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REVIEW

Fertility after uterine artery embolization: a review

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Abstract

Uterine artery embolization (UAE) research has largely been focused on women over 40 years, yet women of reproductive age undergo UAE without any increased morbidity. Some physicians refrain from recommending UAE to women in this age group because of some research findings showing a negative effect on fertility. This review presents a comprehensive discussion of the fertility potential of women undergoing UAE, in terms of pregnancy rates and complications as well as ovarian function and reserve. Findings indicate many benefits for women desiring fertility who undergo UAE over traditional myomectomy.

Key words: *Interventional radiology, uterine artery embolization, minimally invasive procedures*

Introduction

While several papers describe successful pregnancy after uterine artery embolization [UAE] (1–5), authors have questioned the wisdom of UAE as a primary treatment for women desiring childbirth. This review will focus on several points brought up by these authors. Included in this review will be a discussion of ovarian function after UAE, the long-term success of UAE in younger patients, pregnancy results after UAE, and potential benefits accruing to patients who choose UAE and fertility.

Women over the age of 40 have traditionally comprised the prominent age group affected by symptomatic myomata in terms of demographics (6). Indeed, many women learn of myomas while pregnant. We know that myomata are dependent upon estrogen, but know little else to explain this condition that exists in large numbers of women. Estimates of the incidence of myomas vary. However, general agreement would place the number of women suffering from myomata as being >40% of women over the age of 40 years (7). African American women have an even higher incidence, some studies showing this number to be as high as one in two women (7–9). This association may even be present prior to fibroids becoming symptomatic (10). We have less understanding of the frequency of myomata in younger women (11).

The practicing gynecologist will have numerous patients with myomata who present either as teenage girls (12) or young women in their 20s who desire future fertility. Conventional wisdom has been to treat women whose myomata present with symptoms such as menorrhagia, pelvic pain, or pressure (13). Women with asymptomatic myomata are encouraged to attempt pregnancy (14). In addition, data from clinics offering *in vitro* fertilization suggest that even women without symptoms would benefit from treatment of myomata to allow for fertility (15).

Ovarian function and UAE

Soon after the initial report of the success of UAE by Ravina et al. (16) authors noted the association of the onset of menopause in some women who had undergone the procedure (17). Other authors have noted similar findings (18). The mechanism of

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menopause was thought to arise from an anastomosis of the uterine arteries and the ovarian arteries (19). Yet, reports have linked early onset of menopause in women who underwent hysterectomy with the ovaries left *in situ* (20) suggesting another unknown mechanism. As a woman approaches menopause, some have speculated that the ovarian blood supply is more fragile in general (21).

Recent studies have looked at Anti-Mullerian Hormone [AMH] as a marker for ovarian reserve. Many studies suggest AMH as the best marker of ovarian reserve because it is directly related to primordial follicle numbers (22,23). As primordial follicle numbers decline over time AMH declines, therefore AMH levels correlate with age (24). Consequently, age-specific values available from studies of larger populations of women (25,26) are useful in verifying normal ranges. A word of caution here: AMH levels used in these studies are often obtained from women seeking assisted reproduction treatment (25). This population may contain different, yet unknown, factors from the general population. Moreover, we still have relatively few numbers upon which to base 'normal' values.

The measurement of serum AMH has been applied to a wide array of clinical applications, particularly for women seeking assisted reproduction. AMH levels within normal ranges may be used as a potential predictor of pregnancy (27) and AMH assays have been used as a clinical marker for a variety of different pathological conditions of the female reproductive organs (28). Infertility specialists have noted that low AMH may be a prognostic sign for infertility (29) and predictor of the menopause transition (30). Other hormones associated with ovarian function include follicle stimulating hormone [FSH] and Estradiol [E-2]. Fluctuations of FSH within the menstrual cycle are well known (31) as is the variation of this hormone in relation to the menopause (32). Previously FSH levels and E-2 levels have been used as markers of ovarian function following UAE. Multiple studies suggest no effect of UAE on these levels (33,34). These markers, however, provide information on the functioning of the ovary, and not on fertility potential in terms of ovarian reserve.

AMH levels are available for large numbers of women in their 30s and onward, and have become a 'gold standard' for measuring ovarian reserve. A paper from Hehenkamp et al. looked at women who had undergone UAE (35). Comparing this group to those who had not had UAE, diminished ovarian function was noted. This work has been one cited by authors resistant to UAE as a treatment for myomata in women desiring fertility (36). The authors noted in their paper that their cohort included primarily women in their 40s, a group 'relatively old compared to the population of women who have a desire for future pregnancy' (35). The authors noted in their paper that results might vary with younger patients in the reproductive age group from their older cohort. In a recently published study comparing laparoscopic myomectomy and UAE, investigators found a decrease in AMH after 12 months following UAE (37). Yet this finding was again noted in an older cohort of women, at an average age of 40.9 years in the UAE group.

A contrasting study on AMH levels in women <40 years old has been published (38). The report tracked levels of AMH in women six months after their UAE procedure. The results showed no significantly diminished level of AMH in comparison to reported age-specific AMH levels A follow-up to this study measuring AMH levels before and after UAE in women under 40 years of age found no significant difference in AMH levels before and after UAE (39). This report includes results on 27 women with an average age of 34.5 years. Despite the variety in AMH levels and ages in this cohort, 93% had AMH levels within normal ranges following UAE. Some articles suggest that there may be a subgroup of women with abnormally low levels of AMH. This subgroup is already at risk for infertility even without undergoing UAE (40). On rare occasions patients experience premature ovarian failure following UAE. Generally patients who experience ovarian failure are already past reproductive age and are approaching menopause. This occurs in approximately 7% of women undergoing UAE, almost exclusively in those over 45 years of age (41).

The question of fibroids and fertility potential still requires further research to solidify the body of literature surrounding the ideal UAE patient. Particularly, studies including a larger subject pool will allow researchers to determine generalized trends in AMH among women with fibroids undergoing UAE. One such study found lower AMH levels in women with leiomyomatosis (42), yet this study also included women older than reproductive age and a relatively small cohort (n = 30). Yet, women were paired by age in AMH comparison, providing some evidence that a significant difference in ovarian reserve may exist in women with fibroids. Further study of the reliability of AMH as a marker of ovarian reserve should be conducted to establish appropriate guidelines for fertility counseling, particularly in women undergoing fibroid treatment. A further longitudinal study following subsequent pregnancies in women with normal AMH following UAE should be conducted.

Success rates after UAE in younger patients

Overall, UAE has been shown to be a successful treatment for women with symptomatic myomata (43), with technique remaining the same regardless of location or size. Long-term results have revealed a 90% cure rate of myoma symptoms (44–46). Another article published results which indicated less beneficial rates in younger patients (47). However, in a recent study, 104 women <40 years old with myomata were treated using UAE. The range of time of treatment to survey was from six to 40 months. Success rates remained the same as with the general population we have treated. When comparing this younger population to other studies, this group fared equally well (18). The time of failure was consistent for most patients experiencing failure within six months, and only one reporting failure at two years. Thus patients did not experience a higher likelihood of failure over time (48). This short time to failure, and consistency of success of over time has been noted in other smaller studies (49). In this study Kaplan-Meier product limit analysis demonstrated a 93.3% success rate at six months post-UAE and a 91.2% success rate at 12 months to two years. The success rate then remained stable at 89.5% with no further failures at up to $11^1/_2$ years of follow-up.

Physicians should feel comfortable recommending UAE to younger patients, especially those desiring fertility due to long-term stability. This becomes more important due to the high recurrence rate (50) of myomas following myomectomy and the need for subsequent intervention (51).

Pregnancy after uterine artery embolization

Several papers have detailed series of women who have successfully given birth after UAE (1,2,52–55). One particular study looked at women who had become pregnant after the procedure (1). The study population included 44 women who were <40 years old and had indicated a desire for childbearing. Forty-eight percent of women who indicated a desire for children had successful pregnancies with term deliveries of healthy babies. Four women had two pregnancies, and one woman had three deliveries after UAE. In this group, no pregnancy showed growth retardation, fetal distress, or placenta accreta. There were no reports of uterine rupture. Five women delivered vaginally, and 66% percent of women preferred to undergo cesarean section (56). No complications were reported. This paper revealed successful pregnancies as long as 108 months after UAE. UAE candidates are thus not restricted in family planning to immediately after surgery, as is the case with myomectomy (Figure I). No regrowth of myomata was noted in the intervening years. The ability to delay conception is a strong argument in favor of UAE as a technique to preserve the uterus and fertility.

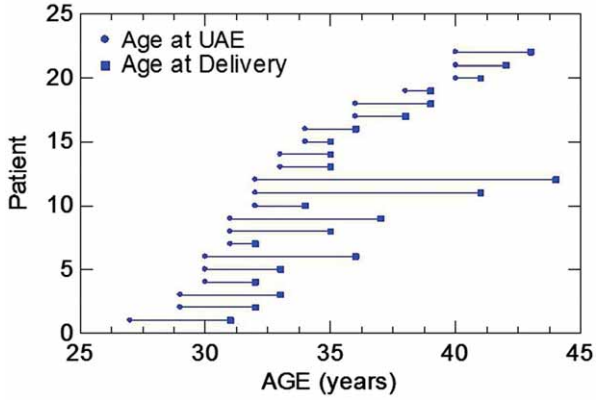

Figure I. Varying lengths of time between UAE and pregnancy. Pregnancies noted up to nine years following UAE.

Authors have listed complications of pregnancy after UAE as follows: increased rate of miscarriage, preterm delivery, intra-uterine growth restriction, mal presentation, abnormal placentation, and post-partum hemorrhage (57,58). Indeed, since UAE only shrinks myomata by 50%, we would expect a higher incidence of premature labor, and mal presentation, which are complications of pregnancy associated with myomata in general (59).

Comparison with myomectomy

We have seen that most of the theoretical considerations about the place of UAE in women desiring fertility remain minor. There are some important considerations favoring UAE over myomectomy in this group of women. First, we discuss the risks of myomectomy. More women undergo myomectomy than UAE. This is a substantial risk for someone desiring fertility. Also, known complications of myomectomy include adhesion formation, which may be a barrier to fertility. Adhesions surrounding the fallopian tubes and ovaries may impede the ability to conceive, and be a source of pain (60). If adhesions occur inside the uterus, causing synechia, the chance of pregnancy is greatly reduced (61). Blood loss and the need for transfusion are described as risks of myomectomy (62,63). For many women the abdominal approach with its four days in the hospital and six week recovery period constitutes a substantial risk (64). Laparoscopic myomectomy will reduce recovery time and incision size (65,66).

Risk of recurrence after myomectomy, whichever method is used, is a greater concern to younger patients. In the younger age group, more than 20 years from menopause, Reed et al. found that at five years, the age-specific cumulative incidence of a subsequent uterine surgery was greatest in women aged 30–34 years (38%), which increased to 44% at seven-year follow-up. The total incidence of repeat surgery is 20.2%, which included repeat myomectomy and hysterectomy (51).

Gynecologists will advise patients to take advantage of the 'golden period' of six months after myomectomy to attempt pregnancy. That will be the time when myomata are less likely to recur (67). Many younger patients are suffering from pelvic pain, and menorrhagia, which force them to seek surgical treatment. Not all of these women are in a relationship and desire immediate fertility. Thus, delaying pregnancy forces many into choices which conflict with their desire for immediate relief. Here, UAE offers significant advantages. That is to say the lack of new myomata gives patients the opportunity to be free of symptoms without the need for immediate pregnancy. Furthermore, pregnancy rates in UAE and myomectomy are comparable. Multiple studies have shown that women are able to become pregnant after UAE, with rates reaching up to 48%, and 46% following myomectomy (Table I) (1,68–74).

If a woman desires two children after traditional myomectomy, she may well be looking at two cesarean sections, and another myomectomy, and four laparotomies in the course of a few years. Not the road many women wish to travel, and with good reason. The risks of uterine rupture must be factored into this approach, as well as the higher incidence of placenta accreta (2). Despite other reports, we have not experienced any occurrences of abnormal placentation, no evidence of the uterus losing its integrity. In fact, placenta accreta is associated with myomectomy (75).

Comparison with other minimally invasive techniques

Recently magnetic resonance guided ultrasound therapy (MRgFU) has been used to treat fibroids non-invasively. Some studies have found that the incidence of follow-up treatment with MRgFU is comparable to other uterine sparing techniques, however lower rates of recurrence are seen in older women (46 years and higher) (76). In addition, this study found that follow-up treatment rates increased over time, 19% at 36 months and 23% at 48 months after MR-guided focused US, suggesting that additional long term studies may be necessary to confirm the reintervention rate.

A few case studies have noted successful term pregnancies following MRgFU, yet no long-term and large studies have confirmed an effect of MRgFu on fertility (77). A cumulative study on all pregnancies occurring after MRgFU reported on 54 pregnancies in 51 women worldwide, occurring an average of eight months following the procedure (78). This evidence is encouraging for women seeking fibroid treatment and fertility, yet the evidence of a higher reintervention rate in younger women and a lack of large long-term studies may suggest otherwise. At present, MRgFU may represent a fertility option similar to myomectomy, with a pregnancy 'golden period'.

Discussion

Embolization is a valid alternative to myomectomy for women desiring fertility, but not a perfect alternative to be sure. The long-term success of UAE in younger patients is comparable to the cohort of older women undergoing the procedure, suggesting that younger women may benefit equally from the procedure. As indicated by pregnancy results after UAE, fertility is possible with the procedure, and is not uncommon. With the smaller, but still present myomata, women may still be at higher risk after UAE for mal

Table I. Pregnancy rates in uterus sparing fibroid treatment techniques.

Group	Procedure type	Total patients	Total patient pregnancies	Term pregnancies	Pregnancy rate
Lissoni et al.	Abdominal myomectomy	8	3	2	25%
Sudik et al.	Abdominal myomectomy	67	39	31	46%
Acien et al.	Abdominal myomectomy	80	9	8	10%
Darai et al.	Laparoscopic myomectomy	70	17	11	16%
Dubisson et al.	Laparoscopic myomectomy	21	7	7	33%
Bernard et al.	Hysteroscopic myomectomy	119	11	9	8%
McLucas et al.	Embolization	53	29	22	39.6%
McLucas et al.	Embolization	44	29	20	47.7%

presentation and premature labor (79). Few women in this younger group experience complications that may affect fertility, such as ovarian failure.

In fact, younger women are at a decreased risk of ovarian failure following the procedure. Premature ovarian failure may be predicted in patients with low AMH (40), with measurement FSH and E-2, other markers of the menopause transition. AMH is the new gold standard of fertility potential in patients undergoing assisted reproduction (80) and has emerged as an important marker in fertility research in women undergoing UAE. Larger longitudinal studies of younger women with normal AMH undergoing UAE may provide more conclusive evidence supporting UAE in this younger cohort. As of now, evidence suggests that UAE does not affect AMH levels in women of reproductive age (38).

Yet, UAE offers some benefits to younger patients that myomectomy does not. UAE treats fibroids noninvasively, leaving the uterus intact. Although UAE may pose the risk of inadvertent non target embolization of the ovarian circulation (81), this complication is rare. Younger women in particular may benefit from UAE over myomectomy, because the risks of recurrence associated with myomectomy are nonexistent. Thus women may not need to plan their conception within the six-month period following surgery. The symptoms of fibroids will be cured, and family planning will not be limited to a small time window.

A potential alternative for women desiring fertility with larger fibroids may be a combination of UAE and myomectomy. Some argue this combination inserts two procedures where one may do, but often UAE may facilitate a less invasive procedure where one may not normally be offered (82). Abdominal myomectomy may be offered in the two weeks after embolization to two specific groups of patients. The first is older nulliparous women who may not want to wait six months to learn that shrinkage was not enough to safely carry a pregnancy (83,84). The second group are women with a larger uterus, greater than the size of an eighteen week gestation, who will not likely have a small enough uterus to carry a pregnancy (85). Although a second procedure is performed, ultimately the younger patient will benefit. Firstly UAE and myomectomy allows for a nearly bloodless field because of the recent devascularization secondary to UAE (86). The second is the 90% chance that no further myomectomy may be needed in the future.

Conclusion

UAE is a valid minimally invasive alternative to myomectomy for women desiring fertility, with some caveats. Proper fertility counseling and assessment should be made prior to UAE to ensure that the patients' fertility goals have the best chance of being achieved.

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