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# Stealth Embolics for Uterine Fibroid Embolization

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**Summary**

Once fibroid ischemia is achieved by the blockade of the uterine arteries with particles, there is no longer the need for these particles which act as permanent foreign bodies in the uterus. They generate inflammation and will compromise the physiological adaptation of the uterine arteries during pregnancy. After having played their role, the particles have to disappear. The time for resorbable biomaterials has come. Promising degradable microspheres are being developed from various biomaterials such as oxidized carboxymethylcellulose combined with chitosan (OCMCC), poly(lactic-co-glycolic acid) (PLGA), saponified poly(vinyl alcohol) (PVA), poly(ethylene glycol) (PEG) hydrogel cross linked with hydrolyzable bridges. They generate more or less inflammation according to their speed of degradation. Their potential to achieve a satisfactory necrosis of the fibroids and a full artery recanalization will be discussed.

## Introduction

Uterine artery embolization (UAE) consists of blocking the blood flow of uterine arteries with small particles in order to necrotize the fibroids (leiomyomas) present in uterus. UAE has been offered initially to a majority of women over the age of 40 at the time of treatment, i.e. to a population of women generally not interested in future pregnancy. UAE is now commonly proposed as an organ preserving treatment to the population of younger women willing to conceive. It has been proven, in a large cohort of women wishing to conceive before embolization, that complete pregnancies can occur after UAE [1]. However, reduction of pregnancy duration, cases of small for gestational age and high rates of spontaneous abortion have been reported in women trying to conceive after UAE [1-5]. Collateral damages to the uterus or ovaries during UAE have been recognized as responsible for these fertility disorders. Multiple lesions such as uterine necrosis, synechiae, ovarian necrosis, have been observed [6-9]. Surprisingly, the embolization particles have not been considered to be responsible for deleterious physiological effect, besides their mechanical role as occlusive agent. In fact, the particles could play a major role in post-UAE fertility disorders by themselves since they induce a durable inflammation in the uterus and impair the recovery of uterine arteries.

### Durable inflammation

Embolization particles are foreign bodies which provoke a prolonged, even mild inflammatory response in the uterus, with potential deleterious effects, such as early miscarriage.

Within seconds after embolization, particles are recognized as foreign bodies; the innate non humoral immune system is immediately activated. Despite their small size, embolics can develop by their number a large surface of activation. For example, 1 ml of microspheres sizing 100 µm diameter contains about one million of beads which develop a total surface of about 315 square centimetre (48 sq.in). Moreover this geometrical surface may be increased hundred or thousand times by the porosity of the material.

This foreign body inflammatory response (FBIR) develops on all embolics, as any other foreign body, and can last months or even years. It rapidly triggers the release of a number of interacting mediators, such as histamine and serotonin, cytokines, bradykinins, leucotriens, prostaglandins (derived from cyclo-oxygenases COX 1 & 2) which sensitize the receptors of the pain pathway (or the sensory receptors) and contribute to hyperalgesia. It therefore contributes to post-embolization pain usually reported by patients and leads to prolonged hospital stay.

Increased levels of cytokines, tumour necrosis factor alpha, interleukin-2 or interferon-alpha, have been shown to be responsible of embryo mortality [10-12], and could explain the low fertility observed in embolized animals [13] and in humans [1-5].

### Impaired uterine arteries

The long-term evolution of embolized vessels may be of major importance for the recovery of a complete uterine arteries functionality, particularly in case of pregnancy. It is known that during pregnancy, the number and diameter of visible uterine arteries and branches increase [14-17] together with uteroplacental blood flow delivering nutrients and oxygen for foetal and placental growth [18]. Cases of intra-uterine growth retardation have been reported after hypogastric artery ligation [3,19] and after UFE [4,20]. The reduction in uteroplacental blood flow by means of ligation [21], clamp [22], occlusion [18,23,24] or embolization [25,26] significantly affects foetal and placental weight.

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The embolics could act as durable obstacle in the UA, disturbing the physiological variations of the diameter that occur during the hormonal cycle and pregnancy, explaining possibly the cases of growth retardation observed in animal and human. In sheep, a high rate of low weight at birth (80%) was observed after complete and bilateral embolization of uterine arteries with poly (vinyl-alcohol) particles [13]. It was clearly related to chronic inflammation and fibrosis around the particles in the uterine arteries [27]. In humans, the percentage of newborns small for gestational age is lower: 22% in Pron's study [1], 14% in Kim's study [22] and 7% in Goldberg's [28], probably due to less extensive embolization than in animal.

Finally, after UFE, the presence of low weight at birth could result from a durable impairment of the uterine arteries to adapt their flow to the foetal growth.

## The time for stealth biomaterials in UFE has come

Once fibroid ischemia is achieved, there is no longer any need for a permanent foreign body in the uterus, since if it remains it will generate a FBIR and compromise the physiological variations of the diameter of the uterine arteries during pregnancy. After having played its role, the embolic must disappear.

Degradable materials on the market are represented by gelatin sponge and collagen-coated PLGA microsphere. Gelatin sponge particles (GSP) are prepared by hand cutting of gelatin foam sheets. Their degradation lasts from 3 weeks to 4 months [29-31] and is accompanied by a chronic inflammatory response [29,32]. Collagen-coated PLGA microspheres (Occlusin™500, IMBiotechnologies) degrade slowly, in several months *in vivo* [33]. Sheep uterine arteries embolized with PLGA microspheres remained fully occluded by fibrous connective tissue at 6M. Actually, the degradation time of these particles is long and associated with vascular damage, chronic inflammation and remodelling which could delay and limit recanalization.

During the past years, a few research teams aimed to develop embolization microspheres having a controllable degradation time. Shomura developed saponified PVA microspheres whose time of resorption, which depends from their degree of saponification, ranges between 30 min for the shortest to a few hours [34]. Nitta developed gelatin microspheres which are degraded by enzymatic hydrolysis in weeks or months [35]. Weng has proposed microspheres made of a combination of oxidized carboxymethylcellulose and chitosan (OCMCC) which degrade *in vitro* by the share action of lysozyme and the hydrolytic cleavage of the crosslink bonds in 6h to 31 days according to composition [36]. The ability of OCMCC and gelatin to be degraded without inflammation is questionable since, as natural polymers, their degradation is governed by an enzymatic process, which is long and linked to inflammation. In these conditions a full and programmable recanalization could be impossible with them.

## A stealth biomaterial

Our team hypothesized that a degradable embolization microsphere should be fully degraded before the onset of a FBIR to guarantee a full recanalization with minimal or no residual arterial damage. To achieve this effect, we sought for a biomaterial which could degrade completely and quickly, by hydrolysis only, without any implication of enzymes. We synthesized degradable embolization microspheres (REM) from a poly(ethylene glycol) (PEG) hydrogel crosslinked with hydrolyzable bridges which are fully degraded by hydrolysis *in vitro* and *in vivo* in 24 hours [37]. These REM were tested in sheep uterine arteries vs. a non degradable microspheres as control, a Gold Standard for UFE [38]. After one week, there was a complete recanalization; the angiographic aspect of the uterus was similar to pre-embolization, both in terms of arterial flow and uterine parenchymography [38]. There was no structural alteration of the arterial wall of vessels. No residual microsphere and no inflammation were seen in REM-embolized tissue, presumably thanks to the rapid hydrolysis of the PEG biomaterial, which confirms previous *in vivo* findings [37,39]. Conversely, with non degradable control, there were arterial blood flow reductions and defects of parenchymography and a limited FBIR comprising macrophages, neutrophils, and foreign body giant cells was observed around non degradable control microspheres, as previously described [40,41].

The absence of FBIR, consistent with the complete disappearance of the material in tissue, clearly distinguishes REM from all other embolics. That no FBIR takes place with REM is an improvement over existing embolics, as well non-degradable as degradable agents such as gelfoam, since it circumvents the chronic inflammation which contributes to the post-embolization syndrome.

## Will stealth microspheres be efficient on fibroids?

The main question arises now about the efficacy of such degradable microsphere: "Is the occlusion time induced by these PEG microsphere sufficiently long to induce an ischemia of the fibroids and their complete necrosis?"

It is commonly admitted that the fibroid are sensitive to ischemia and that a necrosis can be obtained after a reduced blood perfusion of the tissue for a short duration of time. It is established that the immediate reduction in fibroid perfusion after bilateral UFE correlates with uterine fibroid necrosis and with the favourable clinical outcome several months later [42-44]. However, the time of occlusion required for getting a fibroid necrosed is not strictly defined. Scarce information come from the temporary uterine arteries (UA) occlusion by Doppler guided trans-vaginal clamp, a technique which has been proposed as a surgical alternative to UFE [45-47]. The clamp time varies from 5 to 7 hours according to the series [45-47]. Temporary clamp of UA (5 to 170 min) generates after 5 to 170 min a pH drop in uterus, associated to pain, which attests to anaerobic metabolism [46]. Lichtinger observed by laparoscopy that a bilateral UA transient clamp during 26 min (10-59 min) resulted in a complete blanching of the uterus, which was reversible at clamp opening [48]. From these data, we can hypothesize that the minimal duration for achieving a non reversible ischemia should be of a few hours.

In the sheep uterine model, we found that there was similar degree of uterine necrosis in myometrium and endometrium after embolization with REM and non degradable control. This suggests that the duration of arterial occlusion with REM was sufficient to achieve an ischemic necrosis [38]. Since this uterine necrosis is not very different from that of Gold Standard control group, one can expect that the ischemic time induced by REM will be sufficient to cause the necrosis of the fibroids.

The efficacy of REM on fibroid necrosis and UA recanalization shall now be estimated with clinical trials.

In the future, as a complement to its ischemic action on the fibroids achieved by UA occlusion, REM could be loaded to deliver locally a non-steroidal anti- inflammatory drug in the aim to inhibit the proliferation of fibroid cells which is activated by prostaglandins [49]. Such a local delivery of NSAIDs from microspheres in an ischemic tissue releasing pro-inflammatory mediators could also be used to reduce the post-embolization pain.

To conclude, embolization particles for UFE are not satisfactory since they generate a chronic inflammation in the uterus and a durable dysfunction of uterine arteries which compromise fertility and foetal growth. Resorbable embolics are to date promising alternative products which should theoretically reduce or suppress these inconvenient. Clinical trials should assess whether they are actually as efficient as the non degradable materials, and safer than them in terms of fertility and foetal growth.

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