Gynecology and Obstetrics Clinical Medicine 1 (2021) 138–143

Contents lists available at ScienceDirect

Gynecology and Obstetrics Clinical Medicine

journal homepage: www.keaipublishing.com/en/journals/gynecology-and-obstetrics-clinical-medicine

A clinicopathological study of 39 cases of atypical polypoid adenomyoma of the uterus

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ARTICLE INFO

Keywords:
Atypical polypoid adenomyoma (APA)
Clinical and pathological characteristics
Fertility preserving

ABSTRACT

Objective: To clarify the clinical and pathological characteristics of atypical polypoid adenomyoma (APA) in order to improve the criteria used to diagnose and treat this disease.
Study design: In 39 cases of APA, retrospective analysis was performed of theclinical data, pathological characteristics, and the follow-up findings in patients admitted to the Peking University People's Hospital from 2007 to 2019.
Results: The median age was 39.6 years (range 24–60 years). Thirty seven patients were premenopausal (i.e.94.9 %) and eighteen patients were nullipara (i.e. 46.2 %). Abnormal uterine bleeding was the most common presenting symptom. Hysteroscopic transcervical resection (i.e.TCR) identified lesions in 35 cases whereas: a) hysterectomy identified them in 3 cases; b) dilatation and curettage (D&C) identified them in 1 case. Immunohistochemical analysis was performed on 24 samples. In the glandular component, hormone receptors were positively expressed. In all cases, Ki67 expression was detectable in approximately 50 % of the cases. In those samples, its presence was definitive in eighteen of the nineteen cases (94.7 %,18/19), p53 positive expression was present in most cases (68.8 %,11/16), and PTEN positive expression was detected in 40 % (4/10). Stroma immunophenotype expression was exhibited as follows: a)CD10-(12/12), Desmin +(6/7); b) Vimentin +(4/4); c) α-SMA+ (3/3) and; d) p16 positve staining in of 80 %(4/5).The concurrent amount of atypical endometrial hyperplasia with atypical polypoid adenomyoma was 23.1 %(9/39), while its concurrent level of endometrial carcinoma with atypical polypoid adenomyoma was 7.7 % (3/39). Fertility preserving treatments were performed in 20 patients with strong childbearing desires. Their pregnancy success was 15 %(3/20) and the live birth frequency was 10 %(2/10). Follow-up findings were available in 36 cases (92.3 %) with a medial follow-up of 48.1 months (range 4–122 months). Its pathological recurrence and frequency of progression into endometrial carcinoma were both 5 %(1/20). One case died of another type of malignancy, while the other patients were alive.
Conclusions: APA occurs mostly during the years of a women's reproductive period. Its diagnosis is based on the analysis of pathological and immunohistochemical findings. Individuals diagnosed with APA are at risk to coexist with endometrial carcinoma and atypical endometrial hyperplasia. For those individuals who desire retaining fertility, the treatment strategy involves performing TCR completely remove the lesions and close follow-up for surveillance of possible progressive APA recurrence. For those individuals who have no fertility desire, hysterectomy may be a preferred option.

Atypical polypoid adenomyoma(APA) is an uncommon uterine lesion firstly reported by Mazur in 1981.[1] It is comprised of proliferative atypical endometrial glands with squamous morular metaplasia in a typical fibromuscular stroma.[1–5] APA was previously viewed as a benign

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Publishing services by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.gocm.2021.07.003
Received 13 February 2021; Received in revised form 27 June 2021; Accepted 19 July 2021
Available online 20 August 2021

lesion, but it may coexist with atypical endometrial hyperplasia and endometrioid adenocarcinoma as well as with a 30.1 % frequency of either residual or recurrent disease when treated with a fertility-sparing approach.[6] It is currently defined as a potentially malignant lesion,[7] and hysterectomy is considered as the treatment of choice for this condition.[8] However, APA generally affects women in their reproductive and premenopausal periods, most of whom are nulligravida and nullipara[1–5] In those patients, conservative treatment management appears necessary. Given the rarity of APA occurrenceto date there is no consensus on an optimal treatment and follow-up protocol.

In this study, we assembled together 39 cases who were diagnosed with APA and treated in our hospital from January 2007 to August 2019. Their clinicopathological features, the clinical management, and follow-up results are retrospectively reviewed in this report.

1. Material and methods

Clinical records were reviewed of 39 patients that had been diagnosed with APA and treated between Jan. 2007 and Aug. 2019 at the Peking University People's Hospital. The study was approved by the Institutional Review Board of People's Hospital Peking University. As this was a retrospective study. it did not encounter any patient interference since the Institutional Review Board waived the requirement for written informed patient consent.The clinical information, pathological results, treatment strategies, and the follow up results especially the reproductive outcomes of conservative treatments were retrieved from the clinical records. Pathological specimens were rereviewed by two experienced pathologists in our hospital.

The diagnostic criteria adopted for APA were based on those described by Longacre et al.[1-6]: (1) biphasic proliferation of architecturally complex and cytologically atypical endometrial glands with squamous morular and (2) the presence of a typical fibromyomatous stroma.

The plan underwent expedited processing and rapid approval by the hospital review board since it entailed a retrospective analysis of patients' records and didn't interfere with their life quality or breach their privacy.

2. Results

2.1. Demographics and clinical characteristics

The median age of the patients was 39.6 years, with a range from 24 to 60 years. Premenopausal women accounted for 94.9 % (37/39). 18 of them were nullipara (46.2 %) and 12 of them were nulligravida (30.8 %). Thirty patients got married, while 25 had a need for fertility when hospitalized with an infertility rate of 44.0 %(11/25). Body mass index of these patients was 24.1 ± 4.0 (mean ± standard deviation). 34 patients (87.2 %) had abnormal uterine bleeding or menorrhagia; 3 patients underwent hysteroscopy after conservative treatment of atypical endometrial hyperplasia; the other 2 patients (5.1 %) were asymptomatic, but they had abnormal ultrasound imaging findings. 7 patients (17.9 %) had undergone hysteroscopy within 3–12 months before their diagnosis of APA, the previous pathological findings included atypical endometrial hyperplasia in 3 cases, endometrial polyp in 3 cases and endometrial complex hyperplasia without atypia in 1 case. Two patients had a history of myomectomy and 1 patient had a history of ovarian benign tumor resection. Complications consisted of hypertension in 3, diabetes mellitus in 1, and cerebral infarction in 1. One patient had a history of breast cancer (underwent radical surgery and chemotherapy, followed by treatment with tamoxifen for 3 years up until one year before being reexamined. .

All patients underwent transvaginal or transrectal ultrasound tomography while 4 patients had pelvic Magnetic Resonance Imaging (MRI) before treatments. However it was difficult to identify with image analysis any particular characteristics that would lead to establishing a differential diagnosis of an endometrial polyp or a submucosal myoma.

2.2. Pathological and immunohistochemical characterization of APA

Hysteroscopic biopsies diagnosed APA in 89.7 % (35/39) of the patients whereas histological examination of D&C specimens only identified APA in 2.6 % (1/39). In 7.7 % of the (3/39) patients who underwent a hysterectomy for other indications were diagnosed with APA diagnosis. The lesions were mostly located in the uterine fundi in 22 cases (56.4 %), in the lower segment of the uterus in 15 cases (38.5 %), and in the uterine cervix in 2 cases (5.1 %). During hysteroscopy, the lesions presented with a polypoid or submucous myomatoid appearance, with hyperemia or vascular distributions on the surface. The diameters of these APA lesions ranged from 1.0 cm to 4.5 cm (mean 2.1 cm), and the majority of these tumors had hard sections while only 3 cases had soft sections.

Under microscopic inspections, all of these tumors were composed of mild-to-moderate atypical endometrial glands distributing in smooth muscle and cellular smooth muscular or hybrid smooth muscle/fibrous stroma. Squamous metaplasia with various degrees were seen in every case and in 23 cases (59.0 %) this metaplasia presented as squamous morules. On histological examinations, the most common pathologies associated with APA were endometrial polyps (20.5 %,8/39), endometrial carcinoma (7.7 %,3/39), atypical endometrial hyperplasia (7.7 %,3/39), endometrial hyperplasia without atypia (2.6 %,1/39) shown in Figs. 1 and 2.

Immunohistochemical analyses were performed on 24 samples. In the glandular component of APA, estrogen and progesterone receptors were either moderately (20%–40 % positive) or strongly expressed (50%–100 % positive) in all cases. The expression level of Ki67, a proliferation marker, was highly variable, with a labeling index (L.I.) ranging from 3 % to 70 %, mostly less than 50 % in 94.7 %,or 18 out of 19 cases. The expression patterns of p53 were partially to strongly positive in most cases (i.e. 68.8 %,11/16). PTEN expression was detected in 10 cases, at a frequency of 40 %(4/10). In the APA positive periglandular stroma, CD10 staining was either negative or weak and patchy (12/12). The stromal immunphenotype markers were evident as follows: 85.7 % Desmin (+)(6/7), 100 % Vimentin(+)(4/4) and 100 % α-SMA(3/3). In the last two years, stromal p16 expression was analyzed in 5 APA cases where a patchy staining pattern was identified in 4 cases. Mismatch repair proteins were detected in 3 cases These markers (i,e,MLH1, MSH2, MSH6, and PMS2) were omnipresent (i.e. 100 % positive, 3/3). See Table 1.

2.3. Treatments and outcomes

Histopathological analysis confirmed that all of the patients who underwent surgeries were APA positive. Nineteen patients who had no

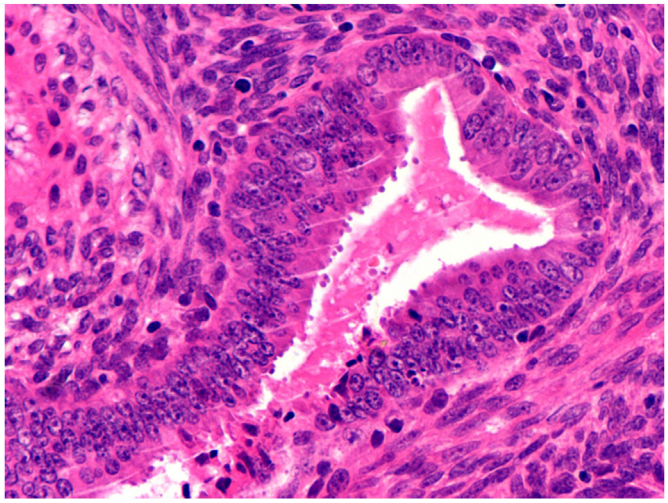

Fig. 1. Atypical glands in APA.

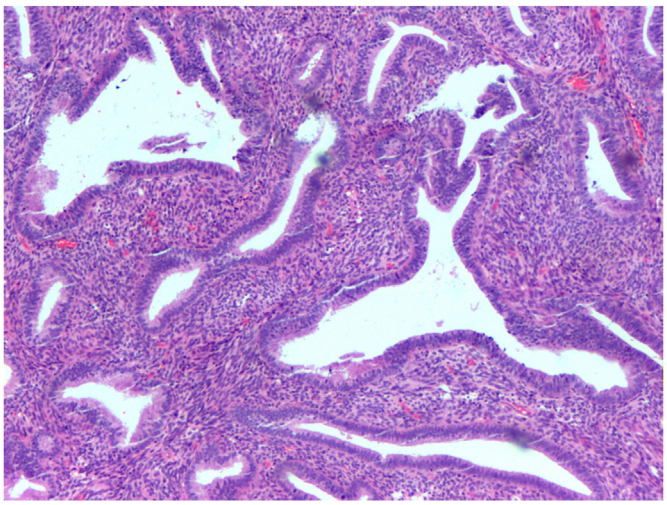

Fig. 2. Celluar myofibromatoid stroma among disorganized glands.

fertility desires were non-conservatively treated within 2–8 weeks after receiving the APA diagnosis. This group included two patients who also had atypical endometrial hyperplasia and another two patients diagnosed with endometrial carcinoma. Ten (52.6%) patients underwent hysterectomy+bilateral salpingectomy,7(36.8%) patients who underwent hysterectomy+bilateral salpingo-oophorectomy. Among these 17 patients, atypical endometrial hyperplasia was discovered in 8 cases after hysterectomy and went through detailed pathological analysis of the endometrium. So totally the frequency of APA cases that coexisted with atypical endometrial hyperplasia was 23.1%(9/39). Amongst this group, there were 2 cases who simultaneously had endometrial carcinoma underwent hysterectomy+bilateral salpingo-oophorectomy+pelvic lymphadenectomy.

Twenty patients who had childbearing demands received fertility-sparing treatments after APA diagnosis., In this group, one patient coexisted with atypical endometrial hyperplasia and another one was diagnosed with an endometrial carcinoma. All of these patients underwent TCR to thoroughly remove the lesions. They were then treated with oral progesterone: 9 cases with medroxyprogesterone acetate, 250 mg daily for at least 3 months; 11 cases with progesterone 200 mg or 20 mg dydrogesterone daily for at least 3 months. Hysteroscopic biopsy was performed every three to six months. If the following hysteroscopic biopsies were negative, the patients were evaluated every 3 months with transvaginal ultrasonography. Among these 20 cases, one patient developed an endometrial carcinoma two years after initial TCR and six months of a large oral dose of progesterone, this patient was surgically treated with a hysterectomy + bilateral salpingo-oophorectomy + pelvic lymphadenectomy; another one underwent hysterectomy because of the recurrence of APA six months after being treated with a large oral dose of progesterone. The pathological findings of the other 18 patients who received a hysteroscopic biopsy following an APA diagnosis showed no evidence of endometrial hyperplasia or carcinoma (known as"complete" regression) after 3–6 months. Although transvaginal ultrasound tomography findings indicated recurrence in two asymptomatic patients one year after an initial TCR, they declined undergoing another hysteroscopy because they were symptom-free. Instead they were closely followed using transvaginal unltrasound surveillance. Two patients conceived 3 times and delivered 2 babies, one of them got pregnant twice by in vitro fertilization and embryo transfer (IVF-ET) but had oncemiscarriage, while one patient got spontaneously pregnant. Eight patients continue to receive medical advice in the reproductive medicine clinic.

2.4. Follow-up results

Except for three patients (all were treated by TAH) who were lost to follow-up, the other thirty-six patients (92.3 %) were followed up for a mean period of 61.1 months (range 24–142 months). These patients were followed up by regularly undergoing transvaginal ultrasonography every 3–6 months. Hysteroscopy and endometrial biopsy were performed at least once in those patients receiving fertility sparing treatments. No pelvic disorders were found in the 16 patients who had undergone a hysterectomy as an initial treatment after receiving the APA diagnosis. Among the other 20 patients who were conservatively treated, one progressed (5%,1/20) to endometrium carcinoma, one patient had a pathological recurrence (5%,1/20) after 6 months. Both of them received non-conservative surgery. In two patients, imaging analysis diagnosed a recurrence. Theydeclined undergoing another TCR because they were symptom-free. The other sixteen patients were completely regressive during the follow-up periods. 35 patients were alive without any metastatic diseases and subsequent death resulting from APA reappearing, while only one patient passed away because of lymphoma. See Table 2.

3. Discussion

Even though APA is a rare endometrial tumor, the medical literature contains many case reports describing its characteristics and therapeutic management. Nevertheless, there are only a few available reviews on this subject.[2,3,5–7] We herein report on a single center's experience describing the criteria used to diagnose APA and approaches used to provide therapeutic management of this disease. In this study the mean age of APA patients was 39.6 years and premenopausal women accounted for 94.9 % of the patients. Almost half of them were nullipara (46.2 %) and the infertility rate was 44.0 %. All of these data are consistent with previous studies.[2,3,5–7,9–12] In Raffone's review of 237 patients,[5] eleven retrospective studies were included. Itturned out that 85.5 % of them were premenopausal and 62.9 % were nulliparous. Matsumoto et al.[9] reported that the majority of patients were premenopausal (93.1 %) and nullipara (86.2 %),and the infertility rate was 35.5 %. In the recent WHO classification, the International Classification of Diseases for Oncology (ICD-O),a grading system ranging between 8932/0 was set up for APA,[13] in which "0" suggests a benign disease. However, it has been reported that the concurrent APA frequency accompanying atypical hyperplasia is about 5.5%–7.2 %, the frequency with endometrial cancer is about 4.8–5.9 %.[5,7] Therefore, it's important for the surgeons to be very cautious when deciding on the most appropriate therapeutic course of action to choose a procedure that preserves the reproductive capacity of patients who hope to be child bearing in the future.

Table 1
Pathological characteristics.

Gross specimen			Coexistent pathology		Immunohistochemistry		
location	uterine fundus	22	endometrial polyp	8	Glandular	ER、PR	100 %+(24/24)
	lower segment	15	endometrial carcinoma	3		Ki67	94.7 %+(18/19)
	uterine cervix	2	atypical endometrial hyperplasia	3		P53	68.8 %+(11/16)
structure	Hard	36	endometrial hyperplasia	1		PTEN	40 %+(4/10)
	Soft	3			Stromal	Desmin	85.7 %+(6/7)
diameter	≤2 cm	21				Vimentin	100 %+(4/4)
	>2 cm	18				SMA	100 %+(3/3)
						p16	80 %+(4/5)

Table 2
Follow up results.

Treatment	pt.n.	follow-up n.	disease progression	disease recurrence	Pregnant	Live birth
Hysterectomy	19	16	0	0	0	0
Fertility-sparing treatment	20	20	1	3(1 pathological recurrence+2 imaging recurrence)	2 pts,3 times	2

The chief complaint of the participants in this report was abnormal uterine bleeding or menorrhagia (87.2 %), even though only 5.1 % were asymptomatic, which is in accord with other values reported in the literature.[2,3,5–7,9–12]Although all of the patients received transvaginal/transrectal ultrasound tomography, the image findings showed few specific characteristics that are associated with endometrial polyps or submucosal myomas. Even though MRI was applied, arriving at a differential diagnosis was very difficult prior to performing a surgical procedure. The findings based on hysteroscopic observations of our patients showed that the uterine fundus (56.4 %) followed by the lower segment of the uterus (38.5 %) were the most common location of the lesions. Their sizes ranged from 1.0 cm to 4.5 cm (mean, 2.1 cm) and had shapes mostly in the form of a polypoid or submucous myomatoid mass. They were clinically diagnosed as an endometrium polyp or a uterine myoma. All of these properties are similar with those reported in the reviews by Young et al.,[2] Longacre et al.,[3] and Raffoneet al.[5] However all of these characteristics were nonspecific and the definite diagnosis depended on the results of pathological and immunohistological examinations.

Histologically, APA lesions are constituted by atypical endometrioid glands, squamous morules, and a myofibromatous stroma.[1–5]The tumors feature a biphasic proliferation of architecturally complex and cytologically atypical endometrial glands within a myofibromatous stroma.[1–5] In these reports, all of the tumors are composed of mild-to-moderate atypical endometrial glands and cellular smooth muscular or hybrid smooth muscle/fibrous stroma. Squamous metaplasia with various degrees are found in every case and in 23 cases (59.0 %) squamous morules are also present. These features conform with the diagnostic criteria used to identify the presence of APA. .

The glandular component possesses endometrioid type glands with an abnormal architecture and varying degrees of cytologic atypia.[14] The morular metaplasia may mimic a solid growth pattern,[15] Reliance sometimes on these features sometimes makes it extraordinarily difficult even for an expert gynecological pathologist to differentiate APA from myoinvasive endometrioid carcinoma. Another possible source of confusion can arise, at the time of the initial APA diagnosis if this condition coexists with atypical endometrial hyperplasia and endometrial cancer. These conditions were defined by Mikos et al.[7] as synchronous atypical endometrial hyperplasia and synchronous endometrial cancer. In recent years, several papers[11,12,14–18] reported on the immunophenotype and immunohistochemical pattern of APA to improve its differential diagnosis. It has been reported that probing for CD10 expression was a useful criterion for differentiating APA from myoinvasive carcinoma. This approach is meaningful because in myoinvasive carcinoma CD10 was locally expressed in an area immediately surrounding the glands (“fringe-like staining pattern”), but in APA it was absent in the stroma. CD10.[12,14,16] In 2019, Bingjian Lu et al.[11] reported that the Ki67 index was significantly lower in the glandular elements of APA (mean ± SD, 20.86%±16.51%) than in endometrial carcinomas (mean ± SD, 32.43 % ± 20.49 %) ($p < 0.05$). In 2019, Kihara et al.[12] firstly compared stromal p16 expression in 12 APA cases and in 84 cases of myoinvasive endometrioid carcinoma. The results showed that in all APA cases there was a diffusive p16 immunhistochemical expression in most cases in the stromal components. On the contrary, immunostaining was negative for p16 in the stroma of myoinvasive endometrioid carcinoma, except for 1 case with focal p16 staining ($P < 0.001$). It was concluded that this significant difference between stromal p16 expression levels in APA and myoinvasive endometrioid carcinoma among endometrial fibroepithelial lesions provides a relevant marker for distinguishing between these two conditions.Also in 2019, a systematic review was performed by Travaglino et al.[14] for the first time to separately assess the immunohistochemical features of the different components in thirteen studies comprising 145 APA cases. APA glands showed prominent expression of hormone receptors (ER & PR) and nuclear β-catenin, endometrioid cytokeratins pattern, Ki67≤50 %, common PTEN loss, and occasional mismatch repair deficiency, all of these features appeared analogous to atypical endometrial hyperplasia. While APA morules exhibited nuclear staining with β-catenin+, positivity with $CD10^{+}$, CDX2+, SATB2+, low with Ki67, and negative with p63 and p40, which were distinguishable immunohistochemically from both conventional squamous metaplasia and solid cancer growth. Stroma immunophenotype resulted in low Ki67, α-smooth-muscle-actin+, h-caldesmon−, either weak or patchy CD10 expression. They concluded that APA immunohistochemically differed from adenosarcoma because of increases in Ki67 and CD10+expression in the periglandular stroma whereas myoinvasive endometrioid carcinoma had elevated levels of expression of h-caldesmon+ in the myometrium and a periglandular fringe-like CD10 pattern). In our patients, immunohistochemical analysis was performed on 24 samples. In the glandular component, hormone receptors were expressed at moderate or very profound levels in all cases, Ki67 expression levels were highly variable. Their levels mostly ranged over 50 % in 94.7 %,18/19). Overall p53 stained positively in most cases (68.8 %,11/16), and PTEN had a positive expression rate of 40 % (4/10). The stromal immunophenotype expression pattern exhibited CD10-(12/12), Desmin +(6/7), vimentin +(4/4) and α-SMA+ 3/3.Stromal p16 expression was detected recently with a positive staining frequency of 80 % (4/5). And mismatch repair proteins were detected in 3 cases, the results showed MLH1, MSH2, MSH6, and PMS2 were universally expressed at high levels(100 % positive, 3/3). Our immunohistochemical findings are consistent with the results reported above and are helpful to make a definitive diagnosis.

The concurrent atypical endometrial hyperplasia frequency and concurrent endometrial carcinoma frequency at the initial diagnosis of APA varied in different reports. In Raffone's[5] systematic review, the former was 5.5 %,and the latter was 5.9 %. In Mikos's[7] systematic review, the former was 7.2 % (15/208), and the latter was 4.8 % (10/208). Matsumoto[9] reported the coexistent frequency of well-differentiated endometrioid adenocarcinoma with APA was 17.2 %. In a systematic review of the English literature, Heatley[6] found the background endometrial hyperplasia frequency and the coexistent frequency of endometrial adenocarcinoma were both 8.8 %. In our report, the concurrent atypical endometrial hyperplasia rate was 23.1 %, and the concurrent endometrial carcinoma rate was 7.7 %. These data suggest that in terms of therapeutic management, the possibility of APA being concurrent with endomerial cancer and atypical endometrial hyperplasia should be taken into consideration. Closer surveillance of the patients who are diagnosed with APA and wish to receive conservative treatment instead of undergoing a hysterectomy is essential and critical.

Since APA generally occurs in women of premenopausal and reproductive ages, and more than half of them are nulligravida and nullipara,[2–9,14] treatments should be individualized. Management choices depend on age, marriage status, desire to have children, and the individual circumstances. On the other hand,if the patient is postmenopausal and the disease is persistent or becomes more progressive even after performing a TCR procedure or administering medication, hysterectomy should be taken as an option.[5,7,9]While if the patient is

young and strongly desires to bear children, fertility-preserving treatment is necessary, and making an accurate histological diagnosis of APA is a precondition that necessitates closely monitoring treatment success.

Chiyoda. et al.[19] retrospectively investigated the clinicopathologic conditions of 35 APA cases who chose fertility-sparing surgery. All of these patients were initially treated with TCR and then again with TCR for recurrence. They reported that in nineteen patients following the first TCR there was a recurrence of 54.3 and the median disease-free interval (DFI) after the first, second, third, and fourth TCR was 12.4, 15.3, 10.5, and 10.9 months, respectively. Any of these DFI would provide a sufficient time span for conception even in recurrent APA patients. Mikos et al.[7] reviewed 15 studies including 208 patients with APA who had been initially treated with uterus preserving treatment. Hysteroscopic removal of the lesions (Transcervical Hysteroscopic Resection of Endometrium-TCRE) was described in 5 studies out of a total of 82 patients. Residual APA rates were significantly lower in those cases treated with all hysteroscopic approaches ($p < 0.0001$) and TCRE ($p < 0.0001$) compared to those who underwent D&C. Similarly, when compared with initial D & C, hysterectomy frequency and cure frequency, APA recurrence was significantly decreased after all hysteroscopic approaches and TCRE (both $p < 0.0001$, respectively) due to the increased effectiveness of the hysteroscopic approach. In Mikos's[7] review, the recurrence rate of APA was 35.1 % (73/208), while the subsequent endometrial cancer frequency was only 10.1 % (21/208). In Raffone. et al.'s[5] systematic review, a total of 169 APA patients were conservatively treated. Fertility-sparing treatments included TCR, D&C, and hormonal therapy (HT) combined with TCR or D&C. They reported that the progression frequency was 16.6 % if the results of all conservative treatments were combined. and the recurrent frequency was 28.9 %. Their results showed that the TCR procedure had a significantly higher initial response frequency ($p < 0.01$) than any other treatment. TCR and TCR + HT produced significantly lower progression frequency ($P < 0.001$), and higher final complete response frequencies ($P < 0.001$) than any other treatment. Among the different TCR techniques, they recommended the 4-step TCR procedure described by Di Spiezio Sardo et al.[20,21] including step 1(resection of APA),step 2(removal of 3–4 mm of endometrium adjacent to the lesion),step 3 (removal of 2–3 mm of myometrium underlying the lesion) and step 4(multiple random endometrial biopsies), which showed significantly lower rates of progression. All of these studies and reviews[5,7,19–21] conclude that TCR is a fertility-sparing method to manage APA under careful observation. In our study, all of the 20 APA patients who had childbearing demands underwent TCR, and were then treated with oral progesterone. The recurrent rate was 5 % (even if the other two imaging results indicating recurrence were included, the recurrent frequency was 15 %) and the frequency of progression to endometrial carcinoma was 5 %, both were much lower than the previous reports.[5,7,19,21] Since TCR was the initial treatment for every patient receiving conservative treatment in our report, perhaps the better outcome is attributable to a higher efficacy of the TCR techniques.

In Chiyoda. et al.'s [19]report, medroxyprogesterone acetate (MPA) was prescribed in recurrent patients following the first TCR. In a retrospective chart review, Nomura et al.[22] identified eighteen patients with histologically diagnosed APA who were treated with MPA for fertility preservation. MPA was administered daily (200–600 mg/day) to each patient after the APA diagnosis. D&C were performed for initial diagnosis and during hormone therapy every 3 months. They reported that fourteen patients (77.8%) achieved either a CR (complete response) or PR (partial response) after the planned treatment while the recurrent frequency was 57.1% and ten patients (55.6%) eventually underwent a hysterectomy. The y concluded that MPA yielded a high response frequency in APA, and it was a safe treatment for younger patients to preserve their fertility for child bearing. Lijuan et al.[23] reported clinical data of 33 APA cases treated with progestin treatment after TCR. The treatments included oral medroxyprogesterone acetate in 18 cases (54.4 %),norgestrel in 7 cases(21.2%), didrogesterone or progesterone in 7 cases (21.2 %),and LNG-IUS in 1 case(3.0 %).They reported the recurrent frequency of 9.1% without progression to carcinoma and recommended long-term progesterone therapy as an alternative for young APA patients after fertility-sparing surgery. In our report, 20 patients who had fertility demands were treated with oral progesterone for at least 3 months after undergoing a TCR procedure. The recurrent frequency (5%) and the rate of progression to endometrial carcinoma (5%) were low and both satisfactory. However in Raffone's[5] systematic review, initial response rates were significantly higher in the TCR group than in the TCR + HT group (98.7 % vs 69.2 %); and there were no significant differences with respect to the other outcomes. This difference may be attributable to the shorter duration of TCR without hormone therapy (HT) over TCR + HT, which allowed for an early start for attempts to conceive. In Mikos's[7] systematic review, MPA (200-400-600 mg bds or tds), dihydrogestone, mergestrol, levonorgestrel releasing intrauterine device had all been applied as conservative treatment for patients with APA. However, their effects on APA recurrent and cure frequency were unsatisfactory. So there is still controversy regarding the use of progestins in providing conservative treatment of APA. In the future, additional studies are necessary to assess whether the expression of certain molecules could predict the responsiveness of APA to progestins, as is now currently possible in choosing a option for treating endometrial hyperplasia and cancer.[5]

In our report, a favorable outcome was realized in all of the patients who received follow-up guidance and support. No deaths occurred from APA except for one patient who passed away because of being afflicted by another unrelated disease. In terms of reproductive outcomes, pregnancy was achieved in 15 % (3/20) of all patients who underwent conservative treatment, with a live birth rate of 10 %(2/10), while 5 patients are being provided with medical advice at a reproductive medicine clinic up until now. In Mikos's[7] review, the data showed that the overall outcome for APA was satisfactory, and there is no available literature linking APA with severe metastatic diseases and subsequent death of the patient. The pregnancy rate was 60.0 % and the live birth rate was 56.4 % in 55 patients wishing to conceive in 8 studies. In Raffone's[5] report, pregnancy was achieved in 25.3 % of all patients who underwent fertility-sparing treatment. Also Raffone's[5] review reported that the DFI was as long as 60 months in four recurrent patients, while one patient underwent hysterectomy 84 months after the beginning of the conservative treatment. Therefore, they recommended a long follow-up duration described by Nomura et al.,[22,24] consisting of D&C or hysteroscopic biopsy plus transvaginal ultrasonography every 3 months for the first 2 years, every 4–6 months for another 3 years, and once a year thereafter.

In conclusion, although the recent WHO classification guideline lists, APA as a benign disease, thetreatment of this disease should be very thorough and cautious considering its malignancy potential. To date, there is no standard therapeutic management protocol of APA, for either a conservative or non-conservative approach. There are currently no standardized recommendations for performing procedures that adhere to preserving childbearing capacity. The purpose of this study was to overcome this hindrance by clarifying how to establish a conservative program of treatment that includes a follow up program of post-surgical care that protects against the loss of child bearing capacity. In our opinion, hysterectomy is the primary therapeutic choice for APA patients who are postmenopausal and who have no reproductive desires. Fertility-preserving treatment of APA with TCR is safe and efficient for those patients who require childbearing capacity. Close follow-up with hysteroscopy, transvaginal ultrasound tomography and pathological examination are necessary and essential for those patients receiving conservative treatment.

Funding

This study was funded by Peking University Medicine Seed Fund for Interdisciplinary Research and the Fundamental Research Funds for the Central Universities. (BMU2020MX003).

Author contribution

Honglan Zhu: Protocol development and manuscript writing. Shanshan Lu and Dongmei Bao:Pathological review. Taji Bai & Zhao Tian: Data collection and analysis. Heng Cui: Manuscript editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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