Amenorrhea after uterine fibroid embolization
A report of six cases

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Background and Objective: Uterine fibroid embolization is an effective treatment alternative for uterine fibroids. However, amenorrhea after uterine fibroid embolization occurs in some patients. This study was to investigate the causes of amenorrhea after uterine fibroid embolization.

Methods: Bilateral transcatheter uterine artery embolization was performed in 487 patients with uterine fibroids. Pingyangmycin (6–16 mg) dispersed in lipiodol (8–15 mL) was used as embolic agent in 104 patients; polyvinyl alcohol (80–150 mg) was used in 158 patients; absorbable gelatin sponge (1–2 g) was used in 225 patients. All patients had been followed up for 1 year to observe amenorrhea occurrence.

Results: Uterine fibroid embolization was effective in 483 (98.97%) patients, but failed in five (1.03%) patients. Amenorrhea after embolization was found in six (1.23%) patients. Of the six patients, three were in lipiodol plus pingyangmycin group with lipiodol deposited in the ovarian region, one was in polyvinyl alcohol group and the other two were in absorbable gelatin group. Except for one patient in absorbable gelatin group, the rest five patients had estradiol (E2) decreasing and follicle stimulating hormone (FSH) rising due to ovarian function failure. In absorbable gelatin group, multiple ultrasonography examinations revealed that the endometrium was only 3 mm thick in one amenorrhea patient who had normal levels of E2 and FSH, and hysteroscopy examination confirmed endometrial atrophy in this patient. Conclusions: Routine embolic agents have the chance in inducing amenorrhea after uterine fibroid embolization. The occurrence rate of amenorrhea after uterine fibroid embolization is about 1.23%. Ovarian function failure and endometrial atrophy are the most related factors.

Uterine fibroid embolization has been gradually accepted as a safe and effective treatment for uterine leiomyoma since it was first reported by Ravina et al.1 in 1995. However, because some uterine leiomyoma patients would develop amenorrhea with unknown reason after uterine fibroid embolization, uterine leiomyoma tends to occur in women of a younger age and women now tend to have children at a relatively older age, the clinical application of uterine fibroid embolization for uterine leiomyoma is affected to a certain extent, especially for young patients.2-4 In order to promote the development of uterine fibroid embolization techniques, we analyzed the clinical data of 487 uterine leiomyoma patients who developed amenorrhea after uterine fibroid embolization and explored underlying causes.

Data and Methods

Clinical data. Regular follow-up was performed in 487 uterine leiomyoma patients who underwent uterine fibroid embolization at the First Affiliated Hospital of Sun Yat-sen University from January 2000 to March 2007. All diagnoses were confirmed by gynecological examination and gynecologic ultrasound examination. The patients were 24–48 years old with a median age of 35 years. Of all patients, 453 showed excessive menstruation or prolonged menses, 28 showed oppressive symptoms such as synchuria and constipation, and six showed no symptoms; 439 had multiple uterine leiomyomas and 48 had single uterine leiomyoma. The volumes of uterine leiomyomas were 47.09–546.84 cm³ with an average of 120.78 cm³.

Therapeutic methods. All patients were subjected to continuous epidural analgesia till the third day after embolotherapy. After anesthesia, bilateral uterine artery catheterization was performed via the right femoral artery approach. A mixture of embolic agents and contrast agents was infused via the catheter (a 5-F Yashiro catheter; Terumo, Japan). When contrast agent retention was observed in the uterine artery, gelatin sponge particles were used to reinforce the embolization of the main trunk of the uterine artery. Angiography was performed again to confirm whether the embolization was satisfactory.

Three different embolic agents were used. Of the 487 patients, 104 (24–48 years old with a median age of 34 years) used lipiodol emulsion (Gubert, France) and pingyangmycin (Tianjin, China) as embolic agents at doses of 8–15 mL (average, 10 mL) and 6–16 mg (average, 8 mg), respectively; 158 (26–45 years old with a median age of 35 years) used polyvinyl alcohol particles (300–700 μm in diameter; COOK, USA) at a dose of 80–150mg (average, 100 mg); 225 (25–43 years old with an average of 36.4 years) used gelatin...
sponge particles (900–1000 μm in diameter; Lianyungang, Jiangsu Province) at a dose of 1–2 g (average, 1.5 g).

Follow-up. All patients were reexamined at one, three, six and 12 months after embolotherapy. After then, the patients were reexamined every six months. The main examinations included gynecological color ultrasound as well as the observation of changes in clinical symptoms and menstrual status. Considering that the amenorrhea present at two years after embolotherapy might be caused by complex factors, the observation endpoint was 12 months after operation.

Criteria for evaluating amenorrhea. According to the definition in gynecology, amenorrhea was concluded if the duration of menstrual cessation was more than six months or three times longer than the duration of past menstrual cycle.

Calculating the volume of the uterus or uterine leiomyoma. According to reference 6, the volume of the uterus or uterine leiomyoma = 0.5233 × the longest longitudinal diameter of the uterus or uterine leiomyoma × the longest transverse diameter × the longest anterior-posterior diameter. The diameter (unit: cm) was measured by ultrasound.

Calculating the volume of multiple uterine leiomyomas. The volume of multiple uterine leiomyomas was calculated by adding the volumes of the three largest leiomyomas of those that could be detected using ultrasound examination.

Calculating volume decrease of the uterus or uterine leiomyoma. The percentage of volume decrease = (the volume before embolization - the volume after embolization)/the volume before embolization × 100%.

Diagnosis criteria of ovarian amenorrhea. According to reference 5, ovarian amenorrhea was diagnosed when the concentration of follicle-stimulating hormone (FSH) increased to ≥ 30 mL/L and that of estradiol (E2) decreased to ≤ 30 pg/L.

Results

Embolization and its clinical efficacy. All patients underwent successful bilateral uterine fibroid embolization and were followed up for one year. During follow-up, 448 of the 453 patients who showed excessive menstruation or prolonged menses recovered after embolization. Clinical symptoms were alleviated in 448 (91.99%) patients. All the 28 patients who showed synchuria and constipation recovered. Six asymptomatic patients showed 50–64% reduction in the volume of uterine leiomyomas one year after embolization when compared with that before embolization by color ultrasound examination, and no blood flow within uterine leiomyomas was observed. The total effective rate was 98.97% (482/487) while the embolization failure rate was 1.03% (5/487). Five patients who had excessive menstruation or prolonged menses showed no symptom alleviation after treatment. Among these five patients, four were treated with traditional Chinese medicine to control symptoms, and the remaining one underwent myomectomy one year after embolotherapy.

The incidence of amenorrhea. Six (1.23%) patients developed amenorrhea after embolization. Of the six patients, three used lipiodol emulsion and pingyangmycin, one used polyvinyl alcohol particles, and two used gelatin sponge particles. Except one patient who used gelatin sponge particles, the remaining five did not resume menstruation any longer after embolization.

Clinical data of patients developed amenorrhea. The clinical data of six patients who developed amenorrhea were shown in Table 1. Except for one patient (case 6) with single uterine leiomyoma, the remaining five had multiple uterine leiomyomas. All six patients showed excessive menstruation or prolonged menses before embolization.

<table>
<thead>
<tr>
<th>Patient’s No.</th>
<th>Age</th>
<th>Uterus volume (cm³)</th>
<th>Fibroid volume (cm³)</th>
<th>Shrinkage of uterus after embolization (%)</th>
<th>Shrinkage of fibroids after embolization (%)</th>
<th>Embolic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>267.76</td>
<td>192.53</td>
<td>68.23</td>
<td>65.19</td>
<td>Lipiodol plus pingyangmycin, 15 mL</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>233.53</td>
<td>188.37</td>
<td>70.53</td>
<td>68.26</td>
<td>Lipiodol plus pingyangmycin, 12 mL</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>229.24</td>
<td>190.27</td>
<td>65.04</td>
<td>60.67</td>
<td>Lipiodol plus pingyangmycin, 10 mL</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>400.32</td>
<td>287.96</td>
<td>53.19</td>
<td>61.91</td>
<td>Polyvinyl alcohol, 100 mg</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>518.06</td>
<td>348.28</td>
<td>60.34</td>
<td>54.33</td>
<td>Gelatin sponge, 1.8 g</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>248.94</td>
<td>70.64</td>
<td>53.62</td>
<td>51.28</td>
<td>Gelatin sponge, 1.1 g</td>
</tr>
</tbody>
</table>

Changes of follicle-stimulating hormone (FSH) and estradiol (E2) in six amenorrhea patients before and after embolization

<table>
<thead>
<tr>
<th>Patient’s No.</th>
<th>Time point</th>
<th>FSH (U/L)</th>
<th>E2 (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Before embolization</td>
<td>18.82</td>
<td>160.00</td>
</tr>
<tr>
<td></td>
<td>After embolization</td>
<td>134.64</td>
<td>30.00</td>
</tr>
<tr>
<td>2</td>
<td>Before embolization</td>
<td>5.45</td>
<td>80.00</td>
</tr>
<tr>
<td></td>
<td>After embolization</td>
<td>54.84</td>
<td>28.00</td>
</tr>
<tr>
<td>3</td>
<td>Before embolization</td>
<td>8.73</td>
<td>98.00</td>
</tr>
<tr>
<td></td>
<td>After embolization</td>
<td>62.32</td>
<td>22.00</td>
</tr>
<tr>
<td>4</td>
<td>Before embolization</td>
<td>10.13</td>
<td>150.00</td>
</tr>
<tr>
<td></td>
<td>After embolization</td>
<td>43.12</td>
<td>27.00</td>
</tr>
<tr>
<td>5</td>
<td>Before embolization</td>
<td>7.58</td>
<td>95.21</td>
</tr>
<tr>
<td></td>
<td>After embolization</td>
<td>36.31</td>
<td>28.36</td>
</tr>
<tr>
<td>6</td>
<td>Before embolization</td>
<td>9.17</td>
<td>103.52</td>
</tr>
<tr>
<td></td>
<td>After embolization</td>
<td>8.92</td>
<td>98.74</td>
</tr>
</tbody>
</table>
changes in FSH and E2 levels in five patients (cases 1–5) suggested ovarian amenorrhea, that is, ovarian function failure.

Uterine artery angiography showed bilateral uterine artery thickening and lengthening, rich blood supply to leiomyomas and arterial network of leiomyomas in these six patients (Fig. 1). Embolic agents were injected via the catheter and the embolization met the requirement. In three patients who used lipiodol emulsion and pingyangmycin, angiography showed ovarian branches in the root of the uterine artery and contrast agents in the ovary, embolic agents were deposited in bilateral ovaries after embolization (Fig. 2).

After embolization, case 6 showed hypomenorrhea, her menstrual period only lasted 2–3 days and gradually decreased, and she developed amenorrhea at four months later. The levels of FSH and E2 showed no significant changes after embolization. After embolization, multiple ultrasound examinations showed that endometrial thickness was only 3 mm and did not change during menstrual cycle. Hysteroscopy showed atrophy and attenuation of endometrium. These results proved that the amenorrhea was a result of endometrial atrophy.

**Discussion**

**Effect of uterine fibroid embolization for uterine leiomyoma on ovarian function.** Although uterine fibroid embolization for uterine leiomyoma has a high success rate, its impact on ovarian function has always attracted extensive attention. Because uterine leiomyoma tends to occur in women of a younger age and women now tend to have children at a relatively older age, the effect of this therapeutic method on the ovarian function of young patients who want to get pregnant has attracted more attention from researchers not only in obstetrics and gynecology but also in interventional radiology. Amenorrhea is not only the most serious side effect of uterine fibroid embolization for uterine leiomyomas but also the greatest threat to patients of childbearing age. Therefore, it is essential to further analyze the reasons underlying the development of amenorrhea.

Among the six patients with amenorrhea in our study, five showed ovarian amenorrhea that was characterized by an increase in FSH level and a decrease in E2 level. These five patients used different embolic agents, suggesting that uterine fibroid embolization may induce a decline in ovarian function no matter which embolic material is used.

The results of previous studies suggested that the effect of embolotherapy on the ovary is mainly related with the age of patients: patients over the age of 45 may develop upward shift of baseline FSH level and might prone to amenorrhea, while young patients won’t have obvious change in ovarian function. However, recent studies found that the effect of embolotherapy on the ovary may be more related to the impairment of ovarian blood supply. The principle of transcatheter uterine fibroid embolization for uterine leiomyomas is to embolize the uterine vascular bed by injecting embolic agents into the uterine artery till the blood flow in the main trunk of the uterine artery is blocked. Anatomically, the ascending branch of the uterine artery sends branches to the ovary near the uterine fundus to provide blood supply to the ovary. Therefore, embolotherapy often leads to disruption of ovarian blood supply via the ovarian branches of the uterine artery. Embolic agents may even enter ovarian vascular network through the ovarian branches of the uterine artery and block ovarian vascular network, thereby inducing ovarian ischemia, ovarian function failure, and eventually amenorrhea. Through examining ovarian artery by color Doppler ultrasound before and after embolization, Ryu et al. found that if ovarian arterial perfusion was decreased while resistance index and pulsation index were increased, non-target embolization of the ovarian artery was indicated. In addition, Payne et al. observed the pathologic changes in embolized specimens and found that embolic agents were present in the terminal branches of the ovarian artery. Thus, they speculated that embolic agents might enter into the ovary via the uterine artery and ovarian artery collaterals, block blood supply to the ovary and lead to ovarian ischemia, thereby inducing ovarian function decline or failure. These studies prove that one reason underlying the development of ovarian amenorrhea is non-target embolization of the ovarian artery which is caused by embolization-induced disruption of blood supply via the ovarian branches of the uterine artery and entering of embolic agents into the ovary via the ovarian branches.

In the three amenorrhea patients who used lipiodol emulsion and pingyangmycin in this study, uterine artery angiography in the process of uterine fibroid embolization showed the ovarian branches of the uterine artery and the ovary, embolic agents were deposited in the ovary after embolization. These results also confirm the above-mentioned speculation, that is, embolic agents can enter into ovarian vascular network via the ovarian branches of the uterine artery and disrupt ovarian blood supply. Since lipiodol emulsion belongs to liquefied embolic material and is even able to enter capillaries, it has the largest effect on the ovarian function and can result in ovarian ischemia, ovarian function failure, and eventually amenorrhea.

In the remaining two amenorrhea patients, although no embolic agents were found to be deposited in the ovary, ovarian amenorrhea still developed after embolization. Some studies have found that the ovarian branches of the uterine artery provide the main blood supply to the ovary in about 6.6% of leiomyoma patients, which
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is regarded as a high risk factor for the development of amenorrhea after embolization.\textsuperscript{11} Therefore, we speculate that, in these two patients, the ovarian branches of the uterine artery are the main arteries to supply blood to the ovary. Although the diameter of polyvinyl alcohol particles and gelatin sponge particles is relatively large (300–700 μm and 900–1000 μm, respectively), the block of the main trunk of the ovarian branches would cause ovarian ischemia and function failure, and lead to amenorrhea.

**Effect of uterine fibroid embolization on the endometrium.** The amenorrhea presented in case 6 was different from those presented in other cases, which was resulted from endometrial atrophy. We found that FSH and E2 levels in this patient, who used gelatin sponge particles as embolic agent, showed no changes after embolization. Although the patient showed no menopausal symptoms, the amount of menstrual bleeding gradually declined and amenorrhea eventually developed. Moreover, her endometrium was attenuated and lost response to sex hormones, and endometrial thickness did not change with menstrual cycle change. Hysteroscopic examination proved endometrial atrophy. Therefore, embolization-induced endometrial atrophy is also an important contributing factor for amenorrhea. Currently, few reports on this contributing factor are seen. Tropeano et al.\textsuperscript{12} reported a 44-year-old uterine leiomyoma

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Figure 2. Angiography of the patient with amenorrhea after uterine fibroid embolization. (A) Right uterine arteriography shows that the right ovarian branch and ovarian area are visualized and stained (the arrow); (B) After right uterine artery embolization, lipiodol entered into the right ovarian area and deposited (the arrow); (C) Right uterine arteriography shows that the right ovarian branch and ovarian area are visualized and stained (the arrow); (D) After right uterine artery embolization, lipiodol entered into the right ovarian area and deposited (the arrow).
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Patient who developed continuous amenorrhea after uterine fibroid embolization: although sex hormone levels and ovarian imaging in this patient showed no changes after embolization, hysteroscopic examination showed attenuation of the endometrium, and endometrial biopsy revealed endometrial atrophy. Their findings are similar to those observed in case 6 in our study. We speculate that it may be associated with the sensitivity of the germinal epithelium of the endometrium to ischemia, which can lead to endometrial dysplasia and thus induce amenorrhea after embolization. However, its exact mechanism is unclear yet.

At present, no satisfactory methods are available to prevent such complications. The main measures currently taken include using of absorbable embolic materials and monitoring of ovarian blood supply by angiography. It is particularly critical to control the degree of embolization.

To sum up, amenorrhea may occur after uterine fibroid embolization for uterine leiomyomas no matter which kind of embolic agent is used, though the incidence is low. The occurrence of amenorrhea may be associated with ovarian dysfunction and endometrial atrophy.

References