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Review article

Clinical presentation and management of atypical polypoid adenomyomas: Systematic review of the literature

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ABSTRACT

The aim of this study is to investigate clinical behavior of Atypical Polypoid Adenomyomas (APAs) and to describe the rates of (i) recurrences, (ii) their association with endometrial hyperplasia and (iii) with endometrial cancer. All studies that reported the outcome of the clinical management of patients with histologically proven APAs were included. A review of the English literature since 1970 was systematically performed (PROSPERO No CRD42018080003). A quality assessment tool was used to assess the scientific value of all the studies. Main contribution of this review is the proposal of new definitions regarding the clinical behaviour of APAs: Cure, Residual or persistent APA, Recurrent APA, Synchronous endometrial hypeprasia, Subsequent endometrial hyperplasia, Synchronous endometrial cancer, and Subsequent endometrial cancer, are terms elucidated in the context of this review. Their rates after initial diagnosis and treatment of APAs are presented as the main outcome measures. 63 studies and 350 patients were included in the systematic review. Fifteen studies that reported 208 patients who did not have hysterectomy as initial treatment were included for further quantitative assessment. The cure rate of APAs in cases where uterus was preserved was 51.0% (106/208), the residual rate of APA was 20.2% (42/208), the recurrence rate of APA was 35.1% (73/208), the concurrent endometrial hyperplasia rate was 7.2% (15/208), the concurrent endometrial cancer rate was 4.8% (10/208), the subsequent endometrial hyperplasia rate of was 6.7% (14/208), and the subsequent endometrial cancer rate of was 10.1% (21/208). Moreover, 56.4% of the patients with APA who opted for uterine sparing treatment and wished to conceive they had a viable pregnancy. The use of hysteroscopic techniques at the initial management of APAs is related with significantly decreased residual rate, and signicantly increased cure rates. In this review, the recurrence rate and the association of APAs with cancer appeared to be higher compared to the previously reported in the literature rates. APAs comprise an intriguing clinical entity that needs individualized treatment, considering the increased association to serious gynecological diseases. Hysterectomy is the appropriate treatment, however uterus-sparing surgery can be offered to selected patients.

Contents

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Introduction

Atypical Polypoid Adenomyomas (APAs) are rare tumors diagnosed as adenomyotic polypoid lesions of the endometrial cavity with architectural complexity or cellular atypia [1,2]. APAs are endometrial polypoid proliferations characterized by markedly atypical glands with squamous metaplasia and a cellular, smooth muscle stroma that may show central necrosis. APAs are defined as potentially malignant lesions, they present as focal and noninvasive usually endometrial growths, and they are characterized by a well-differentiated smooth muscle component. Moreover, APAs histologically resemble to an infiltrating adenocarcinoma or a malignant mixed mullerian tumor and the pathologists frequently discriminate these different enitities with difficulty [3]. According to Longacre, APAs with marked architectural complexity may be associated with myometrial invasion within the lesion and in the adjacent endometrium and therefore are characterized as APAs of low malignant potential (APA-LMP); these lesions warrant closer clinical surveillance as they demonstrate a locally aggressive, infiltrative behaviour with frequent local recurrences [4].

For all the above reasons, APAs attract the interest of the clinicians [1,2]. A previously published report including 136 APAs cases by Heatley et al aggregated all the published cases of APAs up to 2006 and found a rate of residual or recurrence disease of 30.1%, a rate of association with endometrial hyperplasia of 8.8%, and a rate of association with endometrial adenocarcinoma of 8.8% [1]. During the last decade, there is accumulating evidence in the literature based on larger clinical case series with longer follow-up, that allow a more precise description of the clinical course of APAs [2,5–7]. These series provide useful information about a variety of clinical questions that arise when dealing with an APA such as the justification of uterus-sparing surgery, the diagnostic approach, and the follow-up modalities [2,5–7]. Although day-unit endoscopic approach and organ preserving techniques are inherent to the current gynecologic practice [8], the clinician's decision about the management of APAs should be based on clinical and histologic parameters. The contemporary knowledge indicates that the younger women with lesions that are characterized by low architectural index or mild to moderate atypia can be managed with uterus-sparing approaches and close surveillance; however, older women or patients with lesions with high architectural index or severe atypia consistent with adenocarcinoma are candidates for total hysterectomy [2,9].

The aim of this review is to elucidate the clinical behaviour of APAs regarding the following terms: Cure rate, residual or persistent APA rate, recurrent APA rate, synchronous endometrial hyperplasia rate, subsequent endometrial hyperplasia rate, synchronous endometrial cancer rate, and subsequent endometrial cancer rate.

Then, we propose a diagnostic algorithm and therapeutic alternatives for APAs as useful, evidence-based tools for the healthcare providers dealing with this rare entity.

Methods

Definitions

In order to perform this systematic review, specific definitions of the parameters opted for further evaluation was initially set:

(a) Cured APA: this was defined as cases of APAs that were never recurred, nor had any association with endometrial hyperplasia or endometrial cancer during the time of the follow-up of the given study. This should be calculated if there is no evidence of disease after a period of at least 5 years.
(b) Residual or persistent APA: this was defined as confirmation of the diagnosis (incomplete initial removal or re-appearance) of the polypoid lesion in the same as the initially diagnosed uterine area, using the hysteroscope during first follow-up and not longer than 6 months after the initial therapeutic approach
(c) Recurrence of APA: this was defined as a re-appearance of the polypoid lesion in the same or a different from the initially diagnosed uterine area, after having hysteroscopically been proven that the patient was clear of the disease for at least one episode of follow-up
(d) Synchronous endometrial hyperplasia: this was defined as the presence of endometrial hyperplasia on the lesion, around the lesion, or at endometrial sites with no proximity to the lesion diagnosed at the time of the initial diagnosis of the APA; this term is proposed instead of the term "background endometrial hyperplasia" that was described by Heatley
(e) Subsequent endometrial hyperplasia: this was defined as the presence of endometrial hypeprlasia on the lesion, around the lesion, or at endometrial sites with no proximity to the lesion diagnosed during one or more of the follow-up visits; initial or previous pathology did not show evidence of hyperplasia in any occasion.
(f) Synchronous endometrial cancer: this was defined as the presence of endometrial cancer on the lesion, around the lesion, or at endometrial sites with no proximity to the lesion diagnosed at the time of the initial diagnosis of the APA
(g) Subsequent endometrial cancer: this was defined as the presence of endometrial cancer on the lesion, around the lesion, or at endometrial sites with no proximity to the lesion diagnosed during one or more of the follow-up visits; initial or previous pathology did not show evidence of cancer in any occasion.

Systematic review process

Search strategy

This systematic review was registered with PROSPERO database of reviews & meta-analysis (No CRD42018080003). Articles were identified from thorough search into the following electronic databases using individual comprehensive search strategies: MEDLINE (1950 to January 2018), Web of Science (1990 to January 2018) and the Cochrane Central Register of Controlled Trials (The Cochrane Library until January 2018). Specific Medical Subject Headings (MeSH) and/or text words were applied in order to compose the list of citations; the following words alone or in combination were used: atypical [All Fields] AND polypoid [All Fields] AND ("adenomyoma" [MeSH Terms] OR "adenomyoma" [All Fields]). Additional eligible studies were retrieved after critical appraisal of the reference lists of the initially identified articles. The search was conducted by two reviewers (T.M. and D.T.).

Selection criteria

The published articles were selected for further analysis if a pathology report of APA was clearly included in the text for any of the included cases. For the purpose of this systematic review that examines the clinical course of the women who were diagnosed with APA, we included cohort studies, case series, and case reports, and all of them were of retrospective nature. We did not find any randomized trials or any case-control studies. Non-english studies, duplicate publications, and studies published only in abstract form, were excluded.

Study selection and data extraction

Studies were included in the systematic review after a two-stage process (Fig. 1). First, the titles and abstracts from the electronic searches were examined by two reviewers (T.M. and D.T.) and full manuscripts of all articles that met the inclusion criteria were retrieved. Then, full manuscripts were examined in order to make final inclusion or exclusion decisions. Any disagreement in the inclusion/exclusion stage was resolved with arbitration by a third reviewer (GFG).

Quality assessment of studies

All selected articles were assessed for the following: (a) study design, (b) adequate description of patient characteristics, (c) presence of histology definition and description of the extent and the type of the adenomyomas, (d) presence of control group, (e) description of the surgical technique, (f) description of the outcome (use of validated assessment method of symptoms or self-reported), (g) presence of follow-up of time interval, (h) full-length of the follow-up applies for the majority (>75%) of the patients of the study group (i) presence of statistical analysis. A similar assessment tool was used by the authors in a study evaluating the uterus sparing techniques of adenomyosis [10]. Each one of the above-mentioned 9 parameters scored for 1 point if it was satisfied or 0 point if not. After aggregating all available studies, the average number of patients per study and the average length of follow-up (in months) per study were used as cut-offs for grading the studies in these two domains. After calculating the total score, the studies that performed above average were selected for further analysis as “good quality studies” and studies that scored below average were excluded from further

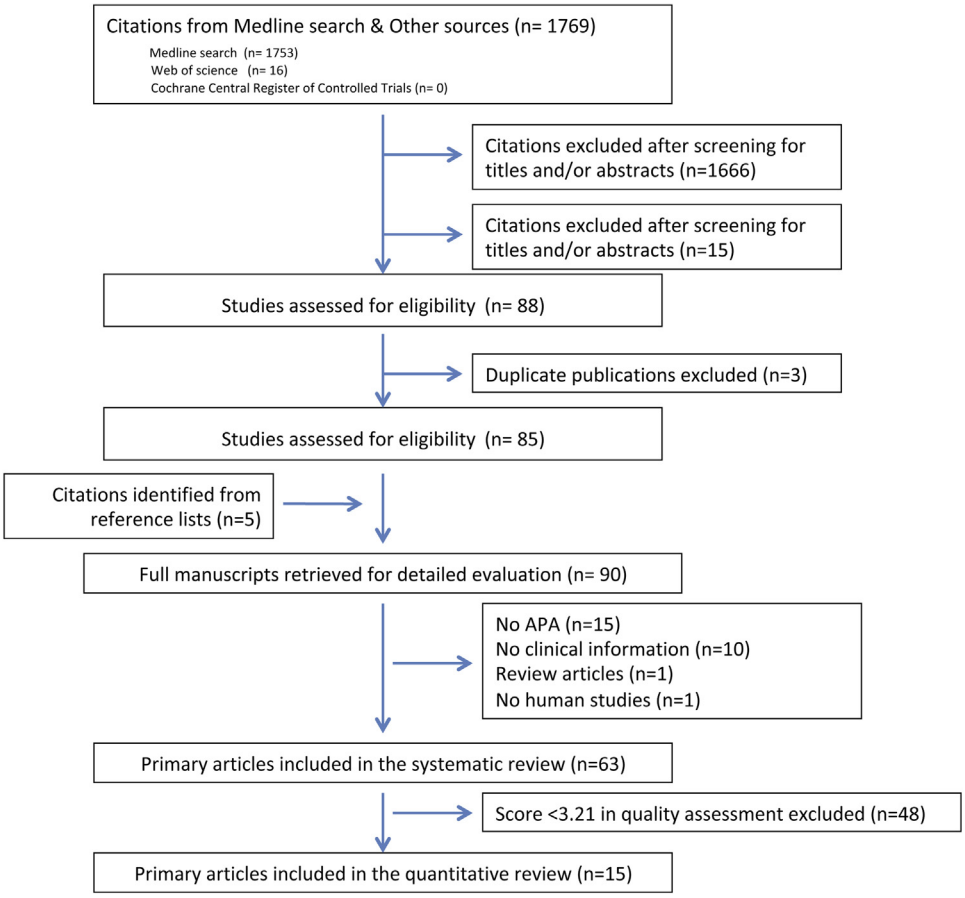

Fig. 1. Flowchart of the study selection.

analysis as "poor quality studies" (Supplemental Table 1 & Supplemental Table 2).

Statistical analysis

All data were compiled and recorded in an electronic database (Microsoft EXCEL; Redmond, WA). Basic descriptive statistics were performed for each parameter. Fisher's chi exact test and Student's *t*-test were used to compare means between nonparametric and parametric indices, respectively. Statistical analyses were performed in order to establish the cure rate, the rate of non-treatment, the rate of recurrence, the rate of concurrent and subsequent endometrial hyperplasia, and the rate of concurrent and subsequent endometrial cancer of the cases of APAs encountered in the studies that were included in this review. Statistical analysis was performed using Microsoft EXCEL and MedCalc 11.4.4.

Results

Study selection

From 1769 studies, 88 were included for further eligibility assessment. After including citations identified from reference lists and excluding double publications, 90 full manuscripts were retrieved for further evaluation. Studies that did not include APAs (n = 15), studies that did not report clinical information (n = 10), review articles (n = 1), and no human studies (n = 1), were excluded. 63 primary articles underwent quality assessment. The average number of patients per study was 4.3 and the average length of follow-up was 27.5 months. The average score of these studies after evaluation was 3.21. Fifteen studies scored above 3.21 points of the quality assessment tool, and these studies were further included in the quantitative analysis (Fig. 1) [2,4–7,11–20].

Risk of bias assessment

No prospective studies were identified. The overall data appear to have poor quality and to be of pure retrospective nature. Six studies scored '6' [2,4–7,20], two studies scored '5' [14,15], and 7 studies scored '4' [11–13,16–19], during the qualitative assessment.

For the field of 'study design', all the fifteen studies were of retrospective design (high risk for bias) [2,4–7,11–20].

For the field of 'number of patients', 8 studies [2,4–7,14,15,20] included more than 4.3 patients (low risk of bias) and 7 studies [11–13,16–19] included less than 4.3 patients (high risk of bias).

For the field of 'mode of diagnosis', all the fifteen studies described histologically confirmed cases of APA diagnosis, recurrence, residual diseases, endometrial hyperplasia, or endometrial cancer (low risk of bias) [2,4–7,11–20].

For the field of 'presence of control group', no study included a control group (high risk for bias).

For the field of 'surgical technique description', all the fifteen studies reported adequately the technique of the removal of the APAs (low risk of bias) [2,4–7,11–20].

For the field of 'outcome evaluation', no study included a structured questionnaire reporting the outcome in clinical, pathological, or surgical terms.

For the field of 'follow-up longer than 27.5 months', all the fifteen studies had longer than 27.5 months follow-up (low risk of bias) [2,4–7,11–20].

For the field of 'adequacy of follow-up', 14 studies [2,4–7,11–13,15–20] had >75% of their cohort followed up adequately (low risk of bias) and 1 study had >75% of its cohort inadequately followed-up (high risk for bias) [15].

For the field of 'presence of statistical analysis', 7 studies [2,4–7,15,20] included statistical analysis (low risk of bias) and 8 studies did not (high risk for bias) [11–14,16–19].

Clinical course of atypical polypoid adenomyomas

The 63 studies included for qualitative review reported information for 350 patients with APA (Supplemental Table 1 & Supplemental Table 2). The 15 studies included for further quantitative review reported information for 208 patients with an APA who had initial organ preserving treatment [2,4–7,11–20].

The cure rate of APAs in cases where uterus was preserved was 51.0% (106/208), the residual rate of APA was 20.2% (42/208), the recurrence rate of APA was 35.1% (73/208), the concurrent endometrial hyperplasia rate was 7.2% (15/208), the concurrent endometrial cancer rate was 4.8% (10/208), the subsequent endometrial hyperplasia rate of was 6.7% (14/208), and the subsequent endometrial cancer rate of was 10.1% (21/208) (Table 1). Fig. 2 describes the Kaplan-Meier survival analysis of the rates of (a) recurrence (Fig. 2a), (b) hyperplasia (Fig. 2b), and (c) cancer (Fig. 2c) in the group of women diagnosed with APA and had follow-up longer than 27.5 months.

Hysteroscopic removal of the APAs (Transcervical Hysteroscopic Resection of Endometrium – TCRE) was described in 5 studies (n = 82 patients) [5–7,12,13]. Residual APA rates were significantly increased after D & C compared to all hysteroscopic approaches ($p < 0.0001$) and TCRE ($p < 0.0001$) (Table 1). Similarly, hysterectomy rates and cure rates after APA treatments were significantly decreased after all hysteroscopic approaches ($p = 0.046$ & $p < 0.0001$, respectively) and TCRE ($p < 0.0001$ & $p < 0.0001$, respectively) when compared with initial D & C, due to the increased effectiveness of the hysteroscopic approach compared to the D & C. However, recurrence rates, concrurrent and subsequent endometrial hyperplasia rates, and concurrent and subsequent endometrial cancer rates did not have any difference between hysteroscopy, TCRE, and D & C (Table 1).

There is no available literature connecting APAs to severe metastatic diseases and subsequent death of the patient.

Pregnancy outcomes after treatment of atypical polypoid adenomyomas

In 8 studies dealing with 106 patients, there were 55 patients wishing to conceive (51.9%), who achieved 33 conceptions (pregnancy rate 60.0%) and delivered 31 babies (live birth rate 56.4%) (Table 2) [2,4,6,11–14,20].

Discussion

What this study adds

According to this systematic review incorporating 350 patients till now, APAs demonstrate a synchronous endometrial hyperplasia rate of 7.2%, and a risk of 4.8% for synchronous endometrial adenocarcinoma. Moreover, after an initial uterus-preserving treatment, the patients with APA have a cure rate of 51.0%, a recurrence of APA rate of 35.1%, a residual disease rate of at 20.2%, an association with subsequent endometrial hyperplasia at a rate of 6.7%, and in the long term there is a risk of 10.1% for endometrial adenocarcinoma.

Clinical interpretation of the results

Our results strongly indicate that APAs have a notorious clinical behaviour and a strong connection with life-threatening conditions like endometrial hyperplasia and endometrial cancer. The current study describes a 13.7% endometrial cancer rates in the patients who are diagnosed with APA (concurrent cancer 4.6% and

Table 1
Clinical outcome in cases of treatment of APAs with initial uterine preservation.

Author, year	No of Patients	Age	TCRE	Duration of Follow up (months)	Residual APA	Recurrence APA	Concurrent Hyperplasia	Subsequent Hyperplasia	Concurrent Cancer	Subsequent Cancer	Hysterectomy	Cure / No Hysterectomy	Comment
Hysteroscopic removal													
Wong, 2007	1	34	–	72	1	2	0	0	0	0	1	0	Danngui Treatment
Yahata, 2011	1	29	+	36	0	0	0	0	0	0	0	1	
Matsumoto, 2013	10	38	+	38.9	0	1	0	0	0	0	0	9	
Yamagami, 2015	3	32.3	+	71	0	3	2	0	1	0	0	2	MPA Treatment
Grimbizis, 2017	9	37.9	–	120	0	2	2	1	1	1	3	6	
Chen, 2017	10	30.1	–	64.5	2	2	5	3	0	1	2	8	MPA Treatment
Chiyoda, 2017	35	35	+	34	1	18	0	5	0	7	9	18	
Ma, 2018	33	55	+	26.9	0	3	0	2	3	0	3	27	
TCRE Subtotal	82	43.2		33.1	1 (1.2)	25 (30.5%)	2 (2.4%)	7 (8.5%)	4 (4.9%)	7 (8.5%)	12 (14.6%)	57 (69.5%)	
Hysteroscopy Subtotal	102	41.4		44.2	4 (3.9%)	31 (30.4%)	9 (8.8%)	11 (108%)	5 (4.9%)	9 (8.9%)	18 (176%)	71 (69.6%)	
D & C													
Young, 1986	24	39.7	–	>6	8	5	3	2	0	0	16	8	
Longacre, 1996	48	39.9	–	27	18	23	2	1	1	0	25	13	
Duggan, 1996	1	29	–	72	1	0	0	0	0	0	1	0	Ovarian Carcinoma
Baschinsky, 1999	1	35	–	36	0	0	0	0	0	0	0	1	
Zhang, 2012	2	36.5	–	60	0	1	0	0	0	2	2	0	
Matsumoto, 2013	11	38	–	38.9	0	4	0	0	0	0	0	7	
Innoue, 2014	1	28	–	96	0	1	0	0	0	1	1	0	
Nomura, 2016	18	33.6	–	96.7	11	8	1	0	4	9	12	6	MPA Treatment
D & C Subtotal	106	38.3		34.4	38 (35.8%)	42 (39.6%)	6 (5.6%)	3 (2.8%)	5 (4.7%)	12 (11.3%)	57 (53.7%)	35 (33.0%)	
Grand Total	208	39.7		39.2	42 (20.2%)	73 (35.1%)	15 (7.2%)	14 (6.7%)	10 (4.8%)	21 (10.1%)	75 (36.6%)	106 (51.0%)	

MPA = Medroxyprogesterone, APA = Atypical Polypoid Adenomyoma, TCRE = TransCervical Hysteroscopic Resection of Endometrium.

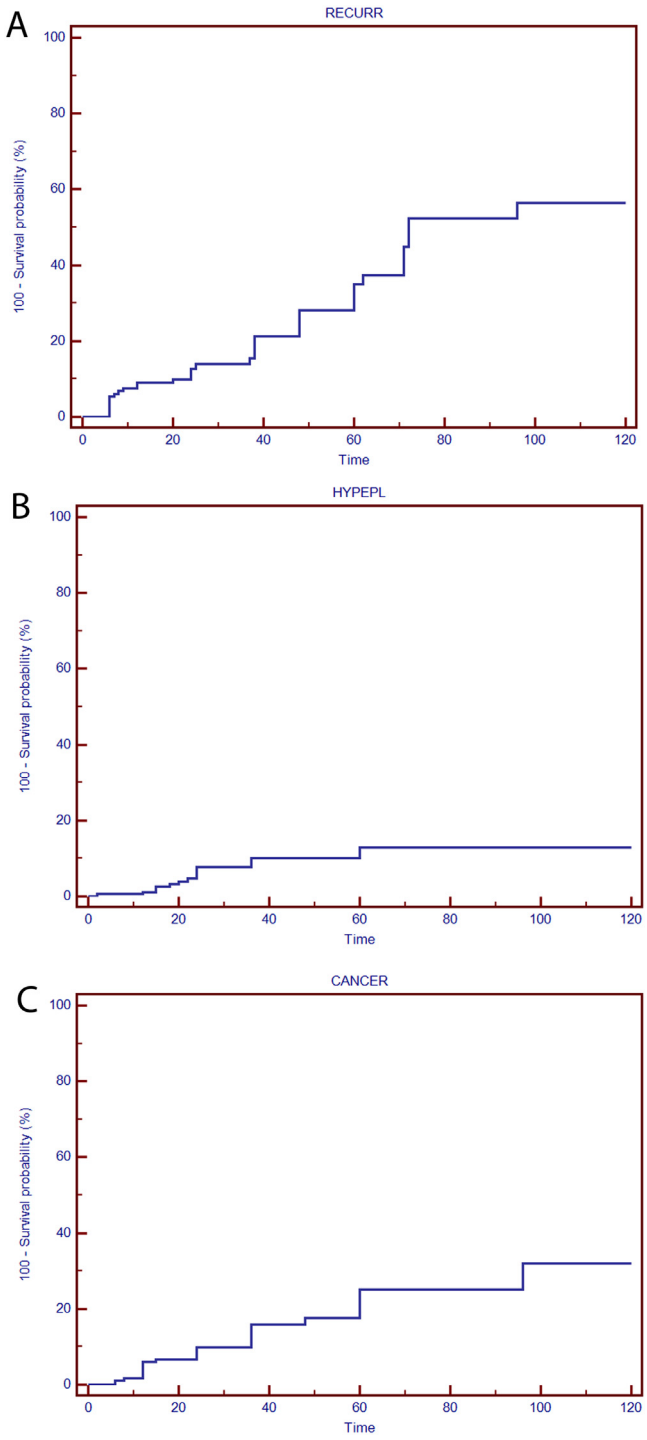

Fig. 2. Clinical outcome after conservative management of APAs. Fig. 2a. Kaplan-Meier survival analysis of the rates of recurrence of APAs. Fig. 2b. Kaplan-Meier survival analysis of the rates of subsequent endometrial hyperplasis. Fig. 2c. Kaplan-Meier survival analysis of the rates of subsequent endometrial cancer.

subsequent cancer 9.1%). Our results are in accordance to the results of the previous largest review on this topic including 136 cases [1]. However, our figures revealed a higher risk of recurrence or residual disease in the long-term, as well as a slightly higher risk of progression to endometrial cancer. Apparently, the co-existence of APA with endometrial hyperplasia, endometrial cancer or other abnormal lesions of the uterine cavity does not imply any aetiologic association. The more likely is that APAs share common risk factors with endometrial hyperplasia. Premenopausal status, nulliparity, infertility, and possibly any previous hormonal treatment, appear to have association to APA [4,5,10,15]; however, the current study is not appropriately designed to investigate this issue. However, the association of APAs with endomerial cancer is challenging in terms of the therapeutic management. In clinical terms, these figures are interpreted as a necessity for closer surveillance of the patients who are diagnosed with APAs and wish to preserve their uterus instead of undergoing a hysterectomy.

So, the most important clinical question after diagnosis of APAs is if preservation of the uterus is an acceptable fertility sparing approach alternative to definite treatment with hysterectomy. It appears that APAs without any evidence of concurrent endometrioid adenocarcinoma permit an initial uterus-sparing option in nulliparous women of reproductive age because the risk of death related to the disease appears to be zero due to the close surveillance. Moreover, in a number of cases it has been described that women can get pregnant after removal of the lesion without any complications and with an acceptable full term pregnancy rate. Therefore, it seems that in women who are willing to conceive, preservation of the uterus may be proposed as an alternative safe option. Nevertheless, it is clearly implicated from our review that the risk of endometrial hyperplasia or endometrial cancer always exists even at a time span of more than 7 years after the initial diagnosis [13]. This possibility implicates that after completion of their family planning, hysterectomy should be offered to these patients eliminating the risk of recurrence to zero.

According to the literature, the factors that predispose to recurrence seem to be: (a) initial D & C, an intervention that increase the possibility of residual disease and/or recurrence; it seems that blind exploration of the uterine cavity does not guarantee the complete removal of the lesion, (b) previous hormonal treatment with estrogens were found to be associated with their growth [9], and (c) Turner's syndrome [9].

The role of conservative treatment and the appropriate follow-up

The effect of conservative medical treatment on APAs has been described in a number of studies. Oral progesterone administration, intra-uterine progesterone release device, and Chinese herbs, have all been proposed as alternative therapies for women with APAs. Medroxyprogesterone acetate (200-400-600 mg bds or tds) [13,20], dihydrogestone, mergestrol [21], levonorgestrel releasing intrauterine device [22], and Danngui [11], have all been applied as conservative treatment for patients with APAs. However, their effect on disease recurrence and cure rate were not as satisfactory as they were expected.

The appropriate length of follow-up in order to safely discharge a patient with APA from close surveillance with no risk of future disease-related complications is another controversial topic. In the literature, there are reported cases with uneventful follow-up lasting up to 72 months [11]. On the other hand, a case of subsequent endometrial cancer has been reported 71 months after initial APA diagnosis [13]. In practice, it appears that even after 6 years of proper follow-up, the patients still have a risk of endometrial hyperplasia and/or endometrial cancer and it appears to be not appropriate to lose them from follow-up. Thus, definitive surgery might be an option for these patients.

APAs and fecundity

It is apparent that previously diagnosed and treated APAs do not affect subsequent pregnancies. It is evident from the available data that both the miscarriage and the preterm pregnancy rates are reduced in women who conceived after treatment of APA: 1 case of intrauterine death in the late 2nd trimester (1/31, 3.2%), and 1 case

Table 2
Pregnancy outcome in patients with APA willing to conceive.

Author, year	No of Patients	Age	Parity	Duration of Follow up (months)	Patients willing to conceive	Number of pregnancies	ART pregnancies	Live Births	Full term pregnancies	Complications	Comment
Hysteroscopic removal											
Wong, 2007	1	34.0	0	72.0	1	2	0	0	1	IUD X 1	
Yahata, 2011	1	29.0	0	36.0	1	1	0	1	0	Preterm labor X 1	
Yamagami, 2015	3	32.3	0	71.0	3	3	1	3	3		IUI X 2
Grimbizis, 2017	9	37.9	1	120	3	2	0	2	2		IUI X 1
Chen, 2017	10	30.1	0	64.5	10	9	3	9	9		
Chiyoda, 2017	35	35	0	34.0	6	6	0	5	5		Ongoing pregnancy X 1
D & C											
Longacre, 1996	29	39.9	–	29,0	13	6	0	6	6		
Nomura, 2018	18	33.6	0	96.7	18	5	0	5	5		CC X 1
Total	106	35,6	0.8	49.9	55	33 (60.0%)	4 (7.3%)	31 (56.4%)	31 (56.4%)		

APA = Atypical Polypoid Adenomyoma, D & C = Dilatation & Currettage, IUD = Intrauterine Death, IUI = Intrauterine Insemination, CC = Clomiphene Citrate.

of premature delivery at 31 weeks of pregnancy (1/31, 3.2%), are the major incidents, whereas 1 miscarriage is reported in this group of patients (1/31, 3.2%) (Table 2). Apparently, obstetric abnormalities do not appear to complicate these pregnancies as well; no cases of abnormal placentation or massive obstetric heamorrhage necessitating hysterectomy have been reported (Table 2) [2,4,6,11–14,20].

On the other hand, the group of patients with infertility and APA is exposed to subsequent change of the hormonal environment by three possible ways. First, this group of patients has been treated with progesterone regimens aggressively in an attempt to control the hormone-dependent APA. Then, many of these patients may need to undergo ovulation induction in order to achieve conception. And for those who finally succeed to conceive after fertility treatment, were confronted with the hormonal milieau that occurs during pregnancy. The influence of each one of these factors independently or synergistically upon the natural history of APAs remains unknown. However, after aggregation of the patients with APAs who had deliveries, it appears that the number of recurrences and the number of hysterectomies needed during the follow-up period is as high as that of the women who are not exposed to these parameters, i.e. in 4 cases hysterectomy was necessary to be performed after delivery (4/31, 12.9%). It seems that pregnancy and full term deliveries neither deteriorates nor ameliorates the clinical course of APAs (Table 2) [2,4,6,11–14,20]. For the evaluation of successful outcome of the conservative hysteroscopic treatment of APAs, the subsequent pregnancy rates should be considered as an important parameter. The hysteroscopic approach appears to have the advantage of the selective resection of the APA and the nearby endometrial surface, allowing superficial biopsies at the rest of the endometrial cavity. By this means full cavity endometrial resection is avoided and the possibility of subsequent pregnancies remains unaffected. Moreover, a second-look hysteroscopy affirms the absence of any endometrial synechiae that may compromise fecundity. Finally, an option for early ART interventions in order that these women get quickly pregnant should be considered, although such evidence is still weak.

Advantages & disadvantages of the study

The strong point of this study is the comprehensive review of the literature including 350 patients and the methodological structure by using strict criteria for evaluation of all relevant studies. However, most of them were found of poor quality as there are only small case series and no studies of prospective design were reported. Moreover, the aforementioned proposed definitions for the description of the clinical behaviour of APAs are subject to criticism. The most controversial issue may be the inclusion of hyperlasia or cancer under one heading using temporal but not topographic discrimination. This means that according to this clinical classification, it is of no clinical relevance where the original site of the hyperplasia or the cancer lies but only if it has been diagnosed in the same time or later compared to the initial diagnosis of APA. Larger studies designed to explore hysteroscopically the endometrial cavity during initial diagnosis and subsequent follow-up appointments, can only further clarify the appropriateness of such a classification. For the time being, grouping the cases together using temporal parameteres facilitates the comparisons between the existing studies and assists in the more detailed description of the natural history of these proliferations.

Another point that merits attention in our study is the use of a non-validated tool for the quality assessment and selection of the studies. In this study, a custom tool previously used with good final results by the authors was applied [10]. This instrument may be a limitation to the study because: (a) it is not possible to determine the quality of it, and (b) a significant number of studies are excluded so that the risk of neglecting significant clinical data is increased. However, the authors were reluctant to use alternative proposed tools (e.g.MINORS), mainly because these instruments are builted for assessment of larger series and may show decreased suitability to assess case reports or case series with very small number of patients (<30 patients) [23].

Proposing an algorith for APAs surveillance

In the group of women who are diagnosed with an APA and do not opt to have hysterectomy, it is proposed to have the following:

(a) Complete hysteroscopic inspection of the endometrial cavity and multiple endometrial biopsies should be taken even in endometrial areas far from the polypoid lesion, especially when the diagnosis has been set only with D&C (Fig. 3a & b),
(b) Six-montly follow up, where clinical examination, transvaginal ultrasound, a guided histological specimen (preferrably with hysteroscopy) and cervical smear test, should be performed,
(c) The length of the follow-up needs to be at least 7 years,

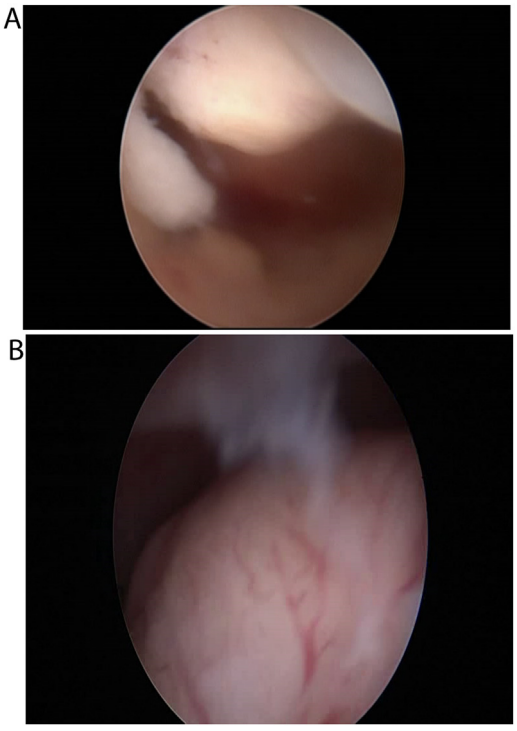

Fig. 3. Hysteroscopic appearance of APA. Fig. 3a. APA arising from the anterior uterine wall. Fig. 3b. APA arising from the posterior uterine wall.

(d) Whenever the patient completes her family or becomes menopausal, a hysterectomy should be offered,
(e) It appears that after hysterectomy no further follow-up is necessary, as no recurrence has been reported after definitive surgery.

The aggregation of our results shows that the possibility of residual disease after hysteroscopic removal is 3.9% compared to 35.8% after D & C ($p < 0.0001$) (Table 1). Therefore, it is recommended as that whenever an APA is diagnosed after D & C, it is mandatory to perform hysteroscopic investigation of the uterine cavity along with biopsies in order to increase the possibility of cure for the patient, whereas the proposed technique for the optimum management of APA appears to be the technique for conservative treatment of stage IA endometrial cancer along with multiple random endometrial biosies [24,25].

Conclusion

In conclusion, APAs are benign endometrial adenomyotic entities that need increased clinical attention. Although, hysterectomy is the safest and the definitive treatment, uterus-sparing surgery is an alternative temporary option for nulliparous women of reproductive age. The gynaecologists should be aware that apart from the increased baseline rate of recurrence or residual disease, APAs are related to endometrial hyperplasia and cancer to a rate over 10% and need close and long-term surveillance in the cases where organ-preserving approach is adopted.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.02.027.

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