

Impact of Uterine Fibroids on Fertility: Still much to Investigate

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Uterine fibroids (UFs) are the most common uterine pathology in women, often show symptoms that negatively affect the quality of life, extending their negative influence also to the female fertility [1], for distortion of uterine cavity and impairment of muscle contractility and impairment of muscle contractility [2]. The UFs evaluation during infertility work up or in preparation for assisted reproductive technology can present a perplexing problem for patients and their providers, especially when fibroids appear to be asymptomatic. The concern is well deserved, since unnecessary surgery for UFs exposes the patient either to risks of future caesarean section to avoid uterine rupture risk during labor and delivery [3], or in adhesion formation that may reduce fertility if adhesions compromise the tubo-ovarian relationship [4]. Anyway, it is difficult to determine the direct UFs impact on fertility, since their incidence increases with age and fertility declines with age [5]. Nevertheless, women with UFs conceive and delivery spontaneously. For this reason and also for other, the choice of surgery for the UFs removal is very delicate. Failure to perform surgery for UFs could impair spontaneous conception or compromise outcomes of fertility treatments or increase the risk of miscarriage and pregnancy-related complications [6].

The UFs location is important in determining the impact on fertility: UFs could impair fertility distorting the uterine cavity, altering the endometrium, and impairing embryo implantation and growth [7]. Sometimes we should include also causes of UFs-related infertility by mechanical obstruction of the tubal ostia [8]. Submucous UFs directly impair fertility and cause adverse reproductive outcomes distorting uterine cavity and endometrium, altering the vascular supply and development of the endometrium (as intramural myomas) or changing growth factors and producing inflammatory substances that may

impair implantation or fetal growth [8]. Submucosal UFs clearly reduce IVF pregnancy and birth rates, and hysteroscopic myomectomy significantly improves pregnancy rates [7]. Also intramural UFs fertility, especially when intramural myomas are 4 cm or larger, and myomectomy appears to restore fertility; in these cases, an endoscopic myomectomy is not clear whether or not the fertility significantly improves [8,9]. The effect of medium and large intramural UFs on IVF outcomes is unclear, and most studies have shown little clinical effect. Subserosal UFs do not appear to affect fertility [8]. Then there is the problem of many patients with fibroids, contemporary positioned in different uterine zone. In these cases, it is absolutely impossible to predict with certainty the direct impact of the various UFs on fertility, so as the relative usefulness of myomectomy on fertility outcome [8,9]. From what has been said in literature, the problem of understanding the UFs impact on fertility is still far from being fully acquired.

Many researches rightly focused on the genetics of UFs, on surgical and pharmacological management, on minimally invasive therapy of fibroids [10,11].

Few investigations focused on the interaction UFs-uterus, on the biological impact of UFs on myometrium, on the biological basis of methods of early and late UFs removal and its consequences, on the problem of uterine healing and scar after myomectomy. Analyzing UFs problem "step by step", it starts from the genesis of the tissue: UFs are thought to be monoclonal tumors that occur via clonal expansion from a single mutated myometrial smooth muscle stem cell [12]. Estrogen and progesterone receptors are present in UFs, and both hormones stimulate fibroid proliferation [13].

UFs are surrounded by a dense fibroneurovascular pseudocapsule [14], a millimetric structure created by myometrium to cope with UFs growth. This

structure has similar architecture to normal myometrium but also contains different nerve fibers and neuropeptides, extremely important in muscular neurotransmission, in the vasculature regulation, in angiogenesis and in tissue regeneration processes [15-18]. It seems strange, but the mechanism of neurotransmission and neuro-vascular tissue and impact on uterine muscle has been poorly studied in the past in pregnant and non-pregnant women. Fibroid is poor of neurofibers and neuropeptides, myometrium is full of these, but the most interesting area for the high concentration of these in such a short structure is the pseudocapsule, as a neurovascular bundle [19]. UFs pseudocapsule is rich of: enkephalin (ENK) and oxytocin (OXT), neurotensin (NT) and protein gene product 9.5 (PGP9.5) and neuropeptide tyrosine (NPY), vasoactive intestinal polypeptide (VIP) and substance P (SP) [15-18]. All of these hormones are involved in a variety of biological processes, not only enhancing uterine contractility, and modulating pain trigger and social behavior, but also possessing antiinflammatory, antioxidative stress and tumorigenic properties. Particularly, they affect muscle contractility, uterine peristalsis and muscular healing and may be involved in the UFs pathophysiology [20].

Probably, pseudocapsule is created by uterus to preserve the integrity of muscular myometrium surrounding the UFs and to aid the successive muscular reconstruction of the damaged muscular tissue, as shown by the uterine scar quality exhibited by patients after laparoscopic myomectomy [21].

The UFs pseudocapsule has an anomalous vascularization, which is similar to malignant neoplastic tissue vessels present in malignant tumors [22]. Since pseudocapsule is characterised by a strong autonomic angiogenic profile [23], may be that it promotes uncontrolled stimulation of the pseudocapsule vessels, with increase of tortuosity, disarray, abnormal branching and the presence of "cul-de-sac" vessels, as in malignant tumors [22]. It is possible that this abnormal vascularity maybe helpful for fertility in uterine healing for a better scar after UF removal.

It is not yet clear, for example, the impact of submucosal myomas in the homeostasis of the micro-vasculature of the endometrium. A recent study analysed this structure in its thickness and location [24] by ultrasound and histology data matching on: subserosal fibroids (SSF); intramural fibroids (IMF) and fibroids near the endometrial cavity (FEC). FEC's pseudocapsules were considerably thicker than those of IMF and SSF measured by US and histology ($P = 0.001$). A clear cut-off existed between FEC pseudocapsule thickness and all other pseudocapsules, with significant differences observed at 2 mm ($P = 0.001$). Similarity between histological and US measurements was observed only with IMF pseudocapsules, whereas FEC or SSF showed significant differences. The pseudocapsule of fibroids is considerably thicker near the endometrial cavity when compared those of both intramural and subserosal fibroids.

Since fibroids closest to the endometrial cavity are the most involved in fertility and infertility [8,9] and fibroid pseudocapsule is considerably thicker near the endometrial cavity, it is possible to hypothesize a direct involvement of fibroid pseudocapsule near on endometrium on fertility and infertility. Moreover, another study [25] examined the presence of collagen IV and laminin in the pseudocapsule of UFs, to clarify different ultra-structural characteristics and their possible role in the UFs' management. In the blood vessels of the pseudocapsules, a reduction in laminin and increase in collagen IV with increasing diameter of UFs was noted. These proteins are related to loss of the basal membrane and to ageing of the tissue. The increase of collagen IV is linked to the increase of amorphous substance, including glycosaminoglycans and glycoproteins. Thus, the authors propose to remove UFs in women seeking pregnancy, before the myoma reaches a size causing compression (6 cm diameter) of the surrounding tissues, which results in the loss of regenerative potential.

Has not yet been established either the impact of hormonal patterns on UFs pseudocapsule, specially focusing on origin, growth and UFs recurrence, or the influence of drugs, embolospheres, and magnetic resonance-guided focused ultrasound on the pseudocapsule and their effects on uterine healing in function of the subsequent search of pregnancy. It was not yet analyzed the neurotransmitter changes in UFs pseudocapsule during women age, to better understand the pseudocapsule involvement in a hormonal environment and the relative involvement of the uterine muscle affected by UF, according to the patient age.

Another area of research should be directed to the understanding of the best treatment to be provided to a patient suffering from UFs. How to remove UF? By what means? Through which endoscopic technique? Nowadays there are hundreds of papers on traditional myomectomy or via laparoscopic, hysteroscopic and robotic approach. There are still no definitive elements to indicate what the best approach for subsequent fertility is. Reported evidences on neurofibers and neuropeptides in the UFs pseudocapsule suggest that the better way to remove UFs is by preserving their pseudocapsule, as a sort of "blood-less" [26,27] intracapsular nerve-sparing laparoscopic "microsurgery" [28] or intracapsular nerve-sparing robotic-assisted "nanosurgery" (in case of robotic magnification), with less postoperative adhesions [29,30]. A great advantage of intracapsular myomectomy is the reproducibility of its application for all myomectomies as a safe, feasible, and minimally damage technique [26, 27], and it can be reproduced also during cesarean section [31].

Thus, after scientific references extensively discussed, being the pseudocapsule thin myometrial tissue [32] containing neuropeptides and neurotransmitter, its preserving during surgery should allow, consequently, reducing myometrial damage during myomectomy, favouring the correct myometrial healing.

In author opinion, these topics should definitely and extensively be largely investigated, in relation to the great impact of UFs on fertility.

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