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GENERAL GYNECOLOGY: ORIGINAL ARTICLE

Levonorgestrel-Releasing Intrauterine Device Use Can Be a Treatment Option in Symptomatic Patients with Isthmocele

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Abstract

Levonorgestrel-releasing intrauterine devices have been used for contraception and treatment of heavy menstrual bleeding. There is only limited data about the effect of this on isthmocele. Here, we aimed to evaluate the effect of levonorgestrel-releasing intrauterine devices in a larger study population with a longer follow-up as compared to the literature on symptomatic patients with isthmocele. A total of 29 patients with symptomatic isthmocele and inserted levonorgestrel-releasing device were included in this prospective study. All patients were included at January 2020 and followed for 18 months. Sociodemographic findings, laboratory parameters, premenstrual spotting, postmenstrual spotting, menorrhagia, dysmenorrhea, and pelvic pain related to isthmocele were recorded. In sonography, width, length, area of isthmocele, and residual myometrial thickness were determined. The frequency of symptoms during follow-up was compared between visits and also compared between groups according to residual myometrial thickness. Premenstrual spotting and pelvic pain were significantly reduced at 6th months (48.3 to 10.3%, $p=0.007$ and 34.5 to 10.3%, $p=0.039$, respectively) and no significant change was detected until the end of follow-up period. Postmenstrual spotting reduced at 6th months (96.6 to 34.5%, $p<0.001$) and also significant change was detected between 6 and 12th months (34.5% vs 13.8%, $p=0.031$). Menorrhagia and dysmenorrhea disappeared at 12th months. No association was found between residual myometrial thickness and the frequency of symptoms for each follow-up. Levonorgestrel-releasing intrauterine devices are useful and reliable therapeutic tools for symptomatic isthmocele patients who do not desire fertility, regardless of residual myometrial thickness.

Keywords Cesarean scar · Isthmocele · Levonorgestrel-releasing intrauterine device · Niche · Treatment

Introduction

Isthmocele, a defect secondary to a previous cesarean section, is an acquired outward diverticulum-like enlargement and thinning of myometrium in cesarean section incision line in a non-pregnant woman [1]. Although there is not a definite diagnostic criteria, it is typically seen as a hypoechoic area in the anterior isthmus of the uterus on ultrasonography [2]. The most common complaints of patients with isthmocele are intermenstrual bleeding (premenstrual spotting, postmenstrual spotting), heavy menstrual bleeding, dysmenorrhea, pelvic pain, and secondary infertility [3, 4]. Accumulation of menstrual blood in noncontractile fibrotic pouch and its inability to be expelled properly is thought to be the cause of postmenstrual spotting, pain, and dysmenorrhea [5]. However, the prevalence of isthmocele is unknown; it nearly exists in 60% of patients after first cesarean section and nearly in all cases after the third cesarean section [6]. Combined estrogen and progesterone therapy and hysteroscopic or laparoscopic repair of isthmocele are main treatment options but the effects of them are still unclear [7]. In the literature, hysteroscopic repair is recommended for cases who have ≥ 3-mm myometrial thickness above the isthmocele and laparoscopic repair if it is less than 3 mm for surgical approach [8, 9]. Hormonal treatment is shown

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to reduce postmenstrual spotting and pelvic pain for the patients who do not desire fertility [5].

Levonorgestrel-releasing intrauterine devices (LNG-IUD) have been used primarily as a method of contraception, but it has become a frequently used treatment modality in heavy menstrual bleeding because it causes thinning of the endometrium and stromal atrophy [10]. There is only limited data about the effect of LNG-IUD on isthmocele. The maximum follow-up period is short and the maximum number of patients is too small in previous studies [4, 11]. Here, we aimed to evaluate the effect of LNG-IUD in a larger study population with a longer follow-up on symptomatic isthmocele patients.

Material and Methods

This prospective study was conducted between the dates of January 2020 and June 2021 at a university-affiliated training and research hospital. It was approved by the institutional review board and ethics committee (approvalnumber:11.12.2019/159) and it complies with the declaration of Helsinki. All participants were informed about the study and written informed consent was taken from all the participants.

In power analysis, the minimum number of patients to be included in the study was found to be 10 with 80% power, 30% difference, and alfa value of 0.05.

Symptoms, followed up in this study, related to the isthmocele were premenstrual spotting, postmenstrual spotting, menorrhagia, postcoital spotting, dysmenorrhea, and pelvic pain. The inclusion criteria were composed of having isthmocele diagnosed by ultrasonography and having symptoms related to isthmocele, having had the last delivery by cesarean section and no expectation of fertility, and being a volunteer for LNG-IUD. After routine gynecological examination, sonography was performed by the same resident (F.K.G) who has 5 years of experience in this field. After confirming the diagnosis of symptomatic istmocele, LNG-IUD (levonorgestrel20 µg/24 h) was applied by the same researcher.

The exclusion criteria were composed of history of previous pelvic infection, presence of endometrial hyperplasia and/or endometrial polyp, having leiomyoma or adenomyosis, presence of pregnancy, history of any kind of cancer, having an ovarian mass or cyst, presence of thyroid disease or hyperprolactinemia, and history of bleeding disorders. Enlarged uterus (greater than 12 weeks of gestation), asymmetric thickness of anterior or posterior wall, heterogeneous echogenicity of the myometrium, and irregular junctional zone under ultrasound were diagnostic criteria for adenomyosis in sonography for exclusion of adenomyosis cases. After the selection was made according to inclusion and exclusion criteria, a total of 33 patients were included in the study. Four of the patients were dropped out because 2 of them decided to get pregnancy, one of them developed 6-cm ovarian cyst, and cervical displacement of IUD was seen in one patient on ultrasonography on 6th month visit. A total of 29 patients completed the follow-up period. All patients were included in January 2020 and followed during 18-month period.

Characteristics of patients such as age, gravida, parity, number of abortion and curettage, weight, height, waist circumference (WC), hip circumference (HC), history of vaginal delivery, comorbid disease, time after cesarean section, number of previous cesarean section, and symptoms related to isthmocele such as premenstrual spotting, postmenstrual spotting, menorrhagia, dysmenorrhea, and pelvic pain were recorded. BMI was calculated as dividing weight to square of height. Blood samples are taken from antecubital vein with a vacutainer system while the patient was in a sitting position. Laboratory parameters such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin, and thyroid-stimulating hormone (TSH) measured by Uni CelDxI 800 chemistry system (Beckman Coulter, Fullerton, CA, USA) were recorded. References values for FSH, LH, E2, prolactin, and TSH were 3.5–12.5 U/L, 14.0–95.6 U/L, 30.9–90.4 ng/L, 4.79–23.3 µg/L, and 0.27–4.2 mU/L respectively. The position of uterus (antervertio, retrovertio), width of isthmocele, length of isthmocele, area of isthmocele, length of uterus, width of uterus, and myometrial thickness on isthmocele were determined and measured while the patient was in the lithotomy position using vaginal probe. Width of the isthmocele was calculated by measuring the length in mm started from the inner surface of the thinnest myometrium to the projection of the healthy myometrium, and length of isthmocele was calculated by measuring the length in mm started from the inner surfaces of mutual healthy myometrium edges. Area of isthmocele was calculated by multiplying the width and the length in mm [2]. Length of uterus was measured starting from the serosa of the fundus to the outermost edge of the cervix. Width of uterus was measured from the serosal surfaces of the largest diameter of the corpus and myometrial thickness on isthmocele was defined the length of the thinnest myometrial tissue from serosa to the endometrial surface corresponding to the kerr incision in mm. For sonographic examination, Mindray M6 ultrasound and 5.0 MHz vaginal probes were used. Three appointments were made in the first examination and the patients were examined and evaluated with ultrasound for any IUD displacement in all visits. In the official notice of LNG IUD (Mirena), it is mentioned that spotting and irregular or heavy bleeding may occur during the first 3 to 6 months [12]. We assessed all kind of light vaginal bleeding after menstruation period as postmenstrual spotting. Irregular heavy bleeding was assessed as menorrhagia. The presence of premenstrual

spotting, postmenstrual spotting, menorrhagia, dysmenorrhea, and pelvic pain recorded in the first visit were followed with 6-month interval for 18 months and the change in the symptoms was compared between visits. The patients were divided into two groups according to the residual myometrial thickness as first group has < 3 mm and second group has ≥ 3-mm thickness on the istmocele because 3 mm is a threshold value in the literature that changes the surgical treatment modalities [8, 9]. The frequency of symptoms was compared between two groups.

Statistical analysis was performed by using SPSS Version 21.0. (IBM Corp. Released2012. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.) software. Shapiro–Wilk test was used to determine whether the variables were distributed normally or not. Demographic continuous variables distributed normally were expressed as mean ± standard deviation; not distributed normally as median (minimum–maximum) and categorical variables as frequency and percentages. Chi-square or Fisher exact test was used to assess the relationship between residual myometrial thickness and symptoms. Moreover, Mc Nemar test was used to evaluate the change of symptoms between periods of times. The level of significance was set at $\alpha = 0.05$.

Results

Demographic characteristics of study participants are shown in Table 1. The median age was 40 years (28–46), parity was 3 (1–4), and number of previous cesarean section was 1 (1–4). The ultrasonographic evaluation results of patients are demonstrated in Table 2 and the hormonal status of the patients is shown in Table 3. No patients had abnormality related to FSH, LH, estradiol, prolactine, and TSH levels.

Table 1 Demographic characteristics of study participants

	(*n* = 29)
Age (years)	40 (28–46)
Gravida (*n*)	3 (1–5)
Parity (*n*)	3 (1–4)
Abortion (*n*)	0 (0–1)
Curettage (*n*)	0 (0–1)
Height (cm)	158.72 ± 5.81
Weight (cm)	70.48 ± 11.88
BMI (kg/m.^{2})	28.18 ± 5.49
Waist circumference (cm)	83.14 ± 12.42
Hip circumference (cm)	110 (90–187)
Hx of vaginal delivery (*n*, %)	6 (20.7%)
Comorbid disease (*n*, %)	13 (44.8%)
Time after cesarean section (month)	21 (16–72)
Number of previous cesarean section (*n*)	1 (1–4)

Table 2 Ultrasonographic findings of patients

	(*n* = 29)
Position of uterus (*n*, %)	
- Antevertio	25 (86.2%)
- Retrovertio	4 (13.8%)
Width of isthmosle (cm)	6.71 ± 2.46
Length of isthmocele (cm)	7.1 (3.8–22)
Area of isthmocele (cm.^{2})	40.96 (15.9–220)
Length of uterus (cm)	82.93 ± 8.46
Width of uterus (cm)	39 (26–65)
Myometrial thickness on isthmocele (cm)	3.64 ± 1.18

The distribution of symptoms related to isthmocele at 0th, 6th, 12th, and 18th months is presented in Table 4. Frequency of premenstrual spotting was 48.3% initially and it decreased to 3.4% at 12th month. The change in frequency of premenstrual spotting was statistically significant between 0 and 6th months and after ($p_{0-6} = 0.007$, $p_{0-12} = 0.001$, and $p_{0-18} = 0.001$), but no significant difference was detected between 6th and12th months and also 12th and 18th months ($p_{6-12} = 0.500$, $p_{12-18} = 1.00$).

The frequency of postmenstrual spotting was decreased from 96.6 to 13.8% at 12th month and to 10.3% at 18th month. Statistically significant alteration in the frequency of postmenstrual spotting was achieved at 6th ($p < 0.001$) months and this improvement was sustained at 12th ($p < 0.001$) and 18th ($p < 0.001$) months. The changement between 6 and 12th months was statistically significant ($p = 0.031$) while it was not between 12 and 18th months ($p = 1.00$).

Significant decrement in the frequency of menorrhagia ($p < 0.001$) and dysmenorrhea ($p < 0.001$) was achieved at 6th month of LNG-IUD insertion and they disappeared at 12th month. The postcoital spotting disappeared at 18th month in all patients.

Lastly, the frequency of pelvic pain was 34.5% at the first visit and decreased to 10.3% in 6th month ($p = 0.039$) and did not alter until the follow-up period ($p_{6-12} = 1.000$, $p_{12-18} = 1.00$). There was no statistically significant change in the frequency of postcoital spotting between the follow-ups.

Table 3 Hormone profile of patients

FSH	8.05 ± 2.75
LH	5.13 (3.17–13.6)
Estradiol	56.24 (12–481.5)
Prolactin	9.39 ± 3.07
TSH	1.45 (0.49–7.45)

Abbreviations: *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *TSH* thyroid-stimulating hormone

Table 4 The distribution of symptoms at 0th, 6th, 12th, and18th months

	(*n* = 29)
Premenstrual spotting 0 month (*n*, %)	14 (48.3%)
Premenstrual spotting 6 months (*n*, %)	3 (10.3%)
Premenstrual spotting 12 months (*n*, %)	1 (3.4%)
Premenstrual spotting 18 months (*n*, %)	1 (3.4%)
Postmenstrual spotting 0 month (*n*, %)	28 (96.6%)
Postmenstrual spotting 6 months (*n*, %)	10 (34.5%)
Postmenstrual spotting 12 months (*n*, %)	4 (13.8%)
Postmenstrual spotting 18 months (*n*, %)	3 (10.3%)
Menorrhagia 0 month (*n*, %)	23 (79.3%)
Menorrhagia 6 months (*n*, %)	2 (6.8%)
Menorrhagia 12 months (*n*, %)	0 (0%)
Menorrhagia 18 months (*n*, %)	0 (0%)
Postcoital spotting 0 month (*n*, %)	7 (24.1%)
Postcoital spotting 6 months (*n*, %)	1 (3.4%)
Postcoital spotting 12 months (*n*, %)	1 (3.4%)
Postcoital spotting 18 months (*n*, %)	0 (0%)
Dysmenorrhea 0 month (*n*, %)	18 (62.1%)
Dysmenorrhea 6 months (*n*, %)	2 (6.8%)
Dysmenorrhea 12 months (*n*, %)	0 (0%)
Dysmenorrhea 18 months (*n*, %)	0 (0%)
Pelvic pain 0 month (*n*, %)	10 (34.5%)
Pelvic pain 6 months (*n*, %)	3 (10.3%)
Pelvic pain 12 months (*n*, %)	3 (10.3%)
Pelvic pain 18 months (*n*, %)	3 (10.3%)

At the end of the study, 34.5% of the patients were amenorrheic and others were still having menstruation.

The distribution of symptoms for residual myometrial thickness groups are shown in Table 5. According to the comparison of the frequency of symptoms between residual myometrial thickness groups, no significant difference was detected for premenstrual spotting, postmenstrual spotting, and pelvic pain at 0th, 6th, 12th, and 18th months. Likewise, no significant difference was detected between two groups in terms of menorrhagia and dysmenorrhea at 0th and 6th months. In addition to this, the rates of postcoital spotting were not different between two groups at 0th, 6th, and 12th months.

Discussion

Isthmocele is a pouch-like anechoic triangular acquired defect of myometrium due to cesarean section and it is also called as niche or cesarean scar defect [13]. The main hypotheses for the development of isthmocele are incomplete closure of incision, the location of cervical incision, and adhesions on uterine scar all of which results in impaired healing of wound [4]. Although most of the patients with isthmocele are asymptomatic, the most common symptom is intermittent postmenstrual bleeding [13]. In the literature, the incidence of postmenstrual bleeding is reported to be 29–82% in isthmocele patients [14]. Isthmocele becomes a reservoir for accumulation of menstrual blood that is assumed to be the reason for postmenstrual spotting [13]. Pelvic pain, dysmenorrhea, and infertility are other

Table 5 The distribution of symptoms for residual myometrial thickness groups

	Residual myometrial thickness < 3				Residual myometrial thickness ≥ 3				*p*
Months	0	6	12	18	0	6	12	18	
Premenstrual spotting (%)	47.6	9.5	0	0	50	12.5	12.5	12.5	$p_0 = 1.000$ $p_6 = 1.000$ $p_{12} = 0.276$ $p_{18} = 0.276$
Postmenstrual spotting (%)	87	33.3	9.5	0	100	37.5	25	12.5	$p_0 = 0.276$ $p_6 = 0.833$ $p_{12} = 0.300$ $p_{18} = 0.276$
Menorrhagia (%)	76.2	0	0	0	87.5	9.5	0	0	$p_0 = 0.647$ $p_6 = 1.000$
Postcoital spotting (%)	12.5	0	0	0	28.6	4.8	4.8	0	$p_0 = 0.366$ $p_6 = 1.000$ $p_{12} = 1.000$
Dysmenorrhea (%)	57.1	0	0	0	75	9.5	0	0	$p_0 = 0.671$ $p_6 = 1.000$
Pelvic pain (%)	28.6	0	0	0	50	14.3	14.3	14.3	$p_0 = 0.278$ $p_6 = 0.540$ $p_{12} = 0.540$ $p_{18} = 0.540$

symptoms related to isthmocele. Impaired sperm motility and implantation are claimed to be the reason of infertility while abnormal myometrial contraction due to the efforts of uterus to empty the accumulated blood in isthmocele is claimed to be the reason of pain [2, 15–17]. In our study, postmenstrual spotting was the most frequent complaint as it was emphasized in the literature and followed by menorrhagia, dysmenorrhea, premenstrual spotting, pelvic pain, and postcoital spotting.

The management of isthmocele is still under debate. Some authors offer expectant therapy for the patients complaining about postmenstrual spotting especially in small size defect that myometrium over the defect is ≥ 3 mm while others prefer hysteroscopic resection of the inferior edge of the isthmocele for the similar population [8, 18]. For larger defect sizes, laparoscopic, laparotomic, or vaginal approaches are suggested [7]. The effect of medical therapy with oral contraceptives on symptoms of isthmocele patients is not clear. Some researchers found it beneficial for patients not desiring fertility while some others did not [19, 20].

LNG-IUD have a wide range of clinical indications such as contraception, abnormal uterine bleeding, endometriosis, adenomyosis, and endometrial protection for estrogen users [19]. LNG-IUD can cause spotting-like or heavy bleeding during the first 3 to 6 months of use but at the end of 6th month, cycles may remain irregular, become infrequent, or even cease [12]. In a systemic review concerning the effect of LNG-IUD use in nulliparous patients revealed that any kind of bleeding including spotting were high at first year compared to more prolonged use [21]. For isthmocele, the symptoms are continuous without any intervention. We assumed that LNG-IUD can be beneficial by cessation of menstruation for a considerable extent. Furthermore, in our study, not all the patient benefited from LNG-IUD and 10.3% of the patient were still suffering from postmenstrual spotting at the 18th month. It may be assessed as a side effect of LNG-IUD or due to some factors related to isthmocele. It can cause total cessation of menstruation due to endometrial thinning and stromal atrophy [10, 22]. In this respect, it was assumed that the mechanism that ends or decreased the menstrual blood flow will indirectly block the accumulation of blood to the isthmocele. However, complaints related to isthmocele are not always due to the accumulation of blood. Donnez et al. described the presence of hypervascularized areas, dendritic vessels with hemorrhage, or polyps at the site of istmocele under hysteroscopic evaluation. In our study, we did not use hysteroscopy neither for diagnosis nor follow-up; therefore, we do not know about the response of these described lesions to LNG-IUD and this topic deserves to be investigated. In the same study, it was referred to the articles that LNG-IUD was effective in eliminating the complaints related to isthmocele, and also it was emphasized that there was a need for studies with a larger population. [23]

There is only a few data in the literature searching the role of LNG-IUD in isthmocele. In the review of Setubal et al., they emphasized that there is no clear evidence about the surgical treatment of isthmocele but it should be offered to symptomatic women and asymptomatic women with no fertility desire. In this review, oral contraceptives and LNG-IUD were searched in medical treatment and only the study of Zhang et al. included for LNG-IUD. Hence, they could not make a suggestion for LNG-IUD for symptomatic isthmocele patients [13]. In a study of Zhang et al.[11] evaluating the five methods used to treat cesarean scar defects, treatment groups were divided into laparoscopy, vaginal surgery, hysteroscopy, combined oral contraceptive, and levonorgestrel intrauterine system groups. Levonorgestrel intrauterine devices were not found to shorten the duration of menstruation. In this study, the study population of LNG-IUD group were composed of only five patients and the follow-up period was 4 months. Moreover, it was lack of the effect of LNG-IUD on symptoms related to isthmocele. Chen et al.[4] reported a preliminary report about the use of a LNG-IUD for the treatment of intermenstrual bleeding due to cesarean scar defect in 2019. Only 6 patients were included, and only intermenstrual bleeding was searched in this study. They concluded that LNG-IUD is an effective treatment for intermenstrual bleeding in isthmocele patients. In 2020, He et al.[14] compared the effect of hysteroscopic resection with LNG-IUD in women with postmenstrual spotting due to isthmocele in their prospective cohort study. The follow-up period was 12 months in this study. Postmenstrual spotting reduced in both groups, but the effectiveness of LNG-IUD was higher during the first year. Hence, the authors claimed that LNG-IUD should be suggested as a first line treatment option in patients with postmenstrual bleeding due to isthmocele who do not desire fertility within 1 year. Another important issue about this study was the investigation of the relationship between thickness of residual myometrium and LNG-IUD insertion. They reported that LNG-IUD could be applied independent of residual myometrial thickness, while hysteroscopy is generally used in patients with myometrial thickness greater than 2.5 mm. In our study, we found that premenstrual spotting and pelvic pain reduced at 6th months and no significant change was detected until the end of follow-up period. Postmenstrual spotting reduced at 6th months and also significant change was detected between 6 and 12th months. Menorrhagia and dysmenorrhea disappeared at 12th months while postcoital spotting disappeared at 18th months. No association was found between residual myometrial thickness and the frequency of symptoms for each follow-up.

Our study has some strengths. First, we have the longest follow-up in the literature with the largest sample size for symptomatic isthmocele patients. Second, we searched the effect of the residual myometrial thickness for each

follow-up for 18 months. Last, the significant changement in frequency of symptoms was evaluated between each follow-up.

Our study has some limitations. First, it is a single center study. Second, we did not have a control group and did not compare LNG-IUD treatment with other treatment options. Third, the diagnosis of isthmocele was based on ultrasonography and magnetic resonance imagining was not used. Last, although our patients had many risk factors for adenomyosis and definite diagnosis is possible only with pathologic evaluation, we excluded adenomyosis cases with ultrasonographic criteria in this study.

In conclusion, LNG-IUD are useful and reliable therapeutic tools for patients who have menorrhagia, dysmenorrhea, pelvic pain, postcoital, premenstrual, and postmenstrual spotting related to isthmocele regardless of the residual myometrial thickness. We should offer this alternative to the patients who do not desire fertility minimum 6-month period.

Data Availability Data can be shared under reasonable request.

Code Availability Not applicale.

Declarations

Ethics Approval It was approved by the institutional review board and ethics committee (approval number: 11.12.2019/159).

Consent to Participate All the participants signed a written informed consent to participate to the study.

Consent for Publication All the participants signed a written informed consent for publication regarding their data.

Conflict of Interest The authors declare no competing interests.

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