THE JOURNAL OF
Obstetrics and Gynaecology Research

The official Journal of Asia and Oceania Federation of Obstetrics and Gynaecology
Japan Society of Obstetrics and Gynecology

doi:10.1111/j.1447-0756.2012.01939.x J. Obstet. Gynaecol. Res. Vol. 39, No. 1: 410–414, January 2013

Fumarate hydratase gene mutation in two young patients with sporadic uterine fibroids

Kristyna Kubinova[1,4], Marketa Tesarova[2,4], Hana Hansikova[2,4], Kamila Vesela[3,4], David Kuzel[1,4] and Michal Mara[1,4]

Departments of [1]Obstetrics and Gynecology, [2]Pediatrics and Adolescent Medicine and [3]Genetics, First Faculty of Medicine, Charles University, and [4]General University Hospital in Prague, Prague, Czech Republic

Abstract

Fumarate hydratase (FH) is a key enzyme of the Krebs cycle. Germline mutations in the *FH* gene encoding fumarate hydratase cause autosomal dominant syndromes multiple cutaneous and uterine leiomyomata and hereditary leiomyomatosis and renal cell cancer (HLRCC). Few data have been published on the role of *FH* gene mutation in development of uterine fibroids outside the context of multiple cutaneous and uterine leiomyomata /HLRCC. We report two *FH* gene mutations, one novel and one previously described, in two young patients with sporadic uterine fibroids and decreased fumarate hydratase activity in lymphocytes. In patient 1, a novel heterozygous mutation c.892G>C was found. In patient 2 we detected heterozygous mutation c.584T>C. Both the patients had a negative family history for renal cancer and cutaneous leiomyomatosis. None of the relatives, however, underwent renal imaging at the time of writing. *FH* mutation carriers may be easily identified by analysis of fumarate hydratase activity in blood lymphocytes. We suggest performing fumarate hydratase activity or *FH* mutation screening in women with onset of uterine fibroids in their 20s and family history of uterine fibroids or other HLRCC-associated malignancies.

Key words: *FH* gene, fumarate hydratase, uterine fibroids.

Introduction

Uterine fibroids are the most common gynecological benign tumors and many uterine fibroids are asymptomatic and remain undiagnosed. Approximately 25% of women with uterine fibroid suffer from pain, metrorrhagia, infertility and pregnancy complications.[1–3] The cause of uterine fibroids is still to be identified. Risk factors have been described, such as hormonal factors, nulliparity, early-onset of menarche before 11 years of age, ethnicity and genetics.[1,4]

Studies of uterine fibroid specimens have shown that up to 50% of these tumors bear cytogenetic chromosomal alteration. Most common are deletion in chromosome 7 and translocation in chromosomes 7, 12 and 14.[4]

Recently the focus on understanding the molecular basis of uterine fibroids has been on mutations in the fumarate hydratase (*FH*) gene. Germline mutations in the *FH* gene are known to cause rare autosomal dominant syndromes of multiple cutaneous and uterine leiomyomata (MCUL1) and hereditary leiomyomatosis and renal cell cancer (HLRCC) characterized by multiple skin leiomyomatosis, early onset of uterine leiomyomas and increased risk of renal cell carcinoma, papillary type II.[1,2,5] The incidence of uterine fibroids in the general population of women increases with age. In women in the 2nd decennium, the incidence rate is 4.3 per 1000 woman-years compared to 22.5 per 1000 woman-years in women aged 40–44 years.[6] However women with HLRCC typically develop uterine fibroids in the 2nd and 3rd decennium.[1,7]

Received: June 15 2011.
Accepted: April 14 2012.
Reprint request to: Dr Kristyna Kubinova, Department of Obstetrics and Gynecology, Apolinarska 18, 128 51 Praha 2, Czech Republic. Email: kristynakubinova@gmail.com

Patients with germline mutation in *FH* show reduced activity of fumarate hydratase (fumarase) in lymphoblastoid and fibroblast cells.[8] Our understanding of the pathways of tumorigenesis in fibroids outside the context of MCUL1/HLRCC is still limited. There is, however, little evidence that somatic *FH* mutation plays a role in development of non-syndromic leiomyomas.[2,9,10] Even though similar in histological structure, the tumorigenesis in HLRCC and sporadic fibroids may occur via a different process.[2]

We report two cases of young patients with multiple sporadic uterine fibroids with a detection of *FH* gene mutation.

Case Report

Proband 1 was a 25-year-old nulliparous Caucasian woman diagnosed with uterine fibroids. She underwent preoperative ultrasound examination that described two fibroids of 5 and 2 cm in the posterior wall location (Fig. 1). Her major complaint was abdominal pain and she underwent laparoscopic myomectomy. The histological examination confirmed the diagnosis of benign leiomyoma. The mother of the proband had suffered from uterine fibroids at 27 years of age and underwent hysterectomy at 40 years of age. The maternal grandmother and sister of the mother were also diagnosed with uterine fibroids. Detailed clinical data obtained for first- and second-degree family members revealed no history of renal cancer or other malignancy, and none of the family members had had renal imaging at the time of writing.

Proband 2 was a 30-year-old nulliparous Caucasian woman with a diagnosis of multiple voluminous uterine fibroids. Preoperative ultrasound examination revealed multiple fibroids of ≥6 cm in the posterior wall (Fig. 2). The proband suffered from menometrorrhagia, anemia and bulky symptoms and underwent open myomectomy. Histology finding verified benign leiomyoma with partial regressive changes. The mother of the proband had a history of uterine fibroids and underwent hysterectomy at 36 years of age. None of the first- and second-degree relatives had developed cutaneous leiomyomatosis, renal cancer (no renal imaging was available at the time of writing) or any other malignancy.

Definitions

We defined the probands as women under 30 years of age with ≥1 symptomatic uterine fibroid sized ≥3 cm. The diagnosis of uterine fibroid(s) was confirmed by ultrasound scan, equipped with a 5–9-MHz vaginal probe and equipped with a 2–5-MHz abdominal probe.

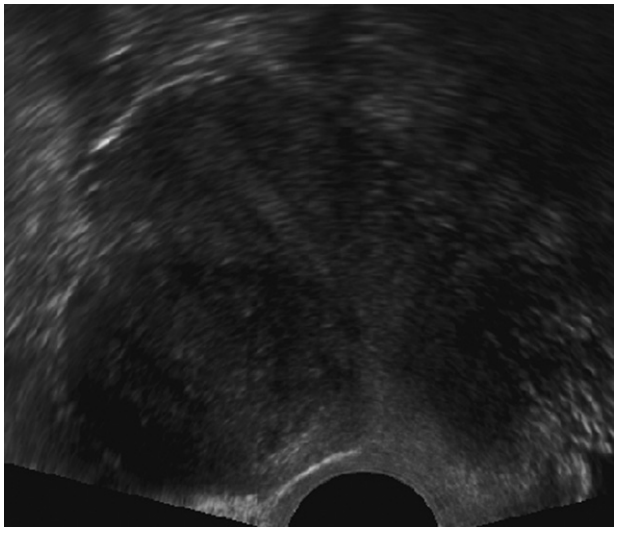

Figure 1 Preoperative ultrasonography image of proband 1.

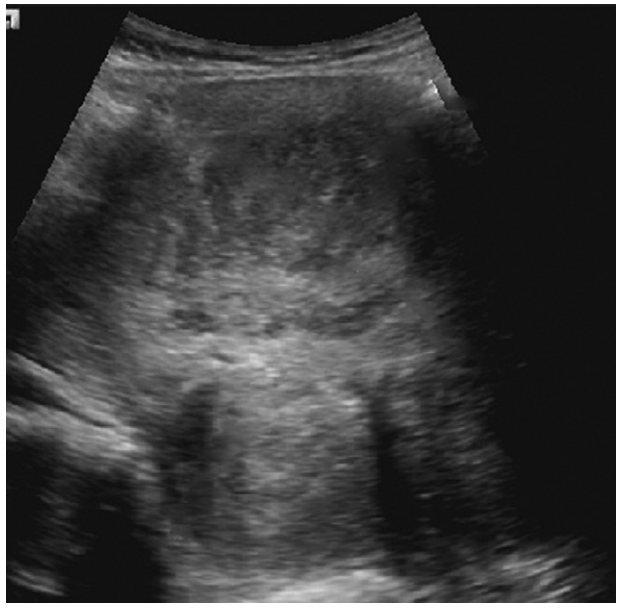

Figure 2 Preoperative ultrasonography image of proband 2.

Healthy controls ($n = 42$) were defined as women younger than 30 years of age with no history of uterine fibroids (confirmed by ultrasound scan) and negative family history for renal cancer and cutaneous leiomyomatosis. All patients from this group were informed on the principles of the study and signed an informed consent. The study design was approved by the ethics committee of the First Faculty of Medicine, Charles University in Prague.

After obtaining the informed consent from probands, analysis of peripheral blood lymphocytes was performed as follows: activities of fumarate hydratase[11] and citrate synthase[12] were measured spectrophotometrically. Activities of fumarate hydratase found in the proband's lymphocytes were compared to activities observed in lymphocytes from healthy controls ($n = 42$). All ten exons and adjacent intronic regions of the *FH* gene were amplified from isolated leukocyte genomic DNA by polymerase chain reaction (PCR) (primers and PCR conditions are available upon request) and sequenced in both directions on an AbiPrism 3100 Avant Genetic Analyser.

Results

Analysis of isolated lymphocytes revealed decreased activity of fumarate hydratase in both probands. In proband 1, the fumarase activity was 11.52 nmol/min/mg of protein (controls 19–32 nmol/min/mg of protein), fumarase activity normalized to activity of control enzyme citrate synthase (CS) was decreased as well (proband 0.11, controls 0.21–0.39). In proband 2, fumarase activity was 8.46 nmol/min/mg of protein (controls 19–32 nmol/min/mg of protein) and fumarase/CS ratio was border low (proband 0.25, controls 0.21–0.39). Mutation analysis of the *FH* gene revealed heterozygous missense mutations in both probands. In proband 1, heterozygous mutation c.892G>C was found. The mutation was also detected in the proband's mother. The mutation changes highly conserved Ala[298] into Pro. According to the LOVD database,[13] the mutation has not been reported previously. The mutation c.892G>C was not found in 200 control alleles. Mutation p.Ala298Pro is localized near the active site[14] and may possibly interfere with catalytic mechanism. In proband 2, heterozygous mutation c.584T>C, inherited from her mother, was found. The mutation results in amino-acid substitution p.Met195Thr and it was previously described in a family with hereditary leiomyomatosis.[15] Mutation p.Met195Thr, localized in core helices, affects the structural integrity of the enzyme by interrupting intra-subunit interactions.[14] In a formalin-fixed paraffin-embedded sample of uterine fibroid of proband 2, molecular genetic analysis confirmed the presence of c.584T>C mutation in the *FH* gene in homozygous status, suggesting loss of heterozygosity in the uterine fibroid.

Discussion

The fumarate hydratase (*FH*) gene is localized at 1q42.3–43 and encodes for two fumarase isoenzymes, mitochondrial and cytosolic. Fumarase is active as a homotetramer, catalyzes hydratation of fumarate to malate as a part of the tricarboxylic acid cycle in mitochondrial matrix, and its deficiency results in rare metabolic autosomal-recessive fumaric aciduria. In 2002, it was demonstrated by genetic studies on HLRCC that *FH* may act as a tumor suppressor gene (citace Nature Genetics 2002).

Studies on families affected by HLRCC have shown that 71–93% of patients have the evidence of *FH* mutation.[15–17] The prevalence of *FH* mutations in sporadic leiomyomas has been reported in three previous studies.[2,5,7] Barker *et al*.[2] found no *FH* mutation in a study on 45 fresh frozen uterine leiomyomas and nine leiomyosarcomas. One germline mutation of *FH* was identified in a patient that did not present any additional clinical features of MCUL1/HLRCC.[2] Kiuru *et al*. found no *FH* mutation in 41 leiomyomas. However, the analysis of 18 uterine leiomyosarcomas in this study harvested one germline mutation.[5] Similarly, Lehtonnen *et al*. found two somatic mutations in 153 leiomyomas from 46 unselected individuals.[9] Barker *et al*. suggests that germline *FH* mutations could cause up to 5% of leiomyomas.[2] A study of MCUL1/HLRCC clinical features has indicated that 7% of FH_{poz} patients had only uterine fibroids and 9% were clinically unaffected.[7] Although Vahteristo *et al*. observed that only approximately 20% of HLRCC families displayed renal cancer, germline *FH* mutations represent an increased risk of renal cancer and therefore clinical surveillance is recommended for all *FH* mutation carriers.[18]

We found germline *FH* mutation in patients and their mothers with sporadic uterine fibroids and negative family history for renal cancer and cutaneous leiomyomatosis. Therefore, yearly magnetic resonance imaging of the abdomen and pelvic region and ultrasound of the kidneys were recommended to all our *FH* mutation carriers.

Carriers of the *FH* gene mutation may be easily detected by fumarase activity measurement in isolated lymphocytes. Both identified mutations resulted in significantly decreased fumarase activity. Moreover, *FH* mutation c.584T>C was homozygous in uterine fibroid sample of patient 2, suggesting a loss of heterozygosity, which is in accordance with the hypothesis of pseudohypoxia response activation providing a growth advantage to cells with fumarase deficiency.[19]

Our data confirm that the *FH* germline mutation can be found in patients with apparently sporadic uterine fibroids with no other clinical features of MCUL1/HLRCC and that the *FH* mutation carriers may be easily selected by analysis of fumarate hydratase activity in blood lymphocytes. Based on our experience and published data, fumarate hydratase activity or FH mutation screening should be performed, especially in women with onset of uterine fibroids in their 20s and family history of uterine fibroids or other malignancies.

Acknowledgments

This work was supported by grants IGA NS 9798-4 and RVO-VFN64165/2012 (M.T.) from the Ministry of Health of the Czech Republic and Grant Agency of the Ministry of Health of the Czech Republic and by institutional research project PRVOUK of the Charles University in Prague-First Faculty of Medicine (program MOLMED; H.H.).

Disclosure

The authors report no conflicts of interest. The authors have no relationships with the companies that may have a financial interest in the information contained in the manuscript.

References

1. Stewart L, Glenn GM, Stratton P *et al*. Association of germline mutations in the fumarate hydratase gene and uterine fibroids in women with hereditary leiomyomatosis and renal cell cancer. *Arch Dermatol* 2008; **144**: 1584–1592.
2. Barker KT, Spendlove HE, Banu NS *et al*. No evidence for epigenetic inactivation of fumarate hydratase in leiomyomas and leiomyosarcomas. *Cancer Lett* 2006; **235**: 136–140.
3. Hodge JC, Morton CC. Genetic heterogeneity among uterine leiomyomata: Insights into malignant progression. *Hum Mol Genet* 2007; **16** (Spec No 1): R7–13.
4. Okolo S. Incidence, aetiology and epidemiology of uterine fibroids. *Best Pract Res Clin Obstet Gynaecol* 2008; **22**: 571–588.
5. Kiuru M, Lehtonen R, Arola J *et al*. Few FH mutations in sporadic counterparts of tumor types observed in hereditary leiomyomatosis and renal cell cancer families. *Cancer Res* 2002; **62**: 4554–4557.
6. Marshall LM, Spiegelman D, Barbieri RL *et al*. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. *Obstet Gynecol* 1997; **90**: 967–973.
7. Alam NA, Barclay E, Rowan AJ *et al*. Clinical features of multiple cutaneous and uterine leiomyomatosis: An underdiagnosed tumor syndrome. *Arch Dermatol* 2005; **141**: 199–206.
8. Pithukpakorn M, Wei MH, Toure O *et al*. Fumarate hydratase enzyme activity in lymphoblastoid cells and fibroblasts of individuals in families with hereditary leiomyomatosis and renal cell cancer. *J Med Genet* 2006; **43**: 755–762.
9. Lehtonen R, Kiuru M, Vanharanta S *et al*. Biallelic inactivation of fumarate hydratase (FH) occurs in nonsyndromic uterine leiomyomas but is rare in other tumors. *Am J Pathol* 2004; **164**: 17–22.
10. Vanharanta S, Pollard PJ, Lehtonen HJ *et al*. Distinct expression profile in fumarate-hydratase-deficient uterine fibroids. *Hum Mol Genet* 2006; **15**: 97–103.
11. Hill RL, Bradshaw RA, John ML. Fumarase: [EC 4.2.1.2 l-Malate hydro-lyase]. In: Lowenstein JM (ed.). *Methods in Enzymology*. San Diego: Academic Press, 1969; 91–99.
12. Srere PA, John ML. Citrate synthase : [EC 4.1.3.7. Citrate oxaloacetate-lyase (CoA-acetylating)]. In: Lowenstein JM (ed.). *Methods in Enzymology*. San Diego: Academic Press, 1969; 3–11.
13. Bayley JP, Launonen V, Tomlinson IP. The FH mutation database: An online database of fumarate hydratase mutations involved in the MCUL (HLRCC) tumor syndrome and congenital fumarase deficiency. *BMC Med Genet* 2008; **9**: 20.
14. Picaud S, Kavanagh KL, Yue WW *et al*. Structural basis of fumarate hydratase deficiency. *J Inherit Metab Dis* 2011; **34**: 671–676.
15. Toro JR, Nickerson ML, Wei MH *et al*. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. *Am J Hum Genet* 2003; **73**: 95–106.
16. Wei MH, Toure O, Glenn GM *et al*. Novel mutations in FH and expansion of the spectrum of phenotypes expressed in families with hereditary leiomyomatosis and renal cell cancer. *J Med Genet* 2006; **43**: 18–27.
17. Perrier-Trudova V, Rustin P, Barrois M *et al*. French National Cancer Institute 'Inherited predisposition to kidney cancer' network. Novel FH mutations in families with hereditary leiomyomatosis and renal cell cancer (HLRCC) and patients with isolated type 2 papillary renal cell carcinoma. *J Med Genet* 2011; **48**: 226–234.
18. Vahteristo P, Koski TA, Näätsaari L *et al*. No evidence for a genetic modifier for renal cancer risk in HLRCC syndrome. *Fam Cancer* 2010; **9**: 245–251.
19. O'Flaherty L, Adam J, Heather LC *et al*. Dysregulation of hypoxia pathways in fumarate hydratase-deficient cells is independent of defective mitochondrial metabolism. *Hum Mol Genet* 2010; **19**: 384 **length polymorphism**4–3851.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Results of fumarate hydratase (*FH*) gene sequencing in DNA isolated from leucocytes of patient 1, patient 2, and control. The red arrow indicates position of the mutation.

Figure S2 Polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP) testing for presence of c.584T>C mutation in *FH* gene in patient 2 leucocytes and uterine fibroid. DNA fragments of 249 bp and 150 bp correspond to wild-type allele. M, molecular size marker.

Table S1 Activities of fumarate hydratase and control enzyme citrate synthase in isolated blood lymphocytes.

Minimally Invasive Therapy. 2012;21:118–124

informa
healthcare

ORIGINAL ARTICLE

Reproduction after myomectomy: Comparison of patients with and without second-look laparoscopy

KRISTYNA KUBINOVA[1], MICHAL MARA[1], PETR HORAK[1], DAVID KUZEL[1], ALENA DOHNALOVA[2]

[1]*Department of Obstetrics and Gynecology Charles University, First Faculty of Medicine and General Faculty Hospital in Prague, Prague, Czech Republic, and* [2]*Department of Physiology and Biostatistics, Charles University, First Faculty of Medicine and General Faculty Hospital in Prague, Prague, Czech Republic*

Abstract

Myomectomy is associated with a high risk of de-novo adhesion formation that may decrease fertility. The purpose of this study was to compare the reproductive outcome of patients after laparoscopic or open myomectomy who underwent second-look (SL) hysteroscopy and laparoscopy including adhesiolysis with patients with no SL intervention. A total of 170 patients underwent open or laparoscopic myomectomy at one centre. All patients were recommended SL. Reproductive results were analyzed in 12 and 24 months intervals following myomectomy. Out of 170 post-myomectomy patients 96 signed informed consent with SL (group A) and 74 withheld (group B). The cumulative pregnancy rate in the 24-months follow-up was: 61.4% and 66.7% ($p = 0.535$) in group A and group B respectively. Adhesions of adnexa were observed and lysed in the overall of 34.0% of patients at the time of SL. Intrauterine synechiae were present in 1.56% of patients at the SL hysteroscopy. No case of uterine rupture during pregnancy or delivery was recorded. Our results show that the pregnancy rate of patients after myomectomy who underwent SL hysteroscopy and laparoscopy is similar to that of patients with no SL procedure. Adhesiolysis performed during SL does not seem to improve the reproductive outcome of post-myomectomy patients.

Key words: *Adhesiolysis, myomectomy, pregnancy rate, reproductive outcome, second-look laparoscopy*

Introduction

Uterine fibroids are the most common benign tumors in women of reproductive age. In the majority of cases uterine fibroids are asymptomatic but in approximately 30% of cases may cause menorrhagia, pelvic pain, and/or infertility (1). Myomectomy still remains the standard of care in symptomatic patients desiring to preserve fertility (2). This procedure is, however, associated with de-novo adhesion formation that may result in bowel obstruction, chronic pelvic pain and infertility (3–6). Pelvic adhesions have been reported to form in up to 95% of patients within the first several weeks after major gynecological surgery (7). Whether these adhesions really deteriorate the reproduction of the patients still remains an enigma. The purpose of this study was to determine whether SL hysteroscopy and laparoscopy (including adhesiolysis) has an impact on reproductive outcome of post-myomectomy patients by means of comparing reproductive results of patients that underwent SL procedure with a group of patients with no SL intervention.

Material and methods

We analyzed 170 women who underwent laparoscopic ($n = 121$) and open ($n = 49$) myomectomy between March 2002 and April 2008 at the Department of Obstetrics and Gynecology of the University Teaching Hospital, Prague, Czech Republic. Patients met the following inclusion criteria: Future reproductive plans, fibroid (s) size ≥ 30 mm, intramural or subserous fibroids requiring myometrium suture, no plausible factor of infertility. Patients with primary pelvic

Correspondence: K. Kubinova, Department of Obstetrics and Gynecology, Charles University, Apolinarska 18, 128 51 Praha 2, Czech Republic. E-mail: kristynakubinova@gmail.com

ISSN 1364-5706 print/ISSN 1365-2931 online
DOI: 10.3109/13645706.2011.573797

adhesions present at myomectomy were excluded from the study. No adhesion-prevention barrier was used during myomectomy. Patients were assigned to open or laparoscopic myomectomy based on size, number and location of fibroids. 5.36% of laparoscopic myomectomies were urgently converted for severe bleeding or technical difficulties in laparoscopic enucleation of myoma. With regards to the inclusion criteria all the patients included in the study were eligible for the second look hysteroscopy and laparoscopy. SL was performed two to six months following myomectomy. All procedures were performed by one team using a unified technique as follows.

Open myomectomy (OM)

In OM a linear vertical incision in the most prominent part of the fibroid was made by means of a monopolar electric scalpel. The fibroid was then grasped by a hooked forceps and enucleated using traction and counter-traction maneuver and a blunt dissection in the right plane. The myoma bed was closed in two or three layers (depending on the size of myoma and on whether the uterine cavity was opened or not) with Vicryl 1-0 (Ethicon Inc., Menlo Park, CA, USA) continuous suture. In the end of the operation uterine suture was lavaged to ensure the absence of bleeding.

Laparoscopic myomectomy (LM)

LM was performed by use of 10 mm scope (Olympus Medical, Inc., Tokyo, Japan) with three ancillary ports. The first step was a longitudinal vertical monopolar incision in the most prominent part of the fibroid. The fibroid was then enucleated combining adequate traction with a Schroeder's tenaculum forceps with counter-traction with a grasper and monopolar coagulation scissors. The myometrium suture was made in two or three layers depending on the uterine wound by means of Vicryl 4-0 (Ethicon Inc.) combining extracorporeal and intracorporeal knotting. Fibroids were then removed with a 12 mm electrical morcelator.

The following baseline data were collected: Patient age, number of fibroids, size and location of the dominant fibroid. All samples were submitted to pathological examination.

All patients were given a detailed explanation of the second look procedure and were offered the SL hysteroscopy and laparoscopy to check the uterine scar tenacity, e.g. predict the risk of uterine rupture, to perform a tubal patency test (patients with no tubal patency were suggested *in vitro* fertilization) and to perform pelvic or intrauterine adhesiolysis in case of presence of adhesions. All patients were informed that the impact of adhesiolysis on pain and infertility might be beneficiary but is still unknown. Seventy-two patients declined the second look. The remaining 94 patients underwent SL hysteroscopy and laparoscopy under general anesthesia with the following technique.

Second look

SL hysteroscopy was performed in lithotomy position. The uterine cervix was dilated and a 5.5 mm rigid hysteroscope (Olympus Medical, Inc.) inserted in the uterine cavity. Normal saline solution (F1/1) was used a distension medium. The uterine cavity was then checked for any abnormality including intrauterine adhesions, intracavitary fibroids, fistula or presence of stitches. In case of intracavitary fibroids resection was performed using a bipolar loop electrode (VersaPoint – Bipolar Resectoscopic System, Gynecare, Ethicon, Inc., Menlo Park, CA, USA) in a distension medium (F1/1 normal saline solution). Intrauterine adhesions, if present, were excised using scissors.

After hysteroscopy the patient was placed in the Trendelenburg position and the SL laparoscopy was performed by a 10 mm scope (Olympus Medical, Inc.) and one to three ancillary ports. The presence, location and severity of intraabdominal adhesions were recorded followed by adhesiolysis. The tenacity of the uterine scar examination as well as the tubal patency test using Methylene blue dye were performed at the end of the operation.

Reproductive follow-up

All patients were referred to our outpatient department for a regular check-up every six months. Patients received a questionnaire regarding reproductive outcome. All the pregnancies and their outcome occurring in a 24-month follow-up period after myomectomy were recorded and included in the study results. We calculated the cumulative pregnancy and delivery rates at 12 and 24 months, as well as all abortions and miscarriages plus all ectopic pregnancies at stated periods. We also registered the proportion of patients with spontaneous conception and patients requiring assisted reproduction techniques.

Statistical analysis

To determine statistical differences between the two groups the following tests were used: For statistical comparison of qualitative parameters from both groups (e.g. pregnancy: YES or NO) Fischer's and χ^2 tests, Student's *t*-test and Mann-Whitney test for quantitative parameters. $P < 0.05$ was determined as statistically significant.

Results

A total of 170 patients underwent laparoscopic or open myomectomy. All patients were eligible for a SL intervention. Ninety-six patients participated in the SL (group A) and 74 patients declined (group B). Five patients were lost to follow-up (four patients in group A and one in group B). The baseline characteristics of the patients in groups A and B are given in Table I. Tables II and III show the baseline characteristics of the subgroups subdivided according to the approach to myomectomy and the findings of SL procedures.

The reproductive results of groups A and B are shown in Table IV. In patients with SL hysteroscopy and laparoscopy we recorded a total of 23 and 43 pregnancies in 12 and 24 months follow-up respectively, with a cumulative pregnancy rate of 25.0% and 46.7%. Five patients required IVF. One induced abortion for 21 chromosome trisomia was performed in this group.

In the group of women without SL procedure 21 and 40 pregnancies were observed in 12 and 24 months follow-up respectively, with cumulative pregnancy rates of 28.5% and 54.1%. Ten patients in this group conceived after IVF. The delivery rate in 24 months of follow-up was significantly higher in this group (31.5% in group A versus 47.9% in group B, $p = 0.032$).

The reproductive outcome of patients with and without SL procedure subdivided according to the type of myomectomy (open, laparoscopic) is demonstrated in Tables V and VI. The number of pregnancies and deliveries were similar in both OM sub-groups. The number of deliveries in patients after LM was significantly higher in a sub-group of patients without SL procedure compared to a sub-group of patients with SL (27 versus 21, $p = 0.038$).

Based on the questionnaire the patients received on their reproductive outcome at the time of a regular check-up, a total of 35 patients (22 in group A and 13 in group B) stated that they did not try to conceive in the 24 months period and were planning to postpone their reproductive plans. Table VII shows the "purged" cumulative pregnancy and cumulative delivery rates in 12 and 24 months follow-up where these patients were excluded. This "purged" delivery rate at 24-month follow-up was also significantly higher in patients without SL: 67.4% in group A vs. 87.5% in group B ($p = 0.03$).

Out of the total of 64 pregnancies that resulted in live births, 53 (82.81%) deliveries were by caesarean

Table I. Baseline characteristics of groups A and B.

	Group A (patients with SL)	Group B (patients without SL)	p value
Number of all patients with myomectomy	96	74	
Open myomectomy	28	21	
Laparoscopic myomectomy	68	53	
Mean age (years)	32.70	32.60	*0.906*
Mean size of dominant fibroid (mm)	61.71	59.34	*0.682*
Number of fibroids removed per patient	1.73	1.62	*0.442*

Table II. Baseline characteristics and results of SL hysteroscopy and laparoscopy in patients with post-myomectomy SL procedure (group A).

	A1 (Open Myomectomy)	A2 (Laparoscopic Myomectomy)
Number of patients	28	68
Mean age (years)	32.11	32.95
Mean size of dominant fibroid (mm)	74.58	56.03
Number of fibroids removed per patient	2.39	1.44
Normal intrauterine finding (%)	96.43	95.31
Intrauterine synechiae (%)	0	1.56
Intracavitary fibroid (%)	3.57	3.23
De-novo inraabdominal adhesions (%)	96.65	71.43
No adhesions (%)	3.35	28.57
Filmy adhesion (%)	20.05	57,14
Dense adhesions (%)	76.60	14,29
De-novo adhesions of adnexa (%)	89.29	10.60
Incomplete adhesiolysis of adnexa	0	0
Fallopian tubes patent (%)	71.43	92.19

Table III. Baseline characteristics of patients without post-myomectomy SL procedure (group B).

	B1 (Open myomectomy)	B2 (Laparoscopic myomectomy)
Number of patients	21	53
Mean age (years)	32.48	32.63
Mean size of dominant fibroid (mm)	74.00	45.21
Number of fibroids removed per patient	1.38	1.15

Table IV. Reproductive results: Comparison of patients with (group A) and without (group B) SL hysteroscopy and laparoscopy.

Group	A	B		A	B	
Number of patients	92	73		92	73	
Follow-up	12 months	12 months		24 months	24 months	
			p value			p value
Pregnancy	23	29	*0.587*	43	40	*0.332*
Cumulative pregnancy rate (%)	28,8	25.0	*0.587*	38.0	49.3	*0.332*
Delivery	16	18	*0.252*	29	35	*0.032*
Cumulative delivery rate (%)	24.70	17.40	*0.252*	47.90	31.50	*0.032*
Miscarriage	1	1	*1.000*	1	1	*1.000*
Missed abortion	5	0	*0.229*	9	1	*0.114*
Abortion	0	1	*0.442*	0	1	*0.442*
Induced abortion	1	0	*1.000*	1	0	*1.000*
Ectopic pregnancy	0	0		1	1	*0.413*
Heterotopic pregnancy	0	1	*0.442*	0	1	*0.442*
Ongoing pregnancy	0	0		2	0	*0.504*
IVF	4	3	*1.000*	5	10	*0.067*
Uterine rupture	0	0		0	0	

section. Forty-three (79.25%) of the caesarean sections were elective due to a fear of uterine rupture during labor, five were acute due to peri-partum fetal distress, in three patients the indication was a non-progressive labor and in two patients fetal macrosomia. Six women (9.38%) had preterm labor (at 26, 32, 33, 35 and 36 weeks) with favorable perinatal outcome.

No case of uterine rupture during pregnancy or delivery or other myomectomy-related complication was observed in our study.

Discussion

At the present time, surgical treatment of uterine myomas is recommended in symptomatic women or, depending on the size and location of fibroids, in women wishing to conceive (2,8). Several studies have been published on reproductive results after laparoscopic or open myomectomy for intramural or subserous myomas suggesting that myomectomy improves the reproductive outcome of fibroid patients

Table V. Comparison of reproductive results of patients after open myomectomy (patients with SL procedure - A1 versus patients without SL - B1).

Group	A1	B1		A1	B1	
Number of patients	28	21		28	21	
Follow-up	12 months	12 months		24 months	24 months	
			p value			p value
Pregnancy	5	4	*1.000*	12	9	*1.000*
Delivery	4	4	*0.710*	8	8	*0.482*
Miscarriage	0	0		0	0	
Missed abortion	0	0		2	0	*0.500*
Abortion	0	0		0	0	
Induced abortion	1	0	*1.000*	1	0	*1.000*
Ectopic pregnancy	0	0		1	1	*1.000*
Heterotopic pregnancy	0	0		0	0	
Ongoing pregnancy	0	0		0	0	
IVF	1	0	*1.000*	2	2	*1.000*

Table VI. Comparison of reproductive outcome in patients after laparoscopic myomectomy (patients with SL procedure - A2 versus patients without SL - B2).

Group	A2	B2		A2	B2	
Number of patients	64	73		64	73	
Follow-up	12 months	12 months		24 months	24 months	
			p value			p value
Pregnancy	18	17	*0.594*	31	31	*0.218*
Delivery	12	14	*0.294*	21	27	*0.038*
Miscarriage	1	1	*1.000*	1	1	*1.000*
Missed abortion	5	0	*0.222*	7	1	*0.184*
Abortion	0	1	*0.448*	0	1	*0.448*
Induced abortion	0	0		0	0	
Ectopic pregnancy	0	0		0	0	
Heterotopic pregnancy	0	1	*0.448*	0	1	*0.448*
Ongoing pregnancy	0	0		2	0	
IVF	3	3	*1.000*	3	8	*0.051*

(1,2,8–10). Our pregnancy rates were comparable to the results published in those studies.

The main aim of uterus-sparing therapy is to preserve or improve the chances of fibroid patients for an undisturbed pregnancy resulting in safe and favorable delivery (8). The choice of operation procedure (open or laparoscopic myomectomy) depends greatly on the experience of the surgeon as well as on the size and location of dominant fibroid and number of fibroids (11). Mais et al. evaluated the benefits of laparoscopic myomectomy during the postoperative period stating that it is associated with a shorter recovery time and less pain (12). Similarly the rupture of the uterus during pregnancy and delivery is a rare complication after laparoscopic myomectomy (13,14). Laparoscopic myomectomy also seems beneficial for a lower prevalence of postoperative adhesions compared to laparotomy. The risk factor of adnexal adhesions is posterior wall myomectomy (6). In our study adnexal adhesions were observed in 10.60% of patients after laparoscopic and in 89.3% of patients after open myomectomy.

Adhesion formation associated with myomectomy is often stated to decrease fertility as well as cause pelvic pain, bowel obstruction and surgical difficulties in re-operation (3,5,13,15–17). Diamond et al. state that infertility is the major morbidity suffered by many women with adhesive disease. The impairment of reproductive performance occurs through a variety of mechanisms. One of the causes is the distortion of normal tubo-ovarian relationship preventing ovum capture and transportation through the fimbriated end of the Fallopian tube (18).

The indications for SL laparoscopy vary from one study to another. At our institution it was suggested to all patients desiring pregnancy in order to evaluate and lyse adhesions not only to affect fertility but also to prevent per-operative complications in subsequent cesarean section (bowel or urinary bladder injury) as well as to check the integrity of the uterine scar and tubal patency.

Few data on reproductive outcome of patients after SL laparoscopy have been published to date.

Table VII. "Purged" pregnancy rates in 12 and 24 months follow-up (patients which have not tried to conceive excluded).

Group	A	B		A	B	
Number of patients	70	60		70	60	
Follow-up	12 months	12 months		24 months	24 months	
			p value			p value
Cumulative pregnancy rate (%)	32.86	35.00	*0.770*	61.43	66.67	*0.535*
Cumulative delivery rate (%)	69.56	85.72	*0.180*	67.44	87.50	*0.030*

In a study on 26 infertile patients with large fibroids who underwent SL laparoscopy including adhesiolysis six weeks after myomectomy Tulandi et al. state a cumulative pregnancy rate of 66.7% at 12 months (19). Pellicano et al. compared the pregnancy rate after laparoscopic myomectomy in patients treated with autocrosslinked hyaluronic acid gel (anti-adhesion barrier) with that of untreated women. The pregnancy rates reported were higher in patients with application of autocrosslinked hyaluronic acid gel (77.8% versus 38.8% in untreated group) (4). However, no clear data on the clinical significance of post-myomectomy adhesions and efficiency of adhesiolysis in infertile patients have been published to date.

The aim of our study was to evaluate the impact of second-look laparoscopy (including adhesiolysis if pelvic adhesions were present) following myomectomy for voluminous intramural or subserous fibroids on pregnancy outcome in patients with short-term fertility plans. We did not observe any statistical difference in pregnancy rates of patients with SL hysteroscopy and laparoscopy and no SL procedure. Actually, the delivery rate in the 24-month follow-up was significantly lower in the group with SL. The result may be slightly affected by two ongoing pregnancies in second and third trimester in this group.

Even though the occurrence of adnexal adhesions in patients after open myomectomy undergoing SL procedure was high, the reproductive results of patients after adhesiolysis in the SL group were not higher than those in the untreated group. Adhesiolysis does not seem to improve reproductive results of post-myomectomy patients and the effect of adhesiolysis on fertility is questionable. Despite of high rates of dense intraabdominal and adnexal adhesions after OM we did not record a higher prevalence of ectopic pregnancies in patients with SL procedure compared to patients with no SL.

Conclusions

Our study has shown that reproductive outcome of patients after myomectomy should not be deteriorated by adhesions, and thus performing SL laparoscopy in order to improve reproductive results of patients after myomectomy is not necessary. We believe, however, that second-look laparoscopy is a safe tool for the evaluation of uterine scar and early adhesiolysis is helpful in prevention of re-operative complications during subsequent caesarian section.

Nevertheless, more data on the clinical and reproductive impact of post-myomectomy adhesion formation are needed.

Acknowledgments

This work was supported by a grant IGA NS 9798-4 from Ministry of Health of the Czech Republic and Grant Agency of the Ministry of Health of the Czech Republic.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Campo S, Campo V, Gambadauro P. Reproductive outcome before and after laparoscopic or abdominal myomectomy for subserous or intramural myomas. Eur J Obstet Gynecol Reprod Biol. 2003;110:215–9.
2. Palomba S, Zupi E, Falbo A, Russo T, Marconi D, Tolino A, et al. A multicenter randomized, controlled study comparing laparoscopic versus minilaparotomic myomectomy: reproductive outcomes. Fertil Steril. 2007;88: 933-41 Epub 2007 Apr 16.
3. Tsuji S, Takahashi K, Yomo H, Fujiwara M, Kita N, Takebayashi K, et al. Effectiveness of antiadhesion barriers in preventing adhesion after myomectomy in patients with uterine leiomyoma. Eur J Obstet Gynecol Reprod Biol. 2005; 123:244–8 Epub 2005 Jun 9.
4. Pellicano M, Guida M, Bramante S, Acunzo G, Di Spiezio Sardo A, et al. Reproductive outcome after autocrosslinked hyaluronic acid gel application in infertile patients who underwent laparoscopic myomectomy. Fertil Steril. 2005;83:498–500.
5. Mais V, Bracco GL, Litta P, Gargiulo T, Melis GB. Reduction of postoperative adhesions with an auto-crosslinked hyaluronan gel in gynaecological laparoscopic surgery: a blinded, controlled, randomized, multicentre study. Hum Reprod. 2006;21:1248–54.
6. Dubuisson JB, Fauconnier A, Chapron C, Kreiker G, Nörgaard C. Second look after laparoscopic myomectomy. Hum Reprod. 1998;13:2102–6.
7. Diamond MP, Daniell JF, Feste J, Surrey MW, McLaughlin DS, Friedman S, et al. Adhesion reformation and de novo adhesion formation after reproductive pelvic surgery. Fertil Steril. 1987;47:864–6.
8. Seracchioli R, Rossi S, Govoni F, Rossi E, Venturoli S, Bulletti C, et al. Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy. Hum Reprod. 2000; 15:2663–8.
9. Marchionni M, Fambrini M, Zambelli V, Scarselli G, Susini T. Reproductive performance before and after abdominal myomectomy: a retrospective analysis. Fertil Steril. 2004; 82:154–9 quiz 265.
10. Vercellini P, Maddalena S, De Giorgi O, Pesole A, Ferrari L, Crosignani PG. Determinants of reproductive outcome after abdominal myomectomy for infertility. Fertil Steril. 1999;72: 109–14.
11. Marret H, Chevillot M, Giraudeau B. A retrospective multicentre study comparing myomectomy by laparoscopy and laparotomy in current surgical practice. What are the best patient selection criteria? Eur J Obstet Gynecol Reprod Biol. 2004;117:82–6.
12. Mais V, Ajossa S, Guerriero S, Mascia M, Solla E, Melis GB. Laparoscopic versus abdominal myomectomy:

a prospective, randomized trial to evaluate benefits in early outcome. Am J Obstet Gynecol. 1996;174:654–8.
13. Dubuisson JB, Fauconnier A, Deffarges JV, Norgaard C, Kreiker G, Chapron C. Pregnancy outcome and deliveries following laparoscopic myomectomy. Hum Reprod. 2000;15: 869–73.
14. Paul PG, Koshy AK, Thomas T. Pregnancy outcomes following laparoscopic myomectomy and single-layer myometrial closure. Hum Reprod. 2006;21:3278–81.
15. Metwally M, Gorvy D, Watson A, Li TC. Hyaluronic acid fluid agents for the prevention of adhesions after fertility-preserving gynecological surgery: a meta-analysis of randomized controlled trials.Fertil Steril. 2007;87:1139–46.
16. Pellicano M, Bramante S, Cirillo D, Palomba S, Bifulco G, Zullo F, et al. Effectiveness of autocrosslinked hyaluronic acid gel after laparoscopic myomectomy in infertile patients: a prospective, randomized, controlled study. Fertil Steril. 2003;80:441–4.
17. Mettler L, Audebert A, Lehmann-Willenbrock E, Schive-Peterhansl K, Jacobs VRA randomized, prospective, controlled, multicenter clinical trial of a sprayable, site-specific adhesion barrier system in patients undergoing myomectomy. Fertil Steril. 2004;82:398–404.
18. Diamond MP, Freeman ML. Clinical implications of postsurgical adhesions. Hum Reprod Update 2001;7: 567–76.
19. Tulandi T, Murray C, Guralnick M. Adhesion formation and reproductive outcome after myomectomy and second-look laparoscopy. Obstet Gynecol. 1993;82: 213–15.

Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2012, Article ID 436174, 6 pages
doi:10.1155/2012/436174

Clinical Study

Effect of a Selective Progesterone Receptor Modulator on Induction of Apoptosis in Uterine Fibroids In Vivo

Petr Horak,[1] Michal Mara,[1] Pavel Dundr,[2] Kristyna Kubinova,[1] David Kuzel,[1] Robert Hudecek,[3] and Roman Chmel[4]

[1] *Department of Obstetrics and Gynaecology, First Faculty of Medicine, Charles University in Prague, Apolinarska 18, 128 00 Prague, Czech Republic*
[2] *Institute of Pathology, First Faculty of Medicine, Charles University in Prague, 128 00 Prague, Czech Republic*
[3] *Department of Obstetrics and Gynaecology, University Hospital Brno, 625 00 Brno, Czech Republic*
[4] *Department of Obstetrics and Gynaecology, Second Faculty of Medicine, Charles University in Prague, 150 06 Prague, Czech Republic*

Correspondence should be addressed to Kristyna Kubinova, kristynakubinova@gmail.com

Received 7 March 2012; Revised 18 May 2012; Accepted 18 May 2012

Academic Editor: Faustino R. Pérez-López

Aim. To determine if hormonal treatment induces apoptosis in uterine fibroids. *Methods*. Immunohistochemical examination of fibroid tissue, using avidin-biotin complex and cleaved caspase-3 antibody for detecting apoptosis, was performed in premenopausal women who underwent 12-week treatment with oral SPRM (6 patients with 5 mg and 5 patients with 10 mg of ulipristal acetate per day) or gonadoliberin agonist (GnRHa, 17 patients) and subsequent myomectomy or hysterectomy for symptomatic uterine fibroids. Ten patients with no presurgical hormonal treatment were used as controls. *Results*. Apoptosis was present in a significantly higher proportion of patients treated with ulipristal acetate compared to GnRHa ($P = 0.01$) and to patients with no hormonal treatment ($P = 0.01$). In contrast to an AI of 158.9 in SPRM patients, the mean AI was 27.5 and 2.0 in GnRHa and control groups, respectively. No statistical difference in the AI was observed between the two groups of patients treated with ulipristal acetate (5 mg or 10 mg). *Conclusion*. Treatment with ulipristal acetate induces apoptosis in uterine fibroid cells. This effect of SPRM may contribute to their positive clinical effect on uterine fibroids.

1. Introduction

Uterine fibroids are the most common benign gynecological tumors. Their prevalence in premenopausal patients is 30–40%, making them one of the most common reasons for gynecological surgery [1].

The etiology and pathophysiology are still unknown. It is considered that various genetic, anthropometric, racial, reproductive, and vascular factors, as well as the role of growth factors or some hormones, particularly ovarian steroids, could play a role [2–7].

Surgery still dominates fibroid treatment; the most common is myomectomy or hysterectomy depending on the age and reproductive status of the patient. Nowadays, pharmacological intervention is used as a symptomatic therapy in smaller fibroids. There are few drugs that have the potential to have a direct effect on fibroid growth. The most promising in this category are the selective progesterone receptor modulators (SPRMs) that have become the subject of intense investigation in recent years but have not yet been introduced into standard clinical practice. The mechanism of action of these drugs is still unknown but the effect on myoma-related symptoms and fibroid shrinkage was proven in early clinical studies [8, 9]. Their selective antiproliferative, proapoptotic, and antifibrinolytic effect on fibroids has been demonstrated in human tissue cultures *in vitro* [10]. The aim of our study was to determine the eventual higher apoptosis rate in fibroids extirpated from patients given SPRM pretreatment compared with controls.

2. Materials and Methods

2.1. Patient Recruitment. Patients with uterine fibroids were given ulipristal acetate (PGL4001) during 12 weeks prior to the planned surgery. This drug, provided by PregLem S.A., Switzerland, belongs to the SPRM group. These patients

had participated in a phase III clinical study with ulipristal acetate. This study, in which patients received daily dose of 5 or 10 mg of ulipristal acetate or placebo, evaluated the efficacy of ulipristal acetate on symptomatic uterine fibroids [11]. Patients that received active treatment and required surgery for their fibroids were included in the present study.

For a comparable group, we chose patients with symptomatic fibroids who were treated with gonadoliberin agonist (GnRHa) triptorelin (Ipsen Pharma Biotech, France) 12 weeks prior to planned surgery at a dose of 3 mg intramuscularly 3 times at 28-day intervals. For controls we enrolled patients with the same diagnosis who were receiving no hormonal pretreatment and were referred to have either a hysterectomy or myomectomy. The operation was always scheduled within 2 weeks from the last SPRM dose or 6 weeks within the last dose of GnRHa.

Our study did not have a randomized or double-blind design. Patient recruitment into each group was dependant on a patient informed choice. In order to reduce anemia and the risk of perioperative blood transfusion and if patients met the inclusion criteria (see below), they were given the option of 12 weeks of hormonal pretreatment with ulipristal acetate (as part of the multicenter placebo-controlled study with SPRM) or triptorelin. If the patients preferred early surgery with no hormonal treatment, they were included in the control group. Patients were fully informed of all known advantages, disadvantages, and differences between the two options of treatment including the fact that if patients choose the SPRM, they could be randomized into the placebo subgroup.

All the patients in the study were administered oral iron supplements (Ferrous sulphate 80 mg once daily) starting either with the administration of hormonal treatment (both groups with hormonal pretreatment) or on the day of the enrolment in the study (control group).

2.2. Inclusion and Exclusion Criteria. Patients aged between 18 and 50 years of age with uterine fibroid/s sized ≥ 3 cm (the largest measurable diameter of myoma measured by vaginal ultrasonography prior to ulipristal or triptorelin administration or before surgery in the control group), typical myoma-related symptoms (menorrhagia with PBAC (Pictorial Bleeding Assessment Chart) score higher than 100 for the 1st–8th days of menstruation; eventually pressure pelvic symptoms) [12, 13] and significant anemia (hemoglobin ≤ 100 g/L) were included in the study.

Exclusion criteria were patients with an overall size of uterus exceeding 16th week of pregnancy, history of uterine surgery, hormonal supplement therapy and hormonal contraception administration or other hormonal treatment with estrogen or progesterone within the last month prior to the study, BMI ≤ 18 or ≥ 40, hemoglobinopathy, atypical hyperplasia or endometrial carcinoma, cervical cancer, ovarian or breast cancer, endometrial polyp larger than 2 cm, and ovarian cyst larger than 4 cm. Patients who refused to sign the informed consent and patients who, regardless of the reasons, wanted to terminate their participation in the study were also excluded. We also excluded women whose histological examination of the extirpated tumor of the uterus or the entire uterus brought a different result than vital (therefore evaluable) leiomyoma and patients (from the study of PregLem S.A.) that used placebo instead of ulipristal acetate.

The study protocol was approved by the Ethics Committee of the first Medical Faculty of Charles University in Prague. All patients enrolled signed an informed consent.

2.3. Laboratory Examination of Fibroids, and Statistical Analysis. All study women who underwent myomectomy (open or laparoscopic) or hysterectomy (laparoscopically assisted vaginal or open) were subject to standard histological examination of the removed myoma or the entire uterus and immunohistochemical tests to detect apoptosis. These examinations were performed and evaluated by the same pathologist who was not informed of whether the patient received any hormonal therapy prior to the surgery.

Immunohistochemistry was performed using the avidin-biotin complex method with antibody against cleaved caspase-3 (dilution 1 : 250, Cell Signaling Technology, Beverly, MA). Antigen retrieval was performed with a sodium citrate buffer (pH 6.0) in a water bath for 40 minutes. The apoptotic index (AI), the number of apoptotic cells of all cells counted, was determined manually using an ocular counting grid at three randomly chosen fields. One thousand cells for each sample were counted [14, 15].

We used a nonparametric Kruskal-Wallis test and Mann-Whitney test (with the Bonferroni adjustment of P values for multiple testing) for statistical comparison of the results of the AI between the subgroups (SPRM versus GnRHa, SPRM versus controls, GnRHa versus controls, and SPRM 10 mg versus SPRM 5 mg). For comparison between patients with an AI higher than 10, a chi-square test and Fisher test were used.

3. Results

A total of 41 symptomatic patients who met the inclusion criteria were recruited to our study between November 2008 and December 2009. Out of these 41 patients, 17 patients preferred GnRHa and 10 patients requested an early operation with no pretreatment. In the placebo-controlled study with ulipristal acetate 14 patients were included, of which 3 patients were subsequently excluded following the unblinding of data revealing placebo administration. Uterine fibroids from the remaining 38 patients were examined histologically after surgery and immunohistochemical tests were performed to detect apoptosis. The baseline characteristics of each group are summarized in Table 1. Patients in each group did not significantly differ in age, BMI, size of dominant fibroid or parity. All the histological findings revealed conventional leiomyomata.

Based on the results of immunohistochemistry, an AI was calculated for each patient. Zero or minimal percentage (less than 1% of 1000 cells examined) of cells with apoptosis were detected in 18.2% of patients receiving preoperative SPRM compared to 76.5% of patients receiving GnRHa and 100% in the control group. The differences between SPRM versus GnRHa ($P = 0.01$, χ^2 test) and SPRM versus controls

Table 1: Baseline parameters of the groups of the study.

Type of preoperative treatment	SPRM (11 patients)	GnRHa (17 patients)	No treatment (10 patients)
Mean age (years)	36.4	33.3	37.9
Mean BMI (kg/m^2)	24.4	23.0	22.8
Mean diameter of dominant fibroid (mm)	58.3	68.1	60.8
Mean number of myomas (larger than 10 mm)	2.5	2.3	2.6
Mean number of deliveries of patients	0.9	0.6	0.8
Mean interval between last tablet intake/last depot injection and surgery (days)	7.5	35.1	—

BMI: body mass index, GnRHa: gonadoliberin agonist, and SPRM: selective progesterone receptor modulator.

Table 2: Apoptotic index (AI) in the subgroups of the study.

Type of preoperative treatment	Number of patients	Mean AI (±SD)	Median of AI	Range of AI	Number of patients with AI > 10
SPRM	11	158.9 (±193.2)	96	0–672	9 (81.8%)
GnRHa	17	27.5 (±62.3)	2	0–196	4 (23.5%)
No treatment	10	2.0 (±2.1)	1	0–6	0

AI: apoptotic index, GnRHa: gonadoliberin agonist, and SPRM: selective progesterone receptor modulator.

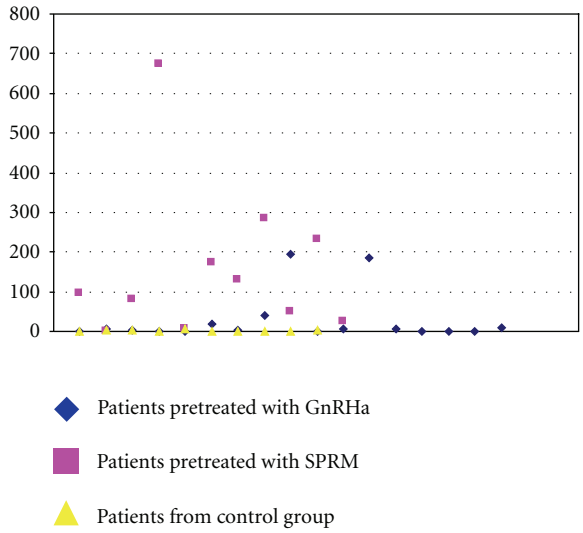

Figure 1: Apoptotic index in separate groups.

($P = 0.001$, Fisher's test), respectively, were statistically significant (see Table 2). The highest average AI value was described in the SPRM group (157.9), which was significantly higher than that in GnRHa group (27.5; $P = 0.01$) and the control group (2.0; $P = 0.01$). The results of each single patient including detailed comparison of the subgroups are shown in Figure 1 and Table 2.

We also tried to determine if there was any difference in the incidence of apoptosis between patients with different doses of ulipristal as well as if a dose-dependent apoptosis rate in the SPRM group could be found (Table 3). In our limited group of 11 patients, we did not observe a higher proportion of cells with apoptosis in women receiving a higher dose of SPRM ($P = 0.144$, Mann-Whitney test).

4. Discussion

Uterus-sparing therapy remains an up-to-date topic even in cases of women no longer desiring pregnancy. Myomectomy remains the most frequently used surgical technique. There is a constant search for alternatives to myomectomy because this operation is both quite invasive for the patient and risky and devastating for the uterus before planned pregnancy. Apart from occlusive methods aimed at fibroid devascularization (uterine artery embolization (UAE), and laparoscopic uterine artery occlusion (LUAO)) new modalities such as thermoablation of fibroids by focused ultrasound or radiofrequency ablation are beginning to be used [16–19].

None of the above-stated methods, however, affect pathophysiology of fibroids or have systematic effects. Some hormonal drugs have the potential to treat the cause of the disease. Many drug groups, such as progesterone (including intrauterine application), Danazol, gonadoliberin agonists and antagonists, selective estrogen receptors modulators, aromatase inhibitors, or antiprogesterone, have been used in this indication [20–25]. None of the drugs have made a significant breakthrough in fibroid treatment.

GnRHa is the most used and studied to date. These drugs cause hypoestrinism, which, after several months of use, leads to a slight fibroid volume reduction [15, 26]. The use of GnRHa is unfortunately accompanied with a number of drawbacks, which is why their use in the treatment of fibroids has been limited to three-month pretreatment in selected patients before myomectomy or hysterectomy [27–29].

Fibroid cells demonstrate higher concentration of estrogen receptors compared to surrounding myometrium, equally higher expression of mRNA and of progesterone receptors

Table 3: Dependence of the number of apoptotic cells on the dose of SPRM.

Daily dose of SPRM	Number of patients	Mean AI (±SD)	Median of AI	Range of AI
Ulipristal 5 mg	6	231.8 (±237.8)	181	26–672
Ulipristal 10 mg	5	71.4 (±71.2)	81	0–173

AI: apoptotic index, SD: standard deviation, and SPRM: selective progesterone receptor modulator.

(PRs) A and B. Increase of mitotic activity and fibroid size in the secretory phase of the cycle has also been described [30–32]. Therefore, the logical effort is to use drugs not only causing hypoestrinism but also affecting PR. In addition to antiprogesterone, Mifepristone, an SPRM, may become one of the drugs used in fibroid treatment [33, 34], due to their targeted mode of action. Unlike Mifepristone, which apart from reduction of menorrhagia and reduction of uterine and fibroid volume leads to hyperplasia of the endometrium, SPRM with its modified both agonistic and antagonistic PR effect does not have this undesirable effect on the endometrium [35, 36]. SPRMs act directly on the endometrium by maintaining its glandular and stromal proliferation at low levels and thus causing amenorrhea in most of the patients without causing hypoestrinism. Similar morphological changes, as well as a reduction in mitotic activity, were detected in cells of leiomyomas examined after hysterectomy of 33 patients receiving 12-weeks treatment with asoprisnil prior to the surgery [37].

In cell cultures SPRMs lead to reduction of cell viability, suppression of expression of growth factors and induced apoptosis through mitochondrial activation and tumor necrosis factor-related apoptosis inducing ligand (TRAIL) [38]. Bcl-2 is considered to be the key protein in the inhibition of apoptosis. It has been demonstrated that a Bcl-2 promoter interacts with PR by progesterone, suggesting in what other ways SPRMs may induce apoptosis [39]. But the proapoptotic effect of an SPRM has not yet been verified in vivo. Asoprisnil (J867) is a typical example of the SPRM, which selectively induces apoptosis in leiomyomas cells in tissue cultures without causing proliferation or apoptosis in normal cells of the myometrium [10, 40]. In our study, we used ulipristal acetate (PGL 4001 or CDB-2914, 17alpha-Acetoxy-11beta-(4-N, N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione), a steroid substance reversibly blocking progesterone receptors. Despite the limited number of patients in the study we observed a significantly higher apoptosis rate in fibroid cells exposed to ulipristal acetate preoperatively compared to fibroids of patients treated with GnRHa as well as in fibroids with no preoperative hormonal treatment. Apoptosis may thus be an important, although apparently not the only, mechanism of an SPRM suppression effect on uterine fibroids. The other factor may be, for instance, uterine artery flow reduction [9]. However, our results should not be generalized to all preparations that modify PR because the group of SPRMs seems to be heterogeneous. The fact that the apoptosis rate was not significantly higher using twice the daily dose of ulipristal acetate (10 mg) suggests that a daily dose of 5 mg ulipristal acetate is sufficient for apoptosis induction and a higher dose apparently does not increase its proapoptotic effect. Unfortunately, at the moment we cannot say if longer use of ulipristal acetate like 6 or 12 months could lead to even larger proapoptotic effect in fibroids or not.

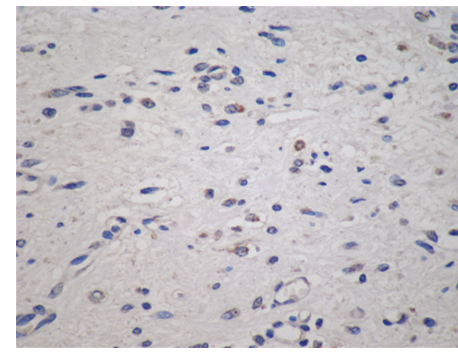

Figure 2: Immunohistochemical analysis using cleaved caspase-3 antibody. Note the granular cytoplasmic positivity in apoptotic cells.

Apoptosis is one of the main types of programmed cell death. It incorporates a series of biochemical processes leading to typical changes in cell appearance. This process is then followed by removal of the cells (without inflammation), making apoptosis in the foundations different from necrosis. The borderline between apoptosis and necrosis is however not clear and sometimes both processes combine making the designation of the cell death ambiguous [41]. The following laboratory methods are used in apoptosis detection: phosphatidylserine-annexin V, DNA fragmentation (ELISA), Laddering, TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling), Fas, TNFR1, and P53 [42]. In our study, we used the method of indirect immunohistochemistry with cleaved caspase-3 antibody (Figure 2). We used an avidin-biotin complex (ABC method) technique with visualization using horseradish peroxidase and diaminobenzidine.

Selective proapoptotic and antiproliferative effects of SPRM preparations could be the ideal mechanism for suppression of uterine fibroids with a permanent or at least longer effect compared to GnRHa without adverse events of hypoestrinism, concurrently with much safer results than the necrosis caused by the UAE. Their big clinical potential (cessation of excessive uterine bleeding, correction of severe anemia, and volume reduction of the fibroids and the uterus) and safety in women with fibroids have been recently proved by two large randomized trials [11, 43]. On the other hand the necrosis after UAE, which can also occur inside the uterine cavity, can greatly reduce the chances for patients to have a successful pregnancy and that is why UAE is considered to be relatively contraindicated in patients planning pregnancy [44–46].

A study by Korean authors comparing occlusive methods in uterine fibroid treatment was targeted at apoptosis detection. Fibroids extirpated 6 months after occlusive treatment were examined with the following results: while the typical finding in fibroids with acute ischemia caused by UAE was necrosis, in cases after LUAO it was apoptosis [47]. In 8 patients, we also examined fibroids removed following LUAO, which was performed within the previous year and had little effect on both fibroid volume reduction and symptoms. These fibroids were examined with the same technique as in all patients in our study. We did not observe a significant apoptosis rate in these 8 patients, the average AI was 19.3 and thus lower than in women treated with GnRHa. However, in all 8 patients, the occlusive treatment failed and was performed in a longer interval prior to myomectomy (and examination for apoptosis), which could have substantially affected the results.

We can summarize that the three-month pre-operative administration of ulipristal acetate induced natural cell death in uterine fibroids in premenopausal women. On the other hand, in women who had three months of preoperative administration of GnRH analogues or no hormonal therapy, a significantly lower proportion of apoptotic cells in leiomyomas were observed.

Acknowledgment

This study was supported by a grant IGA NS 9798-4 from the Ministry of Health of the Czech Republic.

References

[1] E. E. Wallach and N. F. Vlahos, "Uterine myomas: an overview of development, clinical features, and management," *Obstetrics and Gynecology*, vol. 104, no. 2, pp. 393–406, 2004.

[2] A. Arici and I. Sozen, "Expression, menstrual cycle-dependent activation, and bimodal mitogenic effect of transforming growth factor-β1 in human myometrium and leiomyoma," *American Journal of Obstetrics and Gynecology*, vol. 188, no. 1, pp. 76–83, 2003.

[3] L. M. Marshall, D. Spiegelman, R. L. Barbieri et al., "Variation in the incidence of uterine leiomyoma among premenopausal women by age and race," *Obstetrics and Gynecology*, vol. 90, no. 6, pp. 967–973, 1997.

[4] T. Maruo, H. Matsuo, Y. Shimomura et al., "Effects of progesterone on growth factor expression in human uterine leiomyoma," *Steroids*, vol. 68, no. 10–13, pp. 817–824, 2003.

[5] I. Sozen and A. Arici, "Cellular biology of myomas: interaction of sex steroids with cytokines and growth factors," *Obstetrics and Gynecology Clinics of North America*, vol. 33, no. 1, pp. 41–58, 2006.

[6] J. R. Toro, M. L. Nickerson, M. H. Wei et al., "Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America," *American Journal of Human Genetics*, vol. 73, no. 1, pp. 95–106, 2003.

[7] C. L. Walker, "Role of hormonal and reproductive factors in the etiology and treatment of uterine leiomyoma," *Recent Progress in Hormone Research*, vol. 57, pp. 277–294, 2002.

[8] L. K. Nieman, W. Blocker, T. Nansel et al., "Efficacy and tolerability of CDB-2914 treatment for symptomatic uterine fibroids: a randomized, double-blind, placebo-controlled, phase IIb study," *Fertility and Sterility*, vol. 95, no. 2, pp. 767.e2–772.e2, 2011.

[9] J. Wilkens, K. Chwalisz, C. Han et al., "Effects of the selective progesterone receptor modulator asoprisnil on uterine artery blood flow, ovarian activity, and clinical symptoms in patients with uterine leiomyomata scheduled for hysterectomy," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 12, pp. 4664–4671, 2008.

[10] W. Chen, N. Ohara, J. Wang et al., "A novel selective progesterone receptor modulator asoprisnil (J867) inhibits proliferation and induces apoptosis in cultured human uterine leiomyoma cells in the absence of comparable effects on myometrial cells," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 4, pp. 1296–1304, 2006.

[11] J. Donnez, T. F. Tatarchuk, and P. Bouchard, "Ulipristal acetate versus placebo for fibroid treatment prior to surgery," *The New England Journal of Medicine*, vol. 366, no. 5, pp. 409–420, 2012.

[12] J. M. Higham, P. M. S. O'Brien, and R. W. Shaw, "Assessment of menstrual blood loss using a pictorial chart," *British Journal of Obstetrics and Gynaecology*, vol. 97, no. 8, pp. 734–739, 1990.

[13] C. A. H. Janssen, P. C. Scholten, and A. P. M. Heintz, "A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss," *Obstetrics and Gynecology*, vol. 85, no. 6, pp. 977–982, 1995.

[14] K. D. Burroughs, R. Fuchs-Young, B. Davis, and C. L. Walker, "Altered hormonal responsiveness of proliferation and apoptosis during myometrial maturation and the development of uterine leiomyomas in the rat," *Biology of Reproduction*, vol. 63, no. 5, pp. 1322–1330, 2000.

[15] K. N. Khan, M. Kitajima, K. Hiraki et al., "Changes in tissue inflammation, angiogenesis and apoptosis in endometriosis, adenomyosis and uterine myoma after GnRH agonist therapy," *Human Reproduction*, vol. 25, no. 3, pp. 642–653, 2010.

[16] W. M. Liu, "Laparoscopic bipolar coagulation of uterine vessels to treat symptomatic leiomyomas," *Journal of the American Association of Gynecologic Laparoscopists*, vol. 7, no. 1, pp. 125–129, 2000.

[17] J. H. Ravina, D. Herbreteau, N. Ciraru-Vigneron et al., "Arterial embolisation to treat uterine myomata," *The Lancet*, vol. 346, no. 8976, pp. 671–672, 1995.

[18] C. Recaldini, G. Carrafiello, D. Laganà et al., "Percutaneous sonographically guided radiofrequency ablation of medium-sized fibroids: feasibility study," *American Journal of Roentgenology*, vol. 189, no. 6, pp. 1303–1306, 2007.

[19] E. A. Stewart, W. M. W. Gedroyc, C. M. C. Tempany et al., "Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique," *American Journal of Obstetrics and Gynecology*, vol. 189, no. 1, pp. 48–54, 2003.

[20] S. H. Eisinger, S. Meldrum, K. Fiscella, H. D. Le Roux, and D. S. Guzick, "Low-dose mifepristone for uterine leiomyomata," *Obstetrics and Gynecology*, vol. 101, no. 2, pp. 243–250, 2003.

[21] N. Chegini, C. Ma, X. M. Tang, and R. S. Williams, "Effects of GnRH analogues, "add-back" steroid therapy, antiestrogen and antiprogestins on leiomyoma and myometrial smooth muscle cell growth and transforming growth factor-β expression," *Molecular Human Reproduction*, vol. 8, no. 12, pp. 1071–1078, 2002.

[22] T. Maruo, N. Ohara, H. Matsuo et al., "Effects of levonorgestrel-releasing IUS and progesterone receptor modulator PRM CDB-2914 on uterine leiomyomas," *Contraception*, vol. 75, no. 6, pp. S99–S103, 2007.

[23] D. L. Olive, S. R. Lindheim, and E. A. Pritts, "Non-surgical management of leiomyoma: impact on fertility," *Current*

Opinion in Obstetrics and Gynecology, vol. 16, no. 3, pp. 239–243, 2004.

[24] B. W. Rackow and A. Arici, "Options for medical treatment of myomas," *Obstetrics and Gynecology Clinics of North America*, vol. 33, no. 1, pp. 97–113, 2006.

[25] M. Shozu, K. Murakami, T. Segawa, T. Kasai, and M. Inoue, "Successful treatment of a symptomatic uterine leiomyoma in a perimenopausal woman with a nonsteroidal aromatase inhibitor," *Fertility and Sterility*, vol. 79, no. 3, pp. 628–631, 2003.

[26] V. De Leo, G. Morgante, A. La Marca et al., "A benefit-risk assessment of medical treatment for uterine leiomyomas," *Drug Safety*, vol. 25, no. 11, pp. 759–779, 2002.

[27] A. Golan, I. Bukovsky, M. Pansky, D. Schneider, Z. Weinraub, and E. Caspi, "Pre-operative gonadotrophin-releasing hormone agonist treatment in surgery for uterine leiomyomata," *Human Reproduction*, vol. 8, no. 3, pp. 450–452, 1993.

[28] A. Lethaby, B. Vollenhoven, and M. Sowter, "Efficacy of preoperative gonadotrophin hormone releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy: a systematic review," *An International Journal of Obstetrics and Gynaecology*, vol. 109, no. 10, pp. 1097–1108, 2002.

[29] I. Manyonda, E. Sinthamoney, and A. M. Belli, "Controversies and challenges in the modern management of uterine fibroids," *An International Journal of Obstetrics and Gynaecology*, vol. 111, no. 2, pp. 95–102, 2004.

[30] J. Fujimoto, S. Ichigo, M. Hori, M. Nishigaki, and T. Tamaya, "Expression of progesterone receptor form A and B mRNAs in gynecologic malignant tumors," *Tumor Biology*, vol. 16, no. 4, pp. 254–260, 1995.

[31] S. Chrapusta, W. Sieinski, B. Konopka, J. Szamborski, and Z. Paszko, "Estrogen and progestin receptor levels in uterine leiomyomata: relation to the tumour histology and the phase of menstrual cycle," *European Journal of Gynaecological Oncology*, vol. 11, no. 5, pp. 381–387, 1990.

[32] K. Kawaguchi, S. Fujii, I. Konishi, Y. Nanbu, H. Nonogaki, and T. Mori, "Mitotic activity in uterine leiomyomas during the menstrual cycle," *American Journal of Obstetrics and Gynecology*, vol. 160, no. 3, pp. 637–641, 1989.

[33] D. DeManno, W. Elger, R. Garg et al., "Asoprisnil (J867): a selective progesterone receptor modulator for gynecological therapy," *Steroids*, vol. 68, no. 10–13, pp. 1019–1032, 2003.

[34] A. A. Murphy, A. J. Morales, L. M. Kettel, and S. S. C. Yen, "Regression of uterine leiomyomata to the antiprogesterone RU486: dose- response effect," *Fertility and Sterility*, vol. 64, no. 1, pp. 187–190, 1995.

[35] M. Bagaria, A. Suneja, N. B. Vaid, K. Guleria, and K. Mishra, "Low-dose mifepristone in treatment of uterine leiomyoma: a randomised double-blind placebo-controlled clinical trial," *Australian and New Zealand Journal of Obstetrics and Gynaecology*, vol. 49, no. 1, pp. 77–83, 2009.

[36] J. Wilkens, A. R. W. Williams, K. Chwalisz, C. Han, I. T. Cameron, and H. O. D. Critchley, "Effect of asoprisnil on uterine proliferation markers and endometrial expression of the tumour suppressor gene, PTEN," *Human Reproduction*, vol. 24, no. 5, pp. 1036–1044, 2009.

[37] A. R. W. Williams, H. O. D. Critchley, J. Osei et al., "The effects of the selective progesterone receptor modulator asoprisnil on the morphology of uterine tissues after 3 months treatment in patients with symptomatic uterine leiomyomata," *Human Reproduction*, vol. 22, no. 6, pp. 1696–1704, 2007.

[38] T. Maruo, N. Ohara, S. Yoshida et al., "Translational research with progesterone receptor modulator motivated by the use of levonorgestrel-releasing intrauterine system," *Contraception*, vol. 82, no. 5, pp. 435–441, 2010.

[39] P. Yin, Z. Lin, Y. H. Cheng et al., "Progesterone receptor regulates Bcl-2 gene expression through direct binding to its promoter region in uterine leiomyoma cells," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 11, pp. 4459–4466, 2007.

[40] S. Yoshida, N. Ohara, Q. Xu et al., "Cell-type specific actions of progesterone receptor modulators in the regulation of uterine leiomyoma growth," *Seminars in Reproductive Medicine*, vol. 28, no. 3, pp. 260–273, 2010.

[41] K. M. Martel, A. C. Ko, G. M. Christman, and J. M. Stribley, "Apoptosis in human uterine leiomyomas," *Seminars in Reproductive Medicine*, vol. 22, no. 2, pp. 91–103, 2004.

[42] W. R. Duan, D. S. Gamer, S. D. Williams, C. L. Funckes-Shippy, I. S. Spath, and E. A. G. Blomme, "Comparison of immunohistochemistry for activated caspase-3 and cleaved cytokeratin 18 with the TUNEL method for quantification of apoptosis in histological sections of PC-3 subcutaneous xenografts," *Journal of Pathology*, vol. 199, no. 2, pp. 221–228, 2003.

[43] J. Donnez, J. Tomaszewski, and F. Vázquez, "PEARL II Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids," *The New England Journal of Medicine*, vol. 366, pp. 421–432, 2012.

[44] Committee on Gynecologic Practice, American College of Obstetricians, and Gynecologists: ACOG Committee Opinion, "Uterine artery embolization," *Obstetrics & Gynecology*, vol. 103, pp. 403–404, 2004.

[45] D. Kuzel, M. Mara, P. Horak et al., "Comparative outcomes of hysteroscopic examinations performed after uterine artery embolization or laparoscopic uterine artery occlusion to treat leiomyomas," *Fertility and Sterility*, vol. 95, no. 6, pp. 2143–2145, 2011.

[46] H. Homer and E. Saridogan, "Uterine artery embolization for fibroids is associated with an increased risk of miscarriage," *Fertility and Sterility*, vol. 94, no. 1, pp. 324–330, 2010.

[47] K. H. Park, J. Y. Kim, J. S. Shin et al., "Treatment outcomes of uterine artery embolization and laparoscopic uterine artery ligation for uterine myoma," *Yonsei Medical Journal*, vol. 44, no. 4, pp. 694–702, 2003.

Cardiovasc Intervent Radiol (2012) 35:1041–1052
DOI 10.1007/s00270-012-0388-y

Uterine Artery Embolization Versus Laparoscopic Uterine Artery Occlusion: The Outcomes of a Prospective, Nonrandomized Clinical Trial

Michal Mara · Kristyna Kubinova · Jana Maskova · Petr Horak · Tomas Belsan · David Kuzel

Received: 2 November 2011 / Accepted: 25 March 2012 / Published online: 24 April 2012

Abstract
Purpose To compare outcomes of two different types of occlusive therapy of uterine fibroids.
Methods Women with fibroid(s) unsuitable for laparoscopic myomectomy (LM) were treated with uterine artery embolization (UAE) or laparoscopic uterine artery occlusion (LUAO).
Results Before the procedure, patients treated with UAE ($n = 100$) had a dominant fibroid greater in size (68 vs. 48 mm) and a mean age lower (33.1 vs. 34.9 years) than surgically treated patients ($n = 100$). After 6 months, mean shrinkage of fibroid volume was 53 % after UAE and 39 % after LUAO ($p = 0.063$); 82 % of women after UAE, but only 23 % after LUAO, had complete myoma infarction ($p = 0.001$). Women treated with UAE had more complications (31 vs. 11 cases, $p = 0.006$) and greater incidence of hysteroscopically verified intrauterine necrosis (31 vs. 3 %, $p = 0.001$). Both groups were comparable in markers of ovarian functions and number of nonelective reinterventions. The groups did not differ in pregnancy (69 % after UAE vs. 67 % after LUAO), delivery (50 vs. 46 %), or abortion (34 vs. 33 %) rates. The mean birth weight of neonates was greater (3270 vs. 2768 g, $p = 0.013$) and the incidence of intrauterine growth restriction lower (13 vs. 38 %, $p = 0.046$) in post-UAE patients.
Conclusion Both methods are effective in the treatment of women with future reproductive plans and fibroids not suitable for LM. UAE is more effective in causing complete ischemia of fibroids, but it is associated with greater risk of intrauterine necrosis. Both methods have low rate of serious complications (except for a high abortion rate).

Keywords Fertility · Laparoscopic uterine artery occlusion · Uterine artery embolization · Uterine fibroids

M. Mara · K. Kubinova (✉) · P. Horak · D. Kuzel
Department of Obstetrics and Gynecology, General Faculty Hospital and 1st Medical Faculty of Charles University, Prague 2 128 00, Czech Republic
e-mail: kristyna.kubinova@gmail.com

J. Maskova
Department of Radiology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, UK

T. Belsan
Department of Radiology, Central Military Hospital, Prague 6 169 02, Czech Republic

Introduction

Since the introduction of uterine artery embolization (UAE) to clinical practice 15 years ago, uterus-preserving approaches have become a hot topic in the therapy of uterine myomas [1]. Advances in interventional radiology, coupled with increasing patient interest in uterus preservation, have stimulated the efforts of gynecologists to develop uterus-preserving surgical alternatives to conventional treatment, mainly in the field of endoscopy and minimally invasive surgery [2–4]. In addition to increasing interest in laparoscopic myomectomy (LM), which is effective but may carry substantial risks in certain cases, laparoscopic uterine artery occlusion (LUAO) has been introduced as a less-invasive approach [5, 6].

Both UAE and LUAO can be classified as minimally invasive therapy, which preserves fertility, but their routine use in nulliparous or infertile women is controversial and insufficiently studied [7, 8]. Although similarly effective, laparoscopic occlusion is considered to be a safer alternative to embolization (e.g., for lower risk of ovarian failure),

especially in patients who are not eligible for myomectomy. However, only a few studies are available that compare clinical outcomes of radiological and surgical uterine artery occlusion [9–11] and only one study evaluating fertility after those procedures [12].

Materials and Methods

Study Design and Setting

This trial was designed as a prospective, parallel-group, nonrandomized study and was approved by The Ethical Committee of the 1st Medical Faculty of Charles University in Prague. We included 100 patients in each arm of the study. Having a sufficiently large, comparable number of patients, as well as longer follow-up, was essential for comparison of reproductive outcomes. The study was conducted in The Department of Minimally Invasive Surgery of a university hospital that is an international teaching centre for gynecological endoscopy and tertiary care national reference centre for the treatment of uterine myomas in patients with future reproductive plans. We cooperated with the Department of Radiology, which is the leading site in UAE as well as magnetic resonance imaging (MRI) imaging of uterine tumors in the country.

Study Population and Procedure Assignment

Premenopausal women with symptomatic myomas who preferred minimally invasive procedure to hysterectomy or open myomectomy (i.e., because of its burden of high morbidity and a risk of postoperative dense adhesion formation) were screened for the study. We selected patients who were not eligible for LM [13, 14], which is otherwise considered to be the "gold standard" in myoma treatment for patients planning pregnancy [15, 16]. These were patients with myomas in a risky location (uterine margins or isthmus), multiple myomas ($\geq$5 myomas with diameter $>$2 cm), voluminous myoma largely intramural $>$7 cm in diameter, or a history of myomectomy.

Patients were not randomized for one or the other type of treatment; rather, the treatment was chosen based on the patient's preferences (catheterization vs. laparoscopy). Before assignment, Doppler ultrasonographic (USG) and palpation examination of the uterus was performed, and a detailed history was taken. The results were discussed with the patients, and they were fully informed about the pros and cons and potential risks of both procedures.

If they met the inclusion criteria and agreed to participate in the study, the study protocol was explained in detail, and informed consent was signed. Patients were also assured that they could terminate their participation in the study at any time if they wished. Subsequently, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) serum levels (day 3 of the menstrual cycle) was tested, and contrast-enhanced MRI (ce-MRI) was performed. All examinations were performed using the same equipment: (1) USG with Siemens Acuson Antares (Siemens, Siemens Medical Solutions USA, Inc., Malvern, PA) using vaginal probe with frequency 4–9 MHz and abdominal probe with frequency 2–6 MHz and (2) MRI with Signa Excite II (1.5 Tesla; General Electric). Standard MRI scanning protocol consisted of T2-weighted (T2W) images in sagital plane (5 mm slice, 1 mm gap), T2W images (5 mm slice, 1 mm gap) in oblique plain (orthogonal to the long axis of the uterine body), and T1W images (5 mm slice, 1 mm gap) in identical oblique plane before and after gadolinium contrast media administration. Postcontrast scanning was performed to demonstrate perfusion of fibroids.

Inclusion Criteria

Uterine body tumor with the appearance of myoma with diameter $\geq$3 cm by USG and at least one typical myoma-related symptom, e.g., excessive or prolonged menstrual bleeding or pressure in the lower abdomen.

Exclusion Criteria

Age $>$40 years; submucous myomas largely prominent into the uterine cavity (primarily suitable for hysteroscopic resection); largely subserous or pedunculated myoma (easy for LM); predominantly cervical myoma (suitable for laparoscopically assisted vaginal myomectomy); myomas with no perfusion or atypical pelvic tumor (compared with regular myomas) or of suspicious appearance (based on Doppler USG and/or ce-MRI); clinical signs of premature ovarian failure and preference for myomectomy (despite explanation of the risks and invasiveness of this surgery in the particular case); hysterectomy; other treatment or patients not wishing to participate in the study; and preoperative finding (before LUAO) of myoma suited for LM. In contrast, infertility of planned pregnancy was not regarded as exclusion criteria.

Uterine Artery Embolization

Access for the procedure was from the right groin by way of the right common femoral artery. The aim was to bilaterally embolize the ascending branches of the uterine artery supplying the myoma(s) to achieve complete loss of myomas perfusion and at the same time leave free flow in the main stems and in the cervicovaginal branches of both uterine arteries. We refrained from embolizing sites displaying significant utero-ovarian anastomoses of type III

(main ovarian blood supply arises from the uterine artery) [17], which could not be overcome by microcatheter.

The technique of "free-flow embolization" was used to perform all procedures with a 5F catheter (RUC; Cook, Bjeeverskov, Denmark) and always with the aid of a coaxially introduced microcatheter (Embocath; BioSphere, Rockland, MA). Trisacryl gelatin microspheres (TGMs; Embospheres; BioSphere, Roissy, France), >500 μm in size, were used for embolization in all cases.

A single intravenous dose of 1.5 g sultamicillin (or 600 mg clindamycin in case of patient history of allergy to penicillin antibiotics) was administered to every patient 30 minutes before UAE. For pain management during the first 24 h after the procedure, patients were either given epidural analgesia [10 ml 0.5 % bupivacain plus 5 μg sufentanyl in 50 ml normal saline (administered continually from 5 to 10 ml/h)] or intravenous analgesia (5 μg sufentanyl plus 0.15 mg clonidin in 50 ml normal saline (administered as continual infusion at 5–10 ml/h). Nausea and postembolization discomfort during subsequent days were treated by thiethylperazin, diclofenac, and paracetamol.

Embolization leading to bilateral occlusion of ascending branches of uterine arteries and a complete loss of myoma perfusion, as detected by angiography, was considered technically successful. Dissection or severe spasms of uterine arteries (i.e., not reacting to vasodilators), adverse reaction to administered drugs, hematoma in the groin, and other complications of angiography were considered periprocedural complications. All procedures were performed in the same department by two experienced interventional radiologists who had completed at least 30 uterine fibroid embolizations previously.

LUAO

Laparoscopy was performed with the patient in lithotomy position using CO_2 as distension medium and transumbilical approach for Veress needle and the first port. Lateral peritoneum dissection using a harmonic scalpel (SonoSurg Scissors; SonoSurg-G2, Olympus Medical Systems, Tokyo, Japan) was started in the line between the round ligament anteriorly, the infundibulo-pelvic ligament medially, and the pelvic sidewall laterally. The peritoneum was opened, and the paravesical and obturator spaces were developed by blunt dissection. Subsequently, distancing of uterine arteries from the ureter was performed bilaterally to continue with their safe occlusion, and they were cut just medially to their origin from the internal iliac artery.

Surgically treated patients were given the same antibiotics and analgesics after LUAO as patients treated with UAE. Bilateral unequivocal laparoscopic identification and occlusion of uterine arteries was considered technically successful. Significant bleeding from iliac, uterine, ovarian, or obturator vessels (blood loss >300 cc), injury to the ureter, obturator nerve, or bowel, adverse reaction to administered drugs, hematoma at the site of the laparoscopic ports, conversion to laparotomy, and other general complications of laparoscopy were considered periprocedural complications. All surgical procedures were performed in the same department by two experienced laparoscopists working together as a team. They both had performed >30 LUAO procedures before the start of the study.

Follow-Up

From day 1 until day 30 after the procedure, all patients from the study were monitored for the following early postprocedural complications: fever, signs of pelvic infection, severe vaginal bleeding, severe pain not responsive to analgesics, prolonged hospital stay (>48 h after the procedure), necessity for antibiotics or blood transfusion, rehospitalization, allergic reactions, wound complications after surgery, ischemic phenomena after UAE, surgical intervention due to hematoma (pelvic intraperitoneal or retroperitoneal, abdominal wall, or inguinal) or infection, thromboembolic complications, and need for hysterectomy.

Patients were examined (clinically and ultrasonographically) at 1 and 6 months after their procedure and subsequently every 6 months. The levels of FSH, LH, and estradiol (on day 3 of the menstrual cycle or at another time in cases of amenorrhea) were measured, and myoma-related symptoms were evaluated at 6 months after the procedure. FSH level was monitored in the subsequent course of follow-up in women with signs of ovarian failure. ce-MRI was planned 6 months after UAE or LUAO in all patients. Patients were examined immediately in case of difficulties, complications, or signs of pregnancy.

The following late complications were assessed at >30 days after the procedure: signs of uterine infection or sepsis, permanent or transient signs of clinical (i.e., amenorrhea not related to pregnancy, with or without vasomotor symptoms of menopause, requiring hormone-replacement therapy or laboratory tests (i.e., FSH increase >5 IU/l compared with pretreatment values) ovarian failure, ischemic phenomena, chronic pelvic pain or dyspareunia, sudden severe uterine bleeding, chronic malodorous vaginal discharge, signs of paresis of obturator nerve, loss of libido, emergent myomectomy or hysterectomy, transcervical expulsion of myoma (TCEM), and uterine rupture.

Hysteroscopy

Hysteroscopy was performed in all patients at 3–6 months after UAE or LUAO. It was performed using a 3.2 mm rigid hysteroscope with a direct optical system and 7F

bioptic forceps (Versascope; Gynecare, Ethicon, Johnson and Johnson, Somerville, NJ). Normal saline solution was used as distension medium. The procedure was performed either without anesthesia or with the patient under short-duration general anesthesia using propofol at 1.5–2 mg/kg and remifentanyl at 0.1–0.5 ug/kg/min.

The objectives of hysteroscopy were to evaluate the endometrium, to evaluate the symmetry of the uterine cavity, to rule out the intrauterine presence of myoma, and especially to investigate signs of regressive tissue changes. Endometrial biopsy, plus biopsy of the myoma or other abnormal lesion (if detected), was performed during the procedure. All of the specimens were evaluated by one histopathologist. Standard histopathological evaluation was performed and included a description of the type of endometrium as well as any abnormality if present (necrosis and its type, inflammation, presence and localization of embolization particles).

Reinterventions and Reproductive Follow-Up

Reintervention was indicated based on patient symptoms, myoma characteristics per USG and ce-MRI [e.g., size, perfusion, and relationship of myoma(s) to uterine cavity], hysteroscopic findings, and, mainly, patient reproductive plans. In patients with no reproductive plans, reintervention was suggested only in cases with no symptom relief or in cases of worsening symptoms or myoma growth during follow-up. In patients with reproductive plans, reintervention was suggested even in those who were asymptomatic if imaging methods described persisting perfusion of the whole myoma volume and the size of the myoma was $\geq$5 cm in diameter or if the myomas (regardless of perfusion) evidently disfigured the uterine cavity on hysteroscopy.

Reinterventions were divided into the following categories: (1) urgent, i.e., sudden worsening patient health and symptoms and (2) elective, i.e., patient choice based on the previously stated criteria. LM, hysteroscopic myomectomy (HM), or open myomectomy (OM) was chosen as reintervention in both groups according to the size, number, and localization of myoma(s). Only in patients after UAE, sometimes in isolated cases after repeat UAE, was reintervention considered if the risks of LM persisted and the patient was not discouraged by failure of the primary treatment.

Reproductive plans and outcomes were recorded during regular check-ups at every 6 months. In case of missed appointments, patients were contacted by way of email or telephone. The patients were always asked about their attempts to conceive as well as the mode of conception (spontaneous or medically assisted), including the type of eventual assisted reproduction. All of the patients were instructed to report the pregnancy immediately by email and to report the course of the pregnancy at weeks 12, 20, and 30 of the pregnancy as well as after delivery (or miscarriage). After pregnancy, the patient was asked to send her medical report on the delivery (or miscarriage) by mail. Moreover, many patients were monitored during pregnancy and subsequently gave birth in our department.

Analysis of the Results

Statistical analysis was performed using the statistical software SPSS 13.0 (SPSS, Inc, Chicago, IL). For comparison of qualitative parameters from both groups (frequency tables, e.g., periprocedural complication [yes or no]), Pearson chi-square and Fisher's exact tests were used. For comparison of quantitative parameters (e.g., body mass index [BMI]), Mann–Whitney nonparametric test was used due to uneven distribution of baseline data (as tested by Shapiro–Wilk test), and $p < 0.05$ was determined considered statistically significant.

Results

Since September 2004, a total of 207 patients with uterine myomas that were classified as not suitable for LM were enrolled in the study. Seven patients, who were initially assigned to LUAO, were excluded for preoperative findings of myoma suitable for laparoscopic removal. Of the total of 200 patients after radiological or surgical occlusion, 192 completed at least 6 months of follow-up. Seven women failed to undergo imaging examination at 6 months after treatment (however, they maintained telephone contact regarding reproductive results and eventual complications), and 1 patient underwent hysterectomy at 2 weeks after LUAO due to a finding of endometrial stromal sarcoma (ESS) that was misdiagnosed before treatment as leiomyoma. Table 1 lists baseline characteristics of patients in both groups.

Results of Imaging Studies

Shrinkage and perfusion of myomas 6 months after occlusion was evaluated using Doppler USG and ce-MRI (Table 2). In addition to the above-listed eight women, we could not evaluate these parameters in eight patients from the UAE group (seven patients after TCEM and one patient after LM, which was performed at the patient's request 3 months after unilateral UAE due to persistence of symptoms, full perfusion, and unchanged myoma size) and in two women in the surgical group who were in the early stage of pregnancy. After UAE, nonsignificantly greater volume decrease of dominant myoma and significantly greater incidence of patients with myoma shrinkage and

Table 1 Baseline characteristics of 200 patients before UAE or LUAO

Characteristics	UAE ($n = 100$)	LUAO ($n = 100$)	p
Mean age ± SD (year)/range	33.1 ± 3.7/20–39	34.9 ± 4.0/24–39	0.002[a]
Mean BMI ± SD/range	25.2 ± 5.0/18.8–43.3	23.4 ± 3.5/17.6–39.0	0.019[a]
No. of patients with BMI >30	18	5	0.004[b]
Mean length of follow-up ± SD (month)/range	45.5 ± 19.0/8–84	40.4 ± 19.8/6–82	NS[a]
No. of myomas ± SD (on USG)/range[d]	2.0 ± 2.0/1–10	2.1 ± 1.4/1–8	NS[a]
No. of myomas ± SD (on MRI)/range	2.4 ± 2.4/1–13	2.3 ± 1.4/1–9	NS[a]
No. of patients with multiple myomas on USG[e]	36	54	0.011[b]
No. of patients with multiple myomas on MRI[e]	47	65	0.011[b]
Diameter of dominant myoma ± SD (mm) on USG)/range	64.7 ± 17.7/31–107	45.5 ± 11.7/31–86	0.001[a]
Diameter of dominant myoma ± SD (mm) on MRI)/range	68.2 ± 18.2/32–110	48.3 ± 11.1/32–82	0.001[a]
Volume of dominant myoma ± SD (cm^3 on MRI)/range	188.7 ± 39.6/14–630	59.9 ± 41.2/14–243	0.001[a]

NS nonsignificant difference

[a] Tested by Mann–Whitney test

[b] Tested by chi-square test

[c] Tested by Fisher's test

[d] Only myomas >20 mm were counted

[e] Women with >1 myoma >20 mm in size were counted

Table 2 Shrinkage and ischemia of dominant fibroids in patients 6 months after UAE or LUAO

Status of dominant fibroids	UAE ($n = 90$)	LUAO ($n = 92$)	p
USG			
Mean decrease in diameter of dominant fibroid (%)	28.5	22.3	NS[a]
No. of patients with dominant fibroid that shrank (%)	85 (94.4)	72 (78.3)	0.006[b]
No. of patients with dominant fibroid unchanged (%)	2 (2.2)	13 (14.1)	0.013[c]
No. of patients with dominant fibroid that enlarged (%)	3 (3.3)	7 (7.6)	NS[c]
No. of patients with complete ischemia of dominant fibroid[d] (%)	81 (90.0)	62 (67.4)	0.001[b]
MRI			
Mean decrease of volume of dominant fibroid (%)	53.0	39.0	NS[a]
No. of patients with dominant fibroid that shrank (%)	87 (96.7)	72 (78.3)	0.002[b]
No. of patients with dominant fibroid unchanged (%)	0	9 (9.8)	0.01[c]
No. of patients with dominant fibroid enlarged (%)	3 (3.3)	11 (11.9)	NS[c]
No. of patients with complete ischemia of dominant fibroid[e] (%)	74 (82.2)	21 (22.8)	0.001[b]

NS nonsignificant difference

[a] Tested by Mann–Whitney test

[b] Tested by chi-square test

[c] Tested by Fisher's test

[d] According to color Doppler imaging

[e] According to ce-MRI

complete myoma infarction compared with LUAO was recorded.

Clinical Results

Technically successful bilateral occlusion of uterine artery was recorded in 95 UAE and 96 LAUO patients. Of 5 patients with unilateral embolization, 2 underwent OM and 1 underwent LM within 8 months after the primary procedure, in all cases due to nonshrinkage of the dominant myoma, persistent myoma perfusion, and symptoms. In all 3 cases, subsequent histology confirmed the finding of conventional leiomyoma with no regressive changes and sporadic presence of TGMs. One patient with persistent

voluminous vascularized myoma was offered myomectomy, but she refused due to the absence of symptoms and resignation to fertility plans; in 5 years of follow-up her findings are still without progression. In 1 patient after unilateral UAE, complete ischemia and 48 % shrinkage of a solitary myoma was identified, and she is now planning pregnancy. Of 4 women with uncertain identification of 1 of the uterine arteries during laparoscopy, we performed LM in 1 case and OM in 1 case within 6 months (leiomyoma with no regressive changes on histology); the 2 remaining patients are asymptomatic despite the fact that in one of them a myoma of unchanged size still preserves perfusion.

Persistence of myoma-related symptoms in the patients, as well as the recurrence of myomas in 6 months of follow-up, was quite rare and comparable in both groups (Table 3). All eight cases of symptomatic failure of occlusive treatment after LAUO, as well as all four such cases after UAE, correlated with persistent volume and perfusion of the dominant myoma. In three patients 6 month after UAE, bleeding difficulties persisted despite the fact that their myomas shrank and were completely infarcted. In cases of symptomatic recurrence (within 3 years in one patient and 5 years in two patients after UEA and within 3 years in all three patient after LUAO), five times it was due to simultaneous myoma regrowth and reperfusion; only in one patient after LUAO did a nonenlarged myoma showed reperfusion. Patients after UAE or LAUO with myoma regrowth and reperfusion remained asymptomatic in more than half of the cases.

The overall complication rate in this study was relatively low. However, there was a difference between the groups with a greater number of postprocedural complications in UAE group. Equally low was the prolonged hospitalization rate in both groups; the greater incidence of rehospitalization after UAE was due to TCEM cases. In both groups, the gravity of complications was low in most of the cases. In the UAE group, two complications were considered serious: one case of right-sided venous thrombosis of the femoral and iliac veins diagnosed 4 weeks after UAE and one case of repeated myoma expulsion complicated by infection, resulting in the need for laparoscopic revision and peritoneo-vaginal fistula formation. The most serious complications of LUAO, however, with no clear connection to the primary procedure was the finding of uterine leiomyosarcoma and one case of premature ovarian failure 4 years after surgery. Of the ovarian complications, only one case of laboratory and clinically

Table 3 Clinical outcomes of patients with UAE or LUAO

Clinical outcomes	UAE ($n = 100$)	LUAO ($n = 100$)	p
Technical failure of procedure	5	4	NS[c]
Length of hospital stay ± SD (day)/range	2.4 ± 1.1/1–7	2.3 ± 0.8/1–4	NS[a]
Prolonged hospital stay (>48 h after procedure)	4	2	NS[c]
Patients with readmission to hospital (in association with procedure)[d]	7	1	0.032[c]
Patients with significant increase of FSH (until 6 months after procedure)[e]	0	3	NS[c]
Patients with persistence of symptoms (at 6 months after procedure)	7	8	NS[c]
Patients with recurrence of symptoms (any time after 6 months)	3	3	NS[c]
Patients with regrowth of myoma	4	8	NS[b]
Periprocedural complications	**1**	1	NS[c]
Early postprocedural complications (≤30 days)	19	8	0.023[b]
Late postprocedural complications (>30 days)	8	2	0.048[c]
Overall complications	28 (in 26 patients)	11 (in 11 patients)	0.002[b]
All patients with reintervention	39	15	0.001[b]
Patients with reintervention for failure, recurrence, or complication	12	10	NS[b]
Hysterectomy	2	2	NS[c]
Regressive changes (%) of removed fibroid (in histology)	35 (92.1)	8 (53.3)	0.006[b]
Complete regression (%) of removed fibroid (on histology)	29 (76.3)	4 (26.7)	0.002[b]
Adenomyoma or adenomyosis (% on histology)	0	3 (20.0)	0.018[c]

NS nonsignificant difference

[a] Tested by Mann–Whitney's test

[b] Tested by chi-square test

[c] Tested by Fisher's test

[d] Nonurgent reinterventions were not included

[e] At least 5 IU/l increase of FSH (from day 3 of the cycle) at 6 months after the procedure compared with the preprocedural level

demonstrable decrease in ovarian reserve occurred after UAE. In this study, we did not record any cases of sepsis, emergent hysterectomy, or conversion from LAUO to laparotomy (Table 4).

Most notably, the two groups differed in postprocedural evaluation of intrauterine findings. Severe abnormalities of the type of regressively changed myoma communication with the uterine cavity, either in the form of myoma protrusion in the cavity or fistula between the myoma and the cavity, occurred in one third of patients after UAE compared with exceptional cases occurring after LUAO. Macroscopic hysteroscopic evaluation correlated well with histology of bioptic findings of necrotic and/or hyalinized tissues of the uterine cavity (Table 5).

Reinterventions

Reinterventions were more frequent in patients after UAE. Most of the reinterventions were elective due to planned pregnancy or persistent infertility caused by the presence of asymptomatic well-embolized (i.e., complete regression of myomas according to histology in 74 % of cases) but still voluminous myoma compressing or communicating with the uterine cavity. The reintervention rate due to failure of the primary treatment or myoma recurrence was approximately 10 % in both groups (see Table 3). The course of all reinterventions (22 LM, 8 OM, 6 HM, and 1 repeated UAE after UAE plus 6 OM, 5 HM, and 2 LM after LUAO) was uncomplicated and did not differ from comparable surgery

Table 4 List of complications in patients after UAE or LUAO

Timing of complications	Complications after UAE ($n = 100$)	Complications after LUAO ($n = 100$)
Periprocedural	Spasm of uterine artery = 1 (resistant to intra-arterial vasodilators and leading to only unilateral UAE)	Bleeding = 1 (from veins in right infundibulopelvic ligament of ovary)
Early (≤30 days)	Fever/antibiotics = 10 (leading to prolonged hospital stay in 4 cases)	Fever/antibiotics = 3 (leading to prolonged hospital stay in 2 cases)
	Sloughing of myoma = 3 (leading to readmission in all cases)	Right-leg limping = 2[a]
	Hematoma of the right groin = 3	Menorrhagia (ESS-LG) = 1 (leading to readmission)[b]
	Deep venous thrombosis = 1 (leading to readmission)	Tingling of the left thigh = 1
	Menorrhagia = 1	Purulent secretion from laparoscopic suture = 1
	Allergic reaction = 1	
Late (>30 days)	Sloughing of myoma = 4 (leading to readmission in 3 cases)	Dyspareunia = 1
	Dyspareunia/vaginal discharge and odor = 2	Ovarian failure = 1[d]
	Decreased ovarian reserve = 1[c]	
	Decreased libido = 1	

[a] Probably caused by perioperative irritation of obturator nerve, resolved completely using physiotherapy

[b] Menorrhagia 8 days after LUAO indicated to hysteroscopy and biopsy with histological result of endometrial stromal sarcoma: low grade (ESS-LG) in a 27 year-old primipara

[c] Repeated increase of FSH >20 IU/1 (from day 3 of cycle) at 2 years after UAE in a 38 year-old patient with sterility resistant to IVF, who was recommended later for therapy with donated oocytes

[d] Oligomenorrhea and secondary amenorrhea with FSH >50 IU/1 at 4 years after LUAO in a 42 year-old woman without reproductive plans

Table 5 Hysteroscopic findings in patients 3–6 months after UAE and LUAO

Findings	UAE ($n = 91$)	LUAO ($n = 90$)	p
Normal (%)	38.5	86.7	0.001[b]
Minor abnormalities (%)	29.7	7.8	0.001[b]
Major abnormalities (%)	31.9	5.6	0.001[b]
Regressive changes in histology (from biopsy of myoma or endometrium) (%)	30.8	2.9	0.001[b]

[a] Tested by Mann–Whitney test

[b] Tested by chi-squared test

[c] Tested by Fisher's test

with no occlusive pretreatment. Two patients in each group underwent hysterectomy: three patients with no further reproductive plans for myoma recurrence and bleeding 12, 24, and 65 months after occlusive treatment and one patient due to the above-mentioned oncological finding.

Fertility Outcomes

Based on our regularly updated data, 42 women after UAE and 48 women after LAUO have attempted conception thus far. The reproductive results in both groups were comparable despite the fact that there was slight difference in length of follow-up and age (greater in the UAE group) and mean BMI (greater in UAE group). The interval between the procedure and first pregnancy was significantly shorter in patients after surgical treatment (Table 6). Pregnancy, delivery (in women who attempted to conceive), and abortion rates after UAE were 69.0, 50.0, and 34.2 %, whereas after LUAO they were 66.7, 45.8, and 33.3 %, respectively. There was no statistical difference in any of the stated parameters between the two groups (chi-square test). An interesting correlation indicative of possible prediction of pregnancy outcome based on hysteroscopy finding after UAE or LAUO is listed in Table 7.

The perinatal outcome (Table 8) of both groups significantly differed only in lower average newborn birth weight and greater proportion of newborns with intrauterine growth restriction (IUGR) in patients after LAUO. The incidence of severe pregnancy and perinatal complication was, however, low in the whole study.

Discussion

In recent years, we have noted an increasing incidence of women with uterine myomas and reproductive plans, and myomectomy is still, apart from conservative approach or symptomatic pharmacotherapy, the most commonly used treatment. In many cases, however, it is not an optimal treatment. OM for multiple or voluminous myomas is associated with significant morbidity and high prevalence of postoperative adhesions with potential consequences, such as pelvic pain, risk of bowel injury during subsequent surgery, or infertility [18, 19]. Moreover, in some cases, it is practically impossible to identify and remove all myomas, and there is a risk of further growth of the residual myomas and related symptoms. In other cases, myomas are located in a topographically unfavorable location, thus carrying a risk of injury to surrounding organs or major vessels, or the myomas occupy such a significant part of uterine wall and cavity that it can be extremely difficult to reconstruct the uterus after myoma removal so that it can fulfill its physiological functions. Even routine LM of solitary subserous myoma is not entirely without the risk of perioperative bleeding, rupture of the uterus during labor, and need for hysterectomy [20]. Efforts to eliminate these

Table 6 Fertility results of patients trying to conceive after UAE and LUAO

Characteristics	UAE ($n = 42$)	LUAO ($n = 48$)	p
Mean age ± SD (year)/range	33.1 ± 3.5/21–38	34.1 ± 3.1/27–39	NS[a]
Mean BMI ± SD/range	24.5 ± 4.4/18.8–35.3	22.9 ± 3.1/17.6–31.2	NS[a]
Mean length of follow-up ± SD (month)/range	50.8 ± 19.6/8–84	40.3 ± 16.7/11–69	0.008[a]
Mean interval between procedure and first pregnancy ± SD (month)/range	26.7 ± 14.5/7–52	15.1 ± 8.8/5–35	0.001[a]
No. of all pregnancies	42	40	NS [b]
Pregnancies from IVF (%)	4 (9.5)	11 (27.5)	0.0353[b]
No. of pregnant women	29	32	NS[b]
No. of deliveries	23	22	NS[b]
No. of abortions	13	12	NS[b]
No. of women pregnant now	2	4	NS[c]
No. of pregnancy terminations	2	1	NS[c]
No. of ectopic pregnancies	2	1	NS[c]
No. of women with postprocedural sterility	13	16	NS[b]
No. of women with abortion(s) only (and no ongoing pregnancy)	6	6	NS[b]

NS nonsignificant difference

[a] Tested by Mann–Whitney test

[b] Tested by chi-square test

[c] Tested by Fisher's test

[d] All abortions (missed or spontaneous) in the first trimester in both groups

Table 7 Correlation between postprocedural hysteroscopy and fertility results of patients trying to conceive after UAE and LUAO

Correlation of results	UAE ($n = 46$[a])	LUAO ($n = 52$[a])
Prospectively		
Patients with normal hysteroscopy	Pregnancy rate 75.0 %	Pregnancy rate 65.2 %
After UAE = 24	Delivery rate 58.3 %	Delivery rate 43.5 %
After LUAO = 46	Abortion rate 25.0 %	Abortion rate 31.4 %
Patients with abnormal hysteroscopy	Pregnancy rate 54.5 %	Pregnancy rate 66.7 %
After UAE = 22	Delivery rate 31.8 %	Delivery rate 33.3 %
After LUAO = 6	Abortion rate 50.0 %	Abortion rate 33.3 %
p (subgroup with normal HS vs. subgroup with abnormal HS)	NS[b, c]	NS[c]
Retrospectively		
Patients with at least one delivery	Normal HS 66.7 %	Normal HS 91.7 %
After UAE = 21	Abnormal HS 33.3 %	Abnormal HS 8.3 %
After LUAO = 24		
Patients with abortions only	Normal HS 28.6 %	Normal HS 85.7 %
After UAE = 7	Abnormal HS 71.4 %	Abnormal HS 14.3 %
After LUAO = 7		
Patients with postprocedural sterility	Normal HS 37.5 %	Normal HS 84.2 %
After UAE = 16	Abnormal HS 62.5 %	Abnormal HS 15.8 %
After LUAO = 19		
p (subgroup with delivery vs. subgroup with abortions vs. subgroup with sterility)	0.047[b]	NS[b]

HS hysteroscopy; *NS* nonsignificant difference

[a] Four women from each group (UAE and LUAO) were counted twice with respect to the change of their hysteroscopic finding after reintervention

[b] Tested by chi-square test

[c] Tested by Fisher's test

Table 8 Perinatal data of women who delivered after UAE and LUAO

Perinatal data	UAE ($n = 23$)	LUAO ($n = 22$)	p
Mean age of mothers ± SD (y)/range	35.4 ± 3.1/26–40	35.0 ± 3.3/28–41	NS[a]
Mean completed week of gestation ± SD/range	38.1 ± 1.6/32–40	38.0 ± 3.5/24–41	NS[a]
No. of preterm deliveries[d] (<36 weeks' gestation)	1	2	NS[c]
Mean birth weight of all newborns ± SD (g)/range	3270 ± 451/1980–3910	2768 ± 933/490–4130	0.013[a]
Mean birth weight of singletons ± SD (g)/range	3284 ± 469/1980–3910	3098 ± 502/2060–4130	NS[a]
Frequency of newborns with IUGR restriction (<3rd percentile)	12.5 (3/24)	37.5 (9/24)	0.046[b]
Twins	1	2	NS[c]
Pre-eclampsia	1	2	NS[c]
Placenta preavia	0	2	NS[c]
Peripartum bleeding	0	0	–
Placenta accreta[e]	1	0	NS[c]
Fetal malposition (at singletons)	0	0	–
Caesarean section rate (%)	78.3	68.2	NS[b]
Caesarean hysterectomy	0	0	–

NS nonsignificant difference

[a] Tested by Mann–Whitney test

[b] Tested by chi-square test

[c] Tested by Fisher's test

[d] At week 32 after UAE and at weeks 25 and 35 (twins in both cases) after LUAO

[e] Managed conservatively peripartally and using hysteroscopic resection after puerperium

disadvantages of myomectomy and to find alternative treatments are logical as well as the wish of many women for other treatment than hysterectomy and less-invasive treatment than OM.

The role of UAE in patients without fertility plans is well established, yet there is still an absence of studies comparing UAE with minimally invasive hysterectomy (laparoscopic, vaginal, or laparoscopically assisted vaginal). Many patients in their 30s and 40s are interested not only in the clinical effectiveness but also preservation of reproductive potential after UAE. A new randomized British study, regrettably not aimed at fertility outcomes, showed equal results regarding quality of life, shorter hospitalization stay, and lower rate of major complications, but a greater risk of reinterventions within 2 years of follow-up, for women after UAE compared with myomectomy [21]. Nevertheless, embolization is an attractive alternative to myomectomy or hysterectomy in patients generally not suited for surgical treatment, such as obese women or those with a history of multiple surgeries [22].

Initially UAE was used mainly as a symptomatic treatment of uterine myomas in premenopausal women in their 50s. More recently, case reports and small studies evaluating pregnancies after UAE [23–26] and studies comparing fertility outcomes after embolization and myomectomy have emerged [16, 27]. Goldberg et al. [27], who compared 53 pregnancies after UAE with 139 after LM, concluded that women after UAE are at greater risk of preterm delivery (16 %) and malpresentation (11 %) compared with women after LM (3 % for both parameters). The investigators also noted a trend toward greater abortion rate in women after UAE (24 vs. 15 %); IUGR incidence was comparable and low in both groups (5 and 8 %, respectively). A Canadian multicentre study aimed at several aspects of UAE, albeit with no control group, described an increased risk of miscarriage (16.7 %) and prematurity (22.2 %) [25]. In our previous study, patients after UAE had similar chances of conception as patients after myomectomy and favorable perinatal results; however, we recorded a significantly lower delivery rate due to the high frequency of miscarriages [16].

Similar to UAE, the transitory ischemia of the uterus caused by LUAO is technically easier, more generalized, and less traumatizing for the uterus than complicated myomectomy cases. It is an attempt to imitate the physiological processes leading to myoma regression in the puerperium [28] or induction of apoptosis rather than necrosis [11]. Yet, even fewer data are available on fertility outcomes after LUAO than after UAE [29, 30]. Hald et al. [10] conducted a randomized controlled trial of 58 patients comparing the symptomatic effects of UAE and LUAO and found a comparable decrease of menstrual bleeding, greater prevalence of patients with heavy bleeding 6 months after surgical occlusion, and greater use of analgesics after UAE. Volume decrease of the dominant myoma described by individual investigators ranges from 37 to 76 % [6, 9, 31], which is comparable with UAE [32–39]. In our group of patients, the volume decrease of the dominant myoma was greater in UAE compared with LUAO patients [53 vs. 39 % (statistically nonsignificant)] as well as in a number of cases with complete ischemia of myoma on MRI (82 vs. 32 %), which correlates with greater frequency of patients with no volume decrease of myoma after LUAO. Accordingly there was a greater prevalence of cases with complete tissue regression of myoma surgically removed after UAE than after LUAO (Tables 2 and 3). However, the number of necessary reinterventions, which was identical in both groups, does not correlate with these findings. This can be probably explained both by a good symptomatic effect of LUAO, even in cases with incomplete fibroid ischemia, and the smaller mean size of myomas in the surgical group.

The nature of UAE, as a more focused and therefore more effective treatment, but somewhat more aggressive than LUAO, also corresponds with a greater number of early and late postprocedural complications after embolization. Greater prevalence of febrile patients requiring antibiotics within the first week after treatment, as well as expulsion of necrotic, odorous, well-devitalized myoma in seven patients, is an example. Although in older women, myoma expulsion can be considered a successful completion of the treatment, in younger women wishing to conceive, the fertility consequences of this episode are uncertain, even if spontaneous recovery of uterine cavity can be expected [40]. Regrettably, none of these patients in our study has attempted to conceive yet. Interestingly, in our study, we did not observe any cases of TCEM after LUAO, even though it has been described to occur with similar frequency as after UAE [41]. Apart from one case of decreased ovarian reserve and decreased reactivity to hormonal stimulation with in vitro fertilization (IVF) treatment within the first year after UAE, we did not record any ovary-related complication of embolization, which is consistent with data from previous studies on younger women [42, 43].

The images of necrotic myomas communicating with uterine cavity, which were frequent after UAE and rare after LUAO, have also been seen on hysteroscopy (Table 5). The expected negative impact of these findings, at least in the early time period after UAE, is listed in Table 7, showing lower pregnancy and delivery rates and increased abortion rate in patients with abnormal hysteroscopic findings and a greater rate of normal hysteroscopic findings in the subgroup of women who delivered successfully after UAE compared with patients who miscarried or did not conceive.

The only study primarily aimed at reproductive outcomes was published by Holub et al. [12], who showed that 20 pregnant patients after UAE had significantly greater abortion rate (56 %) than 38 pregnant patients after LUAO (11 %). Our study, conducted in a much larger number of patients, did not confirm those findings. Although pregnancy and delivery rate may be affected by longer follow-up in favor of embolization (cumulative frequency of pregnancies and deliveries logically increases in time), abortion rate is not. Pregnancy rate just lower than 70 % in both groups is even comparable with pregnancy rates after LM [44]. The abortion rate was high (respectively, 34.2 vs. 33.3 % compared with 10–15 % in the general population; however, the abortion rate is expected to be greater in all patients with myomas) and surprisingly similar in both the groups. Although in UAE the greater abortion rate can be explained by detrimental effect of embolization on uterine cavity and endometrium, in LUAO in contrast the persistent impact of insufficiently infarcted myoma on myometrium receptivity remains hypothetical.

Likewise, in our study comparing UAE with myomectomy, the further course of pregnancy was uncomplicated because the patients overcame the first trimester. We did not prove greater premature delivery or malpresentation rates as observed in other studies. Perinatal results significantly differed only in the lower average birth weight and greater frequency of IUGR after LUAO. Does complete closure of the main branch of uterine arteries in surgical occlusion present a greater risk of decreased perfusion of the uterus and placenta in pregnancy than more selective UAE?

Limitations

Despite its obvious strengths (large study population, long follow-up, evaluation of current insufficiently studied fertility outcomes), our study has several limitations that warrant discussion. Lack of randomization introduced selection bias, resulting in differences in baseline characteristics of the two groups. Selection of patients with myomas not amenable to LM only limits universality of the outcomes of this study to an entire spectrum of patients with this disease. However, this inclusion restriction was necessary for ethical reasons because clinical and fertility outcomes of patients with myomas amenable to LM are significantly better compared with the previously reported results after UAE or LUAO. The usual drawback of reproductive studies, apart from studies aimed solely at the effectiveness of IVF, is lower predictive value of reproductive results due to other plausible factors of infertility or the inability to compare the motivation of the couple to conceive. Finally, evaluation of some parameters and perinatal complications of lower incidence is limited by the small number of patients who conceived or gave birth.

We conclude that in a highly selected group of women with symptomatic uterine fibroids not suited for standard myomectomy, the radiological or laparoscopic occlusion of uterine arteries offers a minimally invasive treatment with high technical success rate, low risk of serious complications, and high symptomatic effectiveness. UAE ensures greater chances of complete myoma infarction and results in greater volume decrease, but it also carries a greater risk of communication of necrotic myoma with the uterine cavity, which may cause infertility and miscarriages. However, the abortion rate after LUAO is similar (approximately 30 % for both methods) and unlike UAE, LUAO is also associated with a risk of intrauterine growth restriction. Given the low frequency of serious complications, including perinatal, we can consider occlusive therapy of uterine myomas in this preselected group of patients a viable alternative to open myomectomy, which is more invasive and often incomplete. This hypothesis should be confirmed by further studies with randomized, strictly defined design focused on late complications, reinterventions, and fertility.

Acknowledgments The authors thank Alena Dohnalova for statistical consultations and analysis of the results and Pavel Dundr for histopathological examinations of all excised myomas. The study was supported by a grant from the Internal Grant Agency of Ministry of Health of the Czech Republic (Grant No. NS 9798-4).

Conflict of interest All authors state that they have no conflicts of interest to declare.

References

1. Ravina JH, Herbreteau D, Ciraru-Vigneron N et al (1995) Arterial embolization to treat uterine myomata. Lancet 346:671–672
2. Dubuisson JB, Fauconnier A, Chapron C, Kreiker G, Norgaard C (2000) Reproductive outcome after laparoscopic myomectomy in infertile women. J Reprod Med 45:23–30
3. Malzoni M, Sizzi O, Rossetti A, Imperato F (2006) Laparoscopic myomectomy: a report of 982 procedures. Surg Technol Int 15:123–129
4. Nezhat C (1996) The "cons" of laparoscopic myomectomy in women who may reproduce in the future. Int J Fertil Menopausal Stud 41:280–283
5. Holub Z, Kliment L (2002) Laparoscopic ultrasonic dissection of uterine vessels in women with benign uterine pathologies. Clin Exp Obstet Gynecol 29:54–56
6. Liu WM (2000) Laparoscopic bipolar coagulation of uterine vessels to treat symptomatic leiomyomas. J Am Assoc Gynecol Laparosc 7:1251–1259
7. Committee on Gynecologic Practice, American College of Obstetricians and Gynecologists (2004) ACOG Committee Opinion. Uterine artery embolization. Obstet Gynecol 103: 403–404
8. Tulandi T, Sammour A, Valenti D, Child TJ, Seti L, Tan SL (2002) Ovarian reserve after uterine artery embolization for leiomyomata. Fertil Steril 178:197–198

9. Hald K, Langebrekke A, Klow NE, Noreng HJ, Berge AB, Istre O (2004) Laparoscopic occlusion of uterine vessels for the treatment of symptomatic fibroids: initial experience and comparison to uterine artery embolization. Am J Obstet Gynecol 190:37–43
10. Hald K, Klow NE, Qvigstad E, Istre O (2007) Laparoscopic occlusion compared with embolization of uterine vessels: a randomized controlled trial. Obstet Gynecol 109:20–27
11. Park H, Kim Y, Shin S et al (2003) Treatment outcomes of uterine artery embolization and laparoscopic uterine artery ligation for uterine myomas. Yonsei Med J 4:694–702
12. Holub Z, Mara M, Kuzel D, Jabor A, Maskova J, Eim J (2008) Pregnancy outcomes after uterine occlusion: prospective multicentric study. Fertil Steril 90:1886–1891
13. Bajekal N, Li TC (2000) Fibroids, infertility and pregnancy wastage. Hum Reprod Update 6:614–620
14. Dubuisson JB, Fauconnier A, Fourchotte V, Babaki–Fard K, Chapron C, Coste J (2001) Laparoscopic myomectomy: predicting the risk of conversion to an open procedure. Hum Reprod 16:1726–1731
15. Olive DL, Lindheim SR, Pritts EA (2004) Non-surgical management of leiomyoma: impact on fertility. Curr Opin Obstet Gynecol 16:239–243
16. Mára M, Mašková J, Fučíková Z, Kužel D, Belšan T, Sosna O (2008) Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. Cardiovasc Interv Radiol 31:73–85
17. Razavi MK, Wolanske KA, Hwang G et al (2002) Angiographic classification of ovarian artery to uterine artery anastomoses: initial observations in uterine fibroid embolization. Radiology 224:707–712
18. Iverson RE Jr, Chelmow D, Strohbehn K, Waldman L, Evantash EG, Aronson MP (1999) Myomectomy fever: testing the dogma. Fertil Steril 72:104–108
19. Mettler L, Hucke J, Bojahr B, Tinneberg HR, Leyland N, Avelar R (2008) A safety and efficacy study of a resorbable hydrogel for decrease of post-operative adhesions following myomectomy. Hum Reprod 23:1093–1100
20. Pelosi MA 3rd, Pelosi MA (1997) Spontaneous uterine rupture at thirty three weeks subsequent to previous superficial laparoscopic myomectomy. Am J Obstet Gynecol 177:1547–1549
21. Manyonda IT, Bratby M, Horst JS, Banu N, Gorti M, Belli AM (2011) Uterine artery embolization versus myomectomy: impact on quality of life—results of the FUME (fibroids of the uterus: myomectomy versus embolization) trial. Cardiovasc Interv Radiol. doi:10.1007/s00270-011-0228-5
22. Fauconnier A, Pelage JP, Lacombe P, Ville Y (2004) Embolization of uterine fibroids and infertility: is a clinical trial conceivable? Gynecol Obstet Fertil 32:818–824
23. Carpenter TT, Walker WJ (2005) Pregnancy following uterine artery embolisation for symptomatic fibroids: a series of 26 completed pregnancies. Br J Obstet Gynaecol 112:321–325
24. McLucas B, Goodwin S, Adler L, Rappaport A, Reed R, Perrella R (2001) Pregnancy following uterine fibroid embolization. Int J Gynaecol Obstet 74:1–7
25. Pron G, Mocarski E, Bennett J, Vilos G, Common A, Vandenburgh L et al (2005) Pregnancy after uterine artery embolization for leiomyomata: the Ontario multicenter trial. Obstet Gynecol 105:67–76
26. Ravina JH, Vigneron NC, Aymard A, Le Dref O, Merland JJ (2000) Pregnancy after embolization of uterine myoma: report of 12 cases. Fertil Steril 73:1241–1243
27. Goldberg J, Pereira L, Berghella V et al (2004) Pregnancy outcomes after treatment for fibromyomata: uterine artery embolization versus laparoscopic myomectomy. Am J Obstet Gynecol 191:18–21
28. Burbank F (2004) Childbirth and myoma treatment by uterine artery occlusion: do they share a common biology? J Am Assoc Gynecol Laparosc 11:138–152
29. Chen YJ, Wang PH, Yuan Ch, Yang MJ, Yen YK, Liu WM (2002) Pregnancy following treatment of symptomatic myomas with laparoscopic bipolar coagulation of uterine vessels. Hum Reprod 18:1077–1081
30. Liu WM, Wang PH, Chou CS, Tang WL, Wang IT, Tzeng CR (2007) Efficacy of combined laparoscopic uterine artery occlusion and myomectomy via minilaparotomy in the treatment of recurrent uterine myomas. Fertil Steril 87:356–361
31. Holub Z, Jabor A, Lukáč J et al (2004) Mid-term follow-up study of laparoscopic dissection of uterine vessels in symptomatic fibroid. Surg Endosc 18:1349–1353
32. Hutchins FL Jr, Worthington-Kirsch R, Berkowitz RP (1999) Selective uterine artery embolization as primary treatment for symptomatic leiomyomata uteri. J Am Assoc Gynecol Laparosc 6:279–284
33. Katsumori T, Nakajima K, Mihara T, Tokuhiro M (2002) Uterine artery embolization using gelatin sponge particles alone for symptomatic uterine fibroids: midterm results. Am J Roentgenol 178:135–139
34. Lohle PN, Boekkooi FP, Smeets AJ et al (2006) Limited uterine artery embolization for leiomyomas with tris-acryl gelatin microspheres: 1-year follow-up. J Vasc Interv Radiol 17:283–287
35. McLucas B, Adler L, Perella R (2001) Uterine fibroid embolization: nonsurgical treatment for symptomatic fibroids. J Am Coll Surg 192:95–105
36. Pron G, Bennett J, Common A, Wall J, Asch M, Sniderman K et al (2003) The ontario uterine fibroid embolization trial. Part 2. Uterine fibroid decrease and symptom relief after uterine artery embolization for fibroids. Fertil Steril 79:120–127
37. Ravina JH, Aymard A, Ciraru-Vigneron N, Ledreff O, Merland JJ (2000) Arterial embolization of uterine myoma: results apropos of 286 cases. J Gynecol Obstet Biol Reprod 29:272–275
38. Spies JB, Cornell C, Worthington-Kirsch R, Lipman JC, Benenati JF (2007) Long-term outcome from uterine fibroid embolization with tris-acryl gelatin microspheres: results of a multicenter study. J Vasc Interv Radiol 18:203–207
39. Walker WJ, Pelage JP (2002) Uterine artery embolization for symptomatic fibroids: clinical results in 400 women with imaging follow-up. Br J Obstet Gynecol 109:1262–1272
40. Hehenkamp WJ, Volkers NA, Van Swijndregt AD, De Blok S, Reekers JA, Ankum WM (2004) Myoma expulsion after uterine artery embolization: complication or cure? Am J Obstet Gynecol 191:1713–1715
41. Liu WM, Yen YK, Wu YC, Yuan CC, Ng HT (2001) Vaginal expulsion of submucous myomas after laparoscopic-assisted uterine depletion of the myomas. J Am Assoc Gynecol Laparosc 8:267–271
42. Spies JB, Roth AR, Gonsalves SM, Murphy-Skrzyniarz KM (2001) Ovarian function after uterine artery embolization for leiomyomata: assessment with use of serum follicle stimulating hormone assay. J Vasc Interv Radiol 12:437–442
43. Tropeano G, Di Stasi C, Litwicka K et al (2004) Uterine artery embolization for fibroids does not have adverse effects on ovarian reserve in regularly cycling women younger than 40 years. Fertil Steril 81:1055–1061
44. Sizzi O, Rossetti A, Malzoni M et al (2007) Italian multicenter study on complications of laparoscopic myomectomy. J Minim Invasive Gynecol 14:453–462

Genetické faktory v etiopatogenezi děložních myomů

Čes. Gynek.
2012, 77, č. 1
s. 58-60

Genetic factors in etiology of uterine fibroids

Kubínová K., Mára M., Horák P., Kužel D.
Gynekologicko-porodnická klinika VFN a 1. LF UK, Praha, přednosta prof. MUDr. A. Martan, DrSc.

ABSTRACT

Uterine fibroids are the most common pelvic tumors in women of reproductive age. The cause of development of uterine fibroids is still unknown, however recent cytogenetic and genetic studies led to advancement in understanding of etiology of these tumors. In accordance with the latest findings up to 40% of uterine fibroids bear some chromosomal abnormalities. The most common are aberration of chromosomes 6, 7, 12 and 14. Uterine fibroids have been linked to mutations of fumarate hydratase (FH) gene. Germline mutations in FH gene cause autosomal dominant syndromes MCUL1 (multiple cutaneous and uterine leiomyomata) and HLRCC (hereditary leiomyomatosis and renal cell cancer), characterized by multiple uterine and cutaneous leiomyomata and renal cancer. This paper reviews recent findings in the role of genetic in etiology of uterine fibroids.

Key words: **uterine fibroid, cytogenetic, chromosomal aberration.**

SOUHRN

Cíl studie: **Podat přehled nových poznatků o etiopatogenezi děložních myomů.**

Typ studie: **Souhrnný článek.**

Název a sídlo pracoviště: **Gynekologicko-porodnická klinika VFN a 1. LF UK v Praze.**

Metodika: **Analýza dostupných literárních zdrojů.**

Závěry: **Děložní myomy jsou nejčastějšími pánevními nádory žen v reprodukčním věku. Přesná příčina vzniku děložních myomů zůstává do dnešní doby neznámá, přestože v oblasti cytogenetiky a genetiky došlo k značnému pokroku v objasnění etiopatogeneze děložních myomů. Podle nejnovějších poznatků až 40 % děložních myomů vykazuje chromozomální abnormality. Nejčastějším typem jsou aberace chromozomů 6, 7, 12 a 14. Výskyt děložních myomů bývá spojován také s mutacemi genu pro fumarát hydratázu (FH). Germinální mutace tohoto genu způsobují autozomální dominantní onemocnění MCUL1 (multiple cutaneous and uterine leiomyomata) a HLRCC (hereditary leiomyomatosis and renal cell cancer), charakterizované mnohočetnými kožními a děložními leiomyomy a renálním karcinomem. V následujícím článku přinášíme nejnovější poznatky o úloze genetických faktorů v etiopatogenezi děložních myomů.**

Klíčová slova: **děložní myom, cytogenetika, chromozomální aberace.**

ÚVOD

Děložní myomy představují nejčastější novotvary ženského reprodukčního ústrojí. Leiomyomy se mohou vyskytnout i v jiných lokalizacích, nejčastěji však postihují právě myometrium [12]. Se symptomy děložních myomů se setkáváme u 20–25 % žen v reprodukčním věku, ačkoli incidence děložních myomů je ve skutečnosti vyšší. Systematická studie histologických preparátů po hysterektomii u premenopauzálních pacientek prokázala výskyt děložních myomů až u 77 % případů s průměrným počtem myomů 6,5/pacientku [2, 12, 19]. Významné procento děložních myomů je tedy asymptomatických, přesto děložní myomy stále představují značný zdravotní i ekonomický problém.

Mezi nejčastější symptomy děložních myomů řadíme menoragii, bolest, „bulky“ symptomy, infertilitu, a pokud jsou děložní myomy přítomny v graviditě, mohou být příčinou spontánních abortů, předčasných porodů a dystokie [12].

V léčbě děložních myomů stále dominuje léčba chirurgická. U pacientek plánujících graviditu je myomektomie, zachovávající reprodukční schopnosti ženy, atraktivní alternativou k hysterektomii. Dále jsou v léčbě u pacientek s přáním zachovat dělohu využívány metody okluzní a nebo ablační. Léčba hormonální je v současné době využívána spíše jako léčba symptomatická či jako pretreatment před operační léčbou [7, 9, 12, 13].

GENETICKÝ PODKLAD DĚLOŽNÍCH MYOMŮ

Příčina vzniku a růstu děložních myomů zůstává z velké části neobjasněna, ačkoli genetický podklad byl pod-

pořen řadou epidemiologických, molekulárních a cytogenetických studií.

Bylo prokázáno, že děložní myomy se vyskytují častěji u žen s pozitivní rodinnou anamnézou. Příbuzné prvního stupně žen s děložními myomy mají až 2,5krát vyšší riziko vzniku děložních myomů. Stejně tak je popisován vyšší výskyt myomů u monozygotních dvojčat v porovnání s dizygotními. Rizikovým faktorem vzniku děložních myomů je také rasová příslušnost. U Afroameričanek je popisována až 2,9krát vyšší incidence děložních myomů v porovnání s bílým etnikem. Myomy jsou u Afroameričanek častěji mnohočetné, objemné a diagnostikovány v časnějším věku [3, 12, 16, 19].

CYTOGENETICKÉ ABNORMALITY BUNĚK DĚLOŽNÍCH MYOMŮ

Cytogenetické studie vzorků resekovaných leiomyomů vedly ke zjištění, že 40–50 % děložních myomů vykazuje chromozomální aberace. Nejčastějšími jsou translokace chromozomů 12 a 14, delece chromozomu 7 a trizomie chromozomu 12. Rein et al. ve studii na 114 myomech prokázal pozitivní korelaci mezi velikostí myomu a přítomností chromozomální aberace. Myomy s chromozomální aberací byly signifikantně objemnější než myomy s normálním karyotypem, lze tedy říci, že přítomnost cytogenetických abnormalit buněk myomů ovlivňuje růst myomů [21]. Vztah mezi typem aberace, věkem pacientek a paritou nebyl prokázán. Ukazuje se však, že existuje souvislost mezi anatomickou lokalizací myomu a přítomností cytogenetické abnormality. Submukózní myomy vykazují méně abnormalit než myomy intramurální a subserózní (12 % vs. 35 % resp. 29 %) [7, 12, 19].

TRANSLOKACE CHROMOZOMŮ 12 A 14

Přibližně ve 20 % případů myomů s abnormálním karyotypem nacházíme translokaci 12. a 14. chromozomu, která byla zároveň první cytogenetickou abnormalitou popsanou v buňkách leiomyomů [15]. Objev, že chromozomální aberace stejné oblasti genu 12q jsou přítomné i v řadě dalších mezenchymálních tumorů (například fibroadenomy prsu, lipomy, endometriální polypy, angiomyxomy a adenomy slinných žláz), vedl k předpokladu, že klíčové geny pro tumorogenezi se nacházejí právě v oblasti 12q14-15 [4, 5, 12, 17]. Další podrobné mapování této oblasti vedlo k identifikaci skupiny genových proteinů (High Mobility Group) tzv. HMGA. Tyto non-histonové komponenty chromatinu slouží jako architektonické faktory ovlivňující buněčné procesy jako diferenciaci, smrt, růst a proliferaci a jsou pravděpodobně zodpovědné za odlišný růst myomů [20].

ABNORMALITY CHROMOZOMU 7

Dalším častým typem aberace, vyskytujícím se u 17–20 % děložních myomů je delece chromozomu 7. Tento typ aberace se vyskytuje častěji v buňkách děložních myomů než v jiných tumorech, byl však identifikován i v lipomech, endometriálních polypech a u některých hematologických malignit [6]. Delece chromozomu 7 v myomech nalézáme často v kombinaci s dalšími abnormalitami, jako je translokace chromozomů 12 a 14 [12].

Je pozoruhodné, že u buněčných kultur s delecí či translokací chromozomu 7 většinou nacházíme mozaiku, tedy i buňky s normálním karyotypem [23]. Tyto kultury vykazují pomalý růst ve srovnání s buňkami, v nichž je zároveň přítomna translokace chromozomů 12 a 14. Děložní myomy s aberací chromozomu 12 jsou také často objemnější než myomy s abnormalitami chromozomu 7. Tato skutečnost naznačuje, že gen v oblasti 7q22 hraje roli v regulaci buněčného růstu [21].

MÉNĚ ČASTÉ TYPY CHROMOZOMÁLNÍCH ABERACÍ

Aberace chromozomu 6, konkrétně 6p21 jsou popisovány u výše zmíněných mezenchymálních tumorů (lipomy, endometriální polypy, plicní hamartomy) a v děložních myomech se vyskytuje s frekvencí <5 % [18].

Mezi další méně časté chromozomální abnormality pozorované v buňkách děložních myomů patří změny chromozomu X, strukturální přestavby mezi chromozomy 1 a 3, zejména ve formě ring chromozomu 1 a dále momozomie a delece dlouhého raménka chromozomu 10 [12, 14].

FUMARÁT HYDRATÁZA

Významným důkazem o genetickém podkladu děložních myomů je existence dvou vzácných syndromů: multiple cutaneous and uterine leiomyomatosis (MCUL) a hereditary leiomyomatosis and renal cell cancer (HLRCC). MCUL je autozomálně dominantní predispozicí k mnohočetné kožní a děložní myomatóze. HLRCC byl roku 2001 popsán Launonenem et al. ve studii na dvou rodinách s anamnézou výskytu renálního karcinomu, děložních myomů a leiomyomsarkomů, kožních leiomyomů a dalších nespecifikovaných malignit [10]. Později byl identifikován lokus HLRCC a MCUL na chromozomu 1q43. Bylo zjištěno, že germinální mutace genu pro fumarát hydratázu (FH) – kódující fumarát hydratázu, klíčový enzym Krebsova cyklu, vedou k autozomálně dědičné predispozici k děložním a kožním leiomyomům a papilárnímu renálnímu karcinomu typ II [22]. Výskyt děložních myomů je u postižených žen popisován v nízkém věku, mezi 2. a 3. decenniem. FH

má, pravděpodobně, funkci tumor supresorového genu, protože její aktivita je velmi nízká či nulová v buňkách tumorů pacientů postižených MCUL/HLRCC [5].

Identifikace mutací FH u hereditárních, syndromických forem tumorů vedla k výzkumu, zda mutace FH hrají roli i ve vzniku sporadických myomů. Studie zkoumající výskyt mutací FH u non-syndromických myomů prokázaly, že mutace FH jsou u sporadických myomů přítomny v nízkém procentu. Kiuru et al. na 41 vzorcích leiomyomů neprokázal žádnou mutaci FH, Lehtonen ve studii na 153 leiomyomech prokázal 2 mutace FH [8, 11]. Baker et al. se domnívá, že mutace FH by se mohly vyskytovat u 5 % sporadických myomů. Ačkoli mají tedy děložní myomy u pacientek s HLRCC a sporadické děložní myomy shodnou histologickou strukturu, proces tumorogeneze v obou případech pravděpodobně probíhá odlišným mechanismem [1].

ZÁVĚR

Cytogenetické a epidemiologické studie bezpochyby poukazují na genetický podklad vzniku děložních myomů. Ačkoli je výskyt chromozomálních aberací popisován jen u 40–50 % děložních myomů, může jít v ostatních případech o změny sekundární či submikroskopické. Tyto změny se mohou podílet v iniciaci růstu tumoru.

Identifikace mutací genu pro FH spojuje výskyt děložních myomů s dalšími malignitami v rámci syndromů MCUL/HLRCC. Pacientky, u nichž byla identifikována mutace FH, mají kromě výskytu děložních myomů v nízkém věku i zvýšené riziko vzniku renálního karcinomu. Vzhledem k nízké prevalenci těchto syndromů v populaci je otázkou do budoucna vyhledávání těchto pacientek. Vycházíme-li z výše uvedených poznatků, je tedy vhodné u mladých pacientek s děložními myomy a pozitivní rodinnou anamnézou děložních a/nebo kožních leiomyomů či renálního karcinomu provést screening na mutace FH a v případě pozitivity tyto pacientky dispenzarizovat.

Tato práce byla podpořena grantem IGA MZ ČR NS 9798-4.

LITERATURA

1. **Barker, KT., Spendlove, HE., Banu, NS., et al.** No evidence for epigenetic inactivation of fumarate hydratase in leiomyomas and leiomyosarcomas. Cancer Letters, 2006, 235, 1, p. 136-140.
2. **Cramer, SF.** The frequency of uterine leiomyomas. Amer J Clin Pathol, 1990, 94, p. 435-438.
3. **Goedken, J., Rock JA.** Uterine fibroids: Epidemiology and overview. In Tulandi, T. Uterine fibroids: Embolization and other treatments. Cambridge: Cambridge University press. 2003. 147 p.
4. **Hennig, Y., Deichert, U., Bonk, U., et al.** Chromosomal translocations affecting 12q14-15 but not deletions of the long arm of chromosome 7 associated with a growth advantage of uterine smooth muscle cells. Molecular Hum Reprod, 1999, 5, p. 1150-1154.
5. **Hodge, J., Morton, CC.** Genetic heterogeneity among uterine leiomyomata: insights into malignant progression. Hum Molecular Genet, 2007, 16, p. R7-13.
6. **Hodge, J., Park, PJ., Dreyfuss, JM., et al.** Identifying the molecular signature of the interstitial deletion 7q subgroup of uterine leiomyomata using a paired analysis. Genes, Chromosomes & Cancer. 2009, 48, 10, p. 865-885.
7. **Holub, Z., et al.** Management děložních myomů: CSGE doporučení k provádění správné klinické praxe. Čes Gynek, 2005, 70, s. 165-167.
8. **Kiuru, M., Lehtonen, R., Arola, J., et. al.** Few FH mutations in sporadic counterparts of tumor types observed in hereditary leiomyomatosis and renal cell cancer families. Cancer Res, 2002, 62, p. 16.
9. **Kubínová, K.** Perspektivy radiologické léčby myomů. In Mára, M. Děložní myomy: Moderní diagnostika a léčba. Praha: Grada Publishing. 2009. 231 s.
10. **Launonen, V., Vierimaa, O., Kuiru, M., et al.** Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proceedings of the National Academy of Sciences of the United States of America. 2001, 98, s. 3387-92
11. **Lehtonen, R., Kiuru, M., Vanharanta, S., et al.** Biallelic inactivation of fumarate hydratase (FH) occurs in nonsyndromic uterine leiomyomas but is rare in other tumors. Amer J Pathol, 2004, 164, p. 17-22.
12. **Ligon, AH., Morton, CC.** Leiomyomata: heritability and cytogenetic studies. Hum Reprod Update, 2001, 7, p. 8-14.
13. **Mára, M.** Indikace k embolizaci myomů. In MÁRA, M. Děložní myomy: moderní diagnostika a léčba. Praha: Grada Publishing. 2009. 231 s.
14. **Mark, J., Havel, G., Grepp, C., et al.** Chromosomal patterns in human benign uterine leiomyomas. Cancer Genet Cytogenet, 1990, 44, 1, p. 1-13.
15. **Meloni, AM., Surti, U., Contento, AM., et al.** Uterine leiomyomas: cytogenetic and histologic profile. Obstet Gynec, 1992, 80, p. 209-217.
16. **Okolo, S.** Incidence, aetiology and epidemiology of uterine fibroids. BailliŹre, 2008, 22, 4, p. 571-588.
17. **Ozisik, YY., Meloni, AM., Stephenson, CF., et al.** Chromosome abnormalities in breast fibroadenomas. Cancer Genet Cytogenet, 1994, 77, 2, p. 125-128.
18. **Ozisik, YY., Meloni, AM., Altungoz, O., et al.** Translocation (6;10)(p21;q22) in uterine leiomyomas. Cancer Genet Cytogenet, 1995, 79, 2, p. 136-138.
19. **Parker, W.** Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril, 2007, 87, p. 725-736.
20. **Reeves, R.** Molecular biology of HMGA proteins: hubs of nuclear function. Gene, 2001, 277, p. 63-81.
21. **Rein, MS., Powell, WL., Walters, FC., et al.** Cytogenetic abnormalities in uterine myomas are associated with myoma size. Molecular Hum Reprod, 1998, 4, 1, p. 83-86.
22. **Tomlinson, IP., Alam, NA., Rowan, AJ., et al.** Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nature Genet, 2002, 30, p. 406-410.
23. **Xing, YP., Powell, WL., Morton, CC.** The del(7q) subgroup in uterine leiomyomata : genetic and biologic characteristics. Further evidence for the secondary nature of cytogenetic abnormalities in the pathobiology of uterine leiomyomata. Cancer Genet Cytogenet, 1997, 98, p. 69-74.

MUDr. Kristýna Kubínová
Gynekologicko-porodnická klinika
VFN a 1. LF UK
Apolinářská 18
120 00 Praha 2
kristynakubinova@gmail.com

19. **Obermair, A., Ginbey, P., McCartney, AJ.** Feasibility and safety of total laparoscopic radical hysterectomy. J Am Assoc Gynecol Laparosc, 2003, 10, p. 345–9.
20. **Occelli, B., Narducci, F., Lanvin, D., et al.** Learning curves for transperitoneal laparoscopic and extraperitoneal endoscopic paraaortic lymphadenectomy. J Am Assoc Gynecol Laparosc, 2000, 7, p. 51–3.
21. **Pilka, R., Marek, R., Táborská, S., Dzvinčuk, P.** Robotem asistovaný laparoskopický staging karcinomu endometria – srovnání se standardní laparotomií. Čes Gynek, 2011, 76, s. 462–468.
22. **Plante, M., Renaud, M.C., Têtu, B., et al.** Laparoscopic sentinel node mapping in early-stage cervical cancer. Gynecol Oncol, 2003, 91, p. 494–503.
23. **Pomel, C., Rouzier, R., Pocard, M., et al.** Laparoscopic total a pelvic exenteration for cervical cancer relapse. Gynecol Oncol, 2003, 91, p. 616–618.
24. **Possover, M., Krause, N., Plaul, K., et al.** Laparoscopic para-aortic and pelvic lymphadenectomy: experience with 150 patients and review of the literature. Gynecol Oncol, 1998, 71, p. 19–28.
25. **Querleu, D., Dargent, D., Ansquer, Y., et al.** Extraperitoneal endosurgical aortic and common iliac dissection in the staging of bulky or advanced cervical carcinomas. Cancer, 2000, 88, p. 1883–1891.
26. **Querleu, D., Leblanc, E., Cartron, G., et al.** Audit of preoperative and early complications of laparoscopic lymph node dissection in 1000 gynecologic cancer patients. Am J Obstet Gynecol, 2006, 195, p. 1287–1292.
27. **Renaud, MC., Plante, M., Roy, M.** Combined laparoscopic and vaginal radical surgery in cervical cancer. Gynecol Oncol, 2000, 79, p. 59–63.
28. **Scribner, DR. Jr., Walker, JL., Johnson, GA., et al.** Laparoscopic pelvic and paraaortic lymph node dissection: analysis of the first 100 cases. Gynecol Oncol, 2001, 82, p. 498–503.
29. **Scribner, DR. Jr., Walker, JL., Johnson, GA., et al.** Laparoscopic pelvic and paraaortic lymph node dissection in the obese. Gynecol Oncol, 2002, 84, p. 426–430.
30. **Sláma, J., Dundr, P., Dušek, L., et al.** Sentinel lymph node status in patients with locally advanced cervical cancers and impact of neoadjuvant chemotherapy. Gynecol Oncol, 2012 Feb 14. [Epub ahead of print].
31. **Spirtos, NM., Eisenkop, SM., Schlaerth, JB., Ballon, SC.** Laparoscopic radical hysterectomy (type III) with aortic and pelvic lymphadenectomy in patients with stage I cervical cancer: surgical morbidity and intermediate follow-up. Am J Obstet Gynecol, 2002, 187, p. 340–348.

Doc. MUDr. Michal Mára, CSc.
Gynekologicko-porodnická klinika 1. LF UK a VFN
Apolinářská 18
128 00 Praha 2
e-mail: michal.mara@quick.cz

Laparoskopická konzervativní léčba děložních myomů

Čes. Gynek.
2012, 77, č. 4
s. 326-330

Laparoscopic uterus sparing treatment of uterine fibroids

Kubínová K., Mára M., Novotná M., Kužel D.
Gynekologicko-porodnická klinika VFN a 1. LF UK, Praha, přednosta prof. MUDr. A. Martan, DrSc.

ABSTRACT

Objective: **To report up-to date knowledge on laparoscopic, uterine sparing treatment of uterine fibroids.**

Study design: **Review.**

Setting: **Uterine Fibroids Center, Department of Obstetrics and Gynecology, Charles University, Prague.**

Methods: **Analysis of our clinical experience and available literature resources.**

Results: **The management of uterine fibroids depends on the symptoms, location, and size of fibroids and on the reproductive plans of the patient. The surgical treatment has changed from laparotomy to minimally invasive surgery. In general, laparoscopic myomectomy (LM) is considered the best option in symptomatic patients with pregnancy plans. The laparoscopic approach is associated with lower postoperative morbidity as well as lower incidence of massive postoperative adhesion formation compared to laparotomy. The limitation of laparoscopic myomectomy is the size and the number of fibroids but also the location and the accessibility for the laparoscopic suturing. Laparoscopic uterine artery occlusion (LUAO) represents one of the alternatives to LM in patients with multiple small myomas or in patients with fibroids in unfavorable location. LUAO may be advantageously used prior to LM in order to reduce peroperative blood loss or to prevent the persisting fibroids from growing. However there is no universal treatment of uterine fibroids in fertile patients and in each single patient the indication and surgical method should be thoroughly considered.**

Key words: **uterine fibroid, myomectomy, laparoscopy, uterine artery occlusion.**

SOUHRN

Cíl studie: **Podat přehled aktuálních poznatků o laparoskopické, dělohu zachovávající léčbě děložních myomů.**

Typ studie: **Souhrnný článek.**

Název a sídlo pracoviště: **Centrum pro komplexní diagnostiku a léčbu děložních myomů; Gynekologicko-porodnická klinika VFN a 1. LF UK v Praze.**

Metodika: **Analýza našich klinických zkušeností a dostupných literárních zdrojů.**

Závěry: **Léčba děložních myomů závisí na jejich symptomatologii, velikosti a lokalizaci a na reprodukčních plánech pacientky. Chirurgická léčba zaznamenala logický vývoj od otevřeného přístupu k minimálně invazivní chirurgii. Obecně platí, že laparoskopická myomektomie (LM) je u většiny žen plánujících těhotenství metodou volby. Laparoskopický přístup je, ve srovnání s laparotomií, spojen s výrazně nižší pooperační morbiditou a nižším výskytem adhezí. Limitací LM jsou velikost a počet myomů, erudice operatéra (náročnost laparoskopické sutury) a v některých případech i lokalizace a přístup k adekvátní sutuře. Laparoskopická okluze děložních arterií (LUAO) představuje jednu z alternativ k LM u pacientek s mnohočetnou drobnou myomatózou či u pacientek s myomem v nepříznivé lokalizaci. LUAO lze s výhodou provést i před samotnou LM k minimalizaci krevní ztráty během operace nebo k zamezení růstu ponechaných myomů. V současné době neexistuje univerzální metoda na léčbu děložních myomů ve fertilním věku a u každé pacientky je třeba pečlivě zvažovat indikaci a volbu operačního přístupu.**

Klíčová slova: **děložní myom, myomektomie, laparoskopie, okluze děložních tepen.**

ÚVOD

Děložní myomy jsou nejčastější benigní tumory děložního těla, jejichž incidence u žen v reprodukčním věku se udává v rozmezí 6–77 % v závislosti na použité diagnostické metodě [12]. Přibližně 25 % pacientek s myomy je symptomatických, mezi nejčastější příznaky patří pánevní diskomfort, menoragie, infertilita a těhotenské komplikace [25]. U většiny pacientek jsou děložní myomy diagnostikovány náhodně při ultrazvukovém vyšetření či při operaci z jiné indikace [1]. Prevalence myomů se zvyšuje s věkem pacientek a maxima dosahuje ve 4. decenniu. Jejich etiopatogeneze není doposud jednoznačně objasněna, hlavní roli zřejmě hrají faktory hormonální a genové mutace [25]. Proto dodnes neexistuje kauzální léčba a v léčbě pokročilejších nálezů tak dominují chirurgické postupy.

V následujícím textu uvádíme přehled laparoskopických metod léčby myomů u žen preferujících zachování dělohy. Na tyto výkony se na našem pracovišti cíleně zaměřujeme a v posledních 12 letech postupně vstoupily do naší každotýdenní praxe.

LAPAROSKOPICKÁ MYOMEKTOMIE

Minimálně invazivní přístup byl do spektra léčby děložních myomů zařazen před více než dvěma desetiletími [19]. S rozvojem instrumentária a erudicí operatérů se laparoskopická myomektomie (LM) stala dominantní metodou v léčbě děložních myomů u žen s reprodukčními plány a ve většině indikací nahradila myomektomii laparotomickou. Laparotomická myomektomie má však i dnes své místo, zejména u pacientek s objemnými či mnohočetnými myomy. Laparoskopická, minimálně invazivní operativa děložních myomů vyžaduje schopnost provádět laparoskopickou suturu [1, 17]. Pečlivě provedená sutura defektu myometria v několika vrstvách zajišťuje dostatečnou pevnost sutury v graviditě a jen nízké riziko ruptury dělohy v graviditě či během porodu (pod 1 %). V minulosti zveřejněné ojedinělé případy ruptury dělohy v jizvě po LM pravděpodobně souvisely s excesivním použitím elektrokoagulace a s tím související nekrózou tkání a také inadekvátní suturou [1, 3].

V jediné randomizované studii srovnávající fertilitu po laparoskopické a laparotomické myomektomii Seracchioli a spol. udávají vyšší pooperační morbiditu po myomektomii laparotomické (vyšší výskyt febrilií a nutnosti podání krevní transfuze) při kratší době hospitalizace a kratší rekonvalescenci po LM. Reprodukční výsledky obou skupin se statisticky nelišily. Pregnancy rate (55,9 % po laparoskopii a 53,6 % po laparotomii), abortion rate (12,1 % vs. 20 %) a frekvence císařských řezů (77,8 % vs. 65 %) byly srovnatelné v obou skupinách a nebyl zaznamenán žádný případ ruptury dělohy v graviditě či během porodu [23].

Výhodou laparoskopického přístupu ve srovnání s laparotomií je tedy kratší doba hospitalizace, nižší spotřeba analgetik a rychlejší rekonvalescence, oproti tomu je laparoskopie zatížena delším operačním časem a s tím související delší anestezií [1, 9, 17, 18, 21]. Laparotomie je spojena s vyšším výskytem pooperačních adhezí, a to zejména adhezí denzních, hůře rozrušitelných [2].

Výběr pacientek a zkušenosti operatéra, zejména erudice v laparoskopickém šití, jsou klíčové faktory pro úspěch a výsledek LM. Každé pracoviště, zabývající se pokročilejší laparoskopickou operativou, má svá kritéria pro indikace k této operaci. Na našem pracovišti za optimální považujeme pro laparoskopický přístup obecně uznávaná kritéria, tedy velikost myomu do 7 do 8 cm a počet myomů (nad 2 cm) nižší než 5. Je však potřeba individuálně zvážit tato doporučení u každé pacientky s ohledem na lokalizaci dominantního myomu a další faktory, jako jsou obezita či předchozí břišní operace [1, 17, 21].

Předoperační podání analog gonadoliberinu

U pacientek, které nesplňují výše uvedená kritéria, lze před operací zvážit tříměsíční podání analog gonadoliberinu (GnRHa), určené ke snížení prokrvení a zmenšení objemu myomu, a tím vyšší naději na úspěšnou laparoskopickou enukleaci. Jako výhoda tohoto postupu se uvádí korekce předoperační anémie spojená s nižší potřebou perioperační transfuze a nižší peroperační krevní ztráta; k signifikantnímu zkrácení operačního času však podle dostupných údajů nedochází [13]. Použití GnRHa také může vést k vymizení typického vrstvení myomu, což znemožňuje standardní laparoskopickou enukleaci a zvyšuje riziko konverze na laparotomii [4, 9]. Další nevýhodou GnRHa jsou vedlejší klimakterické účinky a bohužel nestandardní objemová redukce myomů, kdy v některých případech se myom zmenší jen nevýrazně. Na naší klinice používáme pre-treatment GnRHa nejčastěji u nálezu solitárního intramurálního myomu o průměru mezi 7 a 10 cm.

Technika laparoskopické myomektomie

LM provádíme v celkové anestezii v Trendelenburgově poloze. Peroperačně aplikujeme single shot antibiotickou profylaxi. Nejčastěji využíváme tři 10mm a jeden 5mm port. Při objemnějším myomu, lokalizovaném zejména ve fundu děložním, lze využít supraumbilikální umístění portu pro kameru.

Operaci obvykle zahajujeme hysteroskopickou vizualizací dutiny děložní k posouzení důležitého faktu, zda a případně jakou částí svého objemu myom(y) zasahuje intrauterinně. U žen sterilních či brzy plánujících otěhotnět je hysteroskopie vhodná také k vyloučení (a ev. současnému řešení) možné přidružené intrauterinní patologie (polypy, vrozené vady). Krvácení navíc vždy nemusí být symptomem pouze děložních myomů, ale setkali jsme se už i u žen mladších 40 let s histologicky verifikovaným nálezem karcinomu endometria či endometriálního stromálního sarkomu.

Pokračujeme laparoskopií. Po zavedení kapnoperitonea zhodnotíme nález v pánvi a vlastní myomektomii zahajujeme incizí serózy dělohy v místě maximálního vyklenutí myomu pomocí monopolární koagulace. Ve velké většině případů preferujeme vedení incize ve vertikálním směru (snížení krvácení, vyhneme-li se děložním rohům a hranám). Jako potenciálně výhodnou, ale nikoli nutnou, vidíme aplikaci roztoku vazokonstrikčního agens (např. zředěný adrenalin nebo vazopresin) mezi myom a zdravé tkáně dělohy. Tento krok obvykle přispívá k redukci krevní ztráty a k snazší enukleaci myomu. Po dosažení vrstvy je myom uchopen do jednozubých amerických kleští a kombinací trakce kleští a tupé i ostré preparace je myom postupně enukleován [1, 17]. Během operace se snažíme vyhnout excesivnímu použití elektrokoagulace, abychom předešli nadměrné nekrotizaci tkání [3] a, pokud je to možné, i nitroděložnímu průniku, což je někdy zvládnutelné i u intrauterinně prominujících myomů, pokud existuje dobré ohraničení myomu od okolních tkání.

Následuje klíčová fáze výkonu a tou je sutura vzniklého defektu děložní stěny ve vrstvách, nejlépe s využitím kulaté jehly a atraumatického návleku. Stehy volíme buď jednotlivé, či pokračující, podle zvyklostí operatéra. Myom z dutiny břišní odstraňujeme elektrickým či mechanickým, většinou 20mm morcelátorem, což upřednostňujeme před využitím zadní kolpotomie nebo minilaparotomie [17]. Ke snížení výskytu pooperačních adhezí lze na závěr operace na oblast sutury po myomektomii aplikovat některý z antiadhezivních, bariérových prostředků [9, 22, 26].

Vedení porodu po laparoskopické myomektomii

Při rozhodování o vedení porodu po LM často hrají roli přidružené indikace (věk, dlouho léčená sterilita, biometrie a poloha plodu, předchozí císařský řez) a motivace rodičky k vaginálnímu porodu. U pacientek, u nichž byl odstraněn objemný (nad 6 cm), hluboce intramurálně zasahující myom vyžadující rozsáhlou suturu myometria nebo došlo-li během myomektomie k průniku do dutiny děložní, doporučujeme primárně porod elektivním císařským řezem, obvykle v ukončeném 39. týdnu gestace. U každé pacientky přistupujeme k vedení porodu přísně individuálně. Pokud se rozhodneme pro vaginální porod, je nutné k rodičce přistupovat stejně jako k rodičkám po císařském řezu [17].

LAPAROSKOPICKY ASISTOVANÁ MYOMEKTOMIE

Laparoskopicky asistovaná myomektomie (LAM) byla do klinické praxe uvedena roce 1994 bratry Nezhaty jako alternativa k laparoskopické a otevřené myomektomii [20]. Technika LAM je shodná s LM, sutura a odstranění myomu jsou však provedeny z minilaparotomie o délce 4–6 cm. Metoda je hodně oblíbená a rozšířená v zemích jihovýchodní Asie, kde jsou tak u štíhlých pacientek operatéři schopni řešit i velmi pokročilé případy myomatóz [16]. Mezi výhody této metody autoři uvádějí možnost přímé palpace dělohy, menší technickou náročnost provedení sutury ve srovnání s LM a možnost odstranit objemnější myomy než při LM [1, 19, 24].

LAPAROSKOPICKY ASISTOVANÁ VAGINÁLNÍ MYOMEKTOMIE

Laparoskopicky asistovanou vaginální myomektomii (LAVM) poprvé popsali roku 2000 Wang a spol. jako alternativu k laparoskopické myomektomii u myomů uložených ve fundu nebo zadní stěně děložní [27]. LAVM se technicky neliší od LAM, rozdílem je odstranění myomu a provedení sutury zadní kolpotomií [10, 27]. Podle studie Holuba a spol. je při LAVM významně zkrácena délka operace ve srovnání s LM [8]. Na našem pracovišti provádíme LAVM v případě tzv. cervikálních myomů, pokud jsou uloženy výrazně kaudálně v oblasti

děložního isthmu a cervixu a pokud alespoň zčásti prominují poševní klenbou do vaginy.

LAPAROSKOPICKÁ OKLUZE DĚLOŽNÍCH ARTERIÍ

V návaznosti na úspěchy intervenčních radiologů s embolizací uterinních arterií (UAE) byla gynekology vyvinuta podobná chirurgická metoda: laparoskopická okluze uterinních arterií s/bez koagulace případných anastomóz a. uterina s a. ovarica [14, 15]. Tato metoda byla dále modifikována Holubem roku 2002, který k retroperitoneální preparaci i k přerušení uterinní arterie v místě odstupu z vnitřní ilické arterie využíval bezpečnější ultrazvukovou energii harmonického skalpelu [6].

Laparoskopická okluze děložních arterií (LUAO) je v porovnání s UAE spojena s nižší spotřebou analgetik post-procedurálně, jde však o chirurgický výkon zatížený všemi riziky spojenými s laparoskopickým výkonem a celkovou anestezií. Hald a spol. publikovali roku 2009 randomizovanou studii srovnávající dlouhodobé výsledky UAE a chirurgické okluze na souboru 66 pacientek. Rekurence myomů byla signifikantně vyšší ve skupině pacientek po LUAO. U pacientek ošetřených embolizací byla zaznamenána významnější objemová redukce myomu a také vyšší procento pacientek s kompletní infarzací myomu [5].

V současné době není k dispozici dostatek statisticky zhodnocených dat o reprodukčních výsledcích pacientek po okluzivní léčbě myomů. Práce tchaiwanských autorů z roku 2003 uvádí vysoký abortion rate u pacientek po LUAO (41,2 %) [11]. Reprodukčními výsledky LAUO a UAE se zabývala studie publikovaná českými autory roku 2008 v časopise Fertility Sterility. Obě skupiny se statisticky nelišily v pregnancy rate (46,9 % po LUAO a 51,2 % po UAE) ani ve frekvenci předčasných porodů (15,3 % vs. 20 %), po UAE byla však významně vyšší frekvence časných abortů (56 % vs. 11,1 %). Ani v jedné ze sledovaných podskupin nebyl prokázán signifikantně vyšší výskyt preeklampsie, IUGR či jiných závažných perinatálních komplikací [7].

Technika laparoskopické okluze děložních arterií

Při LUAO vstupujeme do retroperitonea v trojúhelníku vymezeném anteriorně ligamentem teres, medio-dorzálně ligamentem infundibulo-pelvicum a laterálně pánevní stěnou s vasa ilica externa. Poté postupně, pomocí tupé a ostré disekce vypreparujeme paravezikální a obturatorní fossu. Tahem za ligamentum umbilicale mediale si ozřejmíme a skeletizujeme odstup a. uterina z a. ilica interna. Po vizualizaci ureteru a jeho odsunutí mediálně je možno a. uterina přerušit pomocí bipolárních kleští a/nebo harmonického skalpelu. Peritoneální defekt ponecháváme bez sutury [8]. Výkon je nutné (aby byl dostatečně efektivní), podobně jako v případě UAE, provést bilaterálně, a to nehledě na případnou laterální lokalizaci myomu.

ZÁVĚR

Laparoskopická myomektomie je bezpochyby bezpečnou léčebnou metodou, zatíženou minimálním rizikem komplikací a nízkou morbiditou a je v dnešní době metodou volby u většiny pacientek v reprodukčním věku se signifikantním, symptomatickým děložním myomem či myomy. LM je však zároveň technicky i časově náročnou operací, vyžadující dostatečnou erudici operatéra, zejména v provádění laparoskopické sutury. V léčbě děložních myomů u žen plánujících otěhotnět však ani dnes neexistuje univerzální terapeutická metoda a u každé pacientky je nutno léčbu přísně individualizovat, a to i vzhledem ke zkušenostem operatéra či pracoviště.

Seznam použitých zkratek:

GnRHa – analoga gonadotropin releasing hormonu (gonadoliberinu)
IUGR – nitroděložní růstová retardace plodu
LM – laparoskopická myomektomie
LAM – laparoskopicky asistovaná myomektomie
LAVM – laparoskopicky asistovaná vaginální myomektomie
LUAO – laparoskopická okluze uterinních arterií
UAE – embolizace uterinních tepen

LITERATURA

1. **Agdi, M., Tulandi, T.** Endoscopic management of uterine fibroids. Best Pract Res Clin Obstet Gynaecol, 2008, 22, p.707–716.
2. **Buletti, C., Polli, V., Negrini, V., et al.** Adhesion formation after laparoscopic myomectomy. J Am Assoc Gynecol Laparosc, 1996, 3, p. 533–536.
3. **Dubuisson, JB., Fauconnier, A., Deffarges, JV., et al.** Pregnancy outcome and deliveries following laparoscopic myomectomy. Hum Reprod, 2000, 15, p. 869–862.
4. **Dubuisson, JB., Fauconnier, A., Fourchotte, V.** Laparoscopic myomectomy: predictiong the risk factors of conversion to open procedure. Hum Reprod, 2001, 16, p. 1726–1731.
5. **Hald, K., Noreng, HJ., Istre, O., Klow, NE.** Uterine artery embolization versus laparoscopic occlusion of uterine arteries for leiomyomas: long-term results of a randomized comparative trial. J Vasc Interv Radiol, 2009, 20, p.1303–1310.
6. **Holub, Z., Kliment, L.** Laparoscopic ultrasonic dissection of uterine vessels in women with benign uterine pathologies. Clin Exp Obstet Gynec, 2002, 29, p. 54–56.
7. **Holub, Z., Mára, M., Kužel, D., et al.** Pregnancy outcomes after uterine artery occlusion: prospective multicentric study. Fertil Steril, 2008, 90, p. 1886–1891.
8. **Holub, Z.** Laparoskopická okluze děložních tepen. In: Mára, M. Děložní myomy. Praha: Grada Publishing, 2009, s. 138–144.
9. **Hurst, BS., Matthews, ML., Marshburn, PB.** Laparoscopic myomectomy for symptomatic uterine myomas. Fertil Steril, 2005, 83, p. 1–23.
10. **Goldfarb, HA., Fanarjian, NJ.** Laparoscopic assisted vaginal myomectomy: A case report and literature review. JSLS, 2001, 5, p. 81–85.
11. **Chen, YJ., Wang, PH., Yuan, CC., et al.** Pregnancy following treatment of symptomatic myomas with laparoscopic bipolar coagulation of uterine vessels. Hum Reprod, 2003, 18, p. 1077–1081.
12. **Istre, O.** Management of symptomatic fibroids: conservative surgical treatment modalities other than abdominal or laparoscopic myomectomy. Best Pract Res Clin Obstet Gynaecol, 2008, 22, p. 735–747.

13. **Lethaby, A., Vollenhoven, B., Sowter, M.** Efficacy of preoperative gonadotrophin hormone releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy: a systematic review. BJOG, 2002, 109, p. 1097–1108.
14. **Liu, WM.** Laparoscopic bipolar coagulation of uterine vessels to treat symptomatic leiomyomas. J Am Assoc Gynecol Laparosc, 2000, 7, p. 125–129.
15. **Liu, WM., Ng, HT., Wu, YC., et al.** Laparoscopic bipolar coagulation of uterine vessels: a new method for treating symptomatic fibroids. Fertil Steril, 2001, 75, p. 417–422.
16. **Liu, WM., Wang, PH., Chou, CS., et al.** Efficacy of combined laparoscopic uterine artery occlusion and myomectomy via minilaparotomy in the treatment of recurrent uterine myomas. Fertil Steril, 2007, 87, p. 356–361.
17. **Mára, M.** Laparoskopická myomektomie. In: Mára, M. Děložní myomy. Praha: Grada Publishing, 2009, s. 116–128.
18. **Marret, H., Chevillot, M., Giraudeau, B.** A retrospective multicentre study comparing myomectomy by laparoscopy and laparotomy in current surgical practice. What are the best patient selection criteria? Eur J Obstet Gynecol Reprod Biol, 2004, 117, p. 82–86.
19. **Nezhat, C., Nezhat, FR., Silfen, S.** Laparoscopic myomectomy. Int J Fertil, 1991, 36, p. 275–280.
20. **Nezhat, C., Nezhat, F., Bess, O., et al.** Laparoscopically assisted myomectomy: a report of a new technice in 57 cases. Int J Fertil, 1994, 39, p. 34–44.
21. **Parker, W.** Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril, 2007, 87, p. 725–736.
22. **Pellicano, M., Bramante, S., Cirillo, D., et al.** Effectiveness of autocrosslinked hyaluronic acid gel after laparoscopic myomectomy in infertile patients: a prospective, randomized, controlled study. Fertil Steril, 2003, 80, p 441–444.
23. **Seracchioli, R., Rossi, S., Govoni, F., et al.** Fertility and obstetrics outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy. Hum Reprod, 2000, 15, p. 2663–2668.
24. **Siedman, DS., Nezhat, CH., Nezhat, F., Nezhat, C.** The role of Laparoscopic-Assisted Myomectomy (LAM). JSLS, 2001, 5, p. 299–303.
25. **Stewart, L., Glenn, GM., Stratton, P., et al.** Association of germline mutations in the fumarate hydratase gene and uterine fibroids in women with hereditary leiomyomatosis and renal cell cancer. Arch Dermatol, 2008, l44, p. 1584–1592.
26. **Tsuji, S., Takahashi, K., Yomo, H., Fujiwara M., et al.** Effectiveness of antiadhesion barriers in preventing adhesion after myomectomy in patients with uterine leiomyoma. Eur J Obstet Gynecol Reprod Biol, 2005, 123, p. 244–248.
27. **Wang, CJ, Yen, CF, Lee, CL., et al.** Laparoscopic-assisted vaginal myomectomy. J Am Assoc Gynecol Laparosc, 2000, 7, p. 510–514.

MUDr. Kristýna Kubínová
Gynekologicko-porodnická klinika
VFN a 1. LF UK
Apolinářská 18
128 00 Praha 2

Detection of fetal major structural anomalies at the 11-14 ultrasound scan in an unselected population

Čes. Gynek.
2012, 77, č. 4
s. 330-335

Detekce hlavních fetálních strukturálních anomálií během ultrazvukového vyšetření v 11.-14. týdnu těhotenství v neselektované populaci

Novotná M., Hašlík L., Švabík K., Žižka Z., Belošovičová H., Břešťák M., Calda P.
Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Czech Republic. Chairman Prof. MUDr. A. Martan, DrSc.

ABSTRACT

Objective: **The aim of the study was to determine the efficacy of the 11-14 week scan in detecting fetuses with structural anomalies.**

Study design and methods: **Prospective interventional study in an unselected population of pregnant women in a 5-year period (2003-2008) in a single ultrasound unit. 8889 fetuses with median CRL 65mm (45-84mm) were examined. Continuing pregnancies were rescanned at 20-22 weeks. Actual structural anomalies among newborns from the studied group were obtained from our computerized database.**

Results: **The median maternal age was 30 years (14-50 years). The incidence of anomalies was 16.08 per 1000 (143/8889). Of these, 99 of the 143 were detected with prenatal sonography. 46.9% (67/143) of all anomalies were detected at the 11-14 week scan. Later in pregnancy, another 22.3% (32/143) of structural anomalies were detected.**

Conclusions: **67.7% of all antenatally detected malformations by ultrasound were recognized in the 11-14 week scan. Obviously, the second trimester scan cannot be abandoned, as it provides effective detection of other anomalies.**

Key words: **fetal structural abnormalities, first trimester, prenatal diagnosis, ultrasound.**

SOUHRN

Cíl studie**: Cílem studie bylo zjistit efektivitu ultrazvukového vyšetření v 11.–14. týdnu těhotenství při odhalování plodů se strukturální anomálií.**

Typ studie a metodika: **Prospektivní intervenční studie v neselektované populaci těhotných žen v období 5 let (2003–2008) na jediném ultrazvukovém pracovišti. Bylo vyšetřeno 8889 plodů**