The Egyptian Journal of Hospital Medicine (July 2018) Vol. 72 (2), Page 3979-3985

The Use of Levonorgestrel-Releasing System (Metraplant-E) in the Treatment of Abnormal Uterine Bleeding

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ABSTRACT

Background: Dysfunctional uterine bleeding (DUB) is one of the commonest condition for which patient seeks out medical consultation. The prevalence increases with the increase of age peaking before menopause.

Objective: The aim of this work is to evaluate the effect of this new form of levonorgestrel-releasing IUD on the treatment of patients with abnormal uterine bleeding.

Subjects and methods: A prospective age-specific comparative analysis of 61 peri-menopausal women presented with dysfunctional uterine bleeding who constituted the study group. They underwent hysteroscopy and endometrial sampling during an 18 months period from June 2014 to January 2016 at Ain Shams University Materity Hospital. Prior to metraplant-E application, all the patients in this study were in the age of 25-58 years old.

Results: The role of Metraplant-E in the treatment of abnormal uterine bleeding (AUB) was evaluated. Sixty-one women with failed attempt(s) of medical treatment unwilling or unfit for hysterectomy were treated with Metaplant-E. Menstrual blood loss was assessed by pictoral bleeding assessment chart (PBAC), bleeding index (B.I) and total bleeding score (T.B.S/month). The bleeding patterns in the form of the mean menstrual blood loss estimated by bleeding index and the mean menstrual loss estimated by the total bleeding score/month and PBAC decreased significantly ($p = 0.001$). The quality of life scale (Likert scale) improved significantly ($p = 0.001$). All 15 cases who had endometrial sampling demonstrated progestational effect on histo-pathological examination.

Conclusion: Metraplant-E was found to be effective in managing dysfunctional menorrhagia on both clinical and histopathological levels.

Keywords: Metraplant-E, LNG-IUS, Menorrhagia, Contraceptives

INTRODUCTION

Dysfunctional uterine bleeding (DUB) is one of the commonest condition for which patient seeks out medical consultation. The prevalence increases with the increase of age peaking before menopause. The peri-menopausal women who have anovulatory cycle resulting in DUB. The normal menstrual cycle is defined as having a mean interval of 28 ± 7 days with a men duration of 4 ± 3 days. The upper limit of normal menstruation is 80 ml per menstruation. Any deviation from the normal cycle and the amount of loss is regarded as abnormal uterine bleeding. Dysfunctional uterine bleeding (DUB) is one of the commonest causes of abnormal uterine bleeding. It is defined as heavy and/or irregular menstruation in the absence of detectable pelvic pathology, pregnancy or general bleeding disorder. It affects 20 to 30 % of women and accounts for 12 % of gynecological referrals. DUB can be ovulatory or anovulatory. Anovulatory DUB occurs at extreme reproductive age (adolescence and peri-menopausal age) [1].

Hyperplastic endometrium is abnormal histology finding found in DUB. DUB is more frequent in peri-menopausal age, multiparity and those patients who had undergone tubal ligation. Commonest normal histology of DUB is proliferative endometrium. One third of the patients had initial abnormal histology report which is found more in peri-menopausal age. Peri-menopausal age, irregular menstruation and hypertension are risk factors for hyperplasia. Therefore, it is mandatory to do endometrial sampling in cases of peri-menopausal age with irregular menstruation with or without hypertension [2].

Progesterone intra-uterine devices were originally introduced as contraceptives. However, the addition of levonorgestrel, which induces profound remodeling and differentiation of the oestradiol-primed endometrium, leads to decreased menstrual bleeding [3]. Its action (levonorgestrel) proved to be particularly useful in the treatment of the following conditions: dysmenorrhea associated with endometriosis [4, 5, 6], idiopathic menorrhagia [7,8,9,10,11], adenomyosis and anomalous bleeding [12,13,14,15]. Moreover, it has been proposed for use in the treatment of endometrial carcinoma or as an alternative to surgical treatment in women affected by menorrhagia [16].

Metraplant-E, which is a new levonorgestrel-releasing intra-uterine system used in this study is developed by Azzam in 2013. Metraplant-E design has a T-shaped frame containing levonorgestrel and ethinyl vinyl acetate (EVA) as well as barium sulphate to make it radio-opaque. The whole system is containing levonorgestrel, which is different from other forms of LNG-IUS like mirena or metraplant. It consists of Levonorgestrel hormone (60 mg), EVA (120 mg) and barium sulphate (20 mg) and 20 mg polyethylene. It is designed with a release rate of more than 20 µg/24 h, which allowed it to be used as a contraceptive for more than 5 years. The higher

Received:12/4/2018
Accepted:21/4/2018

initial release just post-application, up to 28 µg/24 has reported by in-vitro studies, may minimize post-insertion bleeding [17].

The most notable advantage for metraplant-E is the polymer that is made of EVA instead of polymethylsiloxane used in mirena and metraplant. EVA is remarkably biocompatible and have been used in the design of biomaterials and drug delivery systems. EVA statistical copolymers can be synthesized via free radical copolymerization. The materials employed for biomedical applications are usually predominately polyethylene (60% of total polymer) [18].

The aim of this work is to evaluate the effect of this new form of levonorgestrel-releasing IUD on the treatment of patients with abnormal uterine bleeding.

Subjects and methods

This was a phase two clinical trial with levonorgestrel-releasing intra-uterine device "Metraplant-E". A prospective age-specific comparative analysis of 61 peri-menopausal women presented with dysfunctional uterine bleeding who constituted the study group. They underwent hysteroscopy and endometrial sampling during an 18 months period from June 2014 to January 2016 at Ain Shams University Maternity Hospital. Prior to Metraplant-E application, all the patients in this study were in the age of 25-58 years old.

Hysteroscopy was done to exclude intra-cavitary gross pathology. All cases had no gross pathology seen by hysteroscopy except two patients who had one or more intra-mural myoma(s) diagnosed by ultrasound examination. Endometrial biopsy was obtained for each participant before application. The women were used as control for themselves.

Patient criteria: Women seeking contraception. Women with history of menorrhagia or metrorrhagia or dysmenorrhea. Pre and peri-menopausal women who are married or previously married. Failure of other medical treatment to control menorrhagia such as hemostatics. Women who did not tolerate copper IUD due to increased amount of menstrual blood loss which could lead to anemia. Women with dysfunctional menorrhagia and taking anticoagulants. Women with simple endometrial hyperplasia.

Pre-treatment evaluation: All women participating in the study were subjected to the following: Personal history. Obstetric history. Menstrual history (with assessment of blood loss). General examination. Thorough abdominal and pelvic examination. Ultrasound examination. Hysteroscopic examination. Endometrial biopsy.

Assessment of menstrual blood loss:

Three numerical systems were used: the bleeding index and bleeding score/month and the PBAC: Total bleeding score / month = summation of daily scores **[19] (**Score 0 No bleeding, Score 1 Spotting 1 pad/day, Score 2 Mild bleeding 2 pads/day, Score 3 Moderate bleeding 3-4 pads/day, Score 4 Severe bleeding 5-6 pads/day). In addition, the PBAC was used to assess the amount of blood loss. Likert scale for patient satisfaction. Pelvic ultrasound. Uterine size and dimensions. Endometrial thickness.Presence of foci of adenomyosis or fibroids. Ovarian size and presence of follicles or cysts. Hysteroscopic examination. Endometrial sampling for histopathology

Metraplant-E

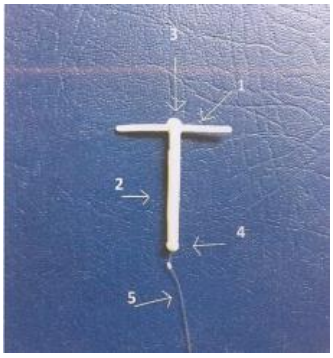

Fig. (1): Metraplant-E structure. 1. Shoulders: Diameter 1.4 mm. 2. Stem diameter: 2.8 mm. 3. Shoulder ball : 3 mm. 4. Tail Ball: 3 mm. 5. Double Naylon threads

1. Insertion of the Metraplant-E:

During any day of the menstrual cycle (range between day 5 – 62). Insertion was done by withdrawal technique exactly as copper T-380 insertion. This was done after informed written consent.

2. Follow up of the patients

The patients were seen after 3 to 29 weeks after Metraplant-E insertion. During the follow up period, the patients were submitted to the following re-evaluation tests:

Clinical history, general, gynecological examination with emphasis on:

1. Menstrual history
2. Side effects
3. Health benefits

Pelvic ultrasound was done in most cases immediately after insertion or during the first month post-insertion to ensure the correct positioning of the device. Unscheduled visits were allowed in case of development of any major side effect or severe bleeding. Four

patients were excluded for incompliance to follow up. The remaining 57 patients represented the study group.

Statistical analysis:

All statistical calculation were done using computer program SPSS (Statistical Package for the Special Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

RESULTS

In this study, women with intra-uterine gross pathology seen by hysteroscopy such as submucous fibroid (partly or totally submucous) were excluded from the study except for two cases where one of them was on antiplatelet therapy after cardiac stent insertion operation and the other with multiple small fibroids refused hysterectomy. However, ultrasonography detected nine cases of intramural, intramural to submucous or intramural to subserous myomatas where six of these cases could not be confirmed by hysteroscopy.

The mean age of participants was 43.11 ± 6.887 years old. The mean parity was 3.36 ± 1.317. The mean number of abortions was 0.56 ± 1.058. The mean duration elapsed since the last deliver/abortion was 10.16 ± 6.105 years.

The mean uterine length among the participants was 83.95 ± 14.797 mm. The mean transverse fundal diameter was 56.89 ± 10.182 mm.

The mean follow-up period was 116.03 ± 91.122 days.

The mean quality of life affection (Likert scale) at the end of the study (after metraplant-E insertion) was 4.93 ± 3.619.

Pre-insertion clinical findings table (1):

Sixteen women (26.23 %) showed endometrial polyps as by histo-pathological examination that were not visible on hysteroscopic examination. Two women had suspected adenomyosis by U.S. evaluation. (3.2 %) were on anticoagulant therapy and (4.92 %) had bleeding with copper T. Six patients had oligomenorrhea.

Pre-insertion Endometrial histo-pathology table (2) :

Endometrial polyps in 16 patients (26.23 %), proliferative endometrium in 15 patients (24.59 %), progesterone effect in 13 patients (21.31 %), chronic endometritis in 13 patients (21.31 %), hyperplastic endometrial polyp in 9 patients (14.57 %), secretory endometrium in 8 cases (13.11 %), disordered proliferative endometrium in 6 patients (9.84 %), simple endometrial hyperplasia in 4 cases (6.56 %) and simple cystic hyperplasia in 4 cases (6.56 %).

There was highly significant reduction of PBAC from 228.4 to 6.87 (p = 0.001). Bleeding index decreased significantly from 22.94 to 2.3 with p value of 0.001. Total bleeding score went from 28.97 to 2.33 with p value of 0.001. Quality of life scale increased from 9.1 to 4.93 with p value of 0.001 (table 3).

Side effects are mentioned in table (4). Breakthrough bleeding appeared in 21 cases, increased body weight in 1 case, increased vaginal discharge in 5 patients, lower backache in 17 cases and expulsion in 9 cases (14.75%).

Histopathology:

Histopathology before and after application of Metraplant-E are presented in fig. (2). Progestogen effect, early and late is presented showing endometrial glandular atrophy and decidualization. Early changes included secretory differentiation of endometrial glands " Pre-decidual changes" and decidual type of changes in the stroma and spiral arterioles (fig. 3).

Long term exposure to Metraplant-E demonstrated stromal decidualization which included: (a) atrophic glandular changes and hemorrhagic infarctions, (c) Surface microvilli, (d) Thin walled ectatic vessels (fig.4 & 5).

The impact of the hormone-releasing system Metraplant-E on endometrial pathology reported before its application is evident. Proliferative hyperplastic endometrium showed marked decidualization in the histopathology after Metraplant-E insertion.

Table (1): Pre-insertion clinical findings

Finding	Prevalence
Polyp in histo=pathological specimen of endometrium taken before "Metraplant-E" insertion (not seen hysteroscopically"	Sixteen women (26.23 %)
Suspected adenomyosis by ultra-sonographic pelvic scan	Two women (3.2 %)
Interstitial leiomyomatas on ultrasonographic pelvic scan	Six women (9.84 %)
Women on anticoagulant therapy	Three women (4.92 %)
Women who were using copper IUCD which was removed before Metraplant-E insertion	Three women (4.92 %)
Women with anovulatory cycles (cycle > 35 days long)	Six women (9.84 %)

Table (2): Pre-insertion endometrial histopathology

Endometrial biopsy	Number and percent
Endometrial polyp	Sixteen cases (26.23 %)
Proliferative endometrium	Fifteen cases (24.59 %)
Progesterone effect	Thirteen cases (21.31 %)
Chronic endometritis	Thirteen cases (21.31 %)
Hyperplastic endometrial polyp	Nine cases (14.57 %)
Secretory endometrium	Eight cases (13.11 %)
Disordered proliferative endometrium	Six cases (9.84 %)
Simple endometrial hyperplasia	Four cases (6.56 %)
Simple cystic hyperplasia	Four cases (6.56 %)

Table (3): Effect of metraplant-E insertion on the bleeding pattern and quality of life scale after 6 months of use:

	Before insertion	After insertion	P value
PBAC	228.44	6.87	0.001
Bleeding index (B.I)	22.94	2.3	0.001
Total Bleeding Score (T.B.S)	28.97	2.33	0.001
Quality of life scale (Likert scale)	9.1	4.93	0.001

Table (4): Side effects among Metraplant-E users

Side effects	Number of users affected	Percent	Comments
Breakthrough bleeding	21	34 %	Tolerated
Increased body weight	1	1.64 %	Tolerated
Increased vaginal discharge	5	8.2 %	Tolerated
Lower backache	17	35.4 %	Mild
Expulsion	9	14.75 %	High risk patients

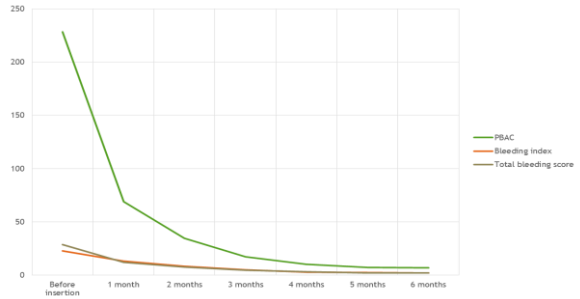

Fig. (2): Graph representing the decrease in the amount of blood loss among the women included in the study after Metraplant-E insertion throughout 6 months (assessment of blood loss was done by

3 methods: 2 numerical (bleeding index and total bleeding score) and 1 chart (PBAC)

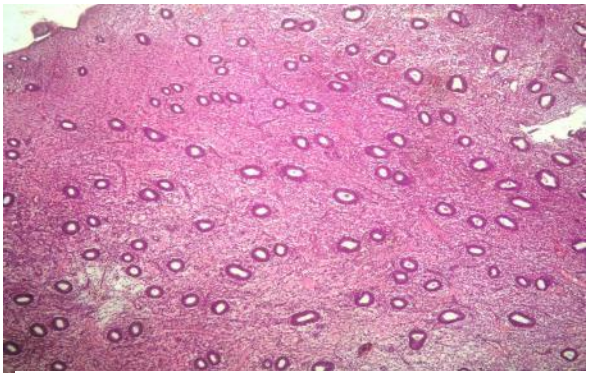

Fig. (3): Histopathology slide representing proliferative endometrium (40 H.P.F) obtained in endometrial sampling prior to Metraplant-E insertion showing non-branching, non-budding, similarly shaped glands evenly distributed throughout the stroma. The stroma is monomorphos and undifferentiated. Uniformly thin-walled blood vessels present.

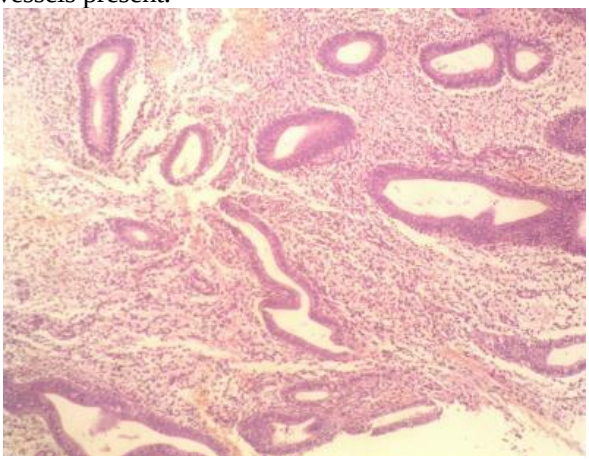

Fig. (4): Histopathology slide representing simple endometrial hyperplasia without atypia obtained in endometrial sampling prior to metraplant-E insertion showing glandular enlargement of proliferative glands and budding.

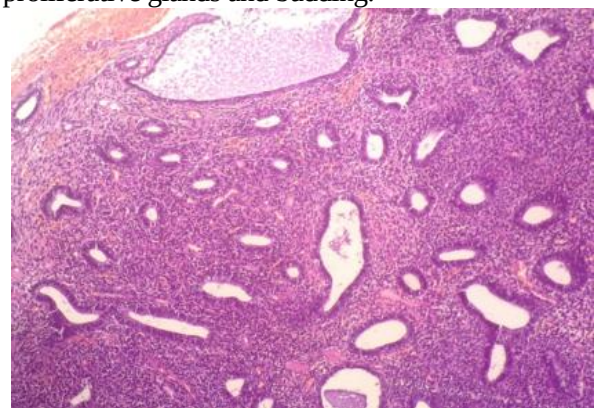

Fig. (5): Histopathology slide representing simple endometrial hyperplasia without atypia (100 H.P.F) obtained in endometrial sampling prior to metraplant-E insertion showing glandular enlargement, cystically dilated glands and abundant cellular stroma.

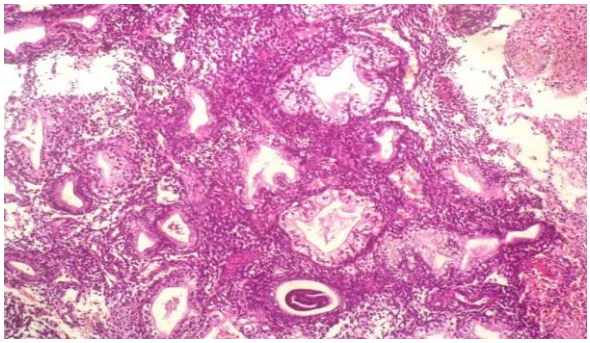

Fig. (6): Histopathology slide representing short term exposure to levonorgestrel-releasing intra-uterine device (metraplant-E) (40 H.P.F) obtained in endometrial sampling after metraplant-E insertion showing classic changes of normal secretory endometrium: secretory differentiation of endometrial glands (pre-decidual changes) and decidual type changes in the stroma and spiral arterioles.

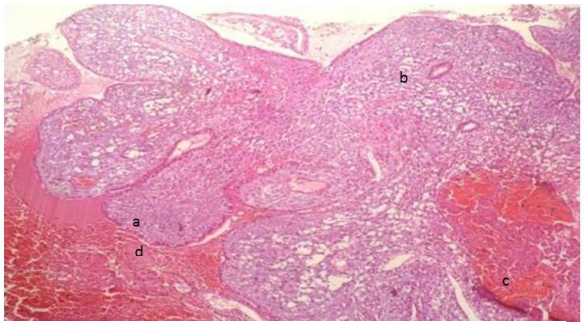

Figure (7): Histopathology slide representing long term exposure to metraplant-E (100 H.P.F) showing stromal decidualization (a), atrophic changes(b), haemorrhagic infarction (c) and surface micropapillae (d).

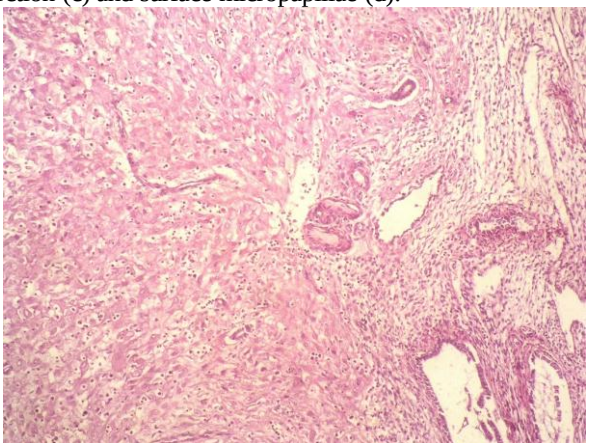

Figure (8): Histopathology slide representing long term exposure to metraplant-E showing stromal decidualization, inactive endometrial glands (atrophic) and lymphocytic infiltration.

DISCUSSION

The therapeutic value of LNG-IUS is documented. Metraplant-E, a levonorgestrel-releasing IUD with EVA as a polymer is used in this study for the treatment of AUB in 57 women with heavy bleeding with different pathological problems including endometrial polyps, adenomyosis, fibroid uterus, hyperplastic endometrium and proliferative endometrium. These patients failed to respond to other forms of treatment. Metraplant-E is proved in the present study to be very effective as a therapeutic tool for this group of relatively high risk women. This is reflected in marked improvement of PBAC chart, bleeding score and bleeding index (table 3) (fig. 2). Results are highly significant p = 0.000. This is comparable to other studies performed on other levonorgestrel-releasing IUDs like Mirena [5,6,7,8], Fibroplant [22] and Metraplant [17].

Also, the improvement of quality of life scale is documented in the present study (table 4). This is also comparable to other studies performed on other forms of LNG IUD.

The in-vitro release of levonorgestrel from Metraplant-E is previously studied in Azzam et al. [9] and is comparable to other reports.

In Metraplant-E, ethylenevinyl acetate (EVA) is used instead of polymethylsilixane polymer in the manufacture of this device. EVA has many advantages. Metraplant-E is manufactured with expected lower price.

The therapeutic effect of Metraplant-E on the endometrium is manifested by the histo-pathological findings of endometrial tissue collected after the use of Metraplant-E (fig. 6).

Histo-pathological changes after Metraplant-E insertion were observed as early as three weeks post-insertion, mainly in the form of decidualization ranging from partly decidualized stroma to decidual cast.

Post-insertion endometrial biopsy was taken within a range between three up to twenty-nine weeks after Metraplant-E insertion.

The levonorgestrel-releasing intra-uterine system (LNG-IUS) produces atrophy of the glandular epithelium, prominent decidualization of the stroma and suppression of the spiral artery formation as well as large, thin-walled, dilated vessels. The large surface area of Metraplant-E compared to Mirena and Metraplant would guarantee wider distribution of the hormone into the endometrial surface.

Evaluation of the endometrium of peri-menopausal women with abnormal uterine bleeding revealed various patterns on histo-pathology and functional causes accounted for the majority of the diagnosis. The most common histology in dysfunctional uterine bleeding is proliferative and hyperplastic endometrium (fig. 3, 4, 5) [2]. Endometritis was a significant pathological diagnosis in the study by (Jetley et al., 2013) [21] and diagnosed in 20 cases (9.1 %). Non-specific chronic endometritis as an aetiology of atypical uterine bleeding in peri-menopausal women, has been reported by Khare et al. to be affecting 6.4 % of their study group [21].

Some of the factors that could have possibly increased the incidence of expulsion might include problematic patients with severe dysfunctional uterine bleeding, pre-insertion manipulation e.g. hysteroscopy and associated endometrial pathology [23, 24].

The rate of expulsion with LNG-IUS is significantly higher in women with adenomyosis 9.1-11.1 % and uterine leiomyomata 14.5 – 15.8 % compared to 3.6 – 4.6 % in normal uterus (p = 0.008) [24].

Metraplant-E is recently used to replace copper-T 380 A, for women who were suffering from AUB and pain. Bleeding, pain, anemia and patient satisfaction improved significantly in the greatest majority of cases. Expulsion, incomplete and complete occurred only in 3 cases (5.1 %) [25].

CONCLUSION

Metraplant-E is effective as a therapeutic tool in dysfunctional uterine bleeding. In the majority of cases, the amount of blood loss significantly reduced, endometrial changes documents the marked progesterone effect. Expulsion rate is relatively high probably due to selection of high risk patients.

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