

High intensity focused ultrasound in management of placenta accreta spectrum: A systematic review

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Abstract

Background: High intensity focused ultrasound (HIFU) is a non-invasive procedure that has been recently studied in management of placenta accreta spectrum (PAS). **Objective:** To appraise efficacy and safety of HIFU in management of PAS and to highlight restrictions of transitioning uterus-preserving studies to clinical practice. **Search Strategy:** A search on Scopus, Cochrane, PubMed and Web of Science was conducted from date of database inception to January 31st, 2020. **Selection Criteria:** Studies on use of HIFU in management of PAS were eligible. Review articles, conference papers, animal studies, and case reports were excluded. **Data Collection and Analysis:** A standardized data collection sheet was used to abstract data from eligible studies. CON-PAS registry was used to include studies on other conservative modalities of management of PAS. **Results:** Out of 30 studies, four were eligible (399 patients). Average residual placental volume was 61.74 cm³ (6.01-339). Treatment was successful in all patients. Normal menstruation recovered after 48.8 days (15-150). Average time for normalization of β -HCG was 16.5 (1-82) days. No major complications were encountered. Sixty-one studies were retrieved from CON-PAS registry; uterine artery embolization (23 studies), Prophylactic balloon placement (15), compression sutures (10), leaving placenta in situ (7), and uterine wall excision (6) were successful in 83.7% 92.9% 87.9%, 85.2%, and 79.3% of patients, respectively. **Conclusions:** HIFU yields promising success and safety profile in management of PAS in certain clinical situations. A global research strategy is recommended to incorporate conservative approaches in selected patients within a comprehensive protocol to manage PAS.

Introduction:

Placenta accreta spectrum (PAS) is a term that comprise abnormal placental invasion disorders of the uterine wall. According to the depth of invasion, it ranges from placental invasion in contact with myometrium (placenta accreta), into myometrium (placenta increta), or beyond myometrium (placenta percreta) (1, 2). PAS is an obstetric emergency that may be complicated by emergency hysterectomy, intraoperative surgical complications, massive transfusion, hemorrhagic shock, and even maternal death if not managed efficiently (3). Previous cesarean deliveries, placenta previa and advanced maternal age are recognized strong risk factors of PAS, all of which, have become more prevalent among contemporary population (4, 5). Therefore, PAS is no longer a rare disorder in modern practice; the incidence of PAS has increased from approximately 1 in 30,000 deliveries before 1950 to 3 in 1000 deliveries in the current decade (6).

Currently, cesarean hysterectomy is the standard management of PAS. Despite surgical risks, loss of uterine function, and psychological sequences, cesarean hysterectomy permits elective intervention under controlled settings to minimize blood loss (7). Several uterus-preserving procedures have been evaluated including preoperative uterine artery embolization via catheterization (2), open surgical devascularization of uterus (8), hysteroscopy resection of residual placenta with or without methotrexate administration (9) and leaving the

placenta in situ (10). However, in most instances, data is derived from case series and small studies, and these procedures may be associated with significant blood loss, infection, bleeding, and secondary hysterectomy (11).

High intensity focused ultrasound (HIFU) is a non-invasive treatment that utilizes ultrasound waves to cause thermal damage of a targeted lesion without affecting adjacent tissue (12). Since 1950s, HIFU has been investigated in management of various benign and malignant solid tumors (13). Uses has extended to uterine fibroids, cesarean scar pregnancy and adenomyosis (14-16). Recently, HIFU has been proposed as a non-invasive treatment that could preserve the uterus in women with PAS without increasing surgical morbidity and risk of significant blood loss. In this systematic review, we aim at assessing clinical outcomes of HIFU and comparing safety and efficacy of this modality to other uterus-preserving procedures in women with PAS. In addition, we aim at investigating inherited restrictions of these studies and future directives that may improve practice of conservative management of PAS.

Material and methods:

Literature search

Literature search on application of HIFU in management of PAS was conducted. Scopus, Cochrane, PubMed and Web of Science databases were searched for relevant articles using the following terms: [“focused ultrasound” OR “ultrasound ablation”] AND [“placenta accreta” OR “placenta percreta” OR “Placenta increta”], from the date of database inception to January, 31st 2020. References from eligible articles were screened for other related articles. For purpose of comparison to other uterus-conserving techniques, studies were retrieved from CON-PAS registry, an online open access registry of studies on conservative management of PAS in the last 20 years, which is provided by Middle-East Obstetrics and Gynecology Graduate Education (MOGGE) Foundation (17). The registry was last updated in April 2020.

Eligibility criteria and study selection

Original studies that assess effectiveness and safety of HIFU in management of PAS were considered eligible. Review articles, conference papers, animal studies, and case reports were excluded. Neither sample size nor language were used for exclusion.

To assess eligibility, titles of retrieved articles were first screened for relevance. Thereafter, abstracts of filtered articles were reviewed for eligibility. Following the second screen, full texts of indeterminate articles were retrieved, and were assessed by 2 researchers, independently. Conflicting decisions were resolved by consensus in collaboration with the principle investigator.

Data abstraction

A data collection sheet was created for the purpose of the study. Target data include author name, type of study, year of publication, time frame of study conduction, study setting, sample size, selection criteria, patients’ characteristics, method and time of diagnosis of PAS, description of treatment strategy including number and duration of sessions, clinical outcomes, and adverse effects. Data were abstracted from the article text, tables, and figures. All articles were published in English and no translation was required.

Quality assessment:

US National Heart, Lung and Blood Institute Quality Assessment Tool for Before-After (Pre-Post) Studies was used for quality assessment of included studies (18). The tool consists of 12 questions on research question, selection criteria, sample size, description of intervention and level of conduction, assessment of outcomes, and statistical analysis. Response to each question is binary (yes or no).

Data analysis:

For purpose of demonstrative analysis, a “MOGGE” systematic review chart was designed to summarize characteristics and results of included studies in comparison to other uterus-conserving interventions. Studies are plotted based on their country of origin. The color, shape and size of the plot reflect objective, design,

and sample size of the corresponding study. A pie chart indicative of total success rate of each treatment modality is provided per country of origin. Empty pie charts indicate a total cohort less than 50 for a treatment modality while a thick black-bordered pie charts indicate a cohort greater than 100 patients.

Results:

Thirty articles were initially retrieved from literature search. Eleven articles were excluded as duplicates. Out of 19 remaining abstracts, 7 articles were excluded for irrelevance, 7 articles were review articles, and 1 article was a conference paper. Eventually, 4 studies with, a total of 399 patients, were eligible for this review (3, 19-21). Selection process and quality assessment of included studies are illustrated in Figure 1 and Figure 2, respectively.

All studies were conducted in China. Three of them were retrospective (3, 20, 21), and one study was prospectively designed (19). Selection criteria were highly consistent in all studies and were confined to clinically stable women with imaging-based diagnosis of PAS, and a residual placental tissue greater than 3 cm. Included women were highly motivated to preserve their uteri and their baseline hemoglobin level was above 70 g/l. Eligibility was confined to women delivered vaginally in one study (19). Otherwise, both women delivered vaginally or by cesarean section were included. Women with active postpartum hemorrhage, genital infection, or extensive abdominal scarring were excluded. Patients with a large residual placental mass occupying more than half of the uterus cavity were not eligible in one study (19), and non-vascularized retained placenta was excluded from another study (20). Study characteristics and selected population are summarized (Table S1).

Diagnosis of PAS was verified by color Doppler ultrasound and magnetic resonant imaging (MRI) findings, which were conducted before and after the procedure in all studies. Average placental volume was 61.74 cm³ (range: 6.01 to 339 cm³) (3, 19, 20). Treatment was delivered in one session in all studies except one study where treatment was delivered in a 3-day course (20). Sonication time ranged between 200 to 2500 seconds (median time ranged between 600 to 701 seconds) (3, 20, 21). In all studies, HIFU was combined with uterine curettage/hysteroscopic resection, at one or more sessions, to remove residual tissue or necrotic debris. Methotrexate was considered in some patients in one study if baseline β -HCG was greater than 100 mIU/mL (20).

In all studies, HIFU was associated with decrease in size and vascularity by ultrasound, and reduced signal intensity and degree of enhancement by MRI. Normal menstruation recovered after 48.8 days on average (range: 15-150 days) (3, 19, 20). Average time for β -HCG to normalize was 16.5 (1-82) days (3, 20). No major complications were encountered in all studies. One patient experienced significant vaginal bleeding requiring uterine evacuation. Skin burn and hyperpyrexia were reported in one patient each (0.25%). Majority of patients (393, 98.5%) had no pain or low pain scores [?] 3. A summary of management and outcomes of included studies is shown in Table S2.

Sixty-one studies were retrieved from CON-PAS registry on common modalities of conservative management of PAS (Figure 3). Uterine artery embolization (UAE) was evaluated in 23 studies with a total of 453 patients. Uterine preservation was reported in 83.7%, and complications were encountered in 19.6% of patients. Prophylactic internal iliac/aortic balloon placement was assessed in 15 studies (651 patients); success and complication rate were 92.9% and 6.8%, respectively. Compression sutures were addressed in 10 studies (265 patients). Uterus was preserved in 87.9%, and complications were described in 16.6% of study cohort. Leaving placenta in situ, with or without systemic methotrexate treatment, was assessed in 7 studies. Management was successful in 85.2% of 122 patients, and 18.6% experienced perioperative complications. Finally, six studies expatiate uterine wall excision and reconstruction. Among 488 patients managed by this technique, uterine preservation was achieved in 79.3% of patients. The rate of complications was 27.5% (Table S3).

Discussion:

The current review appraises HIFU as a new conservative management of PAS. For decades, HIFU has been

recognized as an intervention for various benign and malignant solid tumors including benign uterine lesions. However, it has been recently studied in women with PAS who are highly motivated to avoid hysterectomy. Preliminary results on 399 patients convey high success rate and reassuring safety profile. The incidence of complications was less than 1%.

Although HIFU seems to be more effective and safer compared to other uterus-conserving procedures, selection criteria of included studies, which are substantially consistent, may limit indications of treatment. Eligible patients should be clinically stable with no active bleeding, and residual placenta should be larger than 3 cm, yet not occupying more than half of the uterine cavity (19). Therefore, HIFU may be a favorable option in patients who were not diagnosed antenatally, including women who underwent vaginal delivery with incomplete separation of the placenta. Despite advancement in prenatal diagnostic modalities, antenatal diagnosis may be missed in 47% of women with PAS, and they are at greater risk of hemorrhagic morbidity (22). In this set of patients, HIFU may substitute other conservative procedures, that may be associated with higher risk of intraoperative and postoperative complications (Table S3). In women with antenatally planned conservative management, HIFU is unlikely to serve as a sole intervention unless further studies confirm its capacity to ablate a complete placenta with no significant complications. In the meanwhile, it may be reasonable to consider HIFU as a backup intervention in women managed by other conservative options particularly in clinically stable patients.

Although several uterus-conserving interventions have been proposed in management of PAS, their contribution to evidence-based practice is limited (23), and cesarean hysterectomy is endorsed as the standard intervention (24). Cesarean hysterectomy, without attempting to remove the placenta, may reduce risk of significant bleeding and associated morbidity (25). Leaving the placenta in situ is endorsed as an alternative in patients who refuse hysterectomy being the least invasive uterus-conserving intervention (11, 23).

Nevertheless, the need for evidence-based conservative approaches for PAS cannot be underestimated particularly among women who are highly motivated to preserve their fertility. Despite limited evidence, an international survey indicates that 39% of obstetricians consider conservative management as the primary management. Notably, conservative management was inconsistent among respondents (1). Sixty-one articles were retrieved from our CON-PAS registry on conservative management using UAE (23 studies) (26-48), prophylactic balloon placement (15 studies) (49-63), compression sutures (10 studies) (64-73), leaving placenta in situ (7 studies) (74-80), and uterine wall excision and reconstruction (6 studies) (81-86). Despite the number of conducted studies (61 studies, 1,979 patients), they have not yielded robust evidence-based recommendations. Fifty-four and eighty-nine percent of these studies recruited [?] 20 patients and [?] 50 patients, respectively. Most of these studies are either retrospective or case series, and they tend to describe a surgical technique rather than a patient-based comprehensive protocol. Therefore, determining optimal candidates for these techniques may not be clear.

Although these limitations may be attributed to relative paucity of patients with PAS, geographic distribution of these studies is limited to 17 countries; 54% of them were conducted in China (20 studies), France (7 studies) and Egypt (6 studies) (Figure 3). This raises concerns about amount of missed data from the rest of the world, which would have contributed to clinical evidence of this uncommon disorder. A stepwise research approach may optimize utilization of available data and enhance generalizability of results. This may include conducting international multicenter retrospective studies to secure large data for analysis, thereby promoting assessment of clinical outcomes of different interventions/steps according to patient and disease characteristics. Results from these data would facilitate delineation of safe prospective studies and clinical trials that incorporate conservative management as a part of a comprehensive protocol for all clinical scenarios of PAS. As a part of this approach, an international multicenter retrospective study is currently taking place in 11 medical centers from Europe, Asia, and Africa (clinicaltrials.gov ID: *NCT04384510*).

The current review presents outcomes of a new modality of conservative management of PAS, which seems to yield promising results. In addition, it highlights restrictions of converting uterus-preserving studies into evidence-based recommendations despite the wide adoption of this practice. This review is limited by the retrospective nature of included studies. Furthermore, role of HIFU in women with prenatally diagnosed

PAS is not well defined, and further studies may be warranted to incorporate this procedure in a PAS management protocol.

In conclusion, HIFU is a promising treatment modality particularly when diagnosis of PAS is made intra-partum without significant uterine bleeding. A global research strategy may be warranted to support such modalities as a part of evidence-based protocol in management of PAS who are highly motivated to preserve their fertility.

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Contribution to Authorship:

HSA: literature search, data abstraction, manuscript writing, manuscript reviewing

MMS: literature search, data abstraction, manuscript writing, manuscript reviewing

IAA: Data abstraction, quality assessment of included studies, manuscript writing, manuscript reviewing

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AKA: selection of eligible studies, creation of supplementary tables, manuscript writing, manuscript reviewing

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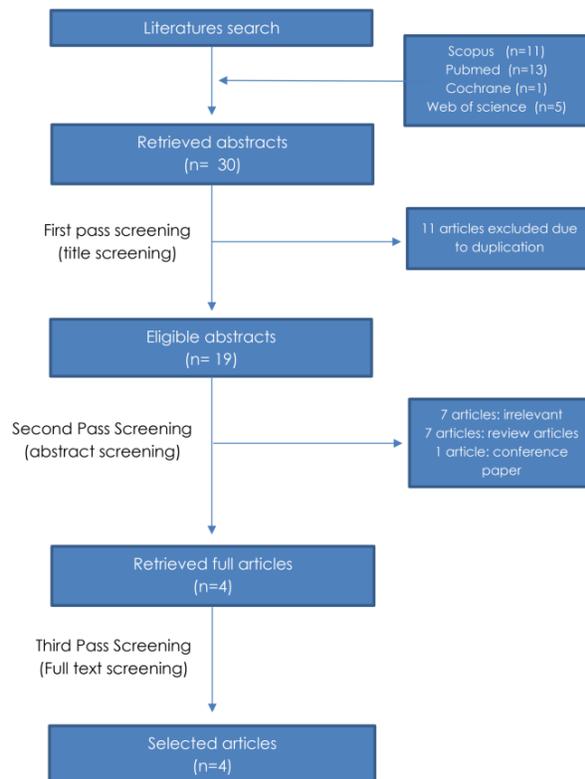
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Figure legend

Figure 1. Flow chart of study selection

Figure 2. Quality assessment of selected articles

Figure 3. MOGGE chart: geographic plotting of studies on conservative management of placenta accreta spectrum based on their objective, design, and sample size



910Z P8Z A	710Z 9A M	810Z 4M	610Z 8umr	
●	●	●	●	1. Was the study question or objective clearly stated?
●	●	●	●	2. Were eligibility/selection criteria for the study population prespecified and clearly described?
●	●	●	●	3. Were the participants in the study representative of those who would be eligible for the intervention in the clinical population of interest?
●	●	●	●	4. Were all eligible participants that met the prespecified entry criteria enrolled?
●	●	●	●	5. Was the sample size sufficiently large to provide confidence in the findings?
●	●	●	●	6. Was the intervention clearly described and delivered consistently across the study population? Selective outcome reporting (reporting bias)
●	●	●	●	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
●	●	●	●	8. Were the people assessing the outcomes blinded to the participants' interventions?
				9. Was the loss to follow-up after baseline 20% or less?
				10. Were statistical tests done that provided p values for the pre-to-post changes?
				11. Did they use an interrupted time-series design?
●	●	●	●	12. If the intervention was conducted at a group level?

