sup>14</sup>

Cumin seeds contain possess numerous phyto-chemicals that are known to have antioxidant, carminative and anti-flatulent properties. The active principles in the cumin may increase the motility of the gastro-intestinal tract as well as increase the digestion power by increasing gastro-intestinal enzyme secretions. This spice is an excellent source of minerals like iron, copper, calcium, potassium, manganese, selenium, zinc and magnesium. It also contains very good amounts of B-complex vitamins such as thiamin, vitamin B-6, niacin, riboflavin, and other vital anti-oxidant vitamins like vitamin E, vitamin A and vitamin C. The seeds are also rich source of many flavonoid phenolic anti-oxidants such as carotenes, zeaxanthin and lutein.<sup>15</sup> It's micronutrients include about 1.4 mg iron, 38 mg potassium and 8 mg magnesium. Magnesium serves a host of functions, including promoting heart health, controlling blood pressure and aiding the absorption of calcium.<sup>16</sup>

Ginger is amongst the important herb described in Ayurveda. It is described as "Mahaushadhi", which means, use of this herb improves growth of the body. General properties of this useful herb are: sweet, pungent, warm, kapha, vatta alleviating. Ginger is a good appetizer, aphrodisiac, pain reliever and anti-inflammatory.<sup>17</sup> Current interest in plant-derived oestrogens or 'phytoestrogens' has increased due to the realization that hormone replacement therapy is neither as safe nor as effective as previously envisaged.<sup>18</sup> Phytoestrogens are defined as any plant compound structurally and/or functionally similar to ovarian and placental oestrogens and their active metabolites. Phytoestrogens affect the regulation of ovarian cycles and oestrous in female mammals and the promotion of growth, differentiation and physiological functions of the female genital tract, pituitary, breast and several other organs and tissues in both sexes<sup>19</sup>.

With the use of the Ovoutoline Forte tablet which contains herbs, satisfactory and excellent results were observed within few days of use, in DUB patients. During every routine visit, general and systemic examination was almost unchanged; there were no reporting of any harmful effect to the patient. Two patients reported pregnancy, positive. With the pre and post investigations, all 57 patients showed significant decrease in DUB symptoms like mid cycle

bleeding, late cycle bleeding and irregular periods with complete treatment of 3 months medication. Hence there is effective treatment for Dysfunctional Uterine Bleeding, proven to be as effective and safer alternatives to conventional drugs. The study indicates that Ovoutoline Forte tablet provides an effective and safer alternative for long term management since it improves symptoms score at the same time positive changes are observed radiographically.

## CONCLUSION

DUB symptoms like mid cycle bleeding, late cycle bleeding and irregular periods were taken care off. No sign of uterine fibroids were observed in upper abdominal USG.

## LIST OF ABBREVIATIONS

ZOFT: Zandu Ovoutoline Forte Tablet

DUB: Dysfunctional Uterine Bleeding

USG: Ultrasonography

Imp.: Improvement

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