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.

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, leukotriens, 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.
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 microspheres. 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-inflamatory 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.

References

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