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Reproductive and obstetric outcomes after uterine artery embolization, high intensity focused ultrasound, and transcervical radiofrequency ablation of uterine fibroids: Systematic review of the three minimally invasive procedures

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Abstract: Objectives: Novel treatment options for uterine fibroids such as uterine artery embolization (UAE), ultrasound-guided and magnetic resonance guided high intensity focused ultrasound (USgHIFU and MRgHIFU), and transcervical radiofrequency ablation (TFA) methods are widely used in clinical practice. This systematic review aims to assess and compare reproductive and obstetric outcomes in women who underwent these minimally invasive approaches for uterine fibroids. **Methods:** This systematic review (CRD42022297312) included studies published in English online by from January 2010 to April 2022, searched from the following databases: PubMed, Google Scholar, and ScienceDirect. The search was performed in PubMed, Google Scholar, ScienceDirect, Cochrane Library, Scopus, Web of Science and Embase using the following keywords: "Uterine fibroids", "Leiomyoma", "Uterine artery embolization", "Ultrasound guided high intensity focused ultrasound", "Magnetic resonance-guided high intensity focused ultrasound", "Transcervical radiofrequency ablation", "Reproductive outcomes", "Obstetric outcomes". Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) and Cochrane guidelines. The articles were selected to meet the following eligibility criteria: 1) research article, 2) human subject research, 3) the study of pregnancy outcomes after treatment of uterine fibroids by either one of three methods - UAE, HIFU, TFA. **Results:** Analysis of 25 eligible original articles shows a similar rate of live births for UAE, USgHIFU, MRgHIFU, and TFA (70.8%, 73.5%, 70% and 75% respectively). The number of pregnancies varied considerably among these studies, as well as the mean age of pregnant women. However, the results of pregnancy outcomes for TFA are insufficient to draw firm conclusions, since only 24 women got pregnant in these studies, resulting in three live births. Miscarriage rate was highest in UAE group (19.2%). USgHIFU was associated with higher rate of placental abnormalities compared to UAE (2.8% vs. 1.6%). The only case of uterine rupture documented after all these

treatment options occurred in USgHIFU group. **Conclusion:** Available evidence confirmed these minimally invasive uterine-sparing treatment options for uterine fibroids as reliable and safe for patients wishing to preserve their fertility, with comparable reproductive and obstetric outcomes among the different techniques.

Keywords: Uterine fibroids; Leiomyoma; UAE; USgHIFU; MRgHIFU; Transcervical radiofrequency ablation; Pregnancy.

1. Introduction

Uterine leiomyoma (or uterine fibroid, uterine myoma) is a benign tumor of the uterus arising from the smooth muscle cells and fibroblasts of the myometrium, mostly affecting women of childbearing age.[1–4] The prevalence of leiomyomas is known to increase with age during the reproductive period. Fibroids vary greatly in pathophysiology, size, location, signs, and symptoms.[2,5,6] Although the exact etiology remains unknown, certain risk factors are significantly associated with the development of uterine fibroids such as reproductive and endocrine factors, namely estrogen and progesterone life cycle, nulliparity, early menarche, obesity, race, hypertension, etc.[2,4,7] In majority of patients, leiomyomas are small and asymptomatic, but in many cases, the symptoms may greatly affect the quality of life and require therapeutic measures.[5,8] The severity of symptoms depends on the number, size, and localization leading to heavy or prolonged menstrual bleeding, pelvic pressure, pain, and even infertility and obstetric complications.[4,5] Pregnant women with uterine fibroids are at increased risk of preterm birth, and various adverse obstetric outcomes like placental abruption, fetal malpresentation, preterm premature rupture of membranes, higher cesarean delivery rate, peripartum hemorrhage and fetal growth restriction.[9,10] Accumulating evidence suggests that submucosal fibroids of any size[11] and intramural fibroids wider than 4 cm in diameter greatly affect fertility and outcomes of assisted reproductive therapy.[12]

The aims of any treatment are to alleviate the symptoms, ~~to~~ reduce risks and morbidity, ~~to~~ improve the quality of life, or ideally ~~to~~ cure the disease.[5,8] The gold standard has been myomectomy for many years, which can be performed by hysteroscopy,[13] vaginally, by open surgery (laparotomy) or minimally invasive approaches (laparoscopy and robotic surgery).[14–18] Nevertheless, myomectomy is associated with greater risks of complications during pregnancy and delivery such as uterine rupture, abnormal placentation, and intrauterine growth restriction (IUGR).[17,18] In addition, recent evidence suggested that laparotomic myomectomy is associated with higher rate of intrauterine adhesions after surgery compared with minimally invasive surgery,[19] and this may further play a detrimental role on fertility.

Although myomectomy and hysterectomy represent the definitive treatment of uterine fibroids, 79% of women with symptomatic leiomyomas prefer uterine-preserving approaches, and 65% of women younger than 40 years of age prefer fertility-preserving methods.[20,21] Alternative treatment options such as uterine artery embolization (UAE), ultrasound-guided high intensity focused ultrasound (USgHIFU) or magnetic resonance imaging-guided high intensity focused ultrasound (MRgHIFU), and the most recent transcervical radiofrequency ablation are being widely investigated.[21–23]

UAE is a minimally invasive treatment, where the blood supply to the fibroids is blocked by using embolizing material under fluoroscopic guidance performed by interventional radiologist.[8,24,25] Fibroid, lacking the blood supply, eventually shrinks without negative impact on fertility.[24,25] The risks of UAE include decreased supply to ovaries due to spread of the embolization particles to ovarian vessels, persistent amenorrhea related to ovarian insufficiency or endometrium atrophy that could compromise future fertility.[26]

Moreover, one of the common complications of acute avascular necrosis which can require hysterectomy.[8,25,26]

Another non-invasive treatment option is HIFU, which targets the fibroid under the guidance of MRI or US, specifically avoiding nearby structures, and delivers focused sound waves into the fibroid to ablate the tissue via the ultrasound transducer.[8,25] Although this method has an advantage of preserving the uterus, it is still not recommended for women wishing to preserve fertility.[27] On the one hand, recent studies compared pregnancy outcome after fibroids management with HIFU and conventional surgery, rising the point that HIFU treatment shorten the preparation time for conception, while there was no significant difference between these groups.[28] ~~On the other hand~~ However, there are reports related to the complication-free course and outcome of pregnancy after HIFU.[29,30]

In recent years, using radiofrequency energy to ablate uterine fibroids has become a topic of growing interest as it integrates the energy delivery and real-time imaging within a single device, and provides greater range of uterine fibroid types to be treated.[21–23,31] Recent studies show clinically significant reduction of symptoms, no adverse events, and a surgical reintervention less than 1% through 1 year.[21,23] However, to date, a small number of studies investigating the long-term safety, efficacy, and pregnancy outcomes are available. Systematic review published in the beginning of 2022 found that radiofrequency fibroid ablation (RFA) is a safe treatment option for women who desire future fertility: indeed, almost all pregnancies after RFA were full-term deliveries with no maternal or neonatal complications.[32] Thus, the aim of this systematic review is to assess and compare reproductive and obstetric outcomes in women who underwent these minimally invasive approaches for uterine fibroids.

2. Methods

2.1. Study registration and methodological standards

The study was registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42022297312). The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[33] and the Cochrane Handbook for Systematic Reviews of Interventions.[34] Reproductive and obstetric outcomes definitions followed the criteria proposed by the CoRe Outcomes in Women's and Newborn health (CROWN) initiative.[35]

2.2. Information Sources and Search Strategy

Articles for the study were manually searched using the following databases: PubMed, Google Scholar, ScienceDirect, Cochrane Library, Scopus, Web of Science, and Embase. Studies limited to the involvement of human subjects and published in English online by from 2010 to present were selected. The search was performed using following keywords: “Uterine fibroids”, “Leiomyoma”, “Uterine artery embolization”, “Ultrasound guided high intensity focused ultrasound”, “Magnetic resonance guided high intensity focused ultrasound”, “Transcervical radiofrequency ablation”, “Course and pregnancy outcomes”. The medical subject heading (MeSH) term “Leiomyoma” (MeSH Unique ID D007889) as major topic and “Uterine artery embolization” (MeSH Unique ID D055357), “High Intensity Focused Ultrasound Ablation” (MeSH Unique ID D057086) and “Pregnancy outcomes” (MeSH Unique ID D011256) were used for the search.

Titles and/or abstracts of studies retrieved using the search strategy, and those from additional sources, were screened independently by 2 review authors to identify studies that potentially meet the aims of this systematic review. The full text of these potentially eligible articles was retrieved and independently assessed for eligibility by other 2 review team members. Any disagreement between them over the eligibility of particular articles was resolved through discussion with a third (external) collaborator.

2.3. Eligibility Criteria and PICO statement

The articles were selected to meet the following eligibility requirements to be included in the study: 1) research article, 2) human subject research, 3) the study of pregnancy outcomes after treatment of uterine fibroids by either one of three methods - UAE, HIFU, TFA. The presence of any of the following did not allow a study to be included: 1) reviews and case reports, 2) irrelevance to uterine fibroids, 3) animal model studies. Abstracts lacking full information about predefined criteria were excluded without further review.

2.4. Data Collection and Synthesis

The search was narrowed by using "Uterine fibroids OR Leiomyoma AND UAE", "Uterine fibroids OR Leiomyoma AND HIFU", "Uterine fibroids OR Leiomyoma AND TFA", "Course AND pregnancy outcomes AND Uterine fibroids OR Leiomyoma after UAE OR HIFU OR TFA". The following data was collected from the studies: first author, year of publication, study type, number of study participants, mean age, number of pregnant women, number of pregnancies, pregnancy outcomes (live births, ongoing pregnancies, miscarriages, gestation of delivery, IVF assistance), time to conception, mode of delivery, birth weight, and any maternal or fetal complications. Due to the heterogeneity of the methodology across different studies, we opted for a narrative synthesis of the results.

Assessment of risk of bias

The selected studies were independently reviewed for inclusion eligibility by three reviewers (A.A., G.A. & M.T.). Any difference in assessment of articles were resolved through discussion. Risk of bias was assessed in terms of deviations from intended interventions, measurement of the outcome criteria, missing outcome data, and selection on the reported result according to guidelines. Non-randomized studies were evaluated according to the Newcastle-Ottawa Scale (NOS)[36] and were determined to have "mild", "moderate", or "severe" risk of bias. The risk of bias of included randomized clinical trial (RCT) was determined by the assessment of selection, comparability, and outcome criteria and assessed according to the Cochrane Handbook for Systematic Reviews of Intervention Quality.[34]

3. Results

3.1. Study identification and selection

During this study, 1673 articles were identified through PubMed, Google Scholar and ScienceDirect searching platforms (Figure 1).

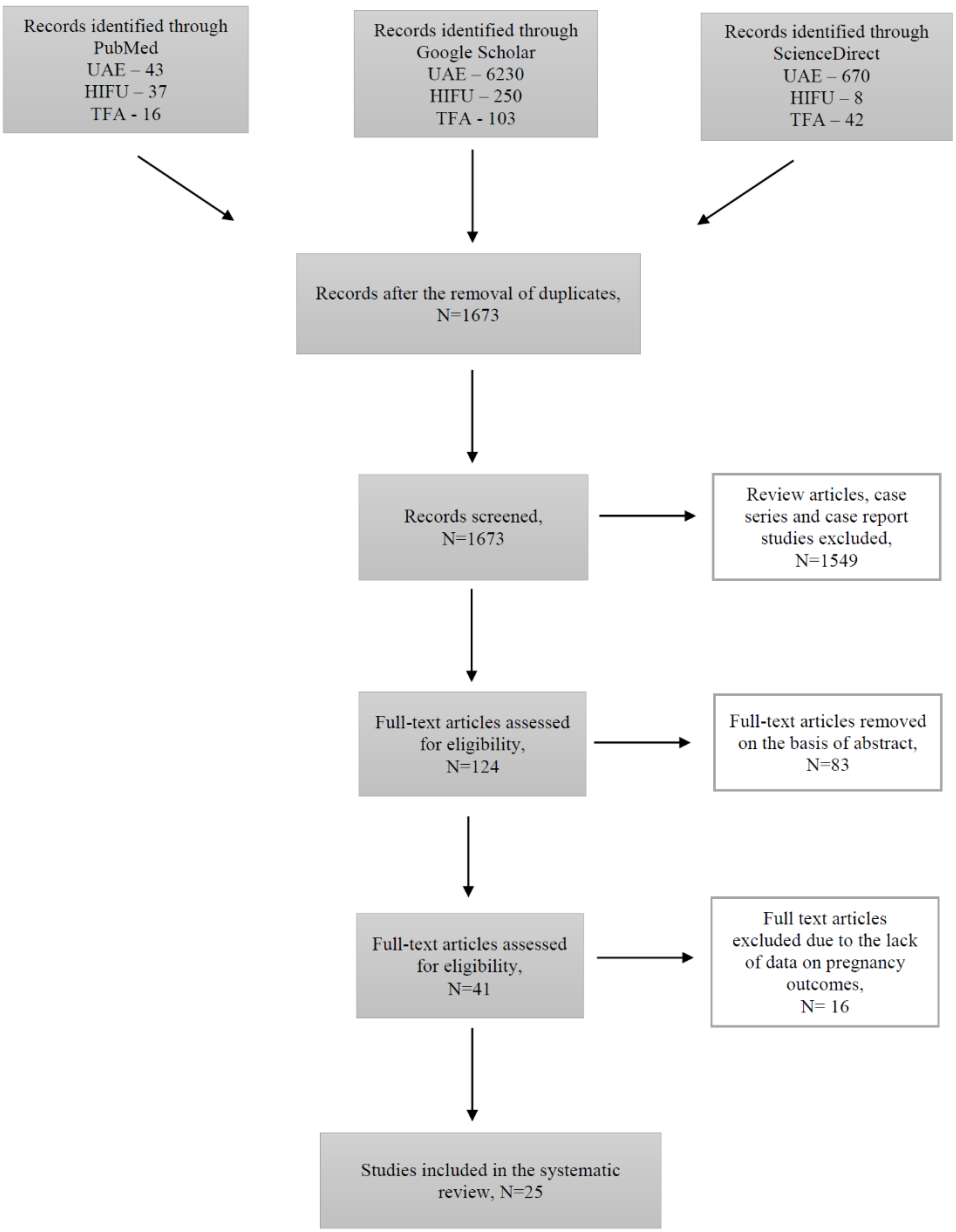


Figure 1. Flow-chart diagram of studies selection.

Out of all articles, 1549 papers were excluded based on the study type including case reports, case series and review articles. Remaining articles were assessed for eligibility based on the abstracts, where 83 articles with irrelevant study aims, design, methods and insufficient results of the studies were excluded. From the remaining 41 articles, 16 articles were excluded at this stage due to the absence of information on pregnancy outcomes, as the desire for a future fertility was one of the exclusion criteria. Finally, 25 articles published during last 10 years investigating the topic of our systematic review were included. Overall, data were available for 250 pregnancies after treatment with UAE, 635 pregnancies after USgHIFU, 55 pregnancies after MRgHIFU, and 40 pregnancies after TFA (Figure 2).

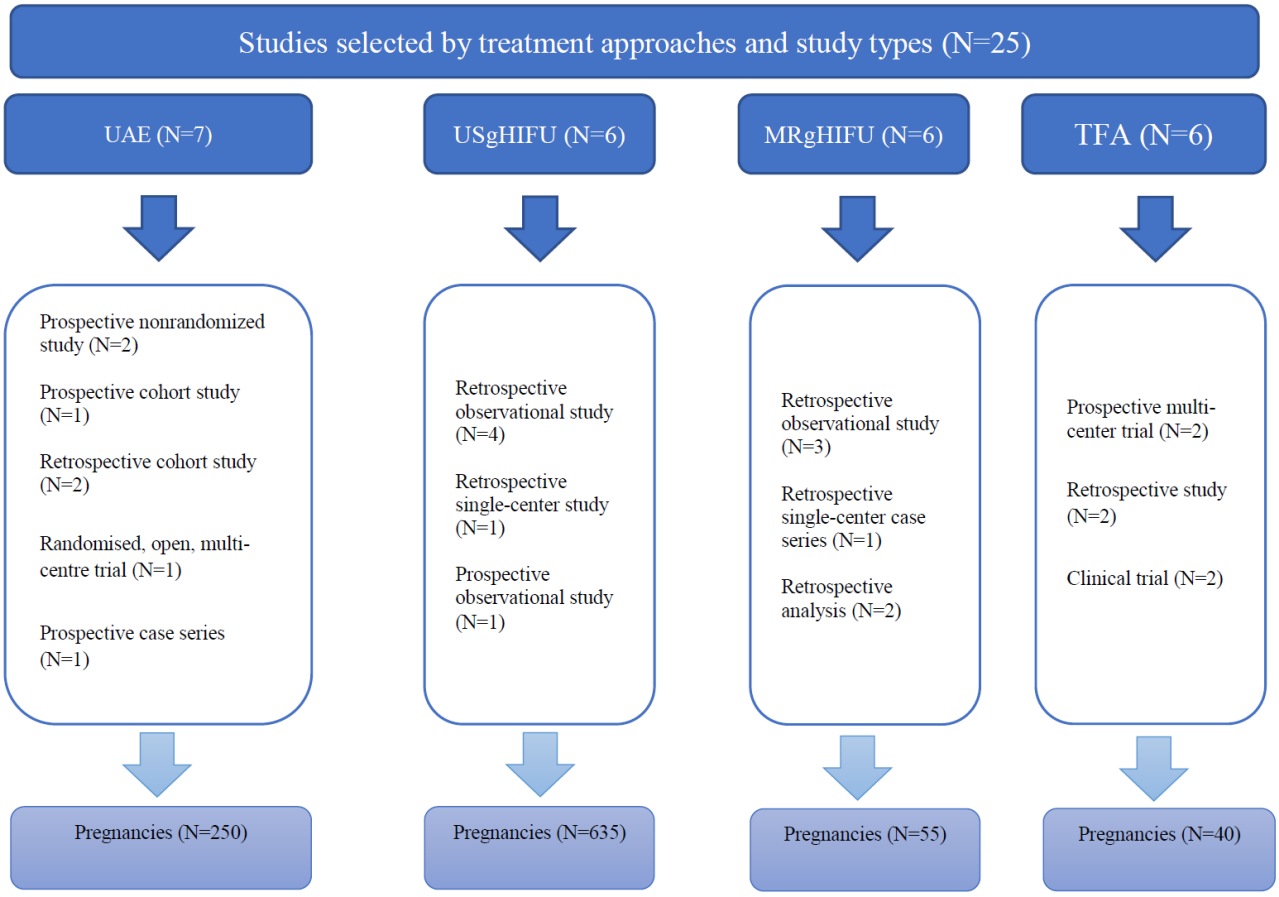


Figure 2. Summary of studies selected by treatment approaches and study types.

3.2. Risk of bias

Of 24 non-randomized studies analyzed, 19 were rated as "mild" risk of bias,[26,27,37,39–48,52–55,57,58] 4 as "moderate" risk of bias,[38,49–51] and 1 as "severe" risk of bias[56] in terms of quality determined by the comparability and outcome criteria (Supplementary Table 1). The bias was mainly caused by discrepancy in gestational age at delivery and pregnancy outcomes reporting. Four studies had "moderate" risk of bias in selection of participants, most studies were at "mild" risk of bias in selection of reported results. One RCT included in the study had "mild" risk of bias (Supplementary table 2).[41]

3.3. Synthesis of results

3.3.1. Uterine Artery Embolization

From 7 studies describing outcomes of 250 pregnancies, the overall live birth rate, ongoing pregnancies, and miscarriage rate were 70,8% (177/250), 1,6% (4/250), and 19,2% (48/250), respectively (Table 1).

Table 1. Course and outcome of pregnancies after UAE.

Study, year	**Study design**	**Mean age, years**	**Total number of women, (N)**	**Number of pregnant women, (N)**	**Pregnancies, (N)**	**Pregnancy outcomes (N)**				**IVF**	**Time to conception, (months)**	**Mode of delivery, (N)**	**Birth weight, (g)**	**Complications, (N)**
						Live birth, (N)	Ongoing pregnancies, (N)	Miscarriages, (N)	Gestational age at delivery, (weeks)					
Torre et al.,[37] 2013	Prospective cohort study	37.3±3.9	66	31	1	0	0	1	-	5	28.9±16.2	-	-	Not reported
Torre et al.,[26] 2016	Prospective non-comparative open-label trial	34.8±4.8	15	8	12	10	1	1	38.0±3.0	3	27.8	VD - 6/10; CS - 4/10.	2857	Moderately low birth weight (i.e. slight- ly below the 10th percentile) - 1
Serres-Cousine et al.,[38] 2021	Retrospective cohort study	37.13± 4.87	398	139	148	109	-	26	-	11	24.82+24	VD - 58/109 (53.2%); CS – 51/109 (46,8%).	3209 g ± 574.9	GDM - 2, Gestational hypertension - 1, Threats of preterm birth - 4, Extra-uterine pregnancy -1, Craniofacial abnormalities - 1, Placenta previa – 1, Fibroid previa - 1,

														"Hard-to-detach" placenta - 1, Intrauterine fetal deaths – 2.
McLucas,[39] 2013	Retrospective chart review	33.4	44	22	28	21	1	3	36.8	1	41	VD – 6; CS – 17.	5lbs 9oz	Borderline oligohydramnios - 1, Low lying placenta -1
Mara et al.,[40] 2012	Prospective, parallel-group, nonrandomized study	33.1 ± 3.7	100	29	42	23	2	13 (abortions spontaneous or missed)	38.1 ± 1.6	4	26.7 ± 14.5/7–52	VD – 5; CS - 18 (78.3%) Pregnancy terminations -2.	3270 ± 451	Preterm birth -1, IUGR -3, Preeclampsia -1, Placenta accreta -1.
Daniels et al., [41] 2021	Randomised, open, parallel multi-centre trial	40.2 ±6.5	127	12	12	7	0	4	-	-	-	Pregnancy terminations -1.	-	-
Redecha et al.,[42] 2012	Prospective case series	38.7	98	6	7	7	0	0	39.0±1.4	-	13.14	VD -6; CS – 1.	3,338.57	PROM - 2
Foot notes: CS – Cesarean section; VD – vaginal delivery; GDM – gestational diabetes mellitus; PROM – premature rupture of membranes; IUGR – intrauterine growth restriction.														

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Mean time to conception after UAE treatment was 27.06 ± 13.73 months. Overall, 27 preterm deliveries were reported in these studies. Studies by McLucas et al. (2013)[39] and Mara et al. (2012)[40] show greater than 61% and 78% rate of Cesarean sections, respectively, whereas Torre et al. (2016)[26] and Redecha et al. (2012)[42] report the greater prevalence of vaginal delivery among live births, 53.3% and 87.5% respectively. From overall 250 pregnancies, complications related to placentation were reported in 4 (1,6%) cases, including placental abnormalities (placenta previa – 1, "hard-to-detach placenta" – 1, low-lying placenta – 1, placenta accreta - 1). Fetal complications were reported in 6% of all pregnancies, 15 (low birth weight - 1, preterm births – 5, craniofacial abnormalities – 1, *in utero* deaths – 2, oligohydramnios – 1, IUGR – 3, preterm premature rupture of membranes (PPROM) – 2). Maternal complications consisted 2% of all pregnancies in the analyzed studies (gestational diabetes – 2, gestational hypertension – 1, fibroid previa - 1, pre-eclampsia – 1). No cases of uterine rupture were reported. The average time for conception after UAE was 27 months, ranging from 13 months to 41 months. From the reported cases, the number of pregnancies achieved by *in vitro* fertilization (IVF) was 24/250 (9,6%). Overall, birth weight was greater than 2,500 g, the minimum birth weight (2,523 g) reported by McLucas (2013).

3.3.2. US-guided HIFU

A total of 635 pregnancies were reported in 1866 women (average age 33,5 years old) recruited to the studies: 467 live births (73,5%), 30 ongoing pregnancies (4,7%), 69 miscarriages (10,9%), 45 terminations (7,1%), (Table 2). Rodríguez et al. (2021)[44] reported in his studies that of the 19 women with miscarriages after USgHIFU, 1 patient had chromosomal mutation, 1 patient with hematologic disease had 4 miscarriages, 1 patient's partner had high sperm DNA fragmentation. One patient with fetal hydrops on her first attempt achieved full-term pregnancy on her second attempt. Five patients with primary and secondary infertility had a miscarriage with successful pregnancies on their second attempt; 3 nulliparous women got pregnant despite the advice of avoiding pregnancy immediately after procedure. The majority of live births were achieved by Cesarean section (59%) due to obstetric factors, social factors and fear of pain. One case of incomplete uterine rupture was documented by Wu et al. (2020)[28] in a group treated by USgHIFU. A total of 28 preterm deliveries were reported. The following complications for the pregnancies after USgHIFU were reported: 50 fetal complications with 19 cases of fetal macrosomia, 65 maternal complications and 18 placental abnormalities (2.8%) with 7 cases of placental abruption and 2 cases of placenta increta in a study by Wu et al (2020)[28]. Average time to conception after USgHIFU was 13,25 ± 7,7 months.

Table 2. Course and outcome of pregnancies after USgHIFU.

Study, year	**Study design**	**Mean age, years**	**Total number of women, (N)**	**Number of pregnant women, (N)**	**Pregnancies, (N)**	**Pregnancy outcomes**				**IVF**	**Time to conception (months)**	**Mode of delivery, (N)**	**Birth weight, (g)**	**Complications (N)**
						Live birth, (N)	Ongoing pregnancies, (N)	Miscarriages, (N)	Gestation of delivery, (weeks)					
Zou et al.,[43] 2017	Retrospective observational study	37.3±3.9	78	78	80	71	5	3	38.1±2.2	4	5.6± 2.7	VD - 15 (19.2%); CS - 56 (80.8%) (PROM -1, fetal distress -2, CPD - 2, oligohydramnios -1); Termination -1.	-	Preterm birth – 3, PROM -1, Fetal distress - 2, Breech presentation - 1, CPD -2, Oligohydramnios - 1, Neonatal asphyxia - 2
Wu et al.,[28] 2020	Retrospective observational study	31.6	320	219	248	178	6	12	-	21	13.6±9.5	VD - 91 (51.1%); CS - 74 (41.6%); Forceps – 13; Pregnancy terminations – 21.	-	Preterm birth - 16, Hypertensive disorder - 13, Intrahepatic cholestasis of pregnancy -6, GDM -15, Fetal distress -5, IUGR - 4, Fetal macrosomia – 14, Placental abruption - 7, Placenta increta 2, Placenta previa -2, Abnormal amniotic fluid volume - 6,

														Umbilical cord abnormalities - 3, Uterine rupture - 1, Postpartum infection - 1, Postpartum hemorrhage – 8.
Rodríguez et al.,[44] 2021	Retrospective observational study	35± 4	560	55	71	43		26	39 ± 2	8	12	VD – 25 (57%); CS – 19 (43%) with indications: Malpresentation - 5, CPD – 1, IUGR – 1, Placenta previa – 2, Fetal distress – 1, Previous myomectomies – 1, Failed labor induction – 4, Fetal bradycardia – 4, "Advice of obstetrician" – 2, Renal colic – 1.	3100 ± 600 (1.4–4.3)	Preterm birth - 4, SGA -2, Congenital malformations - 2, PROM -2, Polyhydramnios -1, Retained placenta with manual removal -3, Svere preeclampsia -1.
Qin et al.,[45] 2012	Retrospective observational study	34.5±4.5	435	24	24	7	0	2	39	-	20±8.85 (for live births only)	CS – 7; Pregnancy termination -14.	3085.71 ± 459.81	-
Liu et al.,[46] 2018	Prospective observational study	31.1±3.8	284	88	81	74	-	9	38	5	16	VD – 21; CS – 53; Pregnancy terminations – 5.		Preterm birth - 5, Fetal macrosomia - 5, Fetal malpresentation - 4, Placenta previa - 1, IUGR -1

Li et al.,[47] 2017	single-center retrospective study	31.4±4.3	189	131	131	94	19	17	-	6	12.3±9.9	VD – 26; CS – 67; Pregnancy terminations – 4.	3.3±0.4	Placenta previa - 5 Placental insufficient - 1 Intrahepatic cholestasis - 1 Abnormal increase of ovarian cysts - 1 Internal orifice of uterus relaxation - 1 Premature rupture of membrane - 1 Fetal distress - 1 Hemorrhoea due to central placenta 1
Foot notes: CS – Cesarean section; VD – vaginal delivery; GDM – gestational diabetes mellitus; PROM – premature rupture of membranes; IUGR – intrauterine growth restriction; SGA – small for gestational age; CPD – cefalopelvic disproportion.														

3.3.3 MRI-guided HIFU

A total of 55 pregnancies were documented among 747 women in 6 different studies (Table 3). The average age of patients was 40 years old. Of them, 40 pregnancies (70%) resulted in live births, 9 (15,5%) were ongoing pregnancies, 9 miscarriages (15,5%). The average time for conception was 17 months. One case of obstructive labor and 2 cases of postpartum hemorrhage were reported by Verpalen et al. (2019)[49].

Table 3. Course and pregnancy outcomes after MRgHIFU

Study, year	**Study design**	**Mean age, years**	**Total number of women, (N)**	**Number of pregnant women, (N)**	**Pregnancies, (N)**	**Pregnancy outcomes**				**IVF, (N)**	**Time to conception**	**Mode of delivery, (N)**	**Complications, (N)**
						Live birth, (N)	Ongoing pregnancies, (N)	Miscarriages, (N)	Gestation of delivery, (weeks)				
Thiburce et al.,[48] 2015	Single-centre retrospective case series	43.5	36	2	2	2	0	0	-	-	2.5 years	VD - 2	-

Łoziński et al.,[27] 2019	Single-center retrospective cohort study	33.2±3.65	276	20	21	11	7	3	38.8	0	-	CS - 7, VD - 4	-
Verpalen et al.,[49] 2019	Retrospective cohort study	44.6 ± 4.7	87	4	9	7	0	2	-	-		CS -3, VD - 2	CPD – 1 Postpartum hemorrhage - 2
Mindjuk et al.,[50] 2014	Retrospective cohort study	42.1 ± 6.9 35.3 ± 3.4	252	15	15	12	2	1	-	-	19.7 months	-	-
Yoon et al.,[51] 2013	Retrospective analysis	41.3±6.3	60	1	1	1	0	0	term	-	4 months	-	NA
Froeling et al.,[52] 2013	Retrospective analysis	36	36	9	10	7	0	3	-	-	16.1 months		NA
Foot notes: CS – Cesarean section; VD – vaginal delivery; CPD – cefalopelvic disproportion.													

3.3.4 Transcervical radiofrequency ablation systems

A total of 470 women were involved in the clinical trials and studies such as FAST-EU, SONATA, VITALITY and SAGE investigating the efficacy of TFA in treatment of uterine fibroids (Table 4). Among 32 women, 40 pregnancies were reported, resulting in 24 live births. However, eight spontaneous abortions and three therapeutic abortions were documented. Although the time of conception after the TFA was not recorded, the earliest pregnancy occurred 3.5 months after TFA. Majority of patients (14/24) underwent Cesarean sections. There were no reported cases of stillbirth, uterine rupture, fetal growth restriction, postpartum hemorrhage, or any placental abnormalities. Obstetric complications included HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome due to maternal antiphospholipid syndrome, premature rupture of membranes (PROM), breech presentation and pyelonephritis at 16 weeks of gestation.

Table 4. Course and pregnancy outcomes after TFA

Study, year	**Study design**	**Mean age, years**	**Total number of women, (N)**	**Number of pregnant women, (N)**	**Pregnancies**	**Pregnancy outcomes**				**IVF, (N)**	**Time to conception, (months)**	**Mode of delivery, (N)**	**Complications, (N)**
						Live birth, (N)	Ongoing	Miscarriages, (N)	Gestation of delivery, (weeks)				

							preg-nan-cies, (N)						
Toub,[53] 2017	Prospective, multi-center trial	37.3±3.9	50	1	1	1	0	0	-	0	6 months	CS -1	Not reported
Lukes and Green,[54] 2020	Prospective, con-trolled, multicenter interventional trial	43	132	2	2	1	0	1	38		30 months	CS -1	Not reported
Garza-Leal,[55] 2019	Retrospective, sin-gle-arm, long-term data-collection study	41-45	17	1	1	1	0	0	term	-	-	CS - 1	Not reported
Christoffel et al.,[56] 2021	Retrospective study	35.6 + 5.0	357	28	36	20	5	8	>37 weeks, except one at 35 6/7	4	NA	VD – 8, CS – 12, Terminations - 3	HELLP syndrome - 1 Fetal macrosomia - 3 Preterm birth - 1
Jiang et al.,[57] 2014	Clinical trial	40.80	46	2	2	2	NA	NA	Term	NA	16,5 months	CS -1, VD - 1	No complications
Brölmann et al.,[58] 2015	Follow-up analysis of clinical trial	41–45 years of age	50	1	1	1	NA	NA	Term	NA	6 months	CS -1	No complications.
Foot notes: CS – Cesarean section; VD – vaginal delivery.													

4. Discussion

To the best of our knowledge, this is the first systematic review comparing minimally invasive uterine-conserving approaches of uterine fibroids treatment such as UAE, USgHIFU, MRgHIFU, and TFA. Since uterine fibroids affect women of reproductive age, the question of fertility preservation and successful pregnancy after treatment is one of the most concerning factors, which affect the choice of treatment. However, limited number of studies investigating the effects of treatment on pregnancy outcomes in terms of number of pregnancies, live births, miscarriages, fetal and maternal complications after fibroids treatment are available. Therefore, this systematic review focuses on the most novel treatment methods of uterine fibroids and their impact on fertility and obstetric outcomes.

4.1. Main findings and its comparison with existing literature

After analyzing 25 original articles including treatment with either UAE, HIFU or TFA, the most significant finding was a similar rate of live births for all approaches: 70.8%, 73.5%, and 70% respectively.[26–28,37–58] The results of the studies of TFA show 10% of participants resulting in live births.[53–58] The low live birth rate could be explained by the fact that the desire for future fertility was the exclusion criteria in these studies. Of note, the number of pregnancies varied considerably among these studies, as well as the mean age pregnant women. As the desire for fertility was the exclusion criteria in participants' selection in TFA trials, the mean age of patients was higher (>40 years old) compared to populations in other studies.

Miscarriage rate was the greatest in UAE group, accounting for 19.2%, which could be explained by the insufficient restoration of uterine cavity anatomy and physiology after this technique, predisposing to first trimester miscarriages. However, increasing maternal age should be considered when interpreting as the odds of any fetal and maternal complications increase considerably after 35 years of age.[59,60] Another complication during pregnancy, sometime associated with uterine fibroids, is uterine rupture and placental abnormalities. Only one case of uterine rupture was documented after USgHIFU (0.16%), which is less than the incidence rate of uterine rupture after myomectomy (0.6%)[61] or other uterine surgeries.[62,63] According the results of meta-analysis of 3685 pregnancies after myomectomy found uterine ruptures at a rate of 0.79%.[32] Although no cases of uterine rupture were reported for patients treated by TFA, the number of patients treated so far is too low to investigate this parameter.[32] Interestingly, USgHIFU resulted in greater incidences of placental abnormalities compared to UAE (2.8% vs. 1.6%).

As expected, increasing age leads to decreasing in pregnancy rate, thus early conception after treatment is preferable. The time of conception after treatment of uterine fibroids was the shortest for USgHIFU group. According to Qin et al. (2012) and Zou et al. (2017), conceiving within a year after USgHIFU ablation did not result in complications.[43,45] Overall, the delivery rate by Cesarean section among all minimally invasive procedures was greater than for general population rate (31.8%), likely due to the intrinsic greater risks of obstetric complications in women with uterine fibroids.[18]

A limited number of a similar studies are available or comparison. One of the recent systematic reviews, which was performed to compare UAE and HIFU for treatment of symptomatic myomas found that compared with HIFU ablation, UAE provided lower pregnancy rate for women with uterine myomas.[64] However, the researchers did not investigate a rate of live births as was done in our study.

4.2. Study strengths and limitations

This is the first systematic review comparing minimally invasive uterine-preserving approaches of uterine fibroids treatment such as UAE, HIFU, and TFA. The main limitation of the study is low total number of pregnancies after TFA available for the analysis. Live birth rate, low rate of miscarriage and the lack of obstetric complications suggest that TFA could be safely used for the treatment of uterine fibroids in patients planning future pregnancies. Moreover, desire for future fertility is outlined as an exclusion criterion for articles studying TFA, leading to potential bias and errors in estimation of pregnancy outcomes. Therefore, future studies investigating pregnancy outcomes after treatment by TFA of uterine fibroids in women planning to conceive should be performed. In addition, this systematic review lacks information on fibroid characteristics (size, location, number), which are known to be a significant disease and treatment prognosis factors. Future studies are needed to establish the pregnancy outcomes after treatment with these methods based on the fibroid characteristics specifically. In addition, the increasing age of participants may also influence the pregnancy outcomes, serving the potential confounder of the study. Finally, a sub-analysis of reproductive and obstetric outcomes according to the type of conception (natural vs. assisted reproduction) after UAE, HIFU, and TFA would be needed.

5. Conclusion

Available evidence confirmed these minimally invasive uterine sparing treatment options for uterine fibroids as reliable and safe for patients wishing to preserve their fertility, as reliable and safe for patients wishing to preserve their fertility, with overlapping reproductive and obstetric outcomes. Despite the current encouraging results, more robust evidence is needed to identify which subpopulation would get most benefits from a technique compared to the other ones. In this scenario, we solicit further studies to investigate both reproductive and obstetric outcomes in women undergoing UAE, HIFU, and TFA, based on the characteristics of the patients, types, number and volume of the fibroid(s), and type of conception (natural vs. assisted reproduction).

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