Gynecol Surg (2010) 7:81–85
DOI 10.1007/s10397-009-0528-9

ORIGINAL ARTICLE

Uterine arterial embolization: collagen analysis of endometrial/uterine biopsy pre and after procedure

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Received: 15 May 2009 / Accepted: 28 September 2009 / Published online: 13 October 2009

Abstract The objective of this study was to evaluate collagen of endometrial/uterine tissue before and after uterine arterial embolization (UAE). Fifteen consecutive patients with a diagnosis of uterine fibroids were included. Clinical diagnosis of uterine fibroids had been confirmed by ultrasonography. Uterine arterial embolization procedure was performed with microsphere with 300–700-my diameter. Selective catheterization of uterine arteries was carried through bilaterally and was guided by angiography. For collagen evaluation, endometrial biopsy was taken in secretory phase with Novak curette before UAE and 3 months after the procedure. Groups were assessed for analysis using Student's *t* test. Collagen fibers percentage was reduced ($p<0.0001$) in the group after UAE (81.05± 1.50) comparing the group before UAE (84.08±1.46). In conclusion, there is a significant reduction in collagen of endometrial/uterine tissue in patients submitted to UAE.

Keywords Uterine arterial embolization · Collagen · Uterine fibroids

Introduction

Uterine fibroids are the most common female pelvic tumor, typically reported to occur in 20–40% of reproductive aged women, and up to 70% of white and 80% of black women by the age of 50 years [1, 2].

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Uterine artery embolization (UAE) is a nonsurgical, minimally invasive therapy that is gaining widespread acceptance as a safe and effective treatment for reducing the symptoms of uterine leiomyomata. An estimated 200,000 UAEs have been performed worldwide since 1995, when this procedure was first utilized by Ravina et al. [3]. The technical goal is to deliver particulate material (typically polyvinyl alcohol particles, PVA microspheres, or gelatin-coated polymer microspheres) into both uterine arteries to produce ischemic change to myomas without causing permanent damage to uterus [4].

The integrity of human body is largely dependent on the composition and arrangement of connective tissue. The connective tissue is composed of several key elements such as fibroblasts and an extracellular matrix (ECM) containing collagen, elastic fibrils, proteoglycans, and glycosaminoglycans organized like a hammock. Structure and distribution of these components and their interactions determine the biomechanical properties of the tissues. ECM is essential for tissue remodeling, and many of its components provide a physical structure support to surrounding cells. More importantly, proteins have a key role in regulating survival, motility, proliferation, and morphology of normal cells and contribute to a variety of cellular functions, including organ development, wound healing, and metabolism [5, 6].

Despite many studies that assessed uterine myoma and infertility, the explanation of how it works on reproduction detrimental effect remains unknown. As the same way, studies evaluating the effect UAE may have on subsequent fertility and pregnancy have yielded conflicting data [7, 8].

Until now, there were no studies that correlate the impact of UAE in endometrial/uterine extracellular matrix which could improve or impair fertility. The objective of this study was to evaluate endometrial/uterine biopsies, especially collagen, before and after UAE in treatment of uterine fibroids.

Material and methods

Fifteen consecutive patients with a diagnosis of uterine fibroids were included. Clinical diagnosis had been confirmed by ultrasonography. Indications for UAE were: menorrhagia subjectively reported by the patient as increased or prolonged menstrual blood loss which causes dysfunction in daily life; pelvic pain; compressive symptoms in urinary/gastrointestinal tract and infertility related to fibroids.

All patients gave their informed consent to participate in this study, and Local Ethics Committee approved the protocol for it. This study was supported by the Department of Gynecology and Department of Image Diagnosis of Federal University of São Paulo, and there was no external sponsor.

Exclusion criteria included subserosal and submucosal fibroids, pelvic infection, gynecologic malignancy, undiagnosed pelvic mass outside of the uterus, unexplained abnormal menstrual bleeding, infection, coagulopathy, history of pelvic irradiation, FSH level >40 IU/L, adenomyosis suspected by magnetic resonance imaging. Patients were also excluded if they wished to become pregnant in future with others options of treatment and uterine volume size >500 cm^3.

Patients had prophylactic antibiotics with 1 g oral azitromicin in previous day and intravenous Cefalotin, 2 g about 60 min before the procedure. Analgesia used was epidural or intradural anesthesia. Selective catheterization of uterine arteries was carried through bilaterally and was guided by angiography. A 4-F or 5-F catheter was introduced into right femoral artery and advanced over aortic bifurcation to contralateral internal iliac artery to identify the origin of uterine artery. UAE was performed with microsphere (trisacryl gelatin microspheres) with 300–700-my diameter, and injection of material was kept until circulation ceasing confirmed by angiography. The procedure was carried through in both uterine arteries. Patient preparation, anesthesia and analgesia details, procedure information, and discharge information were recorded.

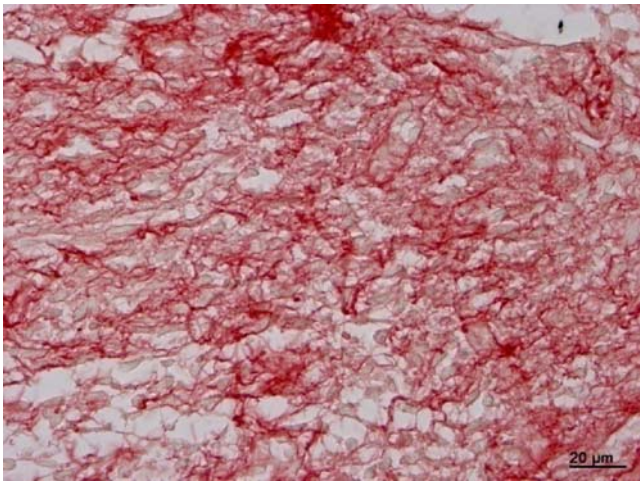

Fig. 2 Biopsy before uterine arterial embolization. Collagen fibers in *red*. Picro-sirius. Magnification ×400

For collagen evaluation, endometrial/uterine biopsy was taken in secretory phase with Novak curette before UAE and 3 months after the procedure.

Material was fixed with 10% buffered paraformaldehyde (Sigma, St. Louis, MO, USA) for 24 h processed routinely and included in similar of paraffin Histosec® (Merck, German). Fragments were dehydrated in ethylene at increasing concentrations, turned translucent by xylol and impregnated with liquid paraffin. Histological courts were adjusted for a thickness of 20 µm. They were placed previously in sheets prepared for routine techniques of coloration in picro-sirius for collagen and muscular fibers.

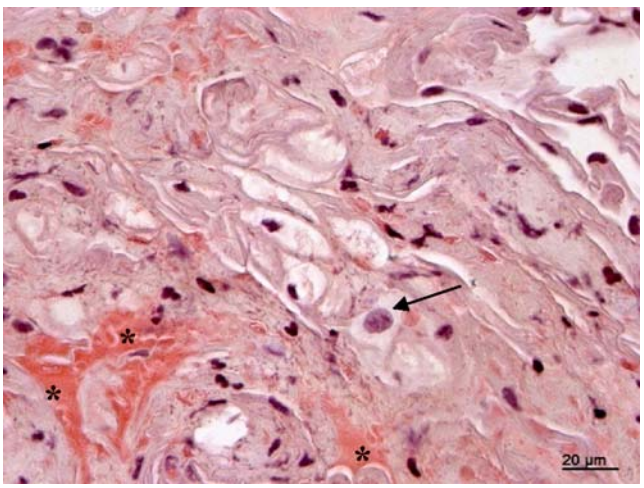

Fig. 1 Biopsy before uterine arterial embolization. Large number of smooth muscular cells with great nucleus (*arrow*) and blood vases (*). Hematoxylin–eosin. Magnification ×400

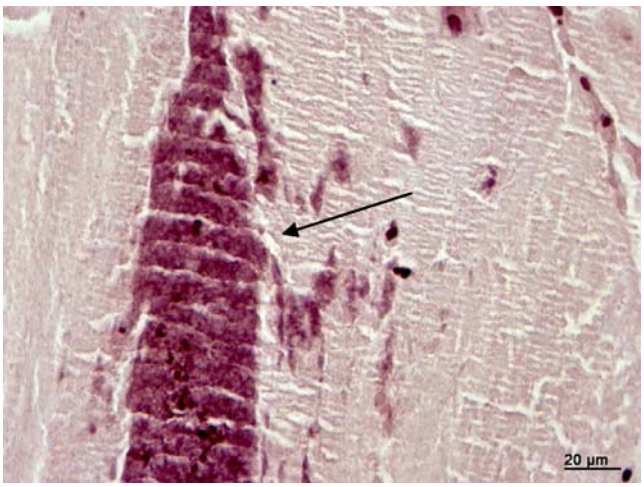

Fig. 3 Biopsy after uterine arterial embolization. Coagulation and necrosis. Hematoxylin–eosin. Magnification ×400

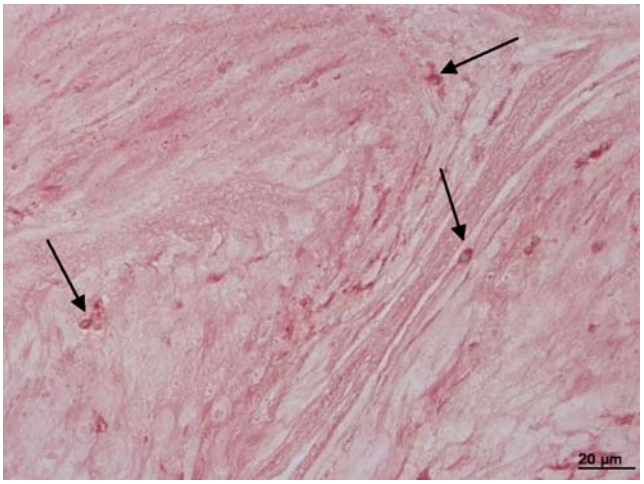

Fig. 4 Biopsy after uterine arterial embolization. Diffuse necrosis and linfoplasmocitary infiltration. Picro-sirius. Magnification ×400

Sheets were maintained in a stove regulated to a temperature of 37°C for 24 h for drying.

For morphometric analysis of collagen and muscular fibers, we used quantification by means of computerized system. It was constituted by a light microscope (Carl Zeiss) with objective 40×, a colored video camera (Sony, Hyper Had), a computer with graphic plate for image acquisition (AxioVision 4.6-Zeiss) software with 640×480 pixels/24 bits and a processing software and image analysis—Imagelab (Softium Informática LTDA).

Statistical analysis

All numerical data were expressed as the mean±standard deviation. The two groups were assessed for comparability using an independent sample *t* test for continuous variables. Level of significance (*p*) was set at ≤05 (α=5%).

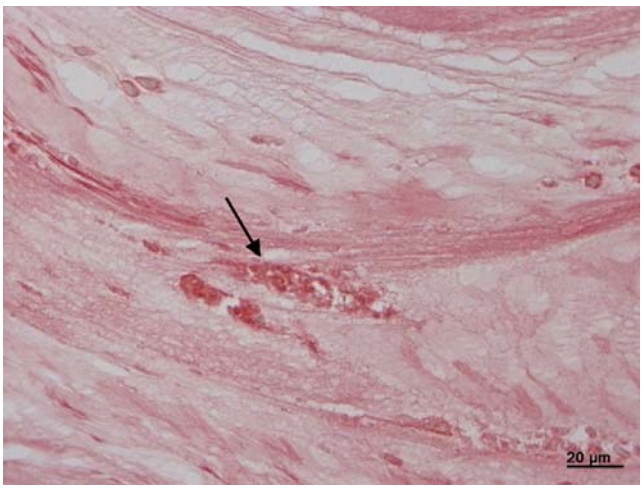

Fig. 5 Biopsy after uterine arterial embolization. Dystrophic calcification. Picro-sirius. Magnification ×400

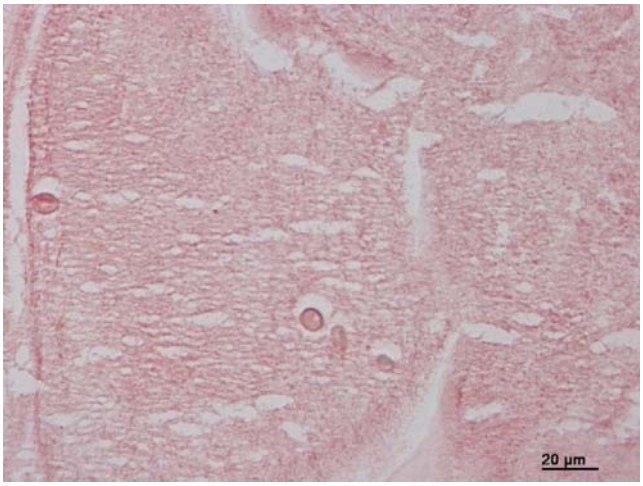

Fig. 6 Biopsy after uterine arterial embolization. Collagen amounts reduction. Picro-sirius. Magnification ×400

Results

Before UAE, we noticed the presence of smooth muscular cells. They contained bulky and central nucleus. These cells were encircled by collagen fibers, blood, vases and fibroblasts (Figs. 1 and 2).

After UAE, we observed diffuse coagulation necrosis, thrombosis vascular, calcification areas, and linfoplasmocitary infiltration (Figs. 3, 4, and 5). In these biopsies, we noticed a clear collagen amount reduction (Fig. 6).

Table 1 Mean percentage of collagen in all 15 patients

Patients	Before UAE	After UAE
1	85.77	82.81
2	83.83	79.89
3	82.77	81.77
4	80.68	78.63
5	85.87	79.36
6	83.15	79.02
7	84.98	82.80
8	84.51	81.79
9	85.15	82.86
10	84.06	81.67
11	84.38	81.22
12	85.57	81.51
13	82.48	81.81
14	83.50	78.81
15	84.28	81.74
Mean	84.08	81.05
Standard deviation	1.46	1.50

Values are given as mean (±standard deviation)

UAE uterine arterial embolization

Analysis of collagen fibers are expressed in Table 1. Collagen fibers percentage was reduced ($p<0.0001$) in group after UAE (81.05±1.50) comparing to group before UAE (84.08±1.46).

Comment

The efficacy of UAE has been recently published by the Cochrane Database. The meta-analysis documented that UAE is efficacious in terms of shorter hospitalization and reduction in blood loss (85% from pretreatment) and uterine size (30–49% from pretreatment) [9]. However, fertility maintenance after UAE is still a conflicting subject. Until now, the impact of this treatment on endometrial functions is not established [10, 11].

Human endometrium is composed of distinct arrangements of cells of different lineages. These include endometrial glands, stromal cells, fibroblasts, lymphoid cells, endothelial cells, and smooth muscle cells that coat vessels of the endometrium. The complex structure of the endometrium undoubtedly requires an array of distinct molecules, which contribute to the cell distribution, cell trafficking, and interaction of cells with each other and with constituents of the endometrial meshwork, including collagen, fibronectin, laminin, and other matrix proteins [12].

Over the years, some investigators have come to recognize the importance of the extracellular matrix in directing growth, differentiation, and function of the underlying epithelium. The major components of basement membranes within human endometrium have been identified. Vascular and glandular basement membranes have been shown to be immunoreactive for collagen IV, laminin, and heparan sulfate proteoglycan during the proliferative, mid and late secretory stages of the menstrual cycle. During the proliferative phase, the most abundant interstitial matrix component is collagen I. The main change is the progressive loss of collagen IV, which starts in the mid secretory phase and continues after implantation [13].

Theoretically, UAE may contribute to difficulties in embryo implantation or maintenance of pregnancy by decreasing vascularity of the uterine myometrium and endometrium. In fact, embolization particles have been identified after UAE in structures adjacent to leiomyomas (myometrium, parametrium, mesovarium) [14]. Most often, myometrium adjacent to embolized leiomyomas is spared from tissue necrosis. In addition, there generally does not seem to be any significant histologic impact on the endometrium, presumably because myometrial vessels trap particles before arrival in the endometrium. Colgan and colleagues [15] reported cervical necrosis, necrotizing myometritis, endomyometritis, or acute endometritis in five of eight hysterectomy specimens that were performed for complications after 555 UAE procedures. Therefore, although the overall risk seems to be low, there is a concern that UAE could produce a deleterious impact on myometrium and endometrium.

Characteristic histological features within leiomyomas included massive necrosis, sometimes with dystrophic calcification, vascular thrombosis, and intravascular foreign material that elicited a histiocytic and foreign-body giant cell reaction. In some cases, intravascular foreign material was present elsewhere in myometrium, cervix, or paraovarian region. In occasional cases, there was focus of myometrial necrosis and microabscess formation. Focus of extra uterine inflammation was also occasionally identified [16].

This study demonstrated statistical significant reduction in collagen, and this observation was present in all patients submitted to procedure. Collagen reduction mainly evidences that UAE is efficient in reducing tumoral myoma mass which is composed by collagen fibers and smooth muscular cells. However, complementary researches are necessary to study functional and biological repercussion of these alterations.

UAE is becoming a popular therapeutic option for symptomatic fibroids. Its role in treatment of fibroid-associated fertility, however, needs further investigation. Indeed, larger prospective randomized trials with control groups are required to better understand the impact of fibroids and its treatment on endometrium extracellular matrix.

Conflict of interest There are no conflicts of interest and no external financial support.

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