Uterine Artery Embolization and Its Effect on Fertility

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ABSTRACT

A systematic review of literature analyzing fertility following uterine artery embolization (UAE) is presented. Twenty-one studies describing pregnancy and complications of pregnancy following UAE were included. Low-level evidence from these studies suggests that pregnancy rates following UAE are comparable to the age-adjusted rates in the general population. Although pregnancy complication rates were similar to those in patients with untreated fibroid tumors, a few studies have reported higher miscarriage rates following UAE. Further randomized controlled trials comparing UAE versus other fertility-preserving treatments are necessary to confirm these findings.

ABBREVIATIONS

ACOG = American College of Obstetrics and Gynecology, PPH = postpartum hemorrhage, UAE = uterine artery embolization

The safety and efficacy of uterine artery embolization (UAE) for the treatment of leiomyomas (ie, fibroid tumors) and postpartum hemorrhage (PPH) are well established; however, the effect of UAE on future fertility is still debated (1,2). At present, professional bodies such as American College of Obstetrics and Gynecology (ACOG) and the Society of Interventional Radiology (SIR) list the desire for future fertility as a relative contraindication to UAE (3,4). Because of the minimally invasive nature of the procedure, increasing numbers of patients with symptomatic fibroid tumors during childbearing age are opting for UAE, which puts their physicians in a dilemma (5). This article systematically reviews the literature to date analyzing pregnancy and complications of pregnancy following UAE.

METHODS

A literature search for studies addressing fertility following UAE was performed in PubMed, Medline, Embase, Ovid, Cochrane database, and ProQuest in January 2013. Search was conducted by using Medical Subject Heading terms and keywords without any date limitation. Searches of key words "uterine artery embolization" or "uterine fibroid embolization" combined with "fertility" or "pregnancy" yielded 123 results. The titles and abstracts were then independently reviewed for appropriateness, which narrowed the results to 34 papers. All studies reporting pregnancy outcomes or complications of pregnancy following UAE for fibroid tumors or PPH were included. Studies presenting pregnancy outcomes without determining the number of patients wishing to conceive were excluded. Full-text articles were retrieved for these 34 articles, and 21 studies were selected for final analysis.

A standardized assessment of methodologic quality of individual studies was not performed because the studies had significant heterogeneity in design and outcome measures. The levels of evidence for individual studies were assessed by using the Oxford Centre for Evidence-based Medicine 2011 guidelines (6), and are indicated in **Tables 1–3** (7–27). The score ranges from I to V, with I being the highest level of evidence. The scores for studies included in the present review range from level II to level IV. Level II evidence denotes low-quality randomized controlled trials and systematic review of cohort/follow-up studies with homogeneity. Studies with level III evidence include nonrandomized cohort or follow-up studies, and those with level IV evidence include poor-quality cohort or case-control studies and case series. In addition, the methodologic quality of individual studies is reported through narrative description.

RESULTS

The results are summarized in **Tables 1–3**. **Table 1** (7–18) summarizes studies analyzing pregnancy rates following

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Table 1. Published Studies of Pregnancy after UAE for Fibroid Tumors (7–18)

Study, Year	Level of Evidence	No. of Pts.	Follow-up Duration (mo)	No. of Pts. Trying to Conceive	Mean Age (y)	Mean Age at Conception (y)	Pregnancies	No. of Pregnant Patients
Mara et al, 2008 (10)	II	58	25	26	33	NS	17	13 (50)
Pisco et al, 2011 (11)	III	74	53	74	NS	36	44	44 (59.5)
Mara et al, 2012 (13)	III	100	50	42	33	NS	42	29 (69)
Holub et al, 2008 (14)	III	112	36	39	NS	32	28	20 (51)
Pron et al, 2005 (12)	III	555	24	35	43	36	24	21 (60)
Firouznia et al, 2009 (15)	III	102	24	23	31	34	15	14 (61)
Kim et al, 2008 (16)	III	87	36	19	37	NS	15	12 (63)
Walker and McDowell, 2006 (18)	IV	1,200	NS	108	NS	37	56	33 (30.5)
Kim et al, 2005 (17)	IV	94	35	6	31	NS	6	5 (83)
Pinto Pabón et al, 2008 (9)*	IV	100	19	57	35	NS	11	10 (17.5)
Dutton et al, 2007 (7)*	IV	649	NS	187	44	38	37	27 (14.4)
McLucas et al, 2001 (8)*	IV	400	NS	131	NS	NS	17	14 (27)

Values in parentheses are percentages.
NS = not specified, UAE = uterine artery embolization.
*Excluded from pooled analysis because of inefficient or incomplete follow-up.

Table 2. Published Studies of Pregnancy after UAE for PPH (19–27)

Study, Year	Level of Evidence	No. of Pts.	Follow-up Duration (mo)	Mean Age (y)	No. of Pts. Trying to Conceive	No. of Pregnancies	No. of Pregnant Patients
Gaia et al, 2009 (19)	III	113	46	NS	29	19	18 (62)
Chauleur et al, 2008 (20)	III	41	NS	27	16	19	16 (100)
Fiori et al, 2009 (21)	III	34	NS	33	15	20	13 (87)
Hardeman et al, 2010 (22)	III	53	NS	34.3	14	14	12 (86)
Descargues et al, 2004 (23)	III	25	NS	NS	9	10	6 (67)
Salomon et al, 2003 (24)	III	17	38	35	6	6	5 (83)
Ornan et al, 2003 (25)	III	28	224	28.6	6	6	6 (100)
Boulleret et al, 2004 (26)	IV	36	NS	NS	3	3	3 (100)
Stancato-Pasik et al, 1997 (27)	IV	17	NS	30.8	3	3	3 (100)

Values in parentheses are percentages.
NS = not specified, PPH = postpartum hemorrhage, UAE = uterine artery embolization.

UAE for leiomyomas. **Table 2** (19–27) summarizes studies analyzing pregnancy rates following UAE for PPH. **Table 3** (7–18) summarizes studies analyzing the complications of pregnancy after UAE for leiomyomas.

Three studies were excluded from the pooled analysis because the pregnancy data reported in these studies were not accurate as a result of incomplete or inefficient follow-up (7–9). The cumulative pregnancy rate and miscarriage rate following UAE for fibroid tumors from the pooled analysis were 58.6% and 28%, respectively. The cumulative live birth rate was 65.2%, with a term delivery rate of 60.7%. The mean preterm delivery and placental abnormality rates were 7.3% and 6.3%, respectively. The mean age of patients with leiomyomas was 35.9 years. In contrast, the cumulative pregnancy rate following UAE for PPH was 87.2%.

CRITICAL APPRAISAL OF INDIVIDUAL STUDIES

The only randomized controlled trial in this review was conducted by Mara et al (10), who reported midterm results of a trial comparing fertility outcomes of UAE with those of myomectomy. The mean duration of follow-up in this study was 23.9 months, with 80% of subjects completing 1 year of follow-up. The longer-term results from this trial are still awaited. Thirteen of 26 patients who underwent UAE and 31 of 40 who underwent myomectomy became pregnant (pregnancy rates, 50% vs 78%; $P = .04$). There was also a significant difference between groups in the incidence of abortions (nine of 17 following UAE vs six of 32 following myomectomy; $P < .05$). Major limitations of

Table 3. Published Studies of Complications of Pregnancy after UAE for Fibroid Tumors (7–18)

Study, Year	Level of Evidence	Pregnant Patients (%)	Mean Age (y)	No. of Pregnancies	Miscarriage	Preterm Delivery	Term Delivery	PA*	Live Births
Mara et al, 2008 (10)	II	13	33	17	9 (60)	0	5 (33)	1 (6)	5 (33)
Pisco et al, 2011 (11)	III	44	NS	44	4 (10)	1 (3)	32 (82)	NS	33 (85)
Mara et al, 2012 (13)	III	29	33.1	42	13 (34)	1 (3)	22 (58)	0	23 (61)
Holub et al, 2008 (14)	III	20	NS	28	14 (56)	2 (7)	8 (32)	2 (7)	10 (40)
Pron et al, 2005 (12)	III	21	43	24	4 (17)	4 (17)	14 (64)	3 (13)	18 (75)
Kim et al, 2008 (16)	III	12	37	15	3 (20)	0	6 (50)	NS	6 (50)
Firouznia et al, 2009 (15)	III	14	31.2	15	2 (13)	0	13 (87)	1 (7)	13 (87)
Walker and McDowell, 2006 (18)	IV	33	NS	56	17 (30)	6 (18)	27 (48)	6 (11)	33 (59)
Kim et al, 2005 (17)	IV	5	31	6	0	1 (17)	5 (83)	NS	6 (100)
Pinto Pabón et al, 2008 (9)†	IV	10	35	11	3 (27)	1 (9)	7 (64)	0	8 (73)
McLucas et al, 2001 (8)†	IV	14	NS	17	5 (29)	1 (6)	10 (67)	1 (6)	10 (67)
Dutton et al, 2007 (7)†	IV	27	43.8	37	15 (41)	NS	NS	NS	19 (53)

Values in parentheses are percentages.
NS = not specified, PA = placental abnormalities, UAE = uterine artery embolization.
*Placental abnormalities.
†Excluded from pooled analysis because of inefficient or incomplete follow-up.

this trial (10) are its small sample size, short duration of follow-up, and high rate of repeat interventions in the UAE group (myomectomy in 32.7% of patients). The study did not specify why this group was kept in the UAE arm of the trial after undergoing both UAE and myomectomy. Whether this high rate of repeat intervention affected the pregnancy and miscarriage rates in the UAE group is unknown.

Pisco et al (11) performed UAE in 74 patients who wanted to become pregnant and prospectively followed them for a total of 4.5 years (11). Forty-four patients became pregnant spontaneously (pregnancy rate, 59.5%). There were 39 completed pregnancies, with 33 live births (84.6%) and four spontaneous abortions (10.3%). The mean delay from UAE to pregnancy was 10.8 months. The authors suggest that the higher proportion of younger patients (89.7% younger than 40 y) likely contributed to the better outcomes (11).

Pron et al (12) reported the pregnancy outcomes from the prospective Ontario multicenter trial, which included 555 patients who underwent UAE at one of eight Ontario hospitals. Patients were followed up with telephone interviews, and 84% completed 2 years of follow-up. Thirty-five patients were actively trying to conceive, among which 21 became pregnant (pregnancy rate, 60%). The mean age of patients who became pregnant was 34 years. There were three cases of placental abnormalities, and the authors suggested the possibility of endometrial disruption from nontarget embolization as the cause (12).

Mara et al (13) also published another prospective study comparing UAE versus laparoscopic uterine artery occlusion. Each arm of this study had 100 patients, all of whom were not eligible for myomectomy as a result of high-risk location or multiplicity or large size of the tumors. Allocation of intervention was based on patient or physician preference. Patients were prospectively followed up at 6 months. The pregnancy rate following UAE was 69% (29 of 42), versus 66.7% (32 of 48) after laparoscopic uterine artery occlusion. The abortion rate and delivery rates following UAE were not significantly different from those in the laparoscopy group (34.2% and 61% vs 27.9% and 51.2%, respectively; $P > .05$). The same group of authors (14) had previously published another observational study comparing the same treatments. At least one of the investigation centers was common to both studies, and there was temporal overlap between the two studies (September 2004 to November 2011 [13] and March 2000 to June 2006 [14]). It is unknown whether there was overlap of patients. Although the paper claims to be a prospective trial, the duration and method of follow-up were not indicated. The mean age of patients was also not mentioned (14). The study reported a pregnancy rate of 51% and a high miscarriage rate of 56% compared with other studies.

Firouznia et al (15) analyzed fertility outcomes in 102 patients undergoing UAE. Patients were prospectively followed for 24 months with questionnaires and telephone interviews. Fourteen of 23 patients who tried to conceive became pregnant (61%). The mean age at conception was 33.8 years. Four patients who became pregnant were older than 40 years. There were two miscarriages (13%), both in patients who were 41 years of age at the time of conception. There was one case of PPH caused by retained placental tissue.

Kim et al (16) studied 87 women younger than the age of 40 years undergoing UAE for symptomatic fibroid tumors. Patients were prospectively followed up for 3 years. They also documented the presence of uteroovarian anastomosis. Nineteen patients attempted to conceive, and 12 women were successful, with 15 pregnancies (63%). Four patients

with uteroovarian anastomoses conceived, and the presence of the anastomosis did not have significant effect on the rate of conception. Another similar small case series (17) followed six patients wishing to conceive after UAE, of which five were successful, with six pregnancies.

Walker et al (18) conducted a retrospective questionnaire study in 1,200 patients who underwent UAE over a period of 9 years. Patients were followed up with questionnaire or telephone interviews. One hundred eight patients attempted conception at some point following UAE, of which 33 became pregnant (30.5%). Although the mean age for the group was not mentioned, the mean age at conception was 37.4 years. There were 17 miscarriages (30.4%) and six preterm deliveries (18.2%). The mean age of patients who had miscarriages was 38.8 years. There were six cases of PPH (18.2%).

Pinto Pabon et al (9) retrospectively analyzed a cohort of 100 women who underwent UAE, 57 of whom expressed a desire to remain fertile. The mean age was not mentioned, but 18 of these 57 patients were older than 40 years of age. The study reported an overall pregnancy rate of 17.5%. The pregnancy rate for patients younger than age 40 years was 25.6%. However, the authors failed to ascertain how many of these 57 patients were actually trying to conceive during follow-up. This study was excluded from the pooled analysis as a result of this major limitation.

Dutton et al (7) presented the reproductive outcomes from a multicenter retrospective comparison of UAE versus hysterectomy for symptomatic fibroid tumors. The authors admit that the fertility data from the study may not be reliable, as, even though 187 patients expressed a desire for future fertility at the time of the procedure, it was not clear how many were actively trying to conceive. This study was also excluded from the pooled analysis.

In a retrospective study, McLucas et al (8) identified 57 women younger than 40 years of age who expressed the desire for future fertility at the time of UAE for fibroid tumors among a group of 400 patients. There were two major flaws in this study. The follow-up was not active; instead, patients who achieved pregnancy were asked to contact the authors. Also, the study did not assess how many patients were actively trying to conceive. This study was also excluded from the pooled analysis.

All the studies assessing fertility following UAE for PPH were observational follow-up studies. They had relatively smaller numbers, and the results are shown in **Table 3**. The populations studied were younger than those who received UAE for leiomyomas, and had better pregnancy outcomes.

DISCUSSION

UAE for the treatment of fibroid tumors was first described by Ravina et al in 1995 (28). The same procedure is also used for the treatment of PPH. The indications for UAE for leiomyomas are menorrhagia, pelvic pain, and pelvic pressure symptoms. The impact of UAE on future fertility is still unclear. Nontarget embolization of the ovaries and endometrium has been proposed as potential cause for infertility following UAE (29). As UAE is becoming popular as the primary treatment modality for symptomatic fibroid tumors, a literature review on this subject would aid clinicians and patients in making an informed decision in cases in which preservation of fertility is desired.

Assessment of fertility following UAE for fibroid tumors is complicated by two confounding factors. One is the advanced age and the second is the presence of the leiomyoma itself, both of which can affect fertility. It is estimated that 2% of infertility is caused by fibroid tumors (30). A metaanalysis of 23 studies (31) showed that women with fibroid tumors were less likely to become pregnant compared with control subjects (relative risk, 0.85; 95% CI, 0.73–0.98). The risk was greater in patients with submucosal or intramural fibroid tumors with cavity distortion (relative risk, 0.36; 95% CI, 0.18–0.74). Patients with fibroid tumors were also at higher risk of spontaneous abortion (relative risk, 1.7; 95% CI, 1.4–2.1). A review of 22 studies (32) showed cumulative miscarriage rates of 20.4% for intramural tumors and 46.7% for submucosal tumors.

Female fertility decreases with advancing age. There is no clear definition of advanced reproductive age; however, several studies have shown significant decline in fertility after the mid-30s (33). "Fecundability" (ie, the probability of achieving pregnancy in one menstrual cycle) begins to decline in the early 30s, with a much more rapid decline after the mid-30s (34). Population-based studies and those from assisted reproduction cohorts support this finding. Menken et al (35) studied seven population groups from around the world and showed a progressive increase in childlessness with age, calculated as the number of childless women who wanted to have children over the total number of women in their age group. The rates of involuntary childlessness in women aged 30–34, 35–39, and 40–44 years were 15.5%, 29.6%, and 63.6%, respectively (35). Dunson et al (36) studied 782 healthy couples in a well designed study and reported the probabilities of pregnancy following intercourse on the most fertile day of the cycle in women aged 27–34 and 35–39 years as approximately 40% and 30%, respectively. In a classic study of 2,193 women undergoing donor insemination for male factor infertility (37), conception rates after 12 cycles for women under the age of 30 years, aged 31–35 years, and older than the age of 35 years were 74%, 62%, and 54%, respectively.

Age is also an important predictor of pregnancy complications such as spontaneous abortions and preterm delivery. In a population-based study involving 1.2 million pregnancy outcomes, Nybo Andersen et al (38) estimated spontaneous abortion rates of 15% among women 30–34 years of age, 24.6% among women 35–39 years of age, 51% among women 40–44 years of age, and 93.4% among women aged 45 years or older. The rate of premature

delivery in the general population is estimated to be 5%–10%, and, in women older than 35 years of age, the risk is approximately doubled (39,40).

The cumulative pregnancy rate from the pooled analysis was 58.6%, and the mean age was 35.9 years. This rate is comparable to the age-adjusted pregnancy rates in the general population. Also considering that there is some degree of subfertility associated with fibroid tumors, these findings contradict the current recommendations from SIR and ACOG. The cumulative miscarriage rate of 28% is also comparable to the rates quoted in patients with untreated fibroid tumors. However, at least two studies have reported miscarriage rates of more than 50%, which cannot be entirely explained by advanced age or the presence of leiomyomas (10,14). The cumulative preterm delivery rate of 7.3% was similar to that in the general population. The population of patients with PPH was not confounded by advanced age or the presence of leiuomyomas, and consequently had better fertility outcomes following UAE. The results from this group are presented in **Table 2**. However, these outcomes should not be directly compared versus those in patients with leiomyomas because of the difference in age, anatomy, and technique of UAE between the two groups.

The results from the present review should be interpreted with caution, as the literature reviewed was of limited quality. Most studies were observational follow-up studies without adequate controls. Retrospective data collection used in some of these studies could have resulted in inaccurate estimation of the pregnancy rate. The only randomized controlled trial in the present review (10) also had significant flaws in the design and follow-up.

In conclusion, there is low-level evidence to suggest that pregnancy rates following UAE are comparable to the age-adjusted rates in the general population. Although pregnancy complication rates were similar to those in patients with untreated fibroid tumors, a few studies have reported higher miscarriage rates. Large, well designed randomized controlled trials comparing UAE versus other fertility-preserving options such as myomectomy are necessary to confirm these findings. Creation of national and regional registries by organizations such as SIR and ACOG to document pertinent fertility-related information would also help in accumulating observational data on this subject.

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