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The current place of medical therapy in uterine fibroid management

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A B S T R A C T

Uterine fibroids (also known as leiomyomas or myomas) are the most common form of benign uterine tumors. Current management strategies mainly involve surgical interventions, but the choice of treatment is guided by patient's age and desire to preserve fertility or avoid “radical” surgery. Surgical and non-surgical approaches include hysterectomy myomectomy by hysteroscopy, myomectomy by laparotomy or laparoscopy, uterine artery embolization, and magnetic resonance-guided focused ultrasound surgery.

The need for alternatives to surgical intervention is very real, especially for women seeking to preserve their fertility.

There is growing evidence of the crucial role of progesterone pathways in the pathophysiology of uterine fibroids, and the efficacy of long-term intermittent use of selective progesterone receptor modulators such as ulipristal acetate was recently demonstrated by randomized controlled studies.

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Introduction

Uterine fibroids (also known as leiomyomas or myomas) are the most common form of benign uterine tumors [1–5]. They are monoclonal tumors of uterine smooth muscle, thus originating from the myometrium [6,7]. They are composed of large amounts of extracellular matrix (ECM) containing collagen, fibronectin, and proteoglycans [6]. Leiomyomas occur in 50%–60% of women, increasing to 70% by the age of 50 [7]. In 30% of cases, leiomyomas cause morbidity because of abnormal uterine bleeding (heavy menstrual bleeding inducing anemia) and pelvic pressure (urinary symptoms, constipation, and tenesmus) [1,8].

Why we need new options [5,8]?

Fibroids are highly prevalent and represent a high health burden. Indeed, about 30% of women with leiomyomas requests treatment because of morbidities such as heavy menstrual bleeding, abdominal pain, pressure symptoms, and/or infertility [5]. Current treatments are mainly surgical and expensive. Among 600,000 hysterectomies performed each year in the USA, 200,000 are for fibroids, and health care costs for the management of leiomyomas were estimated to be over $2 billion per year [9]. The cost of therapy both to the health care system and women with fibroids must be balanced against the cost of untreated disease conditions, and the cost of ongoing or repeated investigations and treatment modalities [10].

The future of medical therapy

Evidence of the crucial role of progesterone pathways in the pathophysiology of uterine fibroids

To date, genetic and epigenetic factors, sex steroids, growth factors, cytokines, chemokines, and ECM components have been identified as being implicated in the pathogenesis of leiomyomas [2,3,11–14]. Of course, estrogen and progesterone and their respective receptors also have a very significant impact on leiomyoma growth [6].

The initial event that triggers the first stages of tumorigenesis nevertheless involves somatic mutations [6].

In the past, estrogen was considered to be the major growth factor in myoma development. However, already in the 1990s, a number of studies reported increased expression of both progesterone receptor A (PR-A) and progesterone receptor B (PR-B) in leiomyoma tissue [15,16] compared with adjacent normal myometrium. Higher proliferative activity, demonstrated by proliferating cell nuclear antigen and the mitotic index, was observed in leiomyomas during the luteal (secretory) phase [16]. Very recently, Tsigkou et al. showed that PR-B mRNA and PR-A and PR-B proteins were more concentrated in leiomyomas than in matched myometrium [17]. There is evidence from histological and pharmacological studies, that progesterone and its receptors play a key role in uterine fibroid growth [6,18–24]. Progesterone can cause rapid, membrane-initiated effects, independent of gene transcription, that alter the production of second messengers involved in cell signaling transduction pathways. Progesterone and growth factor signaling pathways are interconnected and govern numerous physiologic processes such as proliferation, apoptosis, and differentiation [6].

SPRMs and fibroids (Fig. 1)

Four members of the family of compound selective progesterone receptor modulators (SPRMs) have been investigated in phase II clinical trials: mifepristone, asoprisnil, ulipristal acetate (UPA), and telapristone acetate [1–20,25–28]. All were shown to decrease leiomyoma size and reduce uterine bleeding in a dose-dependent manner [5].

Having established the crucial role of progesterone in the growth and development of myomas, we can modulate the progesterone pathway by using SPRMs. SPRMs are synthetic compounds that exert either an agonistic or antagonistic effect on PRs. Their binding allows these receptors to interact with coactivators and/or corepressors, and this is further effected by the presence of coregulators in a

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