Zhou, Q.; Chen, X.; Wu, H.; Ma, S.; Wang, Q. (2023) Diffuse Uerine Leiomyomatosis Complicated with Cerebral Thrombosis After Oral Contraceptive Treatment. : A Case Report And Literature Review.Revista Internacional de Medicina y Ciencias de la Actividad Física y el Deporte vol. 23 (90) pp. 85-96.
DOI: https://doi.org/10.15366/rimcafd2023.90.007

ORIGINAL

DIFFUSE UERINE LEIOMYOMATOSIS COMPLICATED WITH CEREBRAL THROMBOSIS AFTER ORAL CONTRACEPTIVE TREATMENT：A CASE REPORT OF ATHLETIC PATIENTS

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FUNDING STATEMENT: Gansu Provincial Department of Science and Technology---Key research and development program(21YF11FA005) ②Gansu Province Higher Education Innovation Fund project(2021B-165).

Received: March 26, 2022
Accepted: February 19, 2023

ABSTRACT

Objective: We would like to emphasize the differentiations of diagnosis and treatment between general uterine leiomyomas and diffuse uterine leiomyomatosis (DUL), which is a kind of extremely rare disease. Levonorgestrel-releasing intrauterine system (LNG-IUS) is an attainable option provided to treat DUL with cerebral thrombosis, as a feasible novel method. **Case report:** A 21-year-old female patient with DUL was due to cerebral venous thrombosis caused by oral contraceptives. The patient was persistently vaginal bleeding after decreasing intracranial pressure and anticoagulant therapy for 3 days. Subsequently, a hysteroscopic submucosal myomectomy was performed to restore the normal shape of the uterine cavity, and the placement of Mirena was given after surgery, which aimly played a good role in hemostasis, prevention of severe menorrhagia and reconstruction of endometrial function. **Conclusion:** This case report shows that, levonorgestrel-releasing intrauterine system (LNG-IUS) is efficient and secure to treat DUL after hysteroscopic surgery, and simultaneously does not increase the risk of venous thromboembolism (VTE).

KEY WORDS: Diffuse Uterine Leiomyomatosis, Excessived Menstruation, Thrombosis, Oral ontraception

1. INTRODUCTION

Diffuse Uterine Leiomyomatosis (DUL) is a sort of rarely benign diseases of gynecology in women of childbearing age. Its clinical manifestations are dysmenorrhea, menorrhagia, menometrorrhagia, infertility and abortion, etc (Coskun et al., 2008). Pathological features of DUL are a large number of benign fibroid nodules with different sizes (about 0.5-3 cm in diameter), unclear boundaries and mutual interfusion diffusely distributed in the myometrium of the uterus leading to increased uterine symmetry (Mulvany, Ostor, & Ross, 1995), and severe cases even involve the entire uterine body with virtually no normal myometrium visible. Athletic individuals, due to their commitment to rigorous training regimens and peak physical performance, often encounter distinctive health considerations. The interplay between athletic endeavors and medical conditions can create intricate scenarios that require comprehensive understanding and specialized approaches. In the context of DUL, the impact of this condition on an athletic patient's well-being can be particularly significant, potentially affecting both their sports performance and overall quality of life.(Ueda et al., 1999).

DUL is difficult to diagnose because of its low incidence and lack of clinical knowledge. Furthermore, it should be differentiated from common uterine leiomyoma, multiple uterine leiomyoma, adenomyosis, intravascular leiomyomatosis, and uterine malignant tumors, ect (Nevoa et al., 2017). The most total treatment for DUL athletic patients is hysterectomy. Since most athletic patients have the idea of preserving fertility, alternative treatments include transabdominal myomectomy, subuterine myomectomy, uterine artery embolization and hormone therapy：gonadotropin releasing hormone agonists (GnRH-a).

The patient was a young athletic woman and was in the acute phase of cerebral thrombosis. The use of systemic hormones, anticoagulants and GnRH-a was limited. We eliminated most submucous myomas by hysteroscopy and restored normal uterine morphology. In order to subsequent endometrial reconstruction and prevent severe menorrhagia, we performed LNG-IUS placement. Presently, we conducted two clinical reassessments, the first one took place 10 days after operation and another is 3 months after the operation. By far, menstrual patterns and the quality of life were improved significantly.

CASE REPORT

A 21-year-old athletic woman was admitted via the neurology department of our hospital on March 7th, 2021, due to headache, nausea and vomiting aggravated for six days. Her menophania was started in 12 years old, and had a menstrual cycle of 6-7/28-30 days. Beforehand, She had a relatively normal menstruation with moderate dysmenorrhea. Before the hospital stays,

the menstrual volume of the patient gradually increased since 5 months ago, and the menstrual period was extended to 10-15 days. Therefore, the patient was treated in the other hospital with oral ethinylestradiol and cyproterone acetate tablets (Meijieduo, Shanghai Xinyi Tianping Pharmaceutical Co, Ltd.) for 2 cycles, passed for adenomyosis. The patient was regularly given Meijieduo 1 tablet / day from February 11th,2020 to March 3rd,2021. During the period, the vaginal bleeding of the athletic patients continued and the maximum amount of wet permeable 3-4 sanitary towels / day.

After admission, the head CT scan of emergency showed low density in superior sagittal sinus, right transverse sinus, right jugular bulb, external jugular vein and left part of transverse sinus lumen and suspicion of venous sinus thrombosis on March 7th,2021(Figure 1(A)). Gynecological ultrasound showed that the body diameter of the uterus was 75*56 * 60 mm, the echo of the posterior wall of the uterus was uneven (anterior wall thickness 6 mm, posterior wall thickness 43 mm), and the endometrium was unclear about 2 mm. Consider adenomyosis? (Figure 1(B)) Pelvic CT plain scan : enlarged uterus with uneven muscular echo(Figure 1(C)). Laboratory results showed that red blood cell count : 3.62 * 10^{12} / L, white blood cell count : 6.4 * 10^{9} / L, hemoglobin 74g / L, reticulocyte (%) : 2.17, immature reticulocyte : 25.7 %, platelet : 253 * 10^{9} / L, prothrombin activity : 103 %, international normalized ratio (INR) : 0.98, prothrombin time(PT) : 16.2sec, activated partial thrombin time(APTT) : 34.4sec, fibrinogen : 3.75g / L, thrombin time(TT) : 16.2sec, fibrinogen degradation products : 1 : 10.74ug / ml, D-dimer : 3.74ug / mL.The results of cerebrospinal fluid puncture and liver and kidney function showed no obvious abnormality. Then, mannitol 125ml q8h and glycerol fructose 125ml daily were given to reduce intracranial pressure. Low molecular weight heparin calcium 4100IU q12h was given to anticoagulation through hypodermic injection. At the same time, integrate treatment such as anemia resistence, supplement of water and maintaining electrolyte balance was given.

Figure 1. The Imaging results of cranial and pelvic in pre-operative.

A) the head CT scan of emergency showed low density in superior sagittal sinus, right transverse sinus, right jugular bulb, external jugular vein and left part of transverse sinus lumen.
B) Gynecological ultrasound showed uneven echo of posterior uterine wall.
C) Pelvic CT plain scan: uterine enlargement and uneven muscularis echo.

The patient stopped anticoagulant therapy due to continuous vaginal bleeding after headache relief, and then transferred to gynecology. Hysteroscopy Operative system under general anesthesia was performed in our department in March 11th, 2021. Under-hysteroscopy, it can be seen that the uterine cavity was abnormal, and the cavity was filled with multiple myoma-like tumors with uneven sizes (the diameter of the large is about 3 cm, and the smallest is about 0.5 cm), and local vascular congestion was observed. Hysteroscopic surgery using electric loop combined with cold grasper was performed to excise submucous myomas (including 0, I, and II types), residue other intramural myomas in place, and reshape the normal shape of the uterine cavity as possibly as. The intraoperative depth of uterine cavity was about 10cm, so levonorge-strelintrauterine system (LNG-IUS) wasn't be placed because it is easy to fall off or move down in intrauterine. The result of pathological examination was uterine leiomyoma (Figure 2, A and B).

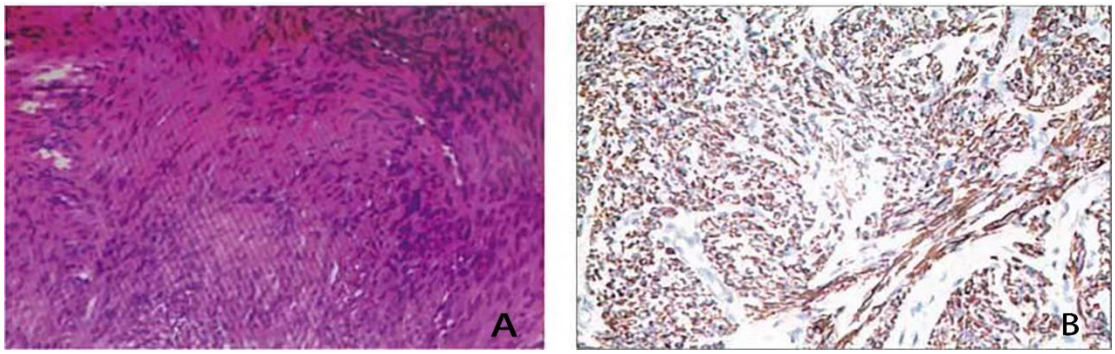

Figure 2. The result of postoperative pathological examination by using hematoxylin-eosin staining (HE) and immunohistochemical (IHC). A) The nucleus was blue-purple and the intercellular was red of HE staining with 40*10 multiple. B) Immunohistoche mi cal staining with 40*10multiple, desmin（+）, caldesmon (+), CD10(-), S-100(-), Ki-67(index:1%)

After operation, the vaginal bleeding symptoms of the patient gradually relieved and the patient was treated with low molecular weight heparin calcium (4100 IU q12h) for anticoagulation and mannitol for lowering intracranial pressure, simultaneously. The symptoms of vaginal bleeding disappeared and headache were relieved. 9 days after surgery, Magnetic resonance imaging (MRI) showed that the flow signal of superior sagittal sinus, sinus confluence, right transverse sinus and sigmoid sinus disappeared, and suspicion of Venous congestion brain changes (Figure3A). Postoperative B-ultrasound examination: 70 * 58 * 62 mm in diameter, uneven echo and unclear endometrium (Figure 3B). Laboratory tests showed: prothrombin activity: 109 %, INR: 0.95, PT : 12.6sec, APTT: 39.5sec, fibrinogen : 3.15g / L,TT: 15.5sec. The depth of uterine exploration was 9cm, considering that the patient with intracranial venous thrombosis had not been completely cured, the LNG-IUS was performed in intrauterine and the patient was discharged from hospital on March 30, 2021.

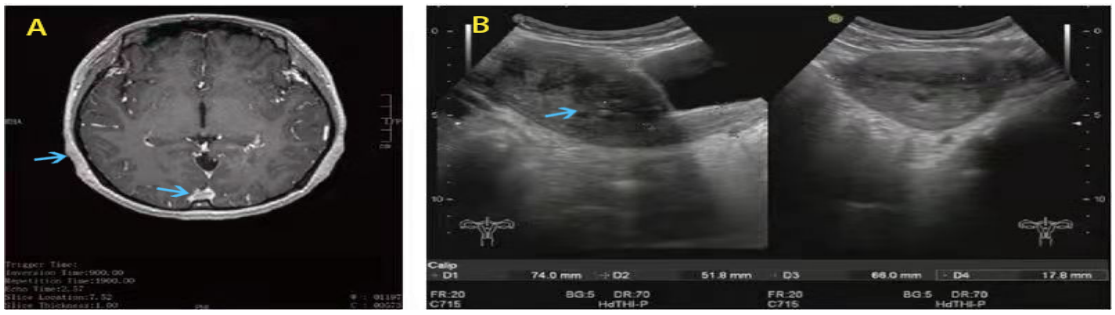

Figure 3. The review results of cranial and pelvic in 9 days post-operative.

A) Brain MRI, disappearance of blood flow signals in superior sagittal sinus, sinus confluence, right transverse sinus and sigmoid sinus. B) Postoperative B-ultrasound: uneven echo.

The follow-up period, 5mg warfarin was given orally and INR was monitored regularly. The patient with menstruation was received oxytocin in local hospitals and menses ended eight days later on April 20th,2021. The second menses occurred on May30,2021 and the menstruation ended spontaneously after 10 days. No severe anemia occurred during the period. Review of Prothrombin activity:06 %, INR: 0.97, PT : 12.8sec, APTT : 37.4sec, fibrinogen : 2.74g / L, TT: 16.9sec, fibrinogen degradation products : 1 : 4.65ug / ml, D-dimer : 0.76ug / ml. Brain MRI + MRV showed signal filling defect in superior sagittal sinus, sinus confluence, right transverse sinus and sigmoid sinus, taking into account venous sinus thrombosis(Figure 4A and B) on May 30,2021. But it obviously alleviated compared with the previous MRI.

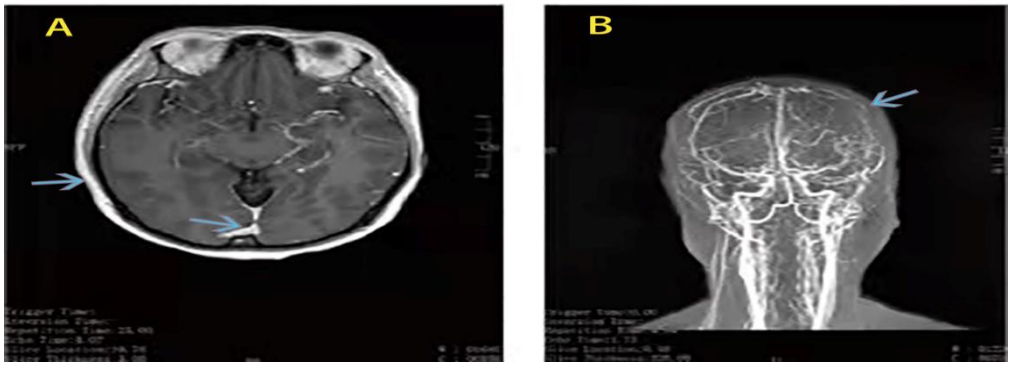

Figure 4. The follow-up results of brain MRI + MRV in 2 months of post-operation.

A) Thrombosis signals (arrow) in superior sagittal sinus, sinus confluence. B) right transverse sinus and sigmoid sinus showed filling defect(arrow).

Three months after operation, the patient ' s self-reported thrombosis by MRI was improved. Pelvic MRI showed he size of the uterus was smaller than pre-operation (69cm * 58* 62mm), irregular thickening of the band and penetration into the muscular layer(Figure 5).

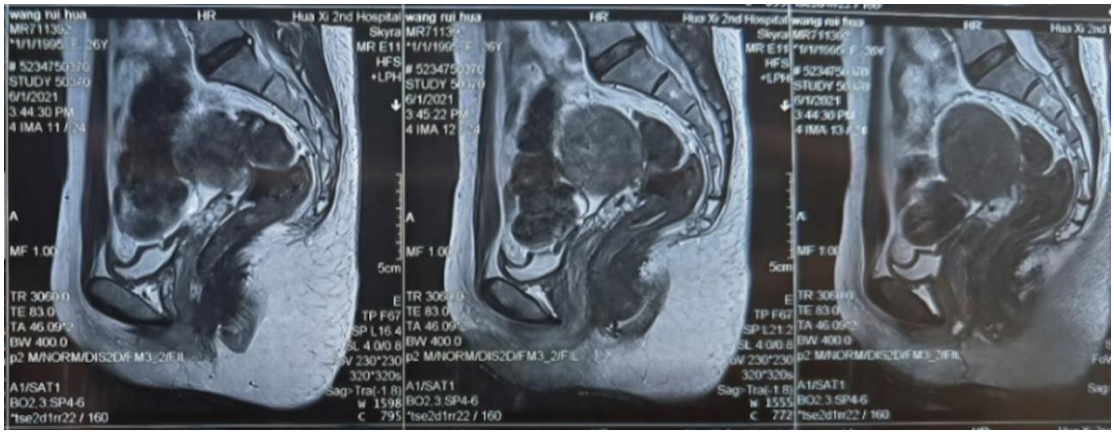

Figure 5. The result pelvic MRI showed hysterauxesis, binding band irregularly thickened, protruding into muscular layer in three months after operation.

2. DISCUSSION

The initial symptoms of DUL are similar to those of leiomyoma of uterus, which are characterized by abdominal pain and abnormal uterine bleeding, as well as excessive menstruation, dysmenorrhea, infertility and pelvic pressure(Coskun et al., 2008). The ultrasonic images of DUL showed diffuse, symmetrical enlargement of uterus and combined, uneven hypoechoic uterine tumors to replace the normal myometrium. It is generally believed that further MRI images display more clearly. Therefore, DUL needs to be distinguished from typical leiomyomas, which have clear boundaries and pseudocapsules. However, the edge of DUL is unclear and combined, causing asymmetric deformation and distortion of the entire uterus(Pai, Coletti, Elkins, Ladino-Torres, & Caoili, 2012).

Since the patient was a virgin, only transabdominal ultrasonography was performed. which is not typical, leading to lower hospitals to diagnose adenomyosis and were given oral contraceptives to stop bleeding. However, the therapeutic effect was not ideal and the cerebral thrombosis of severe adverse reactions was occurred in the patient with this treatment. After admission, the patient underwent pelvic CT examination. The results showed that there were no other special manifestations except enlarged uterus and uneven muscular echo. Therefore, women of childbearing age with menorrhagia should be warned to DUL. MRI diagnosis if necessary to avoid delay.

For DUL athletic patients, traditional hormonotherapy usually fails to control symptoms and it will aggravate anemia and promote tumor growth whether treatment was stopped(Koh et al., 2012). Hysterectomy remains the only permanent treatment for DUL. Taking account into the fertility needs of most athletic patients, there are options for conservative treatment. Traditional myomectomy is considered almost impossible because of the risk of incomplete

removal of fibroids, inevitable endometriosis, recurrence of fibroids and spontaneous rupture of uterus during pregnancy(Zhang et al., 2020).

The development of hysteroscopy provides a new idea for the treatment of DUL. We chose hysteroscopy in the patient with uncontrolled vaginal bleeding and cerebral thrombosis caused by oral contraceptives. This approach not only clarified the etiology of the patient but also effectively stopped bleeding quickly. For young athletic patients with DUL, the most important concern is postoperative fecundity recovery. Yen CF et al. performed hysteroscopic resection of submucous myomas in 8 athletic patients in order to achieve normal endometrium. In this study, all athletic patients of the menstruation was improved and the endometrium recovered in2 to 3 months after the surgery, and besides one suffered a miscarriage, the other 6 cases of successful pregnancy and full-term delivery(Zhao, Yang, Li, Xu, & Feng, 2019). Thus, hysteroscopic surgery is one of the options for DUL athletic patients with less injury and good postoperative reproductive outcome. In this case, we chose the traditional hysteroscopic surgery for emergency hemostasis, and elimination most submucosal fibroids to restore normal uterine morphology, which provided the possibility for the future fertility of the patient.

In addition to the above treatment of direct myomectomy, there are reports that uterine artery embolization (UAE) can also be considered. Jieun Koh et al. studied 7 athletic patients with DUL who underwent uterine artery embolization. Among them, the average uterine volume decreased by 50.1 % in3 months after operation, 5 cases (71 %) had complete necrosis of leiomyoma nodules, 2 cases (29 %) showed that most of the leiomyoma nodules had necrosis. After 16 months, their symptoms of menorrhagia were improved, and even one patient was pregnant at 5 months after operation. No complications occurred until the follow-up to 8 months(Koh et al., 2012). Similarly, Aki Kido et al(Kido et al., 2003). studied 6 athletic patients, of whom 5 athletic patients had permanent remission of symptoms. MRI showed a significant recovery of muscular layer and a reduction and partial discharge of infarcted leiomyoma. However, one patient failed in the treatment of atypical hyperplasia. However, the impact of UAE on fertility has not been determined. It has been reported that the pregnancy rate after UAE is only 38.3 % that is clearly lower than after myomectomy with 53.6–55.9%(Li, Nai, Gao, & Wang, 2016), but the abortion rate and low birth weight are higher than that after myomectomy(Karlsen et al., 2018; Ludwig, Huff, Shanahan, & Stavas, 2020). The above studies suggest that UAE seems to be an option for females with clinically symptomatic fibroids who desire preservation fertility.

For various reasons, women of childbearing age will inevitably take exogenous estrogen-containing drugs such as oral contraceptives (OCs) and hormone replacement therapy (HRT). However, estrogen-containing drugs can promote blood to maintain hypercoagulability and increase the risk of

venous thromboembolism(VTE) complications in all women. The potential pathophysiological mechanism of OCs-related thrombosis risk is still unclear. By affecting the level of activated protein C (APC-R), reducing protein C and protein S, and increasing CRP are considered to be possible mechanisms(Gialeraki, Valsami, Pittaras, Panayiotakopoulos, & Politou, 2018). The most common manifestations of VTE are deep vein thrombosis (DVT) and pulmonary embolism (PE). However, more rare thrombosis events were also observed in women using OCs, such as upper limb and intra-abdominal thrombosis, cerebral sinus thrombosis and superficial venous thrombophlebitis.(de Bastos et al., 2014) Nonetheless, the incidence of VTE among OCs users remains low (8-10 per 10,000 women per year) and the difference is associated with the doses of estrogen and the types of progesterone. At present, the formulation of OCs has been from 150 μg in the first generation to ≤ 30 μg. Rachel E. believed that the risk of myocardial infarction or ischemic stroke in women using OCs increased by 1.6 times, and the risk of tablets containing > 50 μg estrogen was the highest. He thinks OCs pills containing 30μg levonorgestrel are the safest form of oral combined hormone contraceptives(Roach et al., 2015). The patient took OCs (35 μg ethinylestradiol and 2 mg cyproterone acetate) for about 40 days, and severe cerebral thrombosis occurred. At the same time, DUL uterine bleeding was not controlled. The reason is not clear, which may be related to gene heredity. Deeksha analyzed the correlation between different types of progesterone and VET, and concluded that the risk of OCs containing levonorgestrel was the lowest even if athletic patients had genetic risk of VET(Khialani et al., 2020).

For the patient, it is urgent to avoid severe vaginal bleeding after surgery and to control further disease progression. GnRHa is widely recognized in the treatment of DUL. The application of GnRHa in the treatment of DUL can significantly reduce the volume of uterus and myoma, and alleviate the related symptoms such as abnormal uterine bleeding. The main mechanisms include significantly promoting the apoptosis of uterine leiomyoma cells.(Gong et al., 2020) In previous reports, most DUl athletic patients used GnRHa for 6 months before surgery, which helps to improve the operability and success rate of surgery. Another report showed that a 24-year-old athletic woman with DUL had a 50 % reduction in uterine volume after 6 months of using busherelin alone (900 μg / day) and was naturally pregnant until 34 weeks of gestation.(Fedele, Bianchi, Zanconato, Carinelli, & Berlanda, 2004) The above results suggest that GnRHa is optional in the treatment of DUL. However, it is not known whether GnRHa will aggravate cerebral embolism and affect the whole body ' s coagulation function considering the cerebral infarction state of athletic patients (ERGÜDEN, KABASAKAL, & KABAKLI, 2020). Although T.Matsushima1 reported that cerebral thrombosis was caused by oral contraceptives in a patient with adenomyosis, which was later replaced by retrogression therapy with leuprorelin acetate 1.88 mg / month combined with long-term inhalation of bussellin acetate nasal spray for 4 cycles. The therapeutic effect showed that

the cerebral thrombosis in the patient was not aggravated, but no large sample experiment confirmed that GnRHa was completely safe for systemic VTE.

In comparison, the WHO Medical Eligibility Criteria for Contraceptive Use points out that for women with a history of deep venous or pulmonary thromboembolism, the benefits of LNG-IUS are generally considered to exceed their potential risks.(Pisoni, Cuadrado, Khamashta, & Hunt, 2006) At the same time, a large sample study suggests that LNG-IUS is safe for women with coagulation disorders. Whether they use oral anticoagulants or have a history of coagulation or thrombosis, the related menstrual patterns and quality of life can be improved to some extent.(Brull, Fernandes, Monteiro, Bahamondes, & Juliato, 2020) A Brazilian study also confirmed that oral anticoagulants did not induce more frequent and / or longer bleeding in women with thrombosis and / or VTE after LNG-IUS administration.(Braga et al., 2014) A recent study, based on studies of cardiovascular risk factors, found no significant changes in these risk factors after 12 months of LNG-IUS use in women with thrombosis and / or previous venous thromboembolism.(Braga et al., 2020)

3. CONCLUSION

In summary, there is no report on the therapeutic effect of LNG-IUS in athletic patients with DUL combined with cerebral thrombosis. We followed up for 3 months, showing the advantages of LNG-IUS in the maintenance treatment of athletic patients with DUL after hysteroscopic surgery. For female athletic patients with DUL, it is crucial to adopt an individualized approach to treatment, taking into account the specific needs and goals of each athlete. This includes considering the impact of hormonal therapies, such as oral contraceptives, on the growth and complications of uterine leiomyomas. Thorough risk assessment, close monitoring, and informed decision-making are essential to minimize potential adverse effects and optimize overall well-being. Furthermore, healthcare professionals, coaches, and athletes themselves need to be aware of the potential risks associated with DUL and its complications, such as cerebral thrombosis. This awareness can help facilitate early detection, timely intervention, and appropriate modifications to training regimens, ensuring the safety and long-term athletic success of female patients. At the same time, LNG-IUS maintains menstrual volume within a controllable range, and simultaneously does not increase the risk of VTE.

COMPETING INTERESTS

All authors declare no conflict of interest, not to receive any funding of any organization and their agreement for publication.

FUNDING STATEMENT

1. Gansu Provincial Department of Science and Technology---Key

research and development program(21YF11FA005) ②Gansu Province Higher Education Innovation Fund project(2021B-165).

AUTHOR CONTRIBUTION

Xiao-Hong Chen and Qimin Zhou composed the manuscript and literature review; Hui-Fang Wu ，Qing Wang and Shou-Ye Ma had the collection, analysis or interpretation of data for the manuscript. Xiao-Hong Chen revised important intellectual content and final approval of the version to be published, and ensure that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved. Qimin Zhou is the general manager and corresponding author of the article.

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