Impact of previous uterine artery embolization on fertility

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Purpose of review
To describe data on the effects of uterine artery embolization (UAE) on fertility.

Recent findings
UAE is used to treat postpartum hemorrhage (PPH) and fibroids. This effective therapy is replacing surgery in many cases. One of the main goals of UAE is to preserve the uterus and therefore fertility (pregnancies, menses and ovarian reserve). Pregnancies after this technique have been described. The main complications encountered during these pregnancies are not only PPH but also miscarriages and cesarean deliveries after UAE for fibroids. Conflicting results varying from completely well tolerated to serious complications such as definitive negative effect on endometrium and ovary function have been reported. Nevertheless, the series differ in that they included women of different ages and used different material for vessel occlusion (definitive microparticles of varying sizes, temporary pledges of gelatine sponge, etc.). We discuss the impact of these differences on uterus vascularization and fertility.

Summary
UAE is an effective treatment for PPH and fibroids. Pregnancy is possible after UAE. Recurrent PPH is a serious and frequent complication. Synechia is also a potential complication. Desire of childbearing should be considered when choosing embolization or surgery and, in case of embolization, the choice of material used. Further studies on future fertility after UAE are needed as well as information on fertility after surgery.

Keywords
embolization, fibroids, postpartum hemorrhage, pregnancy

Introduction
Uterine artery embolization (UAE) is a vascular radiological technique used to treat postpartum hemorrhage (PPH) \cite{[1–3]} and uterine myomas \cite{[4,5]}. It constitutes a conservative treatment designed to keep the uterus intact. Now, it remains to demonstrate that fertility is really preserved after treatment. This step must take into account that different embolic materials are used depending on the type of treatment: temporary embolotherapy (pledgets of absorbable gelatine sponge, or nonbovine sponge, etc.), and definitive vascular occlusion (microparticles of several sizes, coils, etc.). These materials could potentially have a different impact on uterine and ovarian vascularization.

Literature reports conflicting results on preservation of fertility after UAE \cite{[6–26]}. The goal of our discussion is therefore not only to collect published results but also to point out study limitations which could introduce biases and give misleading conclusions and possibly explain the disputed results.

Embolization for postpartum hemorrhage
PPH is one of the first causes of maternal mortality \cite{[27]}. Once the woman’s life is no longer in danger, if bleeding persists the medical goal is obviously to stop the hemorrhage while preserving the uterus. Obstetricians can opt for conservative surgical options and/or UAE. Although there are no randomized trials comparing these options, embolization of the uterine or other local arteries seems to be highly effective \cite{[1–3]} and to have substantial advantages over surgery.

Techniques
Embolization of pelvic arteries needs a trained radiologist \cite{[2,3,24]}. A unilateral right femoral approach is used and a 4 or 5-French femoral arterial introducer inserted. Initial aorto-iliac angiography is performed to detect the site of bleeding from the pelvic arteries and contralateral internal iliac angiography is then performed. The ipsilateral internal iliac artery and uterine artery are catheterized with the same catheter and via the same puncture
site. Highly selective catheterization of vaginal or ovarian arteries is performed when necessary. Artery occlusions are performed with pledges of absorbable gelatine sponge or nonbovine sponge, or in few cases with definitive material.

Indications
The main indications [28,29] of UAE are PPH after vaginal deliveries, persistent mild bleeding after caesarean and late bleeds [30] as well as some cases of vaginal and cervical trauma when local surgery fails to stop bleeding [28]. Nevertheless, not all patients can benefit from embolization therapy as hospitals with maternity are not always equipped with the necessary specific radiological materials and a vascular radiologist is not always available. Cases of massive hemorrhage with severe shock status [28] and most hemorrhages occurring during caesareans must be treated by surgical procedures.

Efficacy
With a high success rate [1–3], surgery after embolization failure is a rare entity, whereas radical surgery following ineffective conservative surgical therapy is a regular second step. For these reasons, there is now a growing body of literature promoting embolization techniques over surgery except for contraindicated situations [2,28,29].

Fertility after uterine artery embolization for postpartum hemorrhage
Some medical teams have contacted their patients who underwent UAE for PPH to determine whether they desired further pregnancies, the occurrence of pregnancies and sometimes information of the presence and quality of menses.

Pregnancies
The main publications on pregnancies are listed in Table 1. The most frequent reported complications in pregnancies following UAE are PPH [10–12,18,21,23,24,31]. Only three cases of fetal growth restriction were found in the literature [18,32]. Moreover, uterine artery Doppler waveforms were evaluated in two series [12,21] and were normal.

Menses
Bouilleret et al. [11] reported that 91% of the 23 contacted women resumed normal menses and Salomon et al. [10] and Eriksson et al. [31] reported that all the women resumed normal menses but authors [10,11,31] did not indicate if the patients were taking oral contraceptives or not. In the series by Chaulier et al. [18], eight women who used levonorgestrel-releasing intrauterine device or levonorgestrel contraception reported less abundant or more irregular menses, whereas the 33 others resumed normal cycles and menses though we do not know if they were taking estrogenprogestative contraception. Fiori et al. [21] reported regular menses in 30 out of 33 patients (91%) and 14 of whom were on oral hormonal contraception, 6 had an intrauterine device, 1 had an etonorgestrel implant and 9 no contraception. Results from the series of Sentilhes et al. [24] were different as 15 cases (22%) of amenorrhea or decreased flow of menstruation were found in the 68 women, 11/58 in the group UAE alone and 4/10 in the UAE and surgical devascularization group. Synchaecia was found in 8 of the 15 cases. Gaia et al. [23] found that 23 women out of 107 reported oligomenorrhea and 6 amenorrhea, 3 of whom had been embolized using Curaspon powder for UAE for PPH. It is worth noting that the two last authors used microparticles and microcoils for Sentilhes [24] and, for Gaia et al. [23], Curaspon powder. Gaia et al. [23] noted a link between these materials and the occurrence of synchaecia. The 11 women who could not conceive in the Gaia et al. [23] series had synchaecia and/or oligomenorrhea.

Embolization for uterine myomas
Uterine myomas (fibroids) are common benign tumors often found in women of childbearing age. Their location, number, and kind of complications require care and determine the therapeutic strategy. Hormonal treatment and/or surgery were the cornerstone of treatment up to 1995.

Table 1. Pregnancies after uterine artery embolization (UAE) for postpartum hemorrhage (PPH)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Number of patients treated with UAE</th>
<th>Number of contacted women</th>
<th>Number desiring to conceive</th>
<th>Number of pregnant women</th>
<th>Number of pregnancies (all)</th>
<th>Number of pregnancies with babies</th>
<th>Number of abortions</th>
<th>Number of recurrent PPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ornan et al. [9]</td>
<td>28</td>
<td></td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Salomon et al. [10]</td>
<td>28</td>
<td>17</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>4M</td>
<td>2</td>
</tr>
<tr>
<td>Bouilleret et al. [11]</td>
<td>35</td>
<td>23</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1VA</td>
<td>0</td>
</tr>
<tr>
<td>Descargues et al. [12]</td>
<td>31</td>
<td>25</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>3M + 1VA</td>
<td>0</td>
</tr>
<tr>
<td>Eriksson et al. [31]</td>
<td>41</td>
<td>20</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>5 + 2 premature</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chaulier et al. [18]</td>
<td>41</td>
<td>37</td>
<td>16</td>
<td>16</td>
<td>19</td>
<td>18 (2 twin)</td>
<td>1M</td>
<td>1</td>
</tr>
<tr>
<td>Gaia et al. [23]</td>
<td>113</td>
<td>107</td>
<td>29</td>
<td>18</td>
<td>19</td>
<td>18 (1 twin)</td>
<td>1M</td>
<td>3</td>
</tr>
<tr>
<td>Fiori et al. [21]</td>
<td>56</td>
<td>34</td>
<td>2</td>
<td>13</td>
<td>20</td>
<td>12</td>
<td>4VA + 3M + 1EP</td>
<td>1</td>
</tr>
</tbody>
</table>

EP, ectopic pregnancy; M, miscarriage; VA, voluntary abortion.
*Including 10 UAE associated with surgical devascularization.
However, medical treatments have limited effects, and conservative surgery weakens the uterus and delays time of conception. Embolization has thus since emerged as a preferred option and constitutes a new and ‘elegant’ treatment to replace or delay surgery [4,6–8,33,34].

**Techniques**
The main difference between the various protocols currently practiced resides in the choice of material used to obstruct the vessels. Initially, after identifying the uterine vessels by angiography, they were obstructed by nonresorbable microparticles of various sizes [5,16,20,22]. The problem is that these small particles can enter the endometrial arteries causing ischemia with risk of amenorrhea, synecchia or, even ovarian failure if they pass into the utero-ovarian anastomoses [5,13,25,26,33,35–37]. Some teams have therefore recently been using other nonresorbable materials composed of microspheres (Embospheres) which are greater than 500 μm [20,22], to better preserve endometrial and ovarian vascularization. Others prefer to use resorbable materials [38]. Whatever the technique used, embolization causes fibroid ischemia and often leads to pain which has to be treated with pain relief, locoregional anesthesia and sometimes hospitalization.

**Indications**
Uterine fibroids can cause metrorragia or menorrhagia, or pelvic-compression symptoms [39]. These signs might necessitate UAE therapy if medical treatment fails. However, the theoretical or real alteration of endometrial vascularization cast doubts on the risk of secondary infertility and, until recently, a desire of childbearing was a contraindication for embolization [34,40] even though it was still performed in these women. In addition, submucous fibroids surgically accessible by endoscopy are still not an indication for embolization [39]. Similarly, subserous fibroids constitute a contraindication for embolization due to the risk of septic necrobiosis.

**Efficacy**
Considering the different materials used and the varying indications and contraindications applied by one team and another, caution must be applied when comparing published success rates. Furthermore, follow-up is most often short. However, results tend to demonstrate at least the short-term efficacy of embolization in the treatment of fibroids [4,5,19].

**Fertility after uterine artery embolization for myomas**
We have done a literature search on pregnancies following UAE for myomas, and we have also looked for information on menstruation patterns and hormonal follow-up tests.

**Pregnancies**
As a measure of precaution women presenting with fibroids who have a desire for children are not generally eligible for embolization [34]. Thus, there are few studies reporting on subsequent pregnancies. Moreover, it is sometimes difficult to know how many women in these series wanted children. The main studies are reported in Table 2. One large study [13] compiled data from 53 pregnancies after UAE and 139 pregnancies after myomectomy by laparoscopy and showed a higher risk of preterm delivery, malpresentation and caesarean delivery in the UAE group.

**Menses, ovarian preservation**
One case of endometrial atrophy after use of 150–250 μm microparticles was reported by Tropeano et al. [25]. Hegenkamp et al. [26] compared 88 women after UAE and 89 after hysterectomy (H) with a follow-up of 24 months. He measured anti-Mullerian hormone (AMH) and follicle-stimulating hormone (FSH). FSH levels (n = 88 UAE–86 H) increased significantly in the two groups, whereas AMH values (n = 30 UAE–33 H) decreased until 6 weeks after treatment. In the surgery group they then recovered to expected values and remained that way until the end of the follow-up, whereas in the UAE group AMH values remained significantly low after a slight initial recovery. Tropeano et al. [41] evaluated 36 women by hormonal testing after UAE. He reported only one case of changes in menstrual characteristics: irregular cycles (in a woman aged 38 years) and a significant increase in FSH and estradiol levels but not significantly more than hormonal follow-up of a group of 36 matched control women. Mara et al. [42] evaluated FSH levels in 30 women at between 6 and 17 months after UAE, and compared the values with those of 33 women having undergone myomectomy. He found no difference between the two groups.

**Discussion**
With a 90–100% [1–3] success rate in stopping bleeding in women with PPH, the effectiveness of UAE is indisputable. It has largely replaced conservative surgery which only has a proximal action (in ligaturing hypogastric arteries) or semi-distal (other techniques of arterial ligatures). Surgery for fibroids can weaken the uterine wall, whereas UAE for fibroids is effective [4–8,34] and even if efficacy might only be temporary it should allow enough time for pregnancy before surgery. However, UAE could also have a negative impact on further fertility. An important point which differs from study to study, is the material used and this has a strong impact: the smaller the particles the higher the risk of occlusion of the...
endometrial and ovarian arteries. Indeed, smallest polyvinyl alcohol particle emboli have been identified within the cervix, uterine body and adnexa after some cases of radical surgery following UAE [43]. The probable cut-off for material size is 500 μm. For temporary material, Curaspon powder could have the same impact as smallest microparticles [23].

In the few studies evaluating fertility after UAE the number of pregnancies is low [6,7,9–17,19–24,31]. It is likely, however, that the real number of pregnancies is underestimated. Indeed, the ideal evaluation of fertility is the number of subsequent pregnancies and, for various reasons, most women included in the studies mentioned above did not want to become pregnant. One obvious reason is that women with fibroids who desire children are not eligible for UAE [34]. Finally, women having experienced PPH requiring embolization and extensive medical management are generally deeply affected by the possible risks that they entail by subsequent pregnancies and thus hesitate before becoming pregnant again.

This means that teams wishing to evaluate fertility need to adopt an indirect approach by enquiring about the abundance and regularity of the menses. Most studies report no change in menses or cycles [10,11,18]. However, they do not provide any details of estroprogestative contraception making it likely that a certain number of cases are due to withdrawal bleeding rather than real menses and it is thus difficult to draw any conclusions as to the possible presence of ovarian failure.

Reported pregnancies after UAE for PPH are often described as normal until delivery. Two series underlined that uterine artery Doppler waveforms were normal during the pregnancies [12,21], and few cases of fetal growth retardation have been reported [18,32]. One frequent complication after UAE for PPH is the risk of PPH with sometimes serious consequences [10,18,21,23,24].

The risk of infertility after UAE for fibroids is not known. The few pregnancies obtained after UAE for fibroids seem to be complicated by miscarriages, preterm deliveries, abnormal placentation, cesarean deliveries and PPH [16,17,20,22], though these are complications which could also be expected with a myomatous uterus even without treatment [40]. Nevertheless, as these complications could be a consequence of the procedure they must be clearly evaluated in further prospective trials.

Several authors have described synechia as a complication of UAE most often after placenta accreta, and/or the use of the smaller microparticles or Curaspon powder [23–25]. All these materials can potentially reach and obstruct endometrial vessels due to their size. Synechia is
suspected to cause amenorrhoea, oligomenorrhoea and infertility. This opens the question of a systematic diagnostic hysterectomy a few months after UAE to check the integrity of the uterine cavity. We would suggest that a diagnostic hysterectomy should be performed in the case of amenorrhoea, oligomenorrhoea, but also before pregnancy as synchiae could be a risk factor for secondary PPH.

Some series evaluated ovarian reserve after UAE for fibroids by hormonal testing before and after UAE but the results are conflicting and the series have limitations [19,26,36,37,41,44]. There are some reassuring conclusions despite the use of particles smaller than 250 μm but with a short follow-up [42], and without measuring AMH which is more sensitive than FSH. Other results are more worrying [26] as they show loss of ovarian reserve in a population of women with a mean age of 44 years at UAE. However, a more recent study by Tropiano et al. [41] did not demonstrate negative effects of UAE on ovarian reserve in a population of younger women (mean: 35 years). It is important to note that particles greater than 500 μm were used in cases of visible ovarian artery anastomosis in these two series ruling out the effect of the material used [26,41]. The patient’s age is often high, close to 40–44 years, with possible natural disturbances of menses. The hypothesis found in literature is that UAE could precipitate menopause in women aged over 40 or already in a premenopausal status [36,42,44]. Moreover, authors who compared UAE to surgery on the effects of ovarian reserve underlined that surgery has also negative effects [41,42]. This point should be taken into account when interpreting the negative impact of UAE. It is therefore possible that the impact of UAE on fertility is no more negative than that of surgery when appropriate sized particles are used to avoid endometrial lesions.

However, even if it has been demonstrated theoretically that UAE for fibroids using particles greater than 500 μm preserves fertility, there is insufficient evidence to confirm this hypothesis. The use of a solid temporary material such as Curaspon or gelatin sponge for fibroid treatment by UAE could be safer for patients who desire to have children. We would like to stress though that, in all cases of UAE for PPH, the vascular radiologist should avoid using microparticles as the emergency context leaves no room for a meaningful discussion with the patient about further pregnancies.

**Conclusion**

Recurrent PPH is one of the most serious and frequent complications of pregnancies after UAE. Synecchia is a potential complication particularly in case of placenta accreta and, the use of small particles or of Curaspon powder. Therefore, we recommend systematic diagnostic hysteroscopy in case of menses disorder or before starting a pregnancy. Microparticles could induce a real risk of occlusion of endometrial and ovarian vessels. For this reason, except in prospective trials with a fully informed patient, their use is still inappropriate for women with a desire of childbearing. Due to the small size of published series, further studies on future fertility after UAE but also on fertility after surgery are needed to refine these conclusions.

**References**

Impact of previous uterine artery embolization on fertility  Berkane and Moutafoff-Borie  247


