THE NEW ARMENIAN MEDICAL JOURNAL
Vol.16 (2022), Issue 3 p.86-90

DOI: https://doi.org/10.56936/18290825-2022.16.3-86

COMBINED ADMINISTRATION OF DIENOGEST AND LEVONORGESTREL – RELEASING INTRAUTERINE SYSTEM MIRENA

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Received 23.05.2022; accepted for printing 18.08.2022

ABSTRACT

***Objectives**: Intrauterine hormone-releasing systems are now widely applied to treat metrorrhagia (polymenorrhea), endometrial hyperplasia and adenomyosis.*

In previous works we found that risk factors for expulsion of intrauterine device, besides the deformation of the uterine cavity, was the expansion of uterine cavity area > 9 cm^2, associated with increased distance between tubal angles >4.5 cm and after the insertion of Levonorgestrel-releasing Intrauterine System (Mirena), among the patients with indicated parameters of uterine cavity, the expulsion reached 90%. Another widely used medicine for treatment of metrorrhagia (polymenorrhea), endometrial hyperplasia and adenomyosis is dienogest (Vizanna). The objective of this study is to explore the influence of combined administration of dienogest and Levonorgestrel- releasing Intrauterine System with the purpose of prevention of complications and side effects of the Intrauterine System.

***Study design**: This prospective study includes 32 patients with previous Levonorgestrel-releasing Intrauterine System expultions whom Dienogest 2mg daily has been administered within 6 months.*

***Results:** Ultrasound transformation of a myometrium and uterine cavity in 6 months after Vizanna administration was manifested by minimization of uterine cavity and reduction of distance between tubal angles. Mirena was inserted to these patients again.*

Within 12 months of monitoring any case of expulsion was not observed.

***Conclusions:** According to the data received, the combined consistent and simultaneous administration of Dienogest and Mirena reduces the possibility of Intrauterine System expulsion and decreases side effects of the Intrauterine System.*

***Implication statement:** Combined consistent and simultaneous administration of Dienogest and Levonorgestrel-releasing Intrauterine System was used for prevention of complications of Intrauterine System*

***KEYWORDS:** levonorgestrel- releasing Intrauterine system, mirena, dienogest, vizanna, adenomyosis,i ntrauterine system expulsion*

INTRODUCTION

Over the last two decades indications for therapeutic administration of Levonorgestrel- releasing Intrauterine System (LNG-IUS) "Mirena".

Currently it is generally acknowledged that intrauterine hormone-releasing system Mirena, proposed initially as a contraceptive, has additional benefits that make it a preferred choice for management of a number of other gynecologic conditions at the same time, particularly, it became widely used with the purpose of treatment of chronic pelvis pain,

CITE THIS ARTICLE AS:
Tokhunts KA, Khudaverdyan AD, Abgaryan NB, Nahapetyan NA, Manvelyan VL (2022), Combined administration of Dienogest and Levonorgestrel – Releasing Intrauterine System Mirena, The New Armenian Medical Journal, vol.16, issue 3, p.86-90, https://doi.org/10.56936/18290825-2022.16.3-86

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metrorrhagia, dysmenorrhea, endometrial hyperplasia and adenomyosis and for estrogen replacement therapy to protect endometrium [*Hidalgo M et al., 2002; Beatty M, Blumenthal P, 2009; Sheng J et al., 2009; Speroff L, Darney P, 2011; Tariq N et al., 2011; Chen Y et al., 2015*].

Alike to cases of other intrauterine contraceptives , at application of «Mirena» complications, occurring at the moment of insertion, in the process of carriage and deferred – after extraction of the Intrauterine Device, are possible. The most frequent complications of Intrauterine Device application are expulsion, penetration of Intrauterine Device parts [*Merki-Feld G et al., 2008; Kung F, 2011; Bahamondes M et al., 2011; Youm J et al., 2014*].

According to data of certain authors, the expulsion rate is *4* per cent and is most common in the first year after insertion. Risk factors include young age, nulliparity and immediately postpartum. The rate of expulsion is not related to the uterine cavity length [*Bahamondes M et al., 2011*].

In study of G.S. Merki-Feld et *co-authors*, frequency of Levonorgestrel- releasing Intrauterine System expulsion made *2.9–6.5%* [*Merki-Feld G et al., 2008*]. *Kung F, 2011* states up to *29%* of Levonorgestrel-releasing Intrauterine System expulsion in women with different gynecological pathologies (predominantly with uterine myomas of different size and locality, including those with submucous nodes) and up to *15%* in absence of such [*Kung F, 2011*].

High frequency of expulsions in our patients, commensurate with data of *Kung F (2011)*, probably, can be explained by presence of gynecological pathologies in such women, whereas the data, provided in literature relates to «Mirena» expulsion at introduction in healthy women with the purpose of contraception [*Hidalgo M et al., 2002; Beatty M, Blumenthal P, 2009; Zapata L et al., 2010; Kung F, 2011*]. Just like in *Kung F*, 2011 study, in considerable majority of our patients with expulsion *(87%)* hyperpolymenorrhea was observed.

In recent years, in connection to introduction of 3D ultrasound into clinical practice, there came up studies, dedicated to identification of the Intrauterine System expulsion risk factors [*Benacerraf B et al., 2009; Gemzell-Danielsson K et al., 2011*]. In previous works [*Tokhunts K, Hovsepyan L, 2016*] we have established that expulsion risk factors, apart from deformation of uterine cavity, are expansion of uterine cavity virtual area *>9 cm*^{2} and distance between tubal angles *>4.5 cm*, associated with severe adenomyosis. In the meantime, due to the necessity to maintain the reproductive function in such patients the method of choice is long-term contraceptive therapy and in this regard application of Mirena in this cohort is preferable.

Another widely used preparation for treatment of adenomyosis is Dienogest (Vizanna, Bayer AG). Transformation of ultrasound characteristics of myometrium at application of Dienogest with the purpose of adenomyosis treatment, which is manifested, among other things, through significant reduction of thickness of myometrium-endometrium junctional zone and the area of uterine cavity, prompted us the idea to study the influence of Dienogest over ultrasound characteristics of the uterine cavity in patients with previous expulsions of Levonorgestrel- releasing Intrauterine System in case of prescribing administration of Dienogest with the purpose of treatment of adenomyosis.

The goal of this study was to examine the change of sizes of virtual uterine cavity at administration of Dienogest for adenomyosis treatment in patients with previous expulsions of Levonorgestrel- releasing Intrauterine System and to determine the possibility of efficient recurrent insertion of Levonorgestrel- releasing Intrauterine System.

Materials and methods

We conducted concurrent cohort study that included *48 women*, who referred to the department of obstetrics and oynecology, YSMU (Armenia) and "AVAK" medical centre (Armenia) in 2015-2016 after expulsion of Levonorgestrel- releasing Intrauterine System, which occurred within different periods of time after its insertion (*1 to 12 months*) for further observation and treatment.

All these patients were offered conservative treatment of adenomyosis with Dienogest *2mg* daily with the purpose of pain management, reduction of blood loss in periods

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

and dyspareunia during *6 months*. All these women upon referring to us underwent 3D ultrasound of uterine with reconstruction of cavity in coronary section by two independent experts. The ultrasound examination was carried out with ultrasound scanners Voluson E8 and Voluson 730 Expert (GE Healthcare, USA) by transvaginal 3 D curved transducer with frequency of *5–9 MHz* in two- and three-dimension modes [*Benacerraf BR et al., 2009*].

Further same measurements were carried out after *3* and *6* months after taking Dienogest by same methodology. Adenomyosis was diagnosed accordingly to the MUSA statement [*Van den Bosch T. et al.*, 201]. The measurement of distance between tubal angles of virtual uterine cavity and automated measurement of the cavity area were carried out at each 3D ultrasound (VCI plane) [(*Benacerraf BR et al.,, 2009*]. Similar measurements were also carried out in 20 healthy women-carriers of intrauterine system without signs of its dystopia and having no expulsion history.

Statistical processing of research data was carried out by standard methods. Data was represented in the form of M ± SD, minimal and maximal values were presented. Significance of difference was accessed with application of parametrical Student t-test. Difference between mean values was considered to be true at $p<0.05$.

Mean age of women at insertion of Intrauterine System was *37.0 ± 5.9(28 – 48)*. Preceding caesarean section had *9 (28.1%,* other operative interventions on uterus *5 (15.6%)*. Associated menometrorrhagias before insertion of Intrauterine System had*14 (43.8%)* patients, adenomyosis – *17 (53.1%)*, associated recurring hyperplasia of endometrium - *1 (3.1%)*. Bleeding associated with Intrauterine System insertion had *26 (81.3%)*women.

At analysis of ultrasonic images *16* patients with expulsion showed deformations of virtual uterine cavity, conditioned by local thickening of myometrium due to adenomyotic transformations. These patients were excluded from the study due to their high risk of reexpulsion. The study was continued in *32* patients with severe adenomyosis and associated menometrorrhagias and recurring endometrial hyperplasia (*15* of them) with Intrauterine System expulsions without uterine cavity deformations.

After 6 months of taking Dienogest *10* women left the study for different reasons: *4* – due to change of place of residence, *3* – due to being satisfied with treatment redults and refusal from recurrent insertion of Mirena and *3* – due to insignificant reduction of ultrasound parameters of uterine cavity (intertubular distance – by *10%* and cavity area – by *16%*, keeping to increase threshold values, set by us) in which regard we found recurrent insertion of the intrauterine system to be inexpedient.

RESULTS

At examination of sonographic parameters of uterine cavity of same parents in accordance with the methodology stated above, all these patients showed extension of distance between tubal angles *> 4.5 cm* (at average *4.97±0.38 cm*) and cavity area *> 9 cm*^{2} (at average *12.33±1.82 cm*^{2}) which, in our opinion was the cause of Intrauterine System expulsion [*Tokhunts K, Hovsepyan L, 2016*]. After *6* months of Dienogest administration in *92% (23 of 25*) of patients significant weakening of sensation of pain was recorded, *68.8% (22 of 32)* developed amenorrhea and *31.2% (10*) recorded significant reduction of menstrual blood loss, and the volume and duration of menstrual bleeding gradually reduced (*2.6±0.8* days) already starting from the first month of Dienogest administration. By the end of *6*th month of medication administration the duration of menstruation-like hemorrhage was *1.6±0.5* in the average.

Ultrasound transformation of myometrium and uterine cavity parameters before taking Visanne and 6 months after treatment in *22 (68.8%)* patients was manifested by reduction of uterine cavity area in the average from *11.67±1.48* cm^2 down to *7.98±0.63* cm^2 ($p<0.001$) (Fig. 1a) and reduction of distance between tubal angles at the average from *4.80±0.19* cm^2 down to *4.07±0.12 cm* ($p<0.001$) (Fig.1b).

Due to the reduction of these sizes below the thresholds established by us earlier (Fig. 2a), which are risk factors for Intrauterine System expulsion (Fig. 2b) [*Tokhunts K, Hovsepyan L, 2016*], Mirena was reintroduced with their consent, following the instructions for Intrauterine System insertion, followed by ultrasound monitoring (every *3, 6* and *12* months after insertion of Intrauterine System . During this period there were no cases of Mirena expulsion.

It is notable that in the past *81.3 % (26 of 32*) of these women recorded spotting of different in-

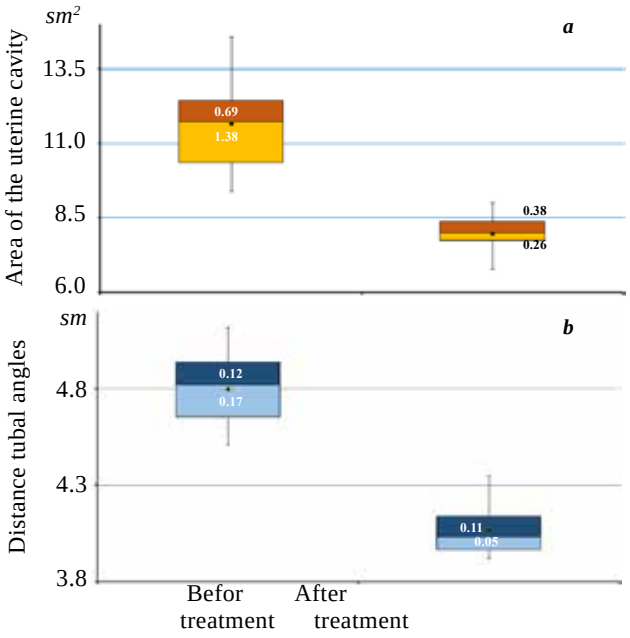

Figure 1. *Diagram of range of values for virtual area of the uterine cavity (a) and distance between tubal angles (b) before and after Dienogest administration.*

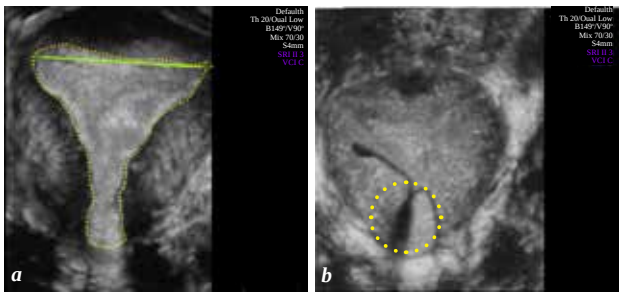

Figure 2. *Adenomyosis. a) Distance between tubal angles of uterine cavity (solid line) 4.65 cm, cavity area (dashed line) 10.95 cm2, b) Intrauterine System expulsion. Helix offset position (dotted circle)*

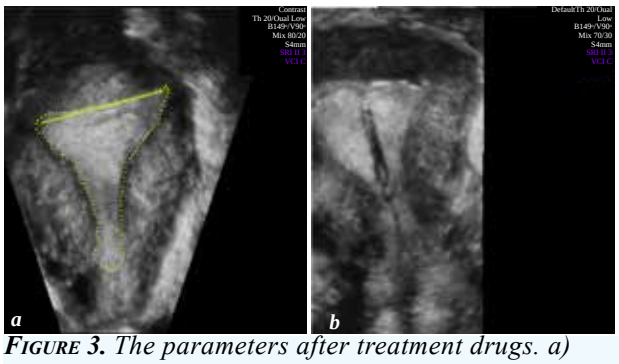

Figure 3. *The parameters after treatment drugs. a) Cavity of the same uterine after 6 months of Vizanna administration. Distance between tubal angles (frim line)3.9 cm, cavity area (dotted line 6.78 cm². b) correct positioning of Mirena in the cavity of the same uterine 1 year after insertion.*

tensity during *3-6* months after insertion of Mirena, whereas preceding administration of Dienogest *68,2% (15 of 22*) of these women had no such complaints.

In *31.8% (7 of 22*) patients after insertion of Intrauterine System spotting of different degree of intensity started again. These patients resumed administration of Dienogest with same dose for *3* more months. Already after *15-20* days of preparation administration spotting stopped and did not resume after its withdrawal, which is yet another benefit of combined administration of Dienogest and Levonorgestrel- releasing Intrauterine System Mirena.

The parameters after treatment of patients, cavity area (6.78 *cm²*) and Distance between tubal angles (3.9 *cm*), as well as the echographic image with the correct location of the intrauterine system in the uterine cavity and with its expulsion and dystopia are shown in (Fig. 3a and Fig. 3b).

After treatment with dienogest and levonorgestrel, during the observation period of several months, inflammatory diseases of the uterus and appendages were not observed.

Conclusion

According to obtained data, as a result of combined successive *(22 patients*) and simultaneous *(7 patients*) administration of Dienogest and Mirena in patients with a decrease in ultrasound parameters of the uterine cavity (distance between tubal angles and cavity area) after the use of Dienogest to the established threshold values for the risk of intrauterine system expulsion and the subsequent introduction of Mirena during the entire observation period, no intrauterine system expulsion and dystopia occurred. In fact, on condition that the size of the virtual uterine cavity is reduced (intertubular distance *<4.5* cm and cavity area, *9.0 cm²*), the effectiveness of re-insertion of the Intrauterine System in the patients studied by us was *100%*.

The obtained results allow recommending, before the introduction of Mirena for the treatment of adenomyosis, accompanied by an increase in the virtual cavity of the uterus, to prescribe Visanna for at least 6 months. The same tactics, in our opinion, should be followed when choosing to reintroduce the Intrauterine System in cases of previously occurring Intrauterine System expulsions associated with an increase in the virtual uterine cavity in absence of its deformation.

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THE NEW ARMENIAN MEDICAL JOURNAL

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The Journal is founded by
Yerevan State Medical
University after M. Heratsi.

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Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS EBSCO THOMSON REUTERS

Copy editor: Tatevik R. Movsisyan

Printed in "VARM" LLC
Director: Ruzanna Arakelyan
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