# Leiomyomas in pregnancy

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#### ABSTRACT

Uterine fibroids are the most common benign tumors affecting female genital tract, responsible for a high morbidity across fertile age women, with a prevalence of 0,1-11% among pregnant women. Although generally asymptomatic, they can lead to a series of symptoms and complications such as pain, infertility, miscarriages, antenatal bleeding, postpartum hemorrhage, preterm labor, fetal malpresentation, placental abruptio and high cesarean section rates. The purpose of review is to update information regarding fibroids specifications and their correlation with pregnancy outcomes as well as fibroids management during pregnancy. Because of uterine fibroids heterogeneity and lack of large, randomized trials there are encountered discrepancies among studies, but it was observed that uterine fibroids increase the risks of negative obstetrical outcomes, especially when it goes to large, multiple, submucous and retroplacental myomas. Conservative management during pregnancy is advised, but in special situations myomectomy could be recommended and possible. Trial of labor should be offered to pregnant women even if they have large uterine fibroids, or previous myomectomy excepting fibroids obstructing the birth canal or patients who underwent extensive surgery for fibroids removal.

Keywords: pregnancy, fibroids, diagnosis, management

#### INTRODUCTION

Leiomyomas or uterine fibroids are the most frequently found benign tumors affecting the female genital system. These smooth muscle cell tumors consist of a larger amount of extracellular matrix than normal myometrium, among myofibroblasts, surrounded by a pseudocapsule, which represent a major morbidity cause for reproductive age women. Clinical studies show that fibroids development relates to ovarian hormones status, therefore they are rarely found before menarche and usually regress after menopause. Risk factors are represented by age, high body-mass-index (BMI), family history of leiomyomas, nulliparity and black women. The prevalence of fibroids reaches 70-80% among women aged 50 and appears to be much higher in black women than white/ Asian/Hispanic women. The real incidence is hard to be determined as there is

no routine screening test and nearly 50% of asymptomatic patients remain undiagnosed until routine ultrasound imaging for pregnancy confirmation. The prevalence among pregnant women is around 0,1% to 11%, of which 20-50% develop symptoms caused by uterine fibroids during pregnancy which are held responsible for 2-3% of the cases of infertility [1-4].

Uterine fibroids can lead to obstetrical complications such as antepartum bleedings, miscarriages, placental abruption, preterm labor and birth, fetal malpresentation, postpartum hemorrhage, depending on the size, type, number and location of the leiomyomas. They can be classified as submucous, intramural and subserous. Sessile fibroids have a large base of implantation to the uterus while pedunculated ones are attached with a stalk. FIGO classification divides them into 9 types as following: 0 –intracavitary pedunculated; 1 – submucous in-

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volving < 50% myometrium; 2 – submucous involving > 50% myometrium; 3 – intramural in contact with the endometrium without distorting the cavity; 4 – intramural without contact with the endometrium or serosa; 5 –subserous involving > 50% myometrium; 6 – subserous involving < 50% myometrium; 7 – subserous pedunculated; 8 – cervical or parasitic; x-y / hybrid – where x defines the submucous part and y the subserous one [3,5].

### MATERIALS AND METHODS

The purpose of this review is to update information regarding fibroids specifications and their correlation with pregnancy outcomes as well as fibroids management during pregnancy. The database of PubMed and UpToDate was searched for literature reviews, case studies and retrospective studies in English regarding uterine fibroids and pregnancy from 2008 to December 2021.

# FIBROID EVOLUTION DURING PREGNANCY AND POSTPARTUM

Fibroid development is known to depend on sex steroid hormones, but the exact mechanism of influence over these benign tumors is not yet fully understood. Studies reveal that 50-60% of fibroids do not increase in size during pregnancy, while 22-32% tend to grow especially during the first trimester, following a non-linear path. The greatest increase is registered below 10 weeks of gestation, usually in larger size fibroids of 5 cm or more [3,6,7]. During the second and third trimesters of pregnancy they appear to pass through a deceleration of growth and even a decrease in size [8]. According to Chill et al. cervical myomas have a higher chance of size increase during pregnancy compared to other fibroid locations [9]. Estrogen and progesterone peak serum levels during pregnancy are achieved during the third trimester in contrast with the rapid and important fibroid growth during the first trimester. Beside their important role in the pathogenesis and growth of myomas, a series of cytokines, hormones and growth factors appear to be involved in their development. Human chorionic gonadotropin (hCG) blood level concentration doubles every 48 hours during the first trimester, achieving a peak around 10 weeks of gestation, followed by a rapid decrease due to progesterone inhibition once the placenta starts increasing progesterone production. In vitro studies shown that hCG stimulates proliferation of myometrial smooth muscle cells, influencing uterine fibroids growth directly or mediated by prolactin secretion, evidence which could suggest hCG involvement in fibroids growth pattern during pregnancy [4,10].

Three to six months postpartum ultrasound reveals up to 90% of the uterine fibroids discovered during pregnancy decrease in size [7].

During pregnancy fibroids can change shape and flatten out as a result of interstitial oedema. As a result of rapid and important growth during the first trimester red degeneration can occur. Ischemia and necrosis of the fibroid's center followed by prostaglandins release are a consequence of the rapid growth of myomas compared with their own vascular supply or due to the change in orientation of the fibroid during uterine growth reported to the blood vessels [3,7].

# ADVERSE PREGNANCY OUTCOMES OF UTERINE FIBROIDS

Complications of fibroids during pregnancy vary according to the number, size, location, type, development, and relation to the placental site of the myomas. The most important impact on pregnancy appears to have FIGO 0-2 or multiple fibroids which distort the uterine cavity, while subserous myomas bear nearly the same risk as the general population pregnant women. There is no consensus of the real impact of intramural fibroids on pregnancy, but it appears that larger ones tend to have a poorer outcome [11,12]. According to recent studies leiomyomas are responsible for 1-3% of infertility cases, leading to a higher rate of miscarriages and early pregnancy bleeding [8]. There are several mechanisms described responsible for reproductive disfunction of which endometrial atrophy, ulceration with local inflammation, venular ectasia, distortion of endometrial glands, distortion of uterine cavity, obstruction of tubal ostia, poor endometrial blood supply, dysfunctional uterine contractility, can interfere with gamete and embryo transport and can impair nidation. Abnormal myocytes found in fibroid uteri affect the calcium metabolism which leads to abnormal uterine contractility and subsequent pregnancy loss. There is a double rate of first or second trimester miscarriages and early pregnancy bleeding among women with fibroids compared to women with normal uteri. The rate is higher in women with large submucous or multiple fibroids and raises if implantation takes place near or over a submucous myoma. Myomectomy can lower the pregnancy loss rate among women with uterine fibroids, but it remains higher compared with the general population [11-13].

The most common symptom of fibroids during pregnancy is pain, which is more often encountered between first and second trimester of pregnancy, corresponding with the maximum growth period of myomas. Almost 40% of pregnant women with fibroids suffer from pain during pregnancy, of which

5-15% require hospitalization, with an increased risk for fibroids greater than 5 cm diameter [14]. It can be associated with red degeneration, caused by rapid growth of the uterus and low vascular supply leading to ischemia, necrosis, and prostaglandin release. Torsion of subserous pediculated fibroids, although rare, can represent another cause for fibroid associated pain. Pain is generally localized, exacerbated by local pressure and can be accompanied by fever, nausea, vomiting, mild leukocytosis and even rebound tenderness. Differential diagnosis should include appendicitis, placental abruptio, ureteric stone, pyelonephritis, ovarian torsion, and preterm labor [15]. A thorough clinical examination and ultrasound findings such as anechoic or cystic spaces through the fibroid mass should help correctly diagnose fibroid pain. Rarely an MRI examination is necessary to elude the diagnosis and conservative treatment including oral analgesia, rest and hydration is usually efficient [3,6,16].

Pressure symptoms such as increased micturition frequency and urinary retention can be caused by large low anterior or cervical fibroids or rarely, as a result of large posterior fibroids that result in a fixed retroversion with pelvic incarceration [3].

Large submucous and multiple fibroids are associated with a 2,5 times higher risk of fetal malpresentation, generally breech position, comparing with general population. There was also found an increased malpresentation incidence among women with retroplacental fibroids, ones located in the lower segment or with diameter greater than 10 cm [6,17-19].

Leiomyomas appear to diminish uterine responsiveness to oxytocin and to affect uterine peristalsis which has been demonstrated in the inner third of the myometrium in pregnant and non-pregnant women. MRI examination revealed uterine peristalsis disturbance in patients with submucous fibroids, which can be explained by the absence of prostaglandins receptors in fibroid tissue, responsible for uterine spontaneous contractions mediating PGF2a action, or by physical disruption of contractile waves. Several studies reported an increased incidence of dysfunctional labor while others could not confirm these findings, showing no statistical difference between uterine responsiveness to oxytocics, labor length, curves or first and second stages of labor comparing women with uterine fibroids to general population [3,6,7]. There is no consensus on whether uterine fibroids are associated with dysfunctional labor, but there have been reported third stage complications such as placenta retention and postpartum hemorrhage (PPH), secondary to inefficient myometrial retraction [20,21]. Postpartum atony and consequently hemorrhage rates appear to be higher in retroplacental lower localized fibroids, with increasing fibroids size and in cesarean delivery [3,16].

Reports show higher rates of cesarean delivery among women with uterine fibroids, with a 3,7-fold increased risk compared with general population. Cesarean section risk is associated with size and location of the fibroids. Among predisposing factors are fetal malpresentation, fibroids in the lower uterine segment obstructing the birth canal, submucosal, large, and multiple fibroids [3,21-24].

Pregnant women with uterine fibroids have a greater risk for preterm labor and preterm birth which are associated with submucous, retroplacental, multiple and larger fibroids. There are two theories involved in the pathogenesis of preterm labor and birth represented by a less distensible uterus with contractions appearing above a certain point of distension and a decrease in oxytocinase activity, leading to an increase in oxytocin levels and furthermore to contractions. Studies show that despite the increased risk of premature labor, uterine fibroids do not represent a predisposing factor for preterm premature rupture of membranes (PPROM). Fibroids are not associated with fetal growth restriction, but it appears that myomas greater than 200 ml (7-8 cm) can be related with small for gestational age infants, congenital torticollis, head deformities and fetal limb reduction [6,20,23].

Blood flow of the myometrium next to uterine fibroids is reduced, fact which suggests a reduced blood flow of the decidua overlying a fibroid leading to abnormal placental perfusion and decidual necrosis associated with an increased risk of antepartum hemorrhage and placental abruption. Submucosal, retroplacental and large fibroids over 200 ml or 7-8 cm diameter are associated with a higher risk of placental abruptio which can lead to adverse neonatal outcomes if not quickly identified and properly managed [6,20,25].

Rare obstetric complications of uterine fibroids are represented by uterine incarceration, intestinal obstruction, acute urinary retention (due to urinary tract obstruction), spontaneous fibroid rupture leading to hemoperitoneum, pyomyoma, sepsis and disseminated intravascular coagulation, deep vein thrombosis, hypercalcemia (result of necrotizing myoma) and puerperal uterine inversion [6,26-28].

# MANAGEMENT OF UTERINE FIBROIDS DURING PREGNANCY

In most of the cases uterine fibroids during pregnancy are asymptomatic. Their most common symptom developed during pregnancy is represented by abdominal pain due to fibroid degeneration or torsion. Conservative management represented by analgesia, rest and hydration is strongly recommended. First line treatment is represented by oral acetaminophen. Use of non-steroidal anti-inflammatory drugs is efficient in pain control, reducing hospitalization rate, but should be used with caution no more than 48 hours and should be avoided after 32 weeks of gestation due to the risks of premature closure of ductus arteriosus, neonatal pulmonary hypertension, platelet dysfunction, necrotizing enterocolitis, intracranial hemorrhage, oligohydramnios, and fetal nephropathy. Opioids or, rarely even, epidural analgesia can be used for acute pain control. In case of pedunculated subserous fibroids and persisting pain when torsion suspicion is raised, surgical removal during pregnancy can be considered. During the first and second trimester of pregnancy laparoscopic approach can be an alternative to open myomectomy due to less invasive procedure, shorter hospitalization, and rapid recovery. For laparoscopic procedures during pregnancy, it is advised that trocar insertion to take place under direct vision using open technique, minimal uterine manipulation, minimal Trendelenburg position accompanied by 15 degree left lateral tilt, slow CO2 insufflation with low pressure and slow exsufflation and monitoring the fetal heart rate before and after surgery [3,5,21]. Myomectomy during pregnancy should be considered only in selected cases after appropriate patient counseling regarding to associated risks. Because of the increased uterine blood flow there is an increased risk of hemorrhage and hysterectomy, while intraoperative manipulation of the uterus can lead to miscarriage, infection, PPROM and preterm birth. Indications for myomectomy in pregnant women are represented by symptomatic torsion of subserous fibroids, necrosis leading to inflammatory peritoneal reaction, pain which lasts more than 72 hours, not responding to conservative management, fast growing myomas and fibroids causing intestinal obstruction or subobstruction [8,29-32].

A rare entity during pregnancy is a prolapsed cervical or submucous myoma, which can lead to excessive bleeding, pain, rarely urinary retention. Routine vaginal myomectomy is not recommended during pregnancy as there are risks of heavy bleeding after the procedure if there is a thick stalk, of premature preterm rupture of membranes, abortion, or preterm delivery, that outweigh the benefits. Conservative management is recommended for asymptomatic fibroids prolapsing into the vagina, excepting cases with heavy bleeding, excessive pain, infection, and urinary tract obstruction which represent reasonable indications for vaginal myomectomy. The procedure depends on the fibroid characteristics such as origin and base thickness, with higher risks involving submucous fibroids with thick stalks situated near the amniotic membranes [6,33,34].

## **DELIVERY METHODS**

Cesarean section risk is higher among women with uterine fibroids. It is advised in cases with fibroids obstructing the birth canal, malpresentation, extensive prior myomectomy and common obstetric indications such as fetal distress, prolonged or dysfunctional labor, placenta previa, etc. Trial of labor should be offered to pregnant women even if they have large uterine fibroids, or previous myomectomy excepting fibroids obstructing the birth canal or patients who underwent extensive surgery for fibroids removal with opening of the endometrial cavity. Uterine rupture risk during pregnancy or vaginal delivery after myomectomy is estimated around 1.5%, with little higher rate involving laparoscopic procedure versus abdominal approach. This can be attributed to single vs. multiple layer suture, technical difficulties during laparoscopic suturing and use of electrosurgical energy. It is recommended a period of 12 months, or shorter for selected cases, between myomectomy and a future pregnancy for proper heal. According to American College of Obstetricians and Gynecologists, cesarean delivery prior to onset of labor is recommended between 37 and 38 weeks of gestation in cases of multiple myomectomies, extensive surgery with significantly myometrium compromise or endometrial cavity opening [6,35,36].

Cesarean section (CS) technique varies according to location, number, and size of the fibroids. Preoperative ultrasound to identify fetal lie, placental position, location, size, and number of the myomas should be taken in order to determine the most suitable site of incision and incision type. Intraoperative ultrasound can be also useful. Incision avoiding the fibroids, at 2 cm distance of the myomas margins and lower segment CS is part of the usual practice whenever possible. Classical CS should be considered when fibroids are localized in the low anterior segment, with greater risk due to difficult hemostasis, higher incidence of postoperative ileus, adhesions, and necessity of future elective CS in order to avoid uterine rupture. Cesarean myomectomy is not a common practice, being discouraged because of the risks of hemorrhage and hysterectomy. Recent studies suggest that it can be considered in carefully selected patients and experienced surgical teams, when it represents the only way to access the uterine cavity, to facilitate closure of the hysterotomy or in case of easily removable fibroids. It has the advantage of avoiding a future anesthesia and surgical intervention, being a cost-effective procedure with outcomes similar to those of patients undergoing cesarean delivery alone [8,21,37].

#### CONCLUSIONS

Uterine fibroids represent common benign tumors affecting reproductive age women, also expressing an impact over pregnant women. Although the data are conflicting, studies suggest that they can be associated with higher rates of miscarriages, antepartum bleeding, fetal malpresentation, abruptio placentae, preterm labor, cesarean section, postpartum hemorrhage, comparing with general population. It appears that large, submucous, multiple and

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retroplacental fibroids are associated with obstetrical negative outcomes, while intramural and subserous myomas have a little or no impact at all. Conservative management during pregnancy is advised, but selected cases may benefit from myomectomy during pregnancy or even during cesarean section. Although there are recorded higher rates of CS among patient with uterine fibroids a trial of labor should be offered regardless of fibroids size, excepting the ones obstructing the birth canal or previous extensive myomectomy.

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