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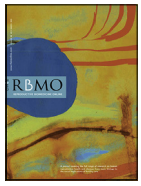

REVIEW

Systematic review of pregnancy outcomes after fertility-preserving treatment of uterine fibroids

BIOGRAPHY

Shen Chuen Khaw is a final year medical student at the University of Edinburgh. His fields of interests include reproductive medicine and benign gynaecology.

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KEY MESSAGE

Myomectomy remains the treatment of choice for uterine fibroids in women wishing to preserve their fertility. This study, however, shows the potential for fibroid ablation in women in whom surgery is contraindicated, but insufficient data are available to assess the outcomes of pregnancy after treatment of fibroids with ulipristal acetate.

ABSTRACT

The aim of this study was to compare pregnancy outcomes after medical (ulipristal acetate [UPA]), surgical (myomectomy) and radiological (uterine artery embolization [UAE] or thermal ablation) therapy for fibroids in women. A systematic review was conducted and *ScienceDirect*, *PubMed*, *Web of Science* and *Cochrane Library* databases were thoroughly searched from 2000 to 2018. Only primary research was included with independent extraction of articles by two reviewers, using a standardized form. Data were available on 12 pregnancies after treatment with UPA, 1575 after myomectomy, 424 after UAE and 420 after fibroid ablation. Results after UPA therapy were not included in the statistical analysis owing to the limited number of cases; most were ongoing pregnancies. High rates of successful pregnancy were seen after myomectomy (75.6%) and fibroid ablation (70.5%), whereas pregnancies after UAE had the lowest live birth rates (60.6%) and highest miscarriage rates (27.4%) (both $P < 0.001$ versus other treatments). In conclusion, myomectomy is associated with better pregnancy outcomes than other fertility-preserving treatments for fibroids. At present, UPA is the only medical treatment for fibroids; however, the evidence on pregnancy outcome is limited. In the absence of randomized controlled trials, these data may be of benefit in advising patients about future pregnancy.

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KEYWORDS
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Uterine artery embolization

INTRODUCTION

Fibroids (leiomyomata) are the most common benign tumours of the pelvis in women of reproductive age group and are more commonly seen in African–American women (*Verkauf, 1992*). In addition to pain and abnormal uterine bleeding, fibroids have been associated with infertility and a higher risk of miscarriage, placenta praevia, fetal malpresentation, preterm labour, the need for caesarean section and peripartum haemorrhage (*Klatsky et al., 2008*). Present evidence indicates that submucosal fibroids of any size and intramural fibroids wider than 4 cm in diameter significantly impair fertility and results of assisted reproductive therapy (*Zepiridis et al., 2016*).

The appropriate approach for the treatment of fibroids depends on multiple factors, including age, fertility wishes, the severity of symptoms and clinical presentation, the type and size of the fibroids, and the woman's overall health, with an emphasis on medical and surgical history or ongoing treatments (*Society of Obstetricians and Gynaecologists of Canada, 2005*; *Flynn et al., 2006*; *Marret et al., 2012*; *van der Kooij et al., 2012*). As fibroids are benign, choice of treatment methods should aim to minimize risk and morbidity.

At present, the management of fibroids in women who wish to preserve their uterus and fertility remains a challenge. The gold standard is myomectomy (*Verkauf, 1992*; *Flynn et al., 2006*; *Flyckt et al., 2017*), which can be carried out by hysteroscopy, laparoscopy, laparotomy or robotic-assisted, each having their pros and cons (*Cinar et al., 2016*; *Adesina et al., 2017*; *Bean et al., 2017*; *Choi et al., 2017*;*Lonnerfors, 2018*). The type of myomectomy used is greatly influenced by the clinical presentation, size, number and location of the fibroids (*Cinar et al., 2016*; *Martinez and Domingo, 2018*).

Alternative medical treatment with ulipristal acetate (UPA) and radiological procedures, including uterine artery embolization (UAE) and fibroid thermal ablation, have been evaluated. Ulipristal acetate is a selective progesterone receptor modulator that has antiproliferative effects on the leiomyoma and endometrium (*Vilos et al., 2015*). It also induces apoptosis and suppresses angiogenic factors, such as vascular endothelial growth factor and adrenomedullin (*Xu et al., 2006*; *Yoshida et al., 2010*). On the other hand, UAE involves selective cannulation of uterine arteries with injection of emboli to occlude blood supply to the leiomyoma (*Viswanathan et al., 2007*). It is, however, associated with potential complications, such as premature ovarian insufficiency and pelvic infection, and has a high re-intervention rate (*Freed and Spies, 2010*; *Torre et al., 2014*). In addition, UAE is relatively contraindicated in women desiring future pregnancies as its effect on fertility has not been clearly defined (*American College of Obstetricians and Gynecologists, 2008*; *Stokes et al., 2010*). Fibroid thermal ablation techniques include radiofrequency volumetric thermal ablation and high-intensity focused ultrasound, magnetic resonance imaging or laparoscopy (*Hesley et al., 2008*; *Chudnoff et al., 2013*; *Vilos et al., 2015*); these induce targeted necrosis in the fibroid. These treatment methods are primarily indicated for women who are unable to undergo surgery for symptomatic fibroids (*Society of Obstetricians and Gynaecologists of Canada, 2005*; *Marret et al., 2012*).

Women who undergo myomectomy or UAE seem to be at higher risk during pregnancy as complications with abnormal placentation and a higher risk of the fetus being small for gestational age have been recorded (*Pron et al., 2005*; *Dutton et al., 2007*; *Marret et al., 2012*). Uterine rupture is of further major concern (*Hortu et al., 2015*; *Pakniat et al., 2016*; *Cho, 2018*).

It is unclear whether the risks to a subsequent pregnancy from conservative approaches to treatment of fibroids differ from surgical myomectomy. Hence, the purpose of this review is to evaluate and compare pregnancy outcomes resulting from currently used therapeutic modalities.

MATERIALS AND METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) approach was used for this study. *ScienceDirect*, *PubMed*, *Web of Science* and *Cochrane Library* databases were thoroughly searched using the following key words: ulipristal acetate, myomectomy, uterine artery embolism, ablation, reduction, fibroid, leiomyoma, leiomyomata, pregnancy, infertility, pregnancy loss and IVF. The articles reviewed were inclusive of primary research, such as randomized controlled trials, cohort studies, prospective studies, retrospective studies, case control studies, case reports and case series from year 2000 to 2018. Additional studies were searched for in the references of all identified publications, including previous narrative reviews and meta-analyses.

Selection criteria

Only studies published as full-length articles were included. Pregnancy outcomes were assessed by rates of live birth, miscarriage, stillbirth, ectopic pregnancy, premature delivery and cases of uterine rupture. The exclusion criteria were women treated for indications other than fibroids and studies that used more than one treatment method.

Data extraction

All identified publications were then independently reviewed by two reviewers (SCK and ZZW). The data were independently extracted using a standardized form, and study design, patient demographics, intervention, time taken to conceive, number of pregnancies, pregnancy outcomes and complications were recorded. Discrepancies were subsequently resolved through consensus. The selection process according to PRISMA is presented in FIGURE 1.

Statistical analysis

Pregnancy outcomes after UPA, myomectomy, UAE or thermal ablation were compared. Statistical software SPSS Version 24.0.0.2 (IBM Corp., USA) was used to analyse the dataset. A chi-squared test of independence was conducted to examine the relationship between treatment modality and pregnancy outcomes. The time taken to conceive was expressed as mean and range. $P < 0.05$ was regarded as statistically significant.

Ethics Review Board approval was not required as all data were abstracted from previously published studies. No funding was received for this study.

RESULTS

The initial literature search retrieved 1805 articles after duplicates were removed. One study was removed from the analysis

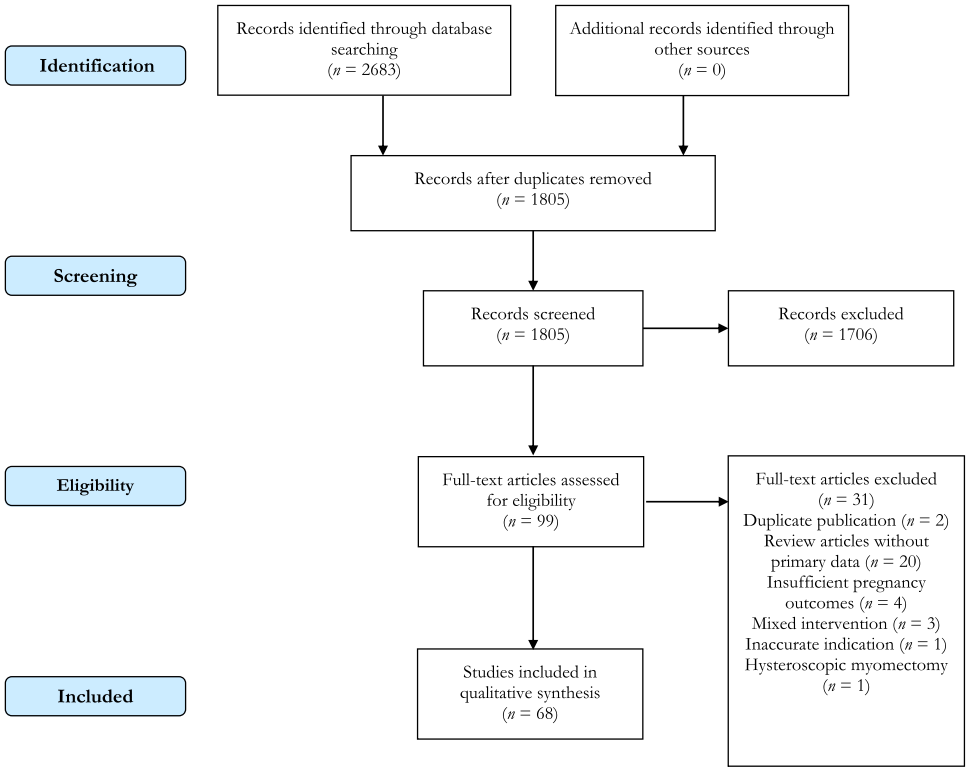

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart.

as it only presented post-hysteroscopic myomectomy data, and therefore has significant differences in techniques used and post-myomectomy risks compared with other studies (*Bernard et al., 2000*). Some articles were excluded for more than one criterion, in which case the first criterion according to the order methodology, intervention and insufficient results is reported. After exclusion, four randomized controlled trials, three cohort studies, 15 prospective studies, 19 retrospective studies, 11 case series and 16 case reports were included; the PRISMA flowchart is presented in FIGURE 1. Details of the study type included for each treatment modality is presented in FIGURE 2. Overall, data were available from 12 pregnancies after treatment with UPA, 1575 after myomectomy, 424 after UAE and 420 after ablation (FIGURE 2).

Ulipristal acetate

The nine reports reviewed included women with fibroids that were intramural or submucosal, ranging from 20 mm to 100 mm in diameter (*Wdowiak, 2013*; *Luyckx et al., 2014*; *Monleon et al., 2014*; *Romer, 2015*; *Tikhomirov, 2015*; *Luyckx et al., 2016*; *Murad, 2016*; *Kale, 2017*; *Hrgovic et al., 2018*). Of the 12 pregnancies (TABLE 1), six (50.0%) resulted in live birth, four (33.3%) were ongoing and two (17.7%) ended in miscarriage. Of the six livebirths, two babies were delivered prematurely at 34 and 36 weeks, respectively (*Monleon et al., 2014*; *Hrgovic et al., 2018*), whereas the others were delivered at term. No cases of intrauterine growth retardation or congenital malformation were recorded. The time to conception after UPA was reported in seven cases, and ranged from 1–3.5 months (*Wdowiak, 2013*; *Monleon et al., 2014*; *Tikhomirov, 2015*; *Luyckx et al., 2016*; *Murad, 2016*; *Kale, 2017*; *Hrgovic et al., 2018*).

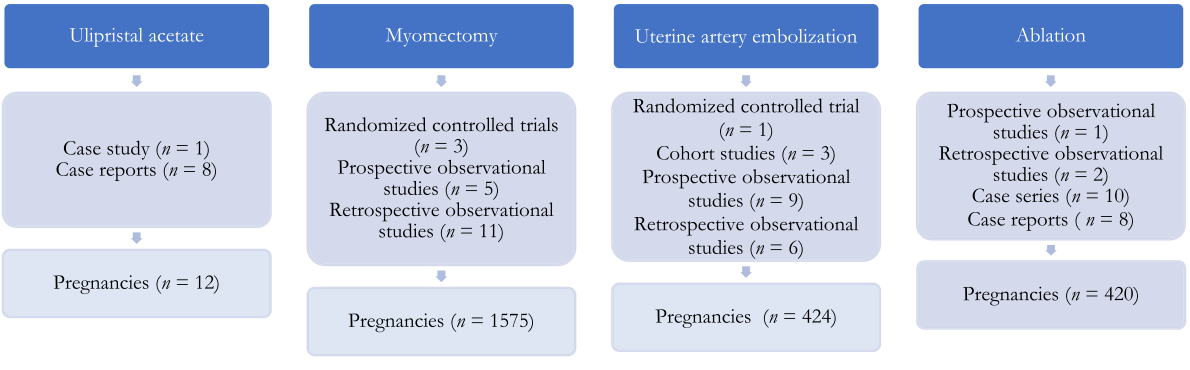

FIGURE 2 Studies included by conservative treatment modality.

TABLE 1 PREGNANCY OUTCOMES AFTER ULIPRISTAL ACETATE THERAPY

Study, year	*Study design*	*Mean age, years*	*Total number of women*	*Number of pregnant women*	*Pregnancies*	*Pregnancy outcomes*				*Time to conception, months*	*Mode of delivery*
						Live birth	*Ongoing pregnancy*	*Miscarriages*	*Gestation at delivery, weeks*		
Luyckx et al., 2014	Case series	36.4	2	2	3	–	1	2	–	NR	–
Hrgovic et al., 2018	Case report	33	1	1	1	1	–	–	36 + 3	3	CS
Kale, 2017	Case report	28.5	2	2	2	–	2	–	–	3	NR
Murad, 2016	Case report	35	1	1	1	1	–	–	38	2	VD
Luyckx et al., 2016	Case report	39	1	1	1	1	–	–	39	3.5	CS
Romer, 2015	Case report	41	1	1	1	1	–	–	Term	NR	VD
Tikhomirov, 2015	Case report	36	1	1	1	1	–	–	38	3	CS
Monleon et al., 2014	Case report	37	1	1	1	1	–	–	34	3	CS
Wdowiak, 2013	Case report	35	1	1	1	–	1	–	–	1	–
Total			11	11	12	6 (50.0%)	4 (33.3%)	2 (17.7%)			

CS, caesarean section; NR not reported; VD, vaginal delivery; –, not-applicable.

Myomectomy

A total of 1575 pregnancies after myomectomy were identified. The surgical approach was reported in 1449 women: 1047 women underwent laparoscopic myomectomy, 107 operations were robotic assisted, 51 were open surgeries or laparotomies, 26 were mini-laparotomies, whereas 218 cases were not clearly stated (TABLE 2). These pregnancies resulted in 1191 live births (75.6%), 42 ongoing pregnancies (2.7%), 299 miscarriages (19.0%), 24 ectopic pregnancies (1.5%) and two stillbirths. Of the 17 pregnancies that were terminated (1.1%), three were caused by fetal anomaly, one was caused by chromosomal abnormalities, whereas the remaining terminations were for either social or maternal medical reasons (*Dessolle et al., 2001*; *Soriano et al., 2003*; *Kumakiri et al., 2005*; *Paul et al., 2006*; *Seracchioli et al., 2006*; *Mara et al., 2008*; *Bernardi et al., 2014*; *Borja de Mozota et al., 2014*; *Sangha et al., 2015*). A total of six placental abnormalities were reported (four placenta previa, one placenta accreta and one placenta percreta (*Dubuisson et al., 2001*; *Paul et al., 2006*; *Tinelli et al., 2012*; *Pitter et al., 2013*). Sixty-three preterm deliveries (5.3%) were reported, in which eight were of extreme prematurity of less than 34 weeks with one case at 24 weeks. Overall, 60.8% were delivered by caesarean section versus 39.2% delivered vaginally.

A total of 10 cases (0.6%) of uterine rupture occurred with one resulting in intrauterine death (*Dubuisson et al., 2001*; *Sizzi et al., 2007*; *Pitter et al., 2013*; *Bernardi et al., 2014*; *Sangha et al., 2015*). One out of 10 woman had undergone open myomectomy, one had undergone robotic-assisted myomectomy and the remaining eight had undergone laparoscopic myomectomy. Two of the women treated with laparoscopic myomectomy had undergone an additional laparotomy for myomectomy and for corneal reanastomosis afterwards. One uterine rupture occurred after a road traffic accident at 24 weeks in a twin pregnancy. Three cases occurred at term, whereas six cases occurred before 35 weeks (range 24–34). The myomectomy-to-conception interval was only reported in four cases, with one patient conceiving 18 weeks after surgery. The other three women conceived more than 12 months from surgery, at 14, 18 and 36 months (*Dubuisson et al., 2000*; *Dubuisson et al., 2001*; *Pitter et al., 2013*). Uterine rupture occurred in two women in whom the uterine cavity had been breached and five women in whom the uterine cavity was not entered, although two of them had undergone repeat laparotomy. The remaining three cases did not indicate whether the uterine cavity was breached (*Sizzi et al., 2007*; *Pitter et al., 2013*; *Sangha et al., 2015*).

Overall, the average time from surgery to pregnancy was 13.0 months (range 5–24 months). This contrasts with the only case series of pregnancy after hysteroscopic myomectomy, the time to pregnancy was shorter in women with no intramural fibroids at 3.1 months (range 2–5 months) compared with 4.8 months in those with intramural fibroids ($P = 0.05$) (*Bernard et al., 2000*).

Uterine artery embolization

From the 19 studies of 424 pregnancies (TABLE 3), the overall live birth rate, ongoing pregnancy rate and miscarriage rate were 60.6% (257/424), 4.0% (17/424) and 27.4% (116/424), respectively. Ten (2.4%) ectopic pregnancies and three (0.7%) stillbirths were reported, whereas the remaining 21 (5%) pregnancies were terminated (*Ravina et al., 2000*; *McLucas et al., 2001*; *Walker and Pelage, 2002*; *Carpenter and Walker, 2005*; *Pron et al., 2005*; *Walker and McDowell, 2006*; *Dutton et al., 2007*; *Holub et al., 2007*; *Mara et al., 2008*; *Holub et al., 2008*; *Kim et al., 2008*; *Pinto Pabon et al., 2008*; *Firouznia et al., 2009*; *Bonduki et al., 2011*; *Pisco et al., 2011*; *Mara et al., 2012*; *Redecha et al., 2013*; *McLucas and Voorhees, 2014*; *Torre et al., 2014*). Overall, 27 premature deliveries were reported, whereas the rest were at term. Most deliveries were by caesarean section (63.5%) compared with 36.5% by vaginal delivery. In 17 reports of placenta abnormalities in 424 pregnancies after UAE, five cases of placenta praevia were reported, four placenta accreta, one placenta membranacea, one placental abruption, and the others were uncategorized (*McLucas et al., 2001*; *Carpenter and Walker, 2005*; *Pron et al., 2005*; *Walker and McDowell, 2006*; *Mara et al., 2008*; *Firouznia et al., 2009*; *Bonduki et al., 2011*; *Mara et al., 2012*). No cases of uterine rupture or intrauterine growth restriction were reported. The average time taken for women to conceive after UAE was 15 months (range 9–36 months) (*Ravina et al., 2000*; *Carpenter and Walker, 2005*; *Pron et al., 2005*; *Dutton et al., 2007*; *Holub et al., 2007*; *Mara et al., 2008*; *Holub et al., 2008*; *Pinto Pabon et al., 2008*; *Firouznia et al., 2009*; *Bonduki et al., 2011*; *Pisco et al., 2011*; *Mara et al., 2012*; *Redecha et al., 2013*; *Torre et al., 2014*).

Fibroid ablation

A total of 420 pregnancies were reported after fibroid ablation, resulting in 296 live births (70.5%), 50 miscarriages (11.9%), 39 terminations (9.3%) and 35 ongoing pregnancies (8.3%) (TABLE 4). All terminations were elective and none were stated to be caused by fetal abnormality (*Rabinovici et al., 2010*; *Qin et al., 2012*; *Bing-Song et al., 2016*; *Li et al., 2017*; *Zou et al., 2017*; *Liu et al., 2018*), although one woman terminated her pregnancy owing to concerns about the potential effects of fibroid ablation on the fetus (*Qin et al., 2012*). Eight successful cases of placental abnormalities were reported (seven placenta praevia and one placental insufficiency) and no cases of stillbirth or ectopic pregnancy (*Rabinovici et al., 2010*; *Li et al., 2017*). A total of 15 preterm deliveries were reported. Most pregnancies were delivered vaginally (61.6%), with the remaining 38.4% by caesarean section. No cases of uterine rupture were reported (*Gavrilova-Jordan et al., 2007*; *Hanstede et al., 2007*; *Morita et al., 2007*; *Funaki et al., 2009*; *Rabinovici et al., 2010*; *Yoon et al., 2010*; *Zaher et al., 2010*; *Bouwsma et al., 2011*; *Kim et al., 2011*; *Zaher et al., 2011*; *Qin et al., 2012*; *Froeling et al., 2013*; *Yoon et al., 2013*; *Garza-Leal et al., 2014*; *Hahn et al., 2015*; *Thiburce et al., 2015*; *Bing-song et al., 2016*; *Li et al., 2017*; *Zou et al., 2017*; *Bends et al., 2018*; *Liu et al., 2018*). The average time taken for women to conceive after thermal ablation was 10 months (range 3–33 months) (*Hanstede et al., 2007*; *Morita et al., 2007*; *Funaki et al., 2009*; *Rabinovici et al., 2010*; *Yoon et al., 2010*; *Zaher et al., 2010*; *Bouwsma et al., 2011*; *Zaher et al., 2011*; *Froeling et al., 2013*; *Yoon et al., 2013*; *Garza-Leal et al., 2014*; *Hahn et al., 2015*; *Thiburce et al., 2015*; *Bing-Song et al., 2016*; *Li et al., 2017*; *Zou et al., 2017*; *Bends et al., 2018*; *Liu et al., 2018*).

Comparison of pregnancy outcomes

As only 12 pregnancies after UPA treatment were reported, it was not included in the statistical analysis. No significant difference was observed in the percentage of live birth in women who received myomectomy or ablation

TABLE 2 PREGNANCY OUTCOMES AFTER MYOMECTOMY[a]

Study, year	Study design	Mean age, years	Management	Total number of women	Number of pregnant women	Pregnancies	Pregnancy outcomes					Mean time to conception (months)	Mode of delivery
							Live birth	Ongoing pregnancy	Miscarriage	Gestation at delivery Gestation, n			
										Gestation	n		
Mara et al., 2008	Randomized controlled trial	32	LM and OM	40	31	32	19	5	6	Preterm	5	13	NR
Palomba et al., 2007	Randomized controlled trial	26	LM and ML	136	62	62	54	0	8	Preterm	2	5	VD (31%); LSCS (69%)
Seracchioli et al., 2000	Randomized controlled trial	34	LM and OM	115	63	63	47	5	10	Preterm	3	NR	VD (28%); LSCS (72%)
Bernardi et al., 2014	Prospective observational study	33	LM	59	44	55	38	0	13	Preterm	5	23.2	VD (24%); LSCS (76%)
Tinelli et al., 2012	Prospective observational study	36.5	LM	235[b]	97	97	97	0	0	Term		10–24 (range)	SVD (42.2%); LCSC (32.9%); vacuum (24.8%)
Sizzi et al., 2007	Prospective observational study	36.1	LM	1683[b]	386	386	309	0	77	Preterm	9	NR	VD (22%); CS (78%)
Campo et al., 2003	Prospective observational study	32.4	LM and OM	41	25	29	25	0	4	Term		NR	NR
Dubuisson et al., 2001	Prospective observational study	33.2	LM	91	43	51	37	4	9	NR		16	NR
Shue et al., 2018	Retrospective observational study	35.7	RM, LM, OM	144	79	79	63	0	14	Preterm	4	NR	CS (100%)
Sangha et al., 2015	Retrospective observational study	NR	LM and OM	124	54	54	31	6	14	Preterm	4	NR	VD (94%); CS (6%)
Borja de Mozota et al., 2014	Retrospective observational study	36.2	Myomectomy	220	54	66	39	7	17	Preterm	7	20.7	VD (72%); CS (28%)
Pitter et al., 2013	Retrospective observational Study	34.8	RM	872[b]	107	127	92	9	24	Preterm	16	12.9	VD (4.3%); LSCS (95.7%)

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Table 2 – (continued)

Study, year	Study design	Mean age, years	Management	Total number of women	Number of pregnant women	Pregnancies	Pregnancy outcomes					Mean time to conception (months)	Mode of delivery
							Live birth	Ongoing pregnancy	Miscarriage	Gestation at delivery Gestation, n			
										Gestation	n		
Paul et al., 2006	Retrospective observational study	30	LM	217[b]	115	141	106	0	28	Preterm	3	8.9	VD (18%); LSCS (82%)
Seracchioli et al., 2006	Retrospective observational study	33.7	LM	233	127	158	106	3	43	Preterm	2	17.8	VD (25.5%); LSCS (74.5%)
Kumakiri et al., 2005	Retrospective observational study	35.5	LM	108	40	47	32	1	11	Preterm	1	13	VD (59%); LSCS (41%)
Seracchioli, 2003	Retrospective observational study	34.9	LM	32	9	9	7	0	2	Term		NR	VD (14%); LSCS (86%)
Soriano et al., 2003	Retrospective Observational Study	35.9	LM and OM	106	52	54	40	0	9	Preterm	1	11.3	VD (74%); LSCS (26%)
Dessolle et al., 2001	Retrospective observational study	36.1	LM	103	42	44	34	0	6	NR		7.5	VD (68%); LSCS (32%)
Rossetti et al., 2001	Retrospective observational study	36	LM	29	19	21	15	2	4	Preterm	3	7.1	VD (26.6%) LSCS (73.4%)
Total				4588	1449	1575	1191 (75.6%)	42 (2.7%)	299 (19.0%)				

[a] Twenty-four ectopic pregnancies, 17 terminations and two stillbirths.

[b] Includes those who did not intend pregnancy.

CS, caesarean section; HM, hysteroscopic myomectomy; LM, laparoscopic myomectomy; LSCS, lower segment caesarean section; ML, mini-laparotomy; NR, not reported; OM, open/laparotomic myomectomy; RM, robot-assisted myomectomy; VD, vaginal delivery.

TABLE 3 PREGNANCY OUTCOMES AFTER UTERINE ARTERY EMBOLIZATION THERAPY[a]

Study, year	*Study design*	*Mean age, years*	*Total number of women*	*Number of pregnant women*	*Pregnancies*	*Pregnancy outcomes*					*Mean time to conception (months)*	*Mode of delivery*
						Live birth	*Ongoing pregnancy*	*Miscarriage*	*Gestation at delivery, weeks*			
									Gestation	n		
Mara et al., 2008	Randomized controlled trial	32.8	26	13	17	5	1	9	Term		18	VD (40%); CS (60%)
Mara et al., 2012	Cohort study	33.1	42	29	42	23	2	13	Preterm	1	26.7	NR
Holub et al., 2008	Cohort study	32.3	112	20	28	10	1	14	Preterm	2	9.1	VD (20%); CS (80%)
Holub et al., 2007	Cohort study	31.9	27	14	17	8	1	7	Preterm	1	9	VD (25%); CS (75%)
Torre et al., 2014	Prospective observational study	37.3	66	1	1	0	1	0	Term		14	NR
Redecha et al., 2013	Prospective observational study	34.4	21	7	7	7	0	0	Term		13.14	VD (87.5%); CS (12.5%)
Firouznia et al., 2009	Prospective observational study	33.8	23	14	15	13	0	2	Term		30.5	CS (100%)
Pinto Pabon et al., 2008	Prospective observational study	35	57	10	11	8	0	3	Preterm	1	15	VD (50%); CS (50%)
Kim et al., 2008	Prospective observational study	36.6	19	12	15	6	0	3	Term		NR	VD (17%); CS (83%)
Pron et al., 2005	Prospective observational study	34	555[b]	21	24	18	0	4	Preterm	4	15	VD (50%); CS (50%)
Walker and Pelage, 2002	Prospective observational study	36	24 + 3[c]	12	13	9	0	2	Preterm	1	NR	VD (89%); CS (11%)
McLucas et al., 2001	Prospective Observational Study	<40	139	14	17	10	2	5	Preterm	1	NR	VD (30%); CS (70%)
Ravina et al., 2000	Prospective observational study	36	184[b]	9	12	7	0	5	Preterm	2	9	VD (75%;) CS (25%)
McLucas and Voorhees, 2014	Retrospective observational study	33	102	23	27	19	2	6	NR		NR	NR
Pisco et al., 2011	Retrospective observational study	36	74	44	44	33	5	4	Preterm	2	10.8	VD (41%); CS (59%)
Bonduki et al., 2011	Retrospective observational study	34.4	75	15	15	13	2	0	Preterm	1	23.8	CS (100%)

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Table 3 – (continued)

Study, year	Study design	Mean age, years	Total number of women	Number of pregnant women	Pregnancies	Pregnancy outcomes					Mean time to conception (months)	Mode of delivery
						Live birth	Ongoing pregnancy	Miscarriage	Gestation at delivery, weeks			
									Gestation	n		
Dutton et al., 2007	Retrospective observational study	38	187	27	37	19	0	15	Term		36	VD (21%); CS (79%)
Walker and McDowell, 2006	Retrospective observational study	37	108	33	56	33	0	17	Preterm	6	NR	VD (27%); CS (73%)
Carpenter and Walker, 2005	Retrospective observational study	37	79	26	26	16	0	7	Preterm	5	20	VD (12%); CS (88%)
Total			1923	344	424	257 (60.6%)	17 (4.0%)	116 (27.4%)				

[a] Ten ectopic pregnancies and three stillbirths.

[b] Includes those who did not intend pregnancy.

[c] Indicates patients who did not intend pregnancy but became pregnant.

CS, caesarean section; NR, not reported; VD, vaginal delivery.

TABLE 4 PREGNANCY OUTCOMES AFTER FIBROID ABLATION.[a]

Study, year	*Study design*	*Mean age*	*Total number of women*	*Number of pregnant women*	*Pregnancies*	*Pregnancy outcomes*					*Mean time to conception (months)*	*Mode of delivery*
						Live birth rate	*Ongoing pregnancy*	*Miscarriage*	*Gestation at delivery, weeks*			
									Gestation	n		
Liu et al., 2018	Prospective observational study	31.1	174	81	88	74	0	9	Preterm	5	23.1	Elective LSCS (72% [53/7]); VD (28% [21/74]).
Zou et al., 2017	Retrospective observational Study	34.5	406	78	80	71	5	3	Preterm	3	5.6	LSCS (79% [56/71]); VD (21% [15/71])
Li et al., 2017	Retrospective observational study	30.3	189	131	133	93	19	17	Preterm	6	12.3	VD (28% [26/93]); LSCS (72% [67/93])
Bing-song et al., 2016	Case series	34.2	169[b]	9	10	3	0	0	Term		12.7	LSCS (100% [3/3])
Thiburce et al., 2015	Case series	–	45[b]	2	2	2	0	0	Term		18	VD (100% [2/2])
Hahn et al., 2015	Case series	31	25[b]	2	2	2	0	0	Term		7.6	VD (100% [2/2])
Garza-Leal et al., 2014	Case series	41	1	1	1	1	0	0	Term		3.5	LSCS (100% [1/1])
Yoon et al., 2013	Case series	–	60[b]	1	1	1	0	0	Term		4	NR
Froeling et al., 2013	Case series	36.2	36[b]	9	10	7	0	3	Term		16.1	NR
Qin et al., 2012	Case series	34.5	435[b]	24	24	7	0	2	Term		<12	LSCS (100% [7/7])
Kim et al., 2011	Case series	39.8	69[b]	3	3	3	0	0	Term		<12	LSCS (33% [1/3]); VD (67% [2/3])
Rabinovici et al., 2010	Case series	37.2	51	51	54	22	11	14	Preterm	1	8	VD 64% [14/22]); LSCS (36% [8/22])
Funaki et al., 2009	Case series	–	91[b]	4	4	2	0	2	Term		12.8	NR
Bends et al., 2018	Case report	33	1	1	1	1	0	0	Term		33	VD
Bouwsma et al., 2011	Case report	37	1	1	1	1	0	0	Term		3	VD
Zaher et al., 2011	Case report	35	1	1	1	1	0	0	Term		10	Emergency LSCS

(continued on next page)

Table 4 – (continued)

Study, year	Study design	Mean age	Total number of women	Number of pregnant women	Pregnancies	Pregnancy outcomes				Mean time to conception (months)	Mode of delivery
						Live birth rate	Ongoing pregnancy	Miscarriage	Gestation at delivery, weeks		
									Gestation n		
Zaher et al., 2010	Case report	39	1	1	1	1	0	0	Term	10	VD
Yoon et al., 2010	Case report	31	1	1	1	1	0	0	Term	4	VD
Gavrilova-Jordan et al., 2007	Case report	38	1	1	1	1	0	0	Term	NR	VD
Hanstede et al., 2007	Case report	40	1	1	1	1	0	0	Term	18	VD
Morita et al., 2007	Case report	30	48[b]	1	1	1	0	0	Term	4	VD
Total			1806	404	420	296 (70.5%)	35 (8.3%)	50 (11.9%)			

[a] Thirty-nine terminations.

[b] Includes those who did not intend pregnancy.

LSCS, lower segment caesarean section; NR, not reported; VD, vaginal delivery.

(75.6% versus 70.5%; $P > 0.05$). After UAE, however, the live birth rate was significantly lower at 60.6% ($P < 0.001$) compared with both myomectomy and ablation groups. Pregnancies after UAE also showed the highest rate of miscarriage (27.4%), followed by myomectomy (19.9%) and ablation (11.9%) ($P < 0.001$).

Five cases of stillbirth were reported, three after UAE and two after myomectomy (*Seracchioli et al., 2006*; *Walker and McDowell, 2006*; *Pisco et al., 2011*; *Bernardi et al., 2014*). Abnormal placentation was more common after UAE at 4% ($n = 17$) than after myomectomy (0.38%; $n = 6$) or after ablation (1.9%; $n = 8$; $P < 0.001$). No placental abnormalities were reported in women who underwent UPA therapy. Ten cases of uterine rupture were recorded after myomectomy and none after UPA, UAE or ablation therapy (*Dubuisson et al., 2001*; *Sizzi et al., 2007*; *Pitter et al., 2013*; *Bernardi et al., 2014*; *Sangha et al., 2015*).

DISCUSSION

This is the first review of pregnancy outcomes comparing medical, radiological and surgical conservative treatment of uterine fibroids, and is limited by the quality of the evidence available, with significant risk of bias. It seems, however, that the live birth rate is highest after myomectomy (75.6%) and ablation (70.5%). Pregnancies after UAE had the lowest live birth rate of 60.6% and the highest rate of miscarriage, at 27.4%, compared with the general population rate of 10–20% (*Stirrat, 1990*; *Regan and Rai, 2000*; *Weeks and Danielsson, 2006*). Live birth rates after UPA were excluded from the statistical analysis owing to the limited number of cases. The stillbirth rates were low (range: 0–3%) with all treatments and are similar to the global average stillbirth rate of 2% (*Blencowe et al., 2016*).

At present, myomectomy is the gold-standard fertility preservation treatment for fibroids and seems to have an advantage over UPA, UAE or ablation for pregnancy outcomes. Surgical complications, such as major haemorrhage requiring transfusion and infections, do occur (*Holzer et al., 2006*; *American College of Obstetricians and Gynecologists, 2008*; *Practice Committee of American Society for Reproductive Medicine in collaboration with Society of Reproductive Surgeons, 2008*; *Marret et al., 2012*; *Ciebiera et al., 2018*; *D'Silva et al., 2018*; *Yang et al., 2018*), and a risk of uterine rupture during pregnancy and labour, of which 10 cases were identified (*Dubuisson et al., 2001*; *Seracchioli et al., 2006*; *Sizzi et al., 2007*; *Kumakiri et al., 2008*; *Gyamfi-Bannerman et al., 2012*; *Kim et al., 2013*; *Pitter et al., 2013*; *Bernardi et al., 2014*; *Koo et al., 2015*; *Kim et al., 2016*; *Chao et al., 2018*). Myomectomy also contributes to postpartum complications by increasing the incidence of placenta praevia and placenta accreta, but the rate of placental abnormalities identified here was only 0.25% (*Campo et al., 2003*; *Pron et al., 2005*; *Dutton et al., 2007*; *Gyamfi-Bannerman et al., 2012*; *Lutomski et al., 2012*; *Kramer et al., 2013*; *Pitter et al., 2013*; *Bernardi et al., 2014*; *Sheldon et al., 2014*; *Mastrolia et al., 2016*; *Tanaka et al., 2016*). Although pregnancy outcomes after myomectomy seem to be better than with other conservative treatments for fibroids, it remains unclear whether myomectomy has a benefit for fertility (*Metwally et al., 2012*; *Lumsden et al., 2015*).

Fibroid ablation using either ultrasonography or magnetic resonance guided focused ultrasound minimizes the damage to surrounding tissue by focusing on the area within the fibroid; however, cases of skin burns and bowel perforation have been reported (*Zupi et al., 2006*; *Bouwsma et al., 2011*; *Bouwsma et al., 2011*; *Chodankar and Allison, 2018*). It is mostly limited to centrally situated fibroids, whereas fibroids usually grow peripherally. To maintain a certain safety margin, its use is limited to fibroids wider than 4 cm. Also, because of the long duration of the procedure, each treatment session is focused on a single fibroid only (*Vilos et al., 2015*; *Chodankar and Allison, 2018*). Radiofrequency volumetric thermal ablation has shown great potential by allowing a higher number of fibroids to be treated, with less intraoperative blood loss and a faster recovery compared with laparoscopic myomectomy (*Brucker et al., 2014*). In this analysis, fibroid ablation had comparable pregnancy outcomes to myomectomy, with similar live birth rates (70.5% versus 75.6%) and low miscarriage rates (11.9% versus 19.0%). No cases of uterine rupture were reported, and it was not associated with higher risk of placental abnormalities. Although promising, fibroid ablation through a focused energy delivery system is relatively new and more controlled trials are required to evaluate its potential for the treatment of fibroids in women who intend pregnancy (*Vilos et al., 2015*; *Chodankar and Allison, 2018*).

After UAE treatment, the disruption of normal uterine blood supply to the endometrium and placental blood supply may explain the suboptimal pregnancy outcomes after UAE compared with myomectomy, UPA and ablation therapy (*Tropeano et al., 2003*; *Bulletti and de Ziegler; 2005*; *Czuczwar et al., 2016*). For these reasons, UAE has often only been offered to women who did not want to retain their fertility. In a prospective cohort (*Torre et al., 2014*), women who had fibroids and intended to conceive yet were unable to undergo myomectomy were offered UAE. Only one out of 31 women who were actively trying for pregnancy after UAE succeeded, but the pregnancy ended in miscarriage. This analysis confirms that UAE should not be considered as first-line conservative management of fibroids for women with fertility wishes. As for UPA and ablation therapy, no controlled trials were conducted on pregnancy outcomes. Therefore, more studies need to establish whether UPA or ablation therapy are indeed associated with a lower live birth rate compared with myomectomy. Both UPA and ablation therapy, however, seem promising in women with leiomyomata who intend to have a subsequent pregnancy.

This analysis is unable to assess pregnancy rates and time taken to achieve pregnancy owing to the limited and potentially selective nature of the data, and the lack of a denominator of women who wished and tried to conceive. Research includes mostly cohort studies or cases series, and pregnancy was not a primary outcome of the randomized controlled trials that were included. In addition, women being advised to wait after surgery before conceiving may also have an effect (*Dicle et al., 1997*), which may also apply to treatment with ablation or UAE. The lack of direct comparisons of different fibroid treatment within studies where pregnancy is desired by a significant proportion of women is, however, the most important limitation to this analysis, as systematic differences may exist in the characteristics of women offered the various treatments in the studies reported.

In conclusion, myomectomy seems to be the treatment modality of choice for women wishing conservative management of fibroids with a view to subsequent pregnancy, although infrequent but specific risks of uterine rupture and abnormal placentation occur. Pregnancy outcomes were similar after fibroid ablation but were worse after UAE, and too few pregnancies have been reported after UPA treatment to allow analysis. In view of this, UAE is perhaps limited to women who have contraindications for other conservative approaches. Until large comparative randomized controlled trials or prospective cohort studies focusing on pregnancy outcomes are carried out, these data may allow more accurate counselling and decision making.

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