

**Review****HEALTHY AND PATHOLOGICAL CHANGES OF MYOMETRIUM:  
PREGNANT MYOMETRIUM, UTERINE FIBROIDS AND  
LEIOMYOSARCOMA****Pasquapina Ciarmela<sup>1\*</sup>, Soriful Islam<sup>1</sup>, Pasquale Lamanna<sup>2</sup>, Andrea Tranquilli<sup>3</sup>,  
Mario Castellucci<sup>1</sup>**<sup>1</sup>*Department of Experimental and Clinical Medicine, Faculty of Medicine, Polytechnic University of Marche, Ancona, Italy.*<sup>2</sup>*Obstetrics and Gynaecology Unit, Profili Hospital, Fabriano, Italy*<sup>3</sup>*Woman's Health Sciences Department, Polytechnic University of Marche, Ancona, Italy***RESUMEN**

El miometrio, la pared muscular del útero, puede modificar su misma masa y las propiedades celulares en el embarazo y también en los tumores como el leiomioma y el leiomyosarcoma. El leiomioma, dicho también fibroma, es un tumor benigno del útero y se considera como una de las causas más frecuentes de infertilidad en el período reproductivo femenino. El leiomyosarcoma, en cambio, es un tumor maligno y agresivo de la musculatura lisa uterina. La presente revisión discute las características generales del leiomioma y el leiomyosarcoma y los relativos tratamientos clínicos actualmente usados y además describe las características del miometrio normal en el embarazo.

**Palabras claves:** miometrio gravídico, leiomioma, leiomyosarcoma

**ABSTRACT**

The myometrium, the muscular wall of the uterus, can modify its mass and cellular properties in pregnancy as well as in tumor conditions such as leiomyoma and leiomyosarcoma. Leiomyomas, also known as fibroids, are benign tumors of the uterus, considered to be one of the most frequent causes of infertility in reproductive years of women. Leiomyosarcomas in turn, are rare aggressive malignant uterine smooth-muscle tumors. The present review is discussing the general features of leiomyoma and leiomyosarcoma with their current treatments and also discussing the characteristics of

normal pregnant myometrium and compare with leiomyoma.

**Kew words:** Pregnant myometrium, leiomyoma, leiomyosarcoma

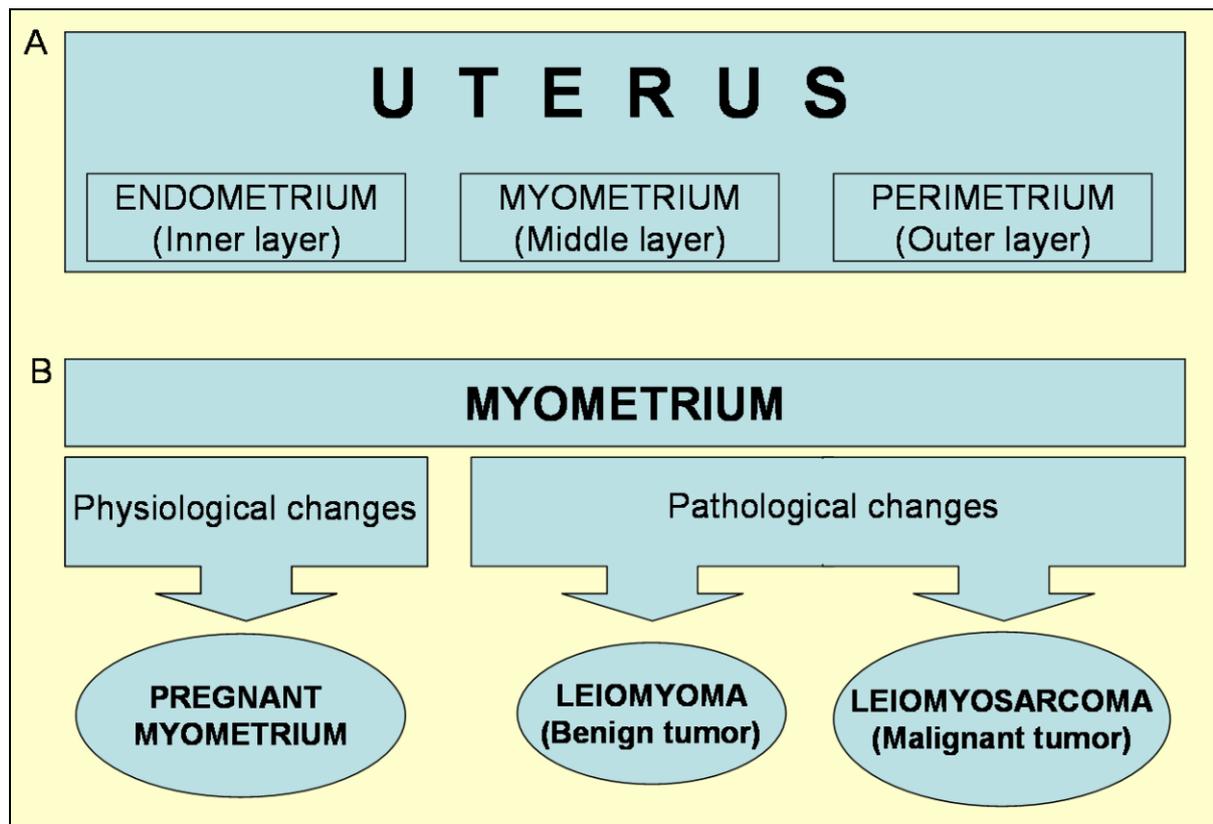
**INTRODUCTION**

Uterus is a muscular organ representing one of the major female reproductive sex organs providing a suitable environment for embryos during reproductive event. The *uterus* is made up of three different layers such as *endometrium*, *myometrium* and *perimetrium* (Fig. 1). The *endometrium* is the innermost layer of the uterus which has many simple tubular glands which, secretion create a special environment in the uterus that is conducive for development of the embryo.

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**Figure 1:** A. Different layer of uterus. B. Possible pathological and physiological changes occurring in myometrium.

There are several pathological conditions of *endometrium* such as adenomyosis (Tamai et al., 2005), endometriosis (Kennedy et al., 2005), endometrial cancer (Amant et al., 2005) and Asherman's syndrome (Yu et al., 2008). The *perimetrium* is the outermost layer of the uterus which has function of support. Myometrium is the middle layer of the uterus which is mostly composed of uterine smooth muscle cells. Its main function is to induce uterine contractions during labor. The *myometrium* undergoes significant changes in size and cellular properties in specific physiological and pathological conditions. The myometrium mass undergoes moderate changes during each reproductive cycle (Burroughs et al., 2000) and dramatic changes throughout pregnancy (Johansson, 1984; Shynlova et al., 2006) and menopause (Wu et al., 2000). Myometrial mass and cellular morphology are also modified in tumoral conditions such as leiomyosarcoma and leiomyoma (Matsuo et al., 1999; Walker and Stewart, 2005). Leiomyosarcoma is a relatively rare malignant tumor of uterine smooth muscle. On the other hand, uterine leiomyomas are

frequent benign tumors of *uterus* originating from myometrial tissue and have significant complications rate on women health in reproductive stage such as abnormal uterine bleeding, anemia and infertility. Despite the high prevalence and significant complications of these tumors on women's health, the etiology is incompletely understood. Consequently, therapeutic options are still limited.

### **PREGNANT MYOMETRIUM**

The uterine mass growth during pregnancy represents one of the most remarkable events in reproduction, with massive increase in both size and number of myometrial smooth muscle cells, to allow the growing *fetus* to have the necessary support. During pregnancy, the *myometrium* mass undergoes changes in cellular phenotype, characterized by an early proliferative phase, an intermediate phase of cellular hypertrophy, and a final contractile/labour phase (Shynlova et al., 2009).

Studies on contractile properties of uterine *myometrium* revealed different behaviour of muscle cells of upper and lower segment of uterine wall during gestation (Lye et al., 1998). Current opinion suggests functional regionalization of the pregnant *uterus* occurs with the lower segment displaying a contractile phenotype throughout gestation changing to a relaxatory phenotype at labor to allow passage of the fetal head, whereas the upper segment has a relaxatory phenotype throughout most of gestation to accommodate the growing *fetus* and adopts a contractile phenotype for expulsion at labor (Lye et al., 1998; Myatt and Lye, 2004). The reported studies on differential contractile characteristics suggest a topographic distribution in the different muscle layers of the myometrium (Myatt and Lye, 2004).

## LEIOMYOMA

Uterine leiomyoma (also referred to as myoma, fibroids, leiomyomata, and fibromyoma) are benign (non-cancerous) tumors originating from the smooth muscle cells of the *myometrium* of the *uterus*. Uterine leiomyomas are found in 20-40% of women during their reproductive age (Wallach and Vlahos, 2004; Ciarmela et al., 2011). Fibroids may be symptomatic or asymptomatic. The severity of symptoms typically depends on size, number of myomas, and tumor location.

**Symptoms:** The common symptoms associated with uterine leiomyoma are irregular and excessive bleeding, very heavy and prolonged menstrual periods, often cause of anaemia, pain in the back of the legs, pelvic pain or pressure, bowel and bladder dysfunctions, pressure sensation in the lower abdomen, pain during sexual intercourse, infertility and recurrent abortion, an enlarged abdomen which may be mistaken for weight gain or pregnancy (Walker and Stewart, 2005; Marsh and Bulun, 2006; Evans and Brunzell, 2007). These tumors tend to grow rapidly during pregnancy and can therefore cause obstructed labour leading to fetal malpresentation and fetal anomalies that often require a Caesarean section; as well as post-partum haemorrhage secondary to uterine atony (Walker and Stewart, 2005).

**Classification (locations):** According to the location, leiomyomas are classified as subserosal, intramural and submucosal (Krysiewicz, 1992; Murase et al., 1999; Ahmadi et al., 2008).

**Subserosal:** These fibroids develop on the outer part of the uterus, just under the covering of the outside of the uterus and continue to grow outward. Subserosal fibroids may also grow on a stalk and referred to as "pedunculated subserosal fibroid". These typically do not affect a woman's menstrual flow but can cause pain due to their size and pressure on other organs.

**Intramural:** This is the most common type of fibroids. These fibroids develop completely within the muscular wall of the *uterus*, which makes the uterus feel larger than normal. Symptoms associated with intramural fibroids are heavy menstrual flow, pelvic pain, back pain, frequent urination, and pressure.

**Submucosal:** Submucosal fibroid is the least common, but most often accounts for symptoms. A submucosal fibroid develops just under the lining of the uterine cavity. Some of these fibroids grow on a stalk. These are referred to as "pedunculated submucosal fibroid". These are the fibroids that have the most effect on heavy menstrual bleeding and the ones that can cause problems with infertility and miscarriage (Krysiewicz, 1992; Murase et al., 1999; Ahmadi et al., 2008).

**Classification (histological types):** Uterine leiomyomas present with different histological types such as usual leiomyoma, cellular leiomyomas, symplastic (bizarre) leiomyoma, haemorrhagic cellular (apoplectic) leiomyoma, lipoleiomyomas, vascular leiomyomas, leiomyoma with haematopoietic elements, myxoid leiomyomas, epithelioid leiomyomas, clear cell and granular cell leiomyomas, intravenous leiomyomatosis, benign metastasizing leiomyoma, perinodular hydropic leiomyoma, multinodular hydropic leiomyoma and cotyledonoid dissecting leiomyoma (Dobashi et al., 1999; Hock et al., 2000; Abramson et al., 2001; Avritscher et al., 2001; Ceyhan et al., 2002; Kim et al., 2002; Kondi-Pafiti et al., 2006; Miettinen and Fetsch, 2006; Toledo and Oliva, 2008; Taran et al., 2010).

**Treatments:** Currently no available medicines are perfect for the management of uterine fibroids. Hysterectomy is the definitive treatment for women with symptomatic uterine fibroids (Farquhar and Steiner, 2002; Edwards et al., 2007). But main drawbacks of this surgical option is loss of fertility. Other disadvantages is that after surgery it takes long time to recover with significant complications such as hemorrhage, bowel or bladder injury, infection and pain (Brölmann and Huirne, 2008). Myomectomy via laparotomy, hysteroscopy, or laparoscopy is

another surgical option to remove uterine fibroids in symptomatic women who wish to preserve their fertility or otherwise desire to keep their uterus (Frishman and Jurema, 2005).

Unfortunately, myomectomy is associated with significant morbidity including haemorrhage, adhesion formation, leiomyoma recurrence, blood transfusion, bowel injury and rarely hysterectomy (Olufowobi et al., 2004). Other treatments of leiomyoma include myolysis/cryomyolysis, MRI-guided focused ultrasound surgery, Uterine artery embolization, Laparoscopic uterine artery occlusion, Doppler-guided uterine artery occlusion, and medical therapy (Evans and Brunzell, 2007; Brölmann and Huirne, 2008).

Gonadotrophin-releasing hormone agonist (GnRHa) is effective medical treatment for shrinking the fibroid size up to 50% of their initial volume and temporary control of bleeding. This type of treatment is restricted to a 3- to 6-month interval, but when treatment stops, usually fibroids came back their pretreatment size. In addition, side effects include menopausal symptoms and bone loss with long term use (Matta et al., 1989; Lethaby et al., 2002; Wallach and Vlahos, 2004; Rackow and Arici, 2006; Sankaran and Manyonda, 2008). Levonorgestrel intrauterine systems (LNG-IUS) can also reduce bleeding association with leiomyomas (Starczewski and Iwanicki, 2000; Wildemeersch and Schacht, 2002; Soysal and Soysal, 2005; Sayed et al., 2010). Currently, several other strategies are under investigation such as GnRHa with add-back therapy (with either progestagen, tibolone, combined oestrogen and progestagen, or raloxifene), GnRH antagonists (abarelix, cetrorelix and ganirelix), selective oestrogen receptor modulators (raloxifene), antiprogestins (tamoxifen and mifepristone), selective progesterone receptor modulator (asoprisnil, CDB-2914, CDB-4124, CP8863 and CP8947) aromatase inhibitors (anastrozole), cabergoline, danazol and gestrinone (Brölmann and Huirne, 2008; Lethaby and Vollenhoven, 2008; Luo et al., 2010; Catherino et al., 2010).

## PREGNANT MYOMETRIUM AND UTERINE FIBROIDS: COMMON CHARACTERISTICS

Pregnant myometrium and uterine fibroids are both characterized by extraordinary myometrial growth rate, apposition of extracellular matrix and changes in physiological attribute (i.e. contraction). Leiomyomas share many characteristics with the parturient *myometrium*, including

increased production of extra-cellular matrix components, the expression of receptors for peptide and steroid hormones and the expression of the gap junction protein connexin 43. The latter is required for cell-cell communication and the synchronous contractions at labor. However, unlike normal *postpartum myometrium*, leiomyomas fail to regress via apoptosis and undergo normal dedifferentiation (Andersen et al., 1993; Andersen and Barbieri, 1995; Walker and Stewart, 2005). Leiomyomas have characteristics of the well-differentiated uterine smooth muscle cells of pregnancy as evidenced by the fact that these tumor cells resemble myometrial cells of pregnancy more closely than they resemble typical myometrial cells of a nonpregnant *uterus* (Andersen et al., 1993; Andersen and Barbieri, 1995; Cesen-Cummings et al., 2003). Leiomyoma and pregnant *myometrium* both present dysregulated patterns of cellular differentiation and gene expression. In general, the major differences as compared to normal non-pregnant *myometrium* are found for estrogen regulated genes including those encoding structural proteins (i.e. collagens) (Andersen and Barbieri, 1995; Shynlova et al., 2009).

## LEIOMYOSARCOMA

Uterine leiomyosarcoma is a rare aggressive malignant uterine smooth-muscle tumors, comprising about 1% of all uterine malignancies and 25~36% of uterine sarcomas (Echt et al., 1990; Emoto et al., 1999).

**Symptoms:** The most common symptoms are abdominal pain (35%), abnormal vaginal bleeding (53%) or palpable abdominal mass (14%) (Wu et al., 2008).

**Classification:** Most leiomyosarcomas have typical histologic features, and variants such as epithelioid leiomyosarcoma, differentiated leiomyosarcoma, myxoid leiomyosarcoma, intravenous leiomyosarcomatosis, osteoclast-like giant cells in smooth-muscle tumours, leiomyosarcoma with a clear cell component, leiomyosarcoma with liposarcomatous differentiation (Mentzel and Fletcher, 1994; Coard and Fletcher, 2002; Miettinen and Fetsch, 2006; Toledo and Oliva, 2008).

**Treatments:** The principle treatment of uterine leiomyosarcoma is surgical excision such as simple hysterectomy and bilateral salpingo-oophorectomy, however, surgical staging

appears to be less important due to rather frequent hematogenous spread (Mayerhofer et al., 1999; Nam, 2011). In postmenopausal women, bilateral salpingo-oophorectomy is recommended (Nam, 2011). Radiotherapy may be useful in controlling local recurrences and chemotherapy with doxorubicin or docetaxel/gemcitabine is now used for advanced or recurrent disease, with response rates ranging from 27% to 36% (Hensley et al., 2008; Hensley et al., 2009). Aromatase inhibitor could be used for the management of uterine leiomyosarcoma (Hardman et al., 2007; O'Cearbhaill et al., 2010).

## CONCLUSIONS

The myometrium is the muscular wall of the uterus which has important functional activities during reproductive cycle, pregnancy and menopause. Myometrium has two important pathological conditions such as leiomyoma and leiomyosarcoma. In this review we summarize the clinical anatomy information regarding leiomyoma, leiomyosarcoma and normal pregnant myometrium.

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