

**VILNIUS UNIVERSITY  
MEDICAL FACULTY**

The Final thesis

**Myomas in Pregnancy**

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**2022**

## 1. SUMMARY

*Background:* Uterine myomas are the most common pelvic tumor in women, causing these monoclonal tumors of the myometrium to play a role in women's health leading to a significant health care burden. A high prevalence of reproduction age in women raises concerns about infertility, adverse pregnancy outcomes obstetrical complications. *Aim:* This literature review aims to explore and investigate the prevalence of myomas, risk factors for the development of these tumors, effects on fertility and implantation, mainly focusing on myomas during pregnancy as well as fetal outcomes, along with the management and treatment of myomas, reviewing and providing a narrative approach of the current literature. *Literature selection strategy:* established mainly through the search on electronic databases such as PubMed and others. *Disease mechanism:* analyzing the pathogenesis and mechanisms of uterine myomas as well as pregnancy-related disease mechanisms. *Clinical description:* myoma growth during pregnancy, adverse pregnancy outcomes such as miscarriage, increased risk for cesarean section, placental abruption, placenta previa, premature rupture of membranes, fetal malpresentation, postpartum hemorrhage, and fetal outcomes such as preterm delivery and small for gestational age has been observed. *Treatment methods:* myomectomy before pregnancy and its effects on future pregnancies and myomectomy during cesarean section. *Conclusion:* important to identify the patient group at risk, further studies are needed to understand the clinical significance of the growth pattern and the relationship to adverse pregnancy outcomes. When discussing treatment further randomized controlled trials are needed.

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### Keywords:

Myomas in pregnancy

Myomas, uterine fibroids, leiomyomas

Risk factors, prevalence

Complications, adverse effects, outcomes

Treatment, Myomectomy, surgical techniques

## 2. INTRODUCTION

The most common pelvic tumor in women is uterine myomas [1], these monoclonal tumors of the myometrium play a role in women's health leading to a significant health care burden [2]. With a high prevalence in women of reproductive age, it raises concerns about unfavorable fertility, adverse pregnancy outcomes as well as obstetrical complications [3].

The prevalence in premenopausal women between the ages of 15-54 years old [2], as it naturally coincides with the reproductive ages of women, pregnancy becomes particularly intriguing showing a prevalence of around 3-12% of pregnant women [4].

In several studies, it was demonstrated that the prevalence is increasing with age and exhibiting a pronounced increase in black women [1].

The increase in prevalence with age reflects the rising incidence of pregnancies with uterine myomas due to the effect of more frequent first pregnancies in older age.

Myomas have been associated with poor pregnancy outcomes, several obstetrical and postpartum complications, as well as infertility [1].

Some of the reported complications that have been shown are increased risk for fetal malpresentation, spontaneous abortion, placenta previa, preterm birth, and cesarian section as well as peripartum hemorrhage among others [4].

The focus of this paper review is mainly on uterine myomas in relation to pregnancy. The goal is to explore the how these tumors arise and the risk factors for developing myomas, the outcomes of pregnancy in women with uterine myomas, to analyze the function of a uterus with myomas, the effects of myomas on implantation as well as obstetrical complications during delivery and postpartum together with fetal outcomes along with appropriate treatments/management that improve or alter the pregnancy outcomes.

### 3. LITERATURE SELECTION STRATEGY

The selection strategy in this literature review was established mainly through an extensive search on electronic databases such as: PubMed, Clinical Key-Elsevier, International Journal of Gynecology & Obstetrics, and Archives of Gynecology and Obstetrics to identify relevant literature.

During the search, the keywords used were “myomas in pregnancy”. Selected publications were meta-analyses, systemic reviews, abstracts, and clinical studies.

All articles with the keywords “myoma in pregnancy” and related synonyms like “fibroid, leiomyoma, fibroleiomyoma” were read and only those of them that were relevant to the literature review were analyzed.

The search was conducted throughout the time period from January 1<sup>st</sup> to May 15<sup>th</sup>. The analysis that was conducted included publication dates collected from 2008-2021. All reports gathered and included in this review were in the English language.

## 4. CLINICAL DESCRIPTION OF THE DISEASE OR CONDITION

### 4.1 Background

The most common benign tumor of the uterus is myomas, with a high prevalence in women of reproductive age, it raises concerns about unfavorable fertility, adverse pregnancy outcomes as well as obstetrical complications [4].

The epidemiology of uterine myomas can be quite difficult to estimate, mainly since fibroids are more often asymptomatic and there is more data on symptomatic women rather than asymptomatic. [1, 2].

In premenopausal women between the ages of 15-and 54-years old, myomas are responsible for 29% of gynecological hospitalizations, in addition to that accounting for 40%-60% of all hysterectomies performed and 30% of hysterectomies for younger women between the ages of 18-44 years. This high prevalence of fibroids is causing a significant health care burden on women. [2].

Ultrasound assessment reported that women of African American descent have a higher incidence of myomas at about 60% by age 35 years and about 40% in Caucasians. However, the incidence increases with age, and it is seen that African Americans have an incidence at 80% by age 50 and Caucasians at 70% [3].

Myomas increase the risk of many obstetrical conditions twice as high as in the general population [4]. These risks of poor pregnancy outcomes raise the big question of how the high prevalence among women reflects in the pregnant population. According to a publication of a literature review by the “International Journal of Gynecology and Obstetrics [1]” many different studies show the prevalence of myomas among pregnant women aged 18 years or older, determined on first-trimester ultrasound, the studies are looking at the prevalence by ethnic origin.

In conclusion, uterine myomas within the gravida population are reported in about 3% to 12% of pregnant women [4].

Similar to the difficulty in estimating prevalence in asymptomatic women, the above-mentioned studies identified women that if they were not pregnant would not have been seen by a doctor and therefore potentially causing the estimation of symptomatic pregnant women to be altered, showing an overestimation of the actual prevalence [1].

## 4.2 Risk factors

There are several risk factors that can influence the development of myomas. Both modifiable and non-modifiable risk factors play a significant role in the pathophysiology of uterine fibroids [2].

Age is a non-modifiable risk factor that is of significance. An increase in the incidence of uterine myomas is seen with aging in women and reaching a peak at 50 years.

Advancing age does not only increase the incidence of myomas but also the number of fibroids, this corresponds to the pathophysiology of uterine myomas which shows that these tumors grow in time and are therefore diagnosed more frequently in older age [2].

Data on younger women of ages 19-35 years usually come from the screening of pregnant women during early pregnancy [2].

The hospitalization rates due to myomas are also seen to increase with age, reaching a peak in women aged 45-49 years, however, a decline is observed in women 50-54 years old [2].

Other risk factors are race and genetics, displaying a 2-3-fold increase in the incidence of myomas presenting in black women, while Caucasians, Asians, and Hispanics have a similar incidence [2]. Comparing white and black women, the lifetime risk for myomas is approximately 70% and more than 80% respectively [2].

In pregnant females with  $\geq 9$ -week gestation uterus with a minimum of one  $>4$ cm tumor or at least one submucosal myoma, it was shown that the incidence reached up to 50% in Black women and 25% in Caucasians [2]. These differences in incidence make the racial variations of great significance and are suggested to have their etiology in the differences in estrogen biosynthesis and/or metabolism most likely caused by a genetically mediated process [2].

Genetic predisposition has been suggested due to some observations seen in genetic linkage studies. Alterations of several genes are also detected to be associated with uterine myomas etiology [2].

Multiple genes are related to the upregulation and downregulation of myoma cells, 100 different genes are associated and some of them being growth hormone receptors, sex-steroid associated genes as well as extracellular matrix genes among many others [5].

Family history of myomas has also been found to increase the risk of uterine fibroids, showing a 2.5 times increased risk in women with a first-degree relative with myomas [5].

When it comes to reproductive factors, women with multiple pregnancies during their reproductive period have been seen to have a protective effect on the development of fibroids. A 5-fold decrease in the risk of developing myomas is observed with high parity, consisting of three or more deliveries [2]. However, the time period between deliveries is of significance, women that gave birth 5 or more years ago had a higher risk of developing myomas than those who gave birth more recently [2].

On the other hand, having myomas and then becoming pregnant can alter the fibroid growth quite powerfully, during pregnancy there are spikes and falls in the production of estrogen and progesterone, which itself can cause an increase in fibroid growth [2,6].

Hormonal risk factors, more particularly estradiol and progesterone are other key players in the pathophysiology of myomas and ovarian activity is fundamental for myoma growth and leads to shrinkage of the fibroid after menopause for most women [2].

Uterine myomas express elevated numbers of progesterone receptors, estrogen works by increasing the cell's responsiveness to progesterone, and together with the high expression of the receptors are associated with the number of tumors [7], making progesterone receptor binding signaling favorable for myoma growth [2].

Gaining weight during adulthood has been shown to be associated with an increase in the risk of myomas [8]. A prospective cohort study was made to investigate surgically treated myomas linked to weight gain, there it was shown that a 10-20kg increase in weight raised the risks for uterine myomas compared to women who gained less than 10kg [9].

An observational study published investigated if fat tissue distribution estimated by ultrasound and the presence of fibroids were associated, finding that visceral fat significantly was associated with uterine fibroids while subcutaneous fat was not [10].

Metabolic syndrome which includes central obesity among other factors also is associated with higher myoma risk [11].

Lastly, other factors are also attributed to the risk for uterine myomas, diet being one, particularly showing that consumption of red meats or ham encompasses a higher risk and a diet high in plants including vegetables and fruits has shown to decrease the myoma risk.

Smoking, physical activity, stress, and caffeine are other factors [2]. In a systematic review and meta-analysis of alcohol consumption and the risk of uterine myoma, it shows that the

correlation is doubtful, making the conclusion that alcohol is not associated with fibroid risk and that further studies are needed [12].

#### 4.3 Fertility and implantation

When it comes to myoma's effect on fertility and a lot of controversiality exists. Infertility in women with fibroids occurs in 3.4% - 31.9% [1]. However, a more recent systematic review and meta-analysis [13] investigated the relationship between fibroids and fertility. Studies used were those that were comparing fertile and infertile women and investigating women with and without myomas to identify if fibroids are a risk factor. It was seen that epidemiological studies could suggest that infertility and fibroid are linked but not demonstrated, one example is the analysis of several studies where pathogenic findings conclude that fibroids can cause subfertility. Despite that, quite a lot of concerns are raised, one explanation highlighted was some methodological difficulties. The conclusion was inconclusive epidemiological studies and the authors urged for more viable evidence [13].

Implantation has been suggested to be altered due to impaired uterine contractility, defective gamete transportation, and overall adverse effects on the endometrium, however, the data is inconclusive, and none of the hypotheses have been proven. Women with submucosal fibroids compared with infertile controls were found to have a 70% decrease in pregnancy rate and were reasoned to be due to a 72% decrease in implantation rate [14].

#### 4.4 Myomas in pregnancy

Myomas during pregnancy have shown to lead to several outcomes in addition to being seen to be having twice as high an increased risk for obstetrical complications than within the general population [4]. Investigating the link between these tumors of the myometrium and the way they could affect pregnant women can help aid practicing obstetricians in better follow-up and treat this patient group.

##### 4.4.1 Changes throughout pregnancy

Pregnant women with myomas are frequently asymptomatic and have unremarked pregnancies, nonetheless, 10% of women with myomas can develop symptoms and potentially develop to become clinically significant [15, 16].



The most common symptom that can manifest in women with myomas during pregnancy is pain. The pain is believed to be caused by degeneration which results from the release of prostaglandins during the rapid growth of the leiomyoma which leads to the perfusion being decreased as well as to ischemia and necrosis. Torsion and necrosis of pedunculated myomas can also be the etiology of the pain [16].

However, symptoms that can accompany pain are discomfort, the sensation of pressure, or vaginal bleeding [16].

Many studies have had an interest in monitoring and closely looking at the size of myoma growth during pregnancy and investigating if this growth can cause adverse pregnancy outcomes. One study explored the possibility of an association between myoma growth and risk factors for fibroids like maternal age, increased body mass index, and parity, but the linkage was not found [17].

The dilemma about myoma growth has been that some authors claim that the growth is increased over the gestation, whilst others describe these tumors growth as unchanged or decreased. A systemic review published in 2018 [18], analyzed all data evidence accessible that reflects uterine myoma growth and size throughout each trimester of pregnancy. The review of the relevant articles revealed that significant growth of myomas was reported in the first trimester of pregnancy. Concerning the second-trimester conflicting data were found, in some studies myomas were found to show a prevalent growing trend while others showed variable growth patterns, including some rising in growth and others even reducing in size [18].

The third trimester also demonstrated conflicting data, showing a reduction significantly in size [18] while the De Vivo study of pregnant women in gestation 11.6 and 20,6 weeks by ultrasound evaluation reported an increase in uterine myoma volume [17].

The HH.Chill retrospective cohort study [15] had similar conclusions as to the systemic review of Vitagliano [18], however, considerable growth was only found in the first trimester of pregnancy, and authors claimed that this trend is later in pregnancy decreased yet showed towards the end of gestation that growth is minimalistic.

Furthermore, Human chorionic gonadotropin is one of the key players been found to expand myomas, and in fact, fibroids increase the diameter associated with the concentration of human chorionic gonadotropin, reported in up to 12<sup>th</sup> weeks of gestation [19].

Another study [20] found an association between the increase in growth patterns of myomas according to female fetal sex. During their analysis of the data, an increase in growth of uterine

myomas was noted for both fetal sexes during first and second trimester of pregnancy, however a faster growth is seen in women expecting a female fetus [20].

#### 4.42 Pregnancy outcomes and obstetrical complications

##### Miscarriage

A systemic literature review made in 2008 by Klatsky [14], reported that women with myomas had an increased risk of miscarriages compared to those without myomas. However, a more recent paper published in 2018 [21] reviewed data from international guidelines including the European Society of Human Reproduction and Embryology, American Society for Reproductive Medicine, and Royal College of Obstetricians and Gynaecologists, on the matter of recurrent pregnancy loss and described that miscarriage risk depends on the type of myomas. Submucosal fibroids were seen to increase miscarriage rates and decrease live birth rates and on the other hand, intramural fibroids were described as that they might increase the risk reflecting on the controversiality, while subserosal fibroids were shown to have no impact on miscarriage [21].

The amount of myomas has also been seen to be a factor increasing the risk for miscarriage, showing that multiple fibroids can make chances for pregnancy loss higher [16].

##### Cesarean section

Many factors can play role in determining whether a woman needs a C-section. Many criteria can influence whether a cesarean section mode of delivery takes place, therefore when evaluating the data of correlation between myomas and cesarean section, these factors must be excluded.

In one large sample of 112,403 deliveries, a retrospective cross-sectional study was made in China [22], where it was confirmed that uterine myomas are associated with an increased risk for cesarean delivery. Pregnant women with myomas had an 85.2% higher cesarean delivery rate compared to 53.5% in women without myomas during pregnancy. This confirmation was done with the exclusion of other factors that can alter the association and requires cesarean section by routine standards, such as placenta previa, placental abruption as well as breech delivery [22]. They also took into account other factors that can complicate pregnancy, such as parity, maternal age, body mass index, hypertensive disorders, premature rupture of membranes, neonatal weight, and gestational age during delivery [22].

Other studies show similar results, a cohort study revealed an overall increased risk for elective cesarean delivery, however, women with a fibroid diagnosis code compared to women without a fibroid diagnosis code have the same risk for acute C-section [23].

Additionally, another meta-analysis reviewed several articles and concluded the same that there is a significantly increased risk of cesarean delivery in association with uterine fibroids [24].

#### Placental abruption

The association between placental abruption and myomas was reviewed during a meta-analysis that included more than 200 000 participants, obtained from case-control and cohort studies [25]. Demonstrating a significant association between placental abruption and uterine myomas among with concluding that myomas are a risk factor for placental abruption [25].

The relationship between placental abruption and uterine fibroids is thought to be related to the location of the lesions. Restriction of local blood flow caused by large submucosal fibroids positioned close to the placenta insertion could lead to ischemia and necrosis. A predisposition for placental abruption might be due to these events [26].

#### Placenta Previa

Compared to placental abruption, placenta previa has been reported in far fewer patients with uterine myomas thus making a controversy rise in question within the analyzed data. According to a large sample, Chinese retrospective study the prevalence of placenta previa was higher in women with myomas but not statistically significant [22]. Despite that, another large meta-analysis found that there is a significant association between placenta previa and myomas. The analysis was done with 255,886 women based on case-control and cohort studies [27].

#### Premature rupture of membranes

Premature rupture of membrane and uterine fibroids association has not been studied much, old reviews suggest that evidence does not show a higher risk for premature rupture of membranes [14].

However, a retrospective cohort study investigating women with myomas, through identification during the second trimester on routine control, found that large myomas are associated with a higher risk of preterm premature rupture of membranes (pPROM) [28].

Lastly, another study also found a strong association between large fibroids and preterm premature rupture of membranes [29]. Finally, a more recent study published in 2022, showed

that 20% of their sample had premature rupture of membrane and concluded that as being one of several significant complications arising from uterine myomas during pregnancy [30].

#### Fetal malpresentation

Primarily, breech presentation has been seen more frequently among women with myomas. In Klatsky review it was shown that malpresentation was 2.5 times higher in women with uterine fibroids compared to the general population [4, 14].

Similarly, another study revealed that breech presentation was found in 12,5% [31] of cases reflecting a comparable frequency to Klatsky's.

The Chinese retrospective analysis also disclosed that the presence of myomas relates to the increased risk of breech presentation [22]. Then as well, a study found that 16,66% of their patient sample showed malpresentation [30].

A meta-analysis was made in 2016 with 232,177 patients [24], resulting in a strong and significant association between fetal malpresentation and uterine fibroids at term.

Finally, one retrospective cohort study found that in addition to the association of myomas and breech presentation, also observed that short cervix was increased in women with myomas and therefore this patient group is at higher risk for a short cervix, however, the number of fibroids did not affect the frequency of short cervix [32].

#### Postpartum hemorrhage

The frequency of postpartum hemorrhage has been reported among women with myomas. Klatsky made an association and reported that 2.5% of women had postpartum hemorrhage [14]. The Chinese multicenter study also showed a higher risk for women with myomas for postpartum hemorrhage [22]. Another study revealed a higher rate of postpartum hemorrhage as well as increased blood loss estimated [33].

One recent retrospective cohort study found a blood loss from 900mL to 3000mL, this was significantly statistically relevant resulting in an increased risk for postpartum hemorrhage. About 30% of these women were in need of blood transfusion [34].

Lastly, another cross-sectional study investigating outcomes in pregnant women with fibroids aimed to record the prevalence and clinical presentation of birth in both maternal and fetal outcomes, there it was shown in their results that they found increased rates of primary postpartum hemorrhage [35].

#### 4.44 Fetal outcomes

##### Preterm delivery

Many studies have shown that preterm birth has a higher incidence in women with uterine fibroids [3, 4, 14, 26].

Ciavattini, during a retrospective cohort study, concluded that in particular large and multiple myomas were associated with a significantly increased risk of preterm delivery [28]. Similarly, a study showed that preterm delivery was most likely in women with multiple myomas rather than those with single fibroids [33].

During an evaluation at 17-23 weeks of gestational age of a routine second-trimester ultrasound during a retrospective cohort study, myomas during pregnancy were strongly and significantly associated with preterm delivery <37 weeks [32]. However, during the Chinese multicenter cross-sectional study an association was not confirmed between preterm birth and myomas [22]. Another study was performed in France, where they made a comparison between patients with uterine myomas and the risk of preterm birth as well as a control group. They had enrolled a quite large sample consisting of 19,866 women, where women 301 at that time had uterine myomas whereas 147 of them had gone through a myomectomy, and the rest had never been operated on. The conclusion showed that women with uterine fibroids are associated with preterm birth as well as after myomectomy [36].

##### Fetal growth and small for gestational age

When it comes to fetal growth, low birth weight, and small for gestational age the literature previously has shown some conflicting results. Some studies found that there was no significant connection between uterine myomas and fetal growth while others suggested that small for gestational age, as well as low birth weight, were associated with women that had myomas [37]. However, the aim of one recent large prospective cohort study was to determine if fibroids are associated with gestational age or birth weight, women during early pregnancy underwent systemic ultrasound screening. The conclusion of the results was that most pregnancies will not alter fetal growth, however, women with multiple myomas show the tendency of impairing fetal growth and cause small gestational age as well as lower birth weight [37].

Finally, another study investigated the association between fetal growth and retroplacental leiomyoma through identification on ultrasound during the second trimester. It was concluded that there was an increased risk of delivering a small gestational age infant if retroplacental leiomyomas were in the mean diameter of >4cm, furthermore, women with retroplacental myomas had a lower mean birth weight born infants than those without myomas [38].

## 5. DISEASE MECHANISMS AND PATHOLOGY

### 5.1 Pathogenesis and mechanisms of development of uterine myomas

Pathogenesis of myomas is very complex and a lot of different factors play a role in the development and growth of fibroids. The changes in cellular and molecular structures leading to the development and growth of these tumors are not precisely understood.

However, one article [39] demonstrated a very thorough review of the pathological mechanisms that are characteristic of fibroids. It was pointed out that one of the most distinguishing characteristics of uterine myomas is the excessive accumulation of extracellular matrix components and those included are fibronectin, collagens as well as proteoglycans [39].

Downstream mediators including Rho, p38 MAPK, ERK, and integrins are stimulated through bidirectional signaling by increased tissue stiffness, a process called mechanotransduction [39]. Key players in the extracellular matrix remodeling are proteolytic enzymes like matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases which are expressed by uterine myomas [39]. The review also stated that several studies show that extracellular matrix function and remodeling are regulated by cytokines, growth factors, and steroid hormones [39].

### 5.2 Pregnancy-related disease mechanism

As previously mentioned myoma growth during pregnancy is more evident in the first trimester, when it comes to the second trimester, controversy exists, and some studies show tumor growth during the second trimester while others do not.

Sex steroid hormones have been suggested to play a crucial role in pregnancy-related growth of myomas [40]. Estrogen is considered the promoter of the growth of these tumors while maintenance and growth are considered to be progesterone dependent. Nonetheless, during a study [40] the authors made a remarkable point, that the rise of these sex hormones does not correlate with fibroid growth, because these hormones rise progressively during pregnancy and reach a peak in the last trimester, however, fibroid growth is more evident in the first and considerably in the second trimester, but a rather decrease in size during the third trimester.

They suggested that many other hormones, as well as proteins, are secreted by fetal, maternal, and placental compartments that can attribute to the proliferation of these tumors [40].

When describing the mechanism of how fibroids can adversely affect pregnancy development, several mechanisms have been suggested [41]. One of them is disturbances in endometrial cytokine expression and changes in uterine contractility. Secondly, chronic endometrial inflammation and abnormal vascularization [41]. Alteration of varying gene expressions has

also been described and the cause being the mechanical stretch of the myometrium and/or endometrium [41].

## 6. TREATMENT METHODS

The management of myomas can differ widely, it is the leading indication of hysterectomies among women, however, not all women are candidates for such procedure since they want to preserve fertility and their uterus.

Therefore, several conservative treatments are an option for this patient group. Some of those include oral contraceptive pills, nonsteroidal anti-inflammatory medications, intrauterine progestin system, and selective estrogen receptor modulators, other alternatives considered for conservative treatment of myomas are radiofrequency ablation, and uterine artery embolization, magnetic resonance imaging-guided focused ultrasound, and uterine artery occlusion [42].

On the other hand, for women who have more symptomatic myomas and that wish to preserve their fertility, the main treatment is myomectomy. When speaking about the method used, laparoscopic versus abdominal myomectomy, the surgical method of choice is foremost based on the number of fibroids, size, and location. However, the data shows shorter recovery time, less invasiveness, and less blood loss as well as reduced postoperative pain during laparoscopic myomectomy [42].

However, during one Cochrane database review [43] it was concluded that evidence of a superior surgical method like laparoscopy or abdominal laparotomy was not indicated in order to improve clinical pregnancy, ongoing pregnancy, preterm birth or rates of live birth as well as miscarriage or cesarean section. It also concluded that there is limited evidence in women with myomas and the role of myomectomy for infertility [43].

How does this procedure affect pregnancy outcomes? Well, one concern following myomectomy is uterus rupture for those women that wish to conceive. Although the incidence is low, uterine rupture is a severe complication of myomectomy [42], and most commonly occurs when the intrauterine pressure is elevated during the third trimester or during labor [44]. Surgical suturing has been suggested to play a role when speaking about uterine rupture as a complication, showing that single-layer suture increases the risk of rupture fourfold compared with double-layer suturing while electrocoagulation leads to a thin scar, moreover, there are several other risk factors like BMI and growth factor characteristics related to the production of the certain individual that can influence the tissue destruction [44].

Other complications of pregnancy after myomectomy that have been noticed and are not associated with the surgical technique are preterm delivery, evidence suggesting that there is an increased risk for preterm delivery during pregnancy after myomectomy, and significant blood loss during delivery has been reported in women with a previous myomectomy [44].

While indications for myomectomy before pregnancy are clear and how it affects can influence some complications arising during pregnancy as well as delivery, indications for myomectomy during a cesarean section has been unclear and much debate has arisen in that matter.

One polish study [45], aimed to determine the factors that influence the intraoperative decision to perform myomectomy during cesarean section, in their study the decision to perform myomectomy during cesarean delivery was mainly performed on younger women who had a higher risk of complications during future pregnancies caused by myomas. It was pointed out that the surgical experience of the obstetrician was of great significance. Most of the study group had multiple myomas as well as subserosal myomas which often led to irregular uterine contractions and obstruction of the birth canal, therefore an indication for cesarean section and candidates for myomectomy. Lastly, they found no statistically significant correlation between location of the fibroids and the decisions to perform myomectomy was found, neither did size of the myoma [45].

Another article [46], investigated the outcomes of cesarean myomectomy and the benefits as well as risk of the procedure. They reviewed literature concerning the outcomes and benefits of cesarean myomectomy. Showing that a lot of controversy exists and current data regarding cesarean myomectomy safety reveals conflicting results. The most common complication described was the risk of intraoperative hemorrhage also mentioning one case of maternal death due to hemorrhage that was massive accompanied by disseminated intravascular coagulopathy after cesarean myomectomy. However, benefits reported on the review was that myomectomy is technically easier to perform on a pregnant uterus rather than non-pregnant, easier placement of stitches due to elasticity and physiological involution in puerperium as well as uterine contractions can reduce hemorrhage. Another benefit is the improvement of the quality of life in these women and reduces the risks for future pregnancies [46].

Regarding the safety of myomectomy during cesarean section, one study [47] conducted in a tertiary center showed that hemoglobin values and blood transfusion rates were of no statistically significant difference in women with cesarean myomectomy compared to only cesarean section. Nonetheless, surgical duration and hospital stay was prolonged in the group



that cesarean myomectomy was performed. The authors concluded that myomectomy during cesarean section was safe and can be applied regardless of the size, location, type, and amount of myomas [47]. But to this day safety has not been proven by larger randomized trials [48].

A recent meta-analysis published in 2021, evaluated cesarean myomectomy trends in the last ten years [48], reporting that most of the studies have shown that hemoglobin is reduced in the cesarean myomectomy group compared to the control group. Additionally, during the meta-analysis it was confirmed that hemorrhage in comparison with cesarean myomectomy and cesarean section alone indicates no difference in the incidence, however, is statistically increased significantly in odds of blood transfusions. Longer operative time was observed with a mean time of 14.7min longer in the cesarean myomectomy surgery, but it is important to keep in mind that it is still less time in comparison to the requirement of a second additional surgery and should not be considered as a contraindication due to the reason that it is not associated with significant morbidity. Pointing out that it saves time and costs for anaesthesia, surgery, and hospital admission for later fibroid surgery in the future. The authors did not find other postoperative morbidities like fever or wound infection as well as anemia and sepsis significantly increased in women who underwent cesarean myomectomy [48].

Similarly, a meta-analysis and systemic review [49] of perioperative complications of cesarean delivery myomectomy, the most evident remarks were that there was no difference in transfusion rates, hemorrhage, or postoperative fever. Prolonged surgical time with approximately a 14-minute prolongation was noted. The conclusion was that a single symptomatic myoma removal that is not localized in the parametria, for the minimization of ureteral injury risk, was not associated with significantly increased morbidity [49].

Although current literature is showing that cesarean myomectomy procedure is safe, obstetricians prefer not to excise myomas during cesarean section, due to potential complications, despite as mentioned before that it can cause future adverse pregnancy outcomes and increased morbidity as well as financial burden on healthcare system. One article [50] aimed in investigate the best techniques to remove these tumors and to clarify the compared the results. Transendometrial myomectomy technique showed more promise and more advantageous compared to conventional technique, main reason being shorter surgery time and less adhesions [50]. Finally, outcomes of endometrial myomectomy compared to serosal myomectomy during cesarean section is considered safer and less risk for adhesions [51].

## 7. CONCLUSIONS AND SUGGESTIONS

Myomas are the most common benign myometrial tumors, leading to a high disease burden and the prevalence shows a higher incidence in women of reproductive age, most of these tumors are asymptomatic and not clinically significant, however, those that are symptomatic can have quite severe symptoms like excessive bleeding, pain, infertility, and adverse pregnancy outcomes. Therefore, it is very important to identify the women that are in risk for developing uterine myomas and monitor them closely, so that we better can control the disease progress as well as the outcomes.

Some studies explored the possibility of fibroid growth and enlargement associated with the overall risk factors of developing myomas during reproductive years, including maternal age, increased body mass index and parity. Further studies are needed to further investigate this claim and might possibly help clinicians furthermore follow up patients in risk and reflect that in obstetrical care when these women become pregnant.

If we have a closer look on the development the last decades on female reproductive behavior it is clearly seen that women bear children in later age therefore delaying pregnancy, this coincides with the diagnosis of myomas as well as the peak incidence, as the incidence increases with age.

An increase in myoma growth during pregnancy is shown in the first and second trimesters. Suggesting that further studies are needed to help in the understanding of the pattern of growth and of such clinical importance, as well as the relation to adverse pregnancy outcomes.

When discussing treatment and management options, it has under a long time been under debate on whether to excise myomas during cesarean deliveries or not, the arguments being the complications of such procedure, more particularly the risk of hemorrhage. However, when analysing the data, there has been shown that there was no marked difference in hemorrhage between women with cesarean myomectomy and only cesarean section, and the procedure is considered safe. Prolonged surgery time was noticed; however, it saves time and costs for future hospital admissions and the risk of avoiding cesarean myomectomy is future adverse pregnancy outcomes and burden on the healthcare system. The decision should be made on a case-to-case matter and future randomized controlled trials are needed as well as more studied surgical techniques to motivate obstetricians to perform myomectomy during cesarean section, finally this will cause less burden on healthcare systems and save patients.

## 8. REFERENCES

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