Journal of Surgery
Fani G, et al. J Surg 10: 11483
www.doi.org/10.29011/2575-9760.11483
www.gavinpublishers.com
Research Article

Is Myomectomy Necessary before IVF Treatment? Narrative Review of Literature

Gkrozou Fani[1*], Koutalia Nikoleta[1], Kalaitzopoulos Dimitrios Rafail[2], Grigoriadis Georgios[3], Daniilidis Angelos[3]

[1]University of Ioannina, Obstetrics and Gynaecology, Ioannina, Greece

[2]Cantonal Hospital of Schaffhausen, 8200 Schaffhausen, Switzerland

[3]1st University Department in Obstetrics and Gynecology, Papageorgiou General Hospital, School of Medicine, Aristotle University of Thessaloniki, 54643 Thessaloniki, Greece

***Corresponding author:** Fani Gkrozou, Assistant Professor in Obstetrics and Gynaecology, University of Ioannina, Stavrou Niarchou Street, Ioannina, 45101, Greece

Citation: Fani G, Nikoleta K, Kalaitzopoulos DR, Grigoriadis G, Angelos G, et al.. (2025) Is Myomectomy Necessary before IVF Treatment? Narrative Review of Literature. J Surg 10: 11483 DOI: 10.29011/2575-9760.011483

Received Date: 31 October 2025; **Accepted Date:** 06 November 2025; **Published Date:** 08 November 2025

Abstract

Background: Uterine fibroids are very common benign tumours that develop in women of reproductive age. They can cause heavy menstrual bleeding, dysmenorrhea, dyspareunia, infertility and other morbidities depending on their size, location and number.

Objectives: Uterine fibroids have been associated with adverse obstetric outcomes like spontaneous abortions, intrauterine growth restriction, preterm labour, abdominal pain during pregnancy due to the excessive growth or necrosis, and higher incidence of caesarean section as well as postpartum haemorrhage. However, the association between infertility and fibroids remains a debate. This study is aiming to recognise when myomectomy is necessary before undergoing assisted conception.

Methods: An electronic database search of all published studies in PubMed, EMBASE and Google Scholar from 2004 to 2024 was performed with following keywords: uterine fibroids, leiomyomas, myomectomy, Assisted Reproductive Technology (ART), In Vitro Fertilisation Treatment (IVF) and infertility. Only scientific papers published in English language were included.

Results: Subserosal fibroids are not associated with infertility, they might influence though uterine contractility and gamete migration, myomectomy though is not suggested before IVF treatment. Intramural fibroids have been associated with lower implantation, clinical pregnancy and live birth rates, as result their removal is advised. There is fair evidence that hysteroscopic myomectomy for submucosal fibroids improves ART outcomes and clinical pregnancy rates.

Conclusions: Data is fair, due to studies' heterogeneity. What is new? Evidence supporting the reproductive benefit of hysteroscopic myomectomy of submucosal fibroids before ART remains limited and inconclusive, whereas removal of large subserosal fibroids may be advisable before treatment.

Abbreviations: ART: Assisted Reproductive Technology; BMI: Body Mass Index; BMP: Bone Morphogenetic Protein; ECDL: Endometrial cavity-distorting leiomyoma; ECM: Extracellular Matrix; ECNDL: Endometrial cavity non-distorting leiomyoma; eNOS: Endothelial Nitric Oxide Synthase; FIGO: International Federation of Gynaecology and Obstetrics; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HOXA: Homeobox A; IVF: In vitro fertilization; LIF: Leukocyte inhibitory factor; MiRNA: MicroRNA; MMPs: Matrix metalloproteinases; NK: Natural Killer; TGF: Transforming growth factor; TIMPS: Tissue Inhibitors of Metalloproteinases; TNF: Tumor Necrosis Factor; VEGF: Vascular Endothelial Growth Factor

Introduction

Uterine fibroids, or leiomyomas, represent the most prevalent type of benign tumors found in women during their reproductive years. Even though, the majority of uterine fibroids are asymptomatic, they can cause heavy menstrual bleeding leading to anaemia, dysmenorrhea, pelvic pressure and pain, dyspareunia, infertility and other morbidities depending on their size, location and number. The risk of developing uterine fibroids is significantly higher in African-American women compared to Caucasian women. Other risk factors that have been described include age, smoking, obesity, nulliparity and prolonged menstrual cycle [1]. Conversely, some epidemiologic studies, as well as a more recent prospective, ultrasound-based cohort study, suggest that cigarette smoking is correlated with a lower incidence of uterine leiomyomata [2,3]. However, these findings should not be regarded as a method of uterine fibroid prevention.

The initial classification of uterine fibroids was based on the location regarding the three anatomic layers of uterus, classifying them as submucosal, intramural or subserosal. In 2011 the International Federation of Gynaecology and Obstetrics (FIGO) introduced a classification system that precisely delineated the topography of fibroids within the uterus [4]. FIGO classification system was revised in 2018, categorizing them into eight different classes [5]. This universally accepted and well-standardized nomenclature enables gynecologists to improve patients counselling and plan their appropriate medical or surgical treatment.

The impact of uterine fibroids on pregnancy has been the subject of extensive research over the years. Uterine fibroids have been associated with adverse obstetric outcomes like spontaneous abortions, intrauterine growth restriction, preterm labour, abdominal pain during pregnancy due to the excessive growth or necrosis, and higher incidence of caesarean section as well as postpartum haemorrhage. In addition, it is estimated that between 5% and 10% of women experiencing infertility are diagnosed with fibroids [6]. Despite research, the link between infertility and fibroids remains a subject of continued controversy. Critical role plays the proximity of them to uterine cavity and the potential distortion of intrauterine environment. Various studies have been conducted on the effect of fibroids on embryo implantation after In Vitro Fertilisation Treatment (IVF). These studies focus on the impact of non-cavity-distorting and cavity-distorting fibroids on embryo – implantation as well as the impact of surgical treatment of these fibroids on IVF fertility outcomes.

The objective of this review is to comment on whether myomectomy should be performed before undergoing assisted conception considering evidence based on bibliography from the last decades.

Materials and Methods

We performed an electronic database search of all published studies in PubMed, EMBASE and Google Scholar from 2004 to 2024. The following keywords were used alone or in combination: uterine fibroids, leiomyomas, myomectomy, Assisted Reproductive Technology (ART), In Vitro Fertilisation Treatment (IVF) and infertility. Only scientific papers published in English language were included.

Results

Fibroids and association with infertility

The association between uterine fibroids and infertility remains a subject of ongoing debate. However, there are many hypotheses on underlying mechanisms which are involved in fibroid-related infertility. The first hypothesis is based on several studies that associate the presence of fibroids with sexual dysfunction due to dyspareunia, dysmenorrhea and heavy menstrual bleeding. Therefore, these symptoms potentially could interfere on the frequency of sexual intercourse, resulting in adverse psychological impact on couple and consecutively reducing the chances of conception [6].

The second hypothetical mechanism is the obstruction of oocyte and sperm transport due to compression of interstitial part of fallopian tubes by subserosal or intramural fibroids or due to distortion of uterine cavity by submucosal fibroids [6]. Furthermore, it is suggested that fibroids are associated with impaired junctional zone peristalsis and consecutively impaired uterine contractility independently of the fibroid location or other fibroid characteristics [7]. However, Yoshino *et al*. concluded that myomectomy restored junctional zone peristalsis, resulting in an increase in the pregnancy rate [8].

The fourth hypothesis is predicated on the assumption that vaginal-uterine microbiome is affected by the presence of

fibroids. Research has shown that uterine microbiota, that is not dominated by Lactobacillus, is associated with a significant decrease in implantation, pregnancy, and live birth rates compared to Lactobacillus-dominated endometrial microbiota [9]. Chen *et al*. concluded that vaginal and cervical samples of women with fibroids were more abundant with Lactobacillus sp., in comparison to women without fibroids, and the cervical mucus of individuals with fibroids was dominated by L. iners [10]. On the other hand, Winters *et al*. found altered vagino - uterine microbiome in patients with fibroids, as the endometrial samples were more abundant with Acinetobacter, Pseudomonas, Comamonadaceae, and Cloacibacterium instead of Lactobacillus species [11]. Further research is required to examine the impact of myomectomy on the female reproductive tract microbiome.

The fifth hypothetical mechanism that correlates fibroids with infertility involves changes in the inflammatory environment of the endometrium. The study by Inagaki *et al*. demonstrated that uterine fibroids could change endometrial inflammatory profile, resulting in the upregulation of MMPs and other inflammatory cytokines such as interleukin-1 and TNF-α [12]. Song *et al*. concluded that the incidence of chronic endometritis was higher in the group of women with submucosal fibroids compared to the group of intramural fibroids [13]. However, another study reported lower pregnancy rates in the group of women with intramural fibroids, even with those not distorting uterine cavity. This could be attributed to increased accumulation of inflammatory cells between the fibroid and corresponding endometrial tissue [14]. Moreover, CD68+ macrophages, which are in endometrium, can induce the production of pro-inflammatory cytokines and increase significantly during the peri-implantation window. These macrophages are in abundance in myometrial site of leiomyoma and in the adjacent tissue compared to distant autologous myometrium. Therefore, they generate the secretion of various growth factors, including Transforming Growth Factor b (TGF-b), leading to the chemoattraction of more macrophages. Interleukin (IL)-11 levels are reduced in patients with fibroids during the window of implantation, resulting in decreased numbers of Natural Killer (NK) cells [15]. This decrease in IL-11 may also contribute to implantation failure in these women. Nevertheless, it has not been clarified yet whether myomectomy restores the normal endometrial inflammatory state. Furthermore, it has been suggested that impaired autophagy, which promotes fibroid growth, could lead to impaired decidualization and consecutively contributes to infertility [6].

The sixth hypothesis refers to changes that are reported in molecular pathways. Homebox A10 (HOXA10) and Homebox A11 (HOXA11) are transcription factors expressed in endometrium during proliferative phase and their expression is upregulated in the midsecretory phase due to the influence of progesterone [16,17]. Proteins encoded by these genes are crucial to implantation as they improve endometrial receptivity. Endometrial expression of HOXA10 and HOXA11 is significantly decreased in women with submucosal fibroids, especially in endometrium which is adjacent to fibroid [18,19]. Considering intramural fibroids, Makker *et al*. reported a significant downregulation of both HOXA10 and HOXA11 and a slight reduction in the expression of E-cadherin during the implantation window, in comparison to fertile women without fibroids [20]. Furthermore, it has been suggested that the expression of HOXA10 and HOXA11 in endometrium of women with intramural fibroids was increased after myomectomy [6]. This effect was not evident in women with submucosal fibroids. HOXA10 expression is regulated by Bone Morphogenetic Protein Type II (BMP2). It is known that fibroids produce significant amounts of TGF-b3, which interact with BMP signaling, leading to the downregulation of BMP receptors [21].

Additionally, there are changes in other molecular pathways which are involved in embryo implantation. Leukocyte Inhibitory Factor (LIF) is also vital for decidualization. LIF levels are decreased in women with submucosal fibroids during luteal phase and a study demonstrated that LIF levels were also significantly decreased in endometrium of women with large (≥3 cm) and non-cavity distorting intramural fibroids [22]. As mentioned above, the presence of fibroids is linked with reduced levels of IL -11, which is crucial for trophoblast invasion. Tumor Necrosis Factor (TNF)-a, a pro-inflammatory cytokine which is also responsible for preimplantation development of embryo and trophoblast invasion, was reported to be increased in uterine flushings of women with fibroids [23].

The last hypothesis is related to dysregulated angiogenesis and inadequate endometrial blood supply. The BMP pathway is a critical regulator of both decidual transformation and successful implantation. Therefore, implantation failure could be attributed to changes in this pathway. BMP regulates TGF - b receptors, which are responsible for endothelial cell function and blood vessel development. Doherty and Taylor and Sinclair *et al.* reported that women with fibroids presented a reduced expression of BMP and its receptors [21,24]. Endometrial Nitric Oxide Synthase (eNOS) is an angiogenic factor which plays a critical role in VEGF – mediated angiogenesis. However, endometrial overexpression of eNOS creates a local oxidative stress resulting in endometrial epithelial apoptosis. A study reported that infertile women with uterine fibroids had higher levels of eNOS compared to fertile controls without fibroids [25]. Furthermore, fibroids and especially those which distort endometrial cavity, can compromise endometrial perfusion. It is known that good endometrial blood flow during assisted reproductive treatment is associated with higher rates of

pregnancy. Therefore, inadequate endometrial blood supply due to uterine fibroids could lead to impaired implantation [26].

Current research focuses on miRNAs, key regulators of gene expression, which are small non – coding RNA molecules, containing approximately 20 nucleotides. Uterine fibroids produce miRNAs, which are subsequently released into the extracellular environment. Studies have reported altered miRNA expression profile in uterine fibroids to normal myometrial tissue. Specifically, the expression of let-7 miRNA family, which is involved in pathways that regulate endometrial receptivity, was significantly upregulated in fibroids compared to matched myometrium [27]. Thus, aberrant expression may contribute to implantation failure. Moreover, miRNA-21 was found to be markedly overexpressed in uterine fibroids, affecting the expression of endometrial genes that are involved in cell adhesion and apoptosis. The miR-29 family is crucial in regulating the expression and remodeling of extracellular matrix components and cell adhesion molecules. A study by Marsh *et al*. reported decreased miR-29a levels in uterine fibroids, compared to normal myometrium [28]. Uterine fibroids expressed significantly reduced levels of miR-29b according to some studies [27,28]. Chuang and Khorram observed that the expression of miR-29c was reduced in fibroids when compared to normal myometrium [29]. MiR-29c reduced expression is associated with abnormal Extracellular Matrix (ECM) remodeling, creating an unfavorable environment for endometrial receptivity and implantation. Furthermore, it has been reported that uterine fibroids express lower levels of miR-200c compared to myometrium [30]. It has been suggested that altered levels of miR-200 could affect endometrial receptivity and result in impaired embryo implantation and development. Kim *et al*. studied the expression of miRNAs in fibroids and specifically the differences in miRNA expression between leiomyomas that distort the endometrial cavity (ECDL) and those which do not distort the Endometrial Cavity (ECNDL) [31]. This study demonstrated the overexpression of miR-15b and the downregulated expression of miR-29a, -29b, -29c, -197, and -200c in fibroids compared to normal myometrium. Moreover, it was reported that ECDL cells expressed lower levels of miR-29b and -200c and the expression of target genes such as estrogen receptor, MMPs and Tissue Inhibitors Of Metalloproteinases (TIMPs) were upregulated compared to ECNDL cells. Therefore, this study suggests that miRNA expression profile of uterine leiomyomas is altered depending on their ability to deform endometrial cavity.

Subserosal Fibroids

Subserosal fibroids develop beneath the outer surface of uterus, underneath serosa. They typically exhibit no symptoms, but larger fibroids may cause noticeable symptoms including pelvic pain, heavy menstrual bleeding and extrinsic compression on nearby organs such as bladder or rectum. In general, they are not regarded as being associated with infertility. However, large fibroids might cause changes in uterine contractility and those located near interstitial part of fallopian tube might cause anatomical distortion and impair gamete migration [6].

In 1998, Elder-Geva *et al*. conducted a retrospective comparative study, including 88 patients with uterine fibroids and 33 of them had fibroids classified as subserosal. They concluded that subserosal fibroids did not affect either pregnancy or implantation rates in patients undergoing Assisted Reproductive Technology (ART) treatment [32,33]. Oliveira *et al*. studied the impact of subserosal fibroids on the outcome of patients undergoing In Vitro Fertilization (IVF). This study demonstrated that patients with fibroids less than 4 cm, in maximum diameter, had comparable IVF outcomes with patients without fibroids. However, patients with fibroids larger than 4 cm tended to have lower implantation and pregnancy rates when compared to patients with fibroids smaller than 4 cm. Therefore, they concluded that this subgroup of patients might require treatment before being scheduled for ART [34]. Pritts *et al*. reported that subserosal fibroids did not have an impact on fertility outcomes, when compared to patients without fibroids [35]. In 2011, another prospective cohort study concluded that small fibroids, with a diameter below 50 mm, that do not encroach the uterine cavity did not affect the IVF success rates. The study included 119 asymptomatic patients undergoing IVF with intramural or subserosal fibroids smaller than 50 mm and 119 controls. However, there were some limitations. Firstly, the study included both intramural and subserosal fibroids based on the lack of consensus on the location-based classification of fibroids at that time. Secondly, some characteristics of the two subgroups were partially different, including BMI and the ovarian stimulation outcome [36]. A more recent review also reported that subserosal fibroids did not have an impact on implantation, clinical pregnancy, live birth and abortion rates [37]. In conclusion, subserosal uterine fibroids don't appear to have any impact on infertility. There is still a debate about whether myomectomy of large subserosal fibroids can improve reproductive outcomes or restore peristalsis in the junctional zone. Additional research is required to assess the benefits of myomectomy in these cases.

Intramural Fibroids

Intramural myomas develop within the myometrium and often lead to symptoms, which can vary based on their number, size or location. According to FIGO classification, type 3 is an intramural fibroid but is encroaching upon the endometrium whereas type 4 is an intramural fibroid that develops within the muscular layer of the uterus. The association between intramural fibroids and infertility has been a matter of ongoing scientific debate and remains inconclusive. There are many questions about whether

there is a specific number, location or a threshold size that affects reproductive outcomes. Moreover, the indications and the efficacy of myomectomy remains a subject for discussion.

Numerous retrospective cohort studies have been conducted over the years. Hart *et al*. performed a prospective, controlled study which included 434 women undergoing ART treatment. The study group included 112 patients with intramural myomas less than 5 cm and the normal control group included 322 women. Implantation and ongoing pregnancy rates were significantly reduced compared to women with no fibroids (11.9% vs 20.2% and 15.1% vs 28.3%, respectively). It is worth mentioning that patients from the study group were on average two years older than controls, a factor that could have influence on fertility outcomes [38]. In 2004, Oliveira *et al.* studied the fertility outcomes of women with intramural and subserosal fibroids undergoing ART treatment. Patients with intramural fibroids larger than 4 cm tended to have lower pregnancy and implantation rates than patients with smaller fibroids. However, there was not significant difference considering live birth rates in patients with fibroids compared to patients without fibroids [34]. That year, Bulletti *et al*. reported increased rates of pregnancy and live birth among patients with intramural fibroids > 5 cm following laparoscopic myomectomy before ART [39]. Another retrospective cohort analysis by Klatsky *et al.* evaluated the impact of non-cavity-distorting fibroids on ART outcomes. Clinical pregnancy and implantation outcomes were similar to those of the control group. Furthermore, patients with fibroids > 4 cm had a 67% pregnancy rate, which was comparable to the pregnancy rate of patients without fibroids [40]. Bozdag *et al*. reported that a single intramural fibroid did not have an adverse effect on ICSI cycles, as the clinical pregnancy per embryo transfer (36 vs 38%) and implantation rates (20 vs 19%) were comparable to the control group. Miscarriage rates were higher in the study group but they did not reach statistical difference [41]. In 2014, another retrospective cohort study was conducted to investigate the effect of fibroids, that do not invade the endometrial cavity, on in vitro fertilization treatment outcomes. In the final analysis 249 patients (198 with intramural and 51 with subserosal) undergoing ART treatment and 249 related matched controls were included. Patients with intramural fibroids larger than 2.85 cm demonstrated a notable reduction in delivery rates compared to controls without fibroids. This study had strict inclusion criteria, and the control group was specifically selected to eliminate confounding variables. However, the study had some limitations. Data were gathered from a single fertility center. Moreover, only fibroid dimensions and delivery rates were considered and some subgroups, including the type 3 fibroid subgroup, had small sample size. It was not clarified that the surgical treatment of intramural fibroids > 2.85 cm would be beneficial for patients undergoing IVF treatment and further research is required to evaluate this cutoff value as an indication for myomectomy for infertile women [42].

As mentioned above, a prospective study designed by Somigliana *et al*., including both intramural and subserosal fibroids, concluded that small fibroids < 50 mm, not distorting the uterine cavity, in asymptomatic patients undergoing IVF treatment did not have a detrimental effect on the success rate of the procedure. Comparable results were observed when specifically focusing on patients with intramural lesions and there were no statistically significant associations between clinical outcomes and the location, number or the dimension of the fibroid [36]. An observational study by Christopoulos *et al*., reported that the presence of multiple fibroids, as well as the presence of non-cavity-distorting fibroids ≥30 mm, was related to significantly lower pregnancy and live birth rates in patients undergoing IVF, when compared to matched control group [43]. Klatsky and colleagues, in a 2008 systematic review, summarized the findings of several cohort studies and concluded that intramural fibroids were linked with a slight reduction in implantation rate, from 22% to 18%, and a rise in spontaneous abortion rate, increasing from 8% to 15%. However, the studies that were included in this review had some limitations, such as some of them were not age matched and the outcomes of many studies did not reach statistical significance [33]. A year later, a systematic review and meta-analysis of controlled studies reached the conclusion that intramural fibroids were associated with lower implantation, clinical pregnancy and live birth rates and significantly higher spontaneous abortion rates. Nevertheless, the benefit of surgical removal of these lesions remained unclear [35]. In 2010, another systematic review and meta-analysis of 19 observational studies focused on the effect of non-cavity distorting intramural fibroids on IVF outcomes. The presence of these lesions was associated with a negative impact on pregnancy outcomes. Some of the limitations of this study included clinical heterogeneity among the studies, differences in the diagnostic methods used to confirm normality of the uterine cavity, variation between the mean dimension and number of fibroids across the studies and the fact that patients with previous myomectomy were excluded in some studies while others did not mention excluding them. Moreover, there was no evidence that routine myomectomy would benefit these patients [44]. A more recent meta-analysis, including 15 studies with 5029 patients, studied also the impact of non-cavity distorting intramural fibroids on live birth rates in women undergoing IVF treatment. The study group showed a 44% decrease in the likelihood of live birth and a 32% decrease in the likelihood of clinical pregnancy compared to the patients of the control group. Lower implantation and higher miscarriage rates were recorded too, although these did not reach statistical significance. Subgroup analysis of patients with only intramural fibroids also revealed a significantly reduced likelihood of both a live birth and clinical pregnancy. However, clinical heterogeneity

between the studies, different diagnostic tools, variation in the assessment of the size and location of fibroids, due to inconsistent reporting, and the fact that most of the studies included were retrospective are some of the weaknesses of this study [45]. The systematic review and meta-analysis by Erden *et al*. included 5 studies in the final analysis. It concluded that noncavity-distorting intramural fibroids 2 - 6 cm sized had an adverse effect on live birth rates in patients undergoing IVF. FIGO type-3 fibroids, ranging from 2 to 6 cm in size, were also associated with markedly reduced live birth rates [46]. The most recent meta-analysis was published in 2024. It involved 13 studies but only eight of them included data considering fibroid size, seven had data about the number of fibroids and only five studies included information regarding myomectomy and subsequent reproductive outcomes. This meta – analysis also concluded that intramural leiomyomas, even smaller than 3 cm, were associated with infertility. Moreover, the presence of more than one fibroid in any location was linked to reduced fertility. The clinical pregnancy rates for patients undergoing myomectomy did not differ from the rates of women who had intramural fibroids in situ. Clinical heterogeneity, biases of age or BMI, retrospective collected data and different diagnostic tools to determine the location of the leiomyomas are some of the limitations of this study [47].

In relation to FIGO type 3 fibroids, a newly published review compiled data from three studies, involving a total of 1,020 patients (324 with fibroids and 696 controls). A significant decline in implantation, cumulative pregnancy, and live birth rates was observed due to the presence of FIGO type 3 fibroids. An increase in both the size and number of fibroids was associated with a higher incidence of adverse IVF outcomes. Despite existing data, whether myomectomy of FIGO type 3 fibroids improves IVF outcomes continues to be debated [48]. Hysteroscopy is considered to be the most effective method of surgical removal of type 3 leiomyomas. Hysteroscopic intracapsular myomectomy, preserving the pseudocapsule of the fibroid, results in a greater preservation of myometrial fibers. Multiple procedures may be needed to achieve a normal endometrial cavity. Even though hysteroscopic myomectomy is regarded as a safe and feasible procedure, there are still concerns regarding its impact on reproductive outcomes.

Submucosal Fibroids

Submucosal fibroids form beneath the uterine lining and extend into the uterine cavity. As mentioned above, the FIGO classification system provides a more efficient categorization of leiomyomas according to their location. According to this classification, submucosal fibroids are divided into three subcategories. A type 0 fibroid is a pedunculated intracavitary fibroid, a type 1 is a submucosal fibroid with a minimal intramural component and type 2 is ≥ 50% intramural. These fibroids tend to be symptomatic, causing severe hemorrhagic symptoms and heavy menstrual bleeding, anaemia, fatigue, pelvic or lower back pain.

The association between submucosal fibroids and infertility has been studied extensively over the years. As referenced above, Eldar-Geva *et al.* assessed the outcomes of ART cycles in patients diagnosed with uterine fibroids. The study included only 9 patients with submucosal fibroids and concluded that both pregnancy and implantation rates were significantly reduced in patients with submucosal fibroids [32]. Klatsky *et al.* conducted a systematic literature review, summarizing the findings of controlled studies. Regardless of the limitations of each study, the presence of submucosal myomas decreases the cumulative implantation rate from 11,5% to 3% and the clinical pregnancy rate from 30% to 14%, compared to women free of fibroids [33].

In past decades, the association between surgical treatment of submucosal myomas and reproductive outcomes has been extensively studied. A prospective, controlled study of patients with submucosal fibroids was performed to assess the reproductive outcome with and without hysteroscopic myomectomy. This study included 52 patients with submucosal fibroids ≤ 4 cm, suffering from infertility for at least one year. A subgroup of 30 women underwent hysteroscopic myomectomy, whereas 22 patients did not undergo surgery, continuing their attempts to conception. Following a one-year follow-up, the first group of patients demonstrated 43,3% clinical pregnancy rate with a miscarriage rate of 38,5%, whereas the corresponding rates of the second group were 27,2% and 50,0%. Pregnancy rates showed a statistically significant difference. Another separate group of 42 patients with both intramural and submucosal myomas was studied and pregnancy rate in women who underwent hysteroscopic myomectomy was 36.4% (8/22) compared to 15.0% (3/20) in women who did not. However, among the study's limitations were a relatively small sample size, the inclusion of only a single fibroid with a maximum diameter of 4 cm, and the absence of data on live birth rates [49].

A systematic literature review compared women who underwent hysteroscopic myomectomy with two types of control groups: women having fibroids remaining in situ and infertile patients with normal uterine cavities. The clinical pregnancy rate was statistically significant when compared to patients with fibroids remaining in situ, but comparable rates of clinical pregnancy were observed when compared to infertile patients without fibroids. Live-birth and miscarriage rates failed to reach statistical significance compared to control subjects in both groups [35].

A retrospective cohort study by Vimercati *et al*. examined the effect of myomectomy on implantation and pregnancy rates before receiving ART treatment. The study consisted of three groups. Group A consisted of 51 women with fibroids, undergoing 97

treatment cycles; Group B included 63 patients with a history of prior myomectomy, who underwent 127 cycles; and Group C comprised 106 controls without fibroids who underwent 215 cycles. There was no statistically significant difference noted between these groups in terms of pregnancy and live birth rate [50]. Data from retrospective cohort studies that have been conducted the past decades demonstrate that women with submucosal fibroids who undergo surgical treatment have higher clinical pregnancy rates, even though the statistical significance varies among the studies. Moreover, birth rates are not assessed in all these studies [51].

The Society of Obstetricians and Gynaecologists of Canada published a new guideline in 2024 addressing the hysteroscopic management of patients with infertility. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) was applied to evaluate the strength and quality of the summary statements and recommendations. According to this guideline, both conclusions that hysteroscopic myomectomy is associated with improved unassisted and assisted pregnancy rates and myomectomy could be considered in patients trying to conceive whether unassisted or with ART, have low quality of evidence and a weak strength of recommendation. However, it is proposed that this guideline should not replace personalized patient care [52].

Conclusively, a 2020 review that included four randomized controlled trials with a total of 442 participants was published. The first study evaluated the effects of myomectomy on reproductive outcomes versus no treatment, whereas the other three studies compared different surgical techniques for performing myomectomy. According to the first study, there was no sufficient evidence supporting the benefit of myomectomy on both clinical pregnancy and miscarriage rate compared to no treatment. Ongoing pregnancy, preterm birth, live birth and caesarean section rates were not reported. Two separate studies compared the fertility outcomes associated with laparotomy and mini-laparotomy procedures against those of laparoscopic myomectomy, though neither surgical approach demonstrated clear superiority. The third study evaluated the impact of utilizing a monopolar versus a bipolar resectoscope during hysteroscopic myomectomy on reproductive outcomes. There were also inconclusive results considering the superiority of a specific hysteroscopic approach. Overall, the validity of the presented evidence in this review was considered to be low [53]. Further research is required to provide conclusive evidence regarding the benefit of myomectomy or the optimal surgical approach.

Discussion

The association between uterine fibroids and infertility remains a field of research over the last decades. Many hypothetical mechanisms have been proposed. Various hypotheses are considered to be responsible for the adverse impact of fibroids on fertility. Some of them are mechanical pressure on the interstitial part of fallopian tubes or endometrium, dysfunctional uterine contractility, changes on inflammatory, angiogenic or molecular profile or altered vagino-uterine microbiome. However, the effect of fibroids on fertility can vary, based on their location, number, vascularization and molecular expression. Current research focuses on miRNA expression profile of uterine fibroids, which can provide valuable insights into molecular mechanisms that associate fibroids with infertility.

Fibroids are classically described as subserosal, intramural or submucosal, according to their location. The FIGO classification system is also used to categorize the location and characteristics of uterine fibroids. Before enrolling in IVF treatment, women undergo an imaging scan to detect potential uterine pathologies, including fibroids, to assess any potential impact on fertility.

Subserosal are classified as the fibroids that develop on the outer layer of the uterus with minimum protrusion into the myometrial muscle layer. Research has demonstrated that subserosal fibroids do not have a significant impact on IVF outcomes. Therefore, they are not associated with infertility, though they might influence uterine contractility and gamete migration. In most cases, myomectomy is not suggested prior to IVF treatment. There is still a debate on whether the surgical removal of large subserosal fibroids confers benefit.

Considering intramural fibroids, a lot of research is conducted to examine the effect of them on fertility. They develop within muscular wall of uterus, and they can be symptomatic, depending on their size or location. Intramural fibroids have been associated with lower implantation, clinical pregnancy and live birth rates. As stated by the latest meta – analysis published in 2024, intramural fibroids, even those smaller than 3 cm, have an adverse effect on reproductive outcomes. According to recent studies, FIGO type 3 fibroids, which are considered intramural but encroach upon endometrium, are also linked to poorer IVF outcomes. Nevertheless, the benefit of surgical removal of intramural fibroids remains controversial, as there is limited evidence regarding the effectiveness of myomectomy on improving fertility outcomes.

Submucosal fibroids extend partially or completely into uterine cavity, leading to the anatomical distortion of it. This type of fibroids is often associated with multiple symptoms such as heavy menstrual bleeding, anaemia, pelvic or lower back pain. Most studies suggest that submucosal fibroids are linked to reduced implantation and pregnancy success rates. Current evidence suggests that hysteroscopic myomectomy may improve fertility outcomes, as compared with expectant management or leaving

submucosal fibroids in situ. However, its positive effect on ART success remains uncertain. In conclusion, there is an urgent demand for up-to-date and high-quality randomized controlled studies to determine the benefit of myomectomy on fertility outcomes before IVF treatment.

References

1. Navarro A, Bariani MV, Yang Q, Al-Hendy A (2021) Understanding the Impact of Uterine Fibroids on Human Endometrium Function. Front Cell Dev Biol 9: 633180.
2. Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K (2012) Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. BMC Womens Health 12: 6.
3. Wesselink AK, Wegienka G, Coleman CM, Geller RJ, Harmon QE, et al. (2023) A prospective ultrasound study of cigarette smoking and uterine leiomyomata incidence and growth. Am J Obstet Gynecol 229:151.e1-151.e8.
4. Munro MG, Critchley HOD, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders (2011) FIGO classification system (PALM□COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynecol Obstet 113: 3-13.
5. Munro MG, Critchley HOD, Fraser IS, the FIGO Menstrual Disorders Committee (2018) The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynecol Obstet 143: 393-408.
6. Don EE, Mijatovic V, Huirne JAF (2023) Infertility in patients with uterine fibroids: a debate about the hypothetical mechanisms. Hum Reprod 38: 2045-2054.
7. Kido A, Ascher SM, Hahn W, Kishimoto K, Kashitani N, et al. (2014) 3 T MRI uterine peristalsis: Comparison of symptomatic fibroid patients versus controls. Clin Radiol 69: 468-472.
8. Yoshino O, Nishii O, Osuga Y, Asada H, Okuda S, et al. (2012) Myomectomy Decreases Abnormal Uterine Peristalsis and Increases Pregnancy Rate. J Minim Invasive Gynecol 19: 63-67.
9. Moreno I, Codoñer FM, Vilella F, Valbuena D, Martinez-Blanch JF, et al. (2016) Evidence that the endometrial microbiota has an effect on implantation success or failure. Am J Obstet Gynecol 215: 684-703.
10. Chen C, Song X, Wei W, Zhong H, Dai J, et al. (2017) The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. Nat Commun 8: 875.
11. Winters AD, Romero R, Gervasi MT, Gomez-Lopez N, Tran MR, et al. (2019) Does the endometrial cavity have a molecular microbial signature? Sci Rep 9: 9905.
12. Inagaki N, Ung L, Otani T, Wilkinson D, Lopata A (2003) Uterine cavity matrix metalloproteinases and cytokines in patients with leiomyoma, adenomyosis or endometrial polyp. Eur J Obstet Gynecol Reprod Biol 111:197-203.
13. Song D, Feng X, Zhang Q, Xia E, Xiao Y, et al. (2018) Prevalence and confounders of chronic endometritis in premenopausal women with abnormal bleeding or reproductive failure. Reprod Biomed Online 36: 78-83.
14. Miura S, Khan KN, Kitajima M, Hiraki K, Moriyama S, et al. (2006) Differential infiltration of macrophages and prostaglandin production by different uterine leiomyomas. Hum Reprod 21(10):2545-2554.
15. Ikhena DE, Bulun SE (2018) Literature Review on the Role of Uterine Fibroids in Endometrial Function. Reprod Sci 25: 635-643.
16. Taylor HS, Arici A, Olive D, Igarashi P (1998) HOXA10 is expressed in response to sex steroids at the time of implantation in the human endometrium. J Clin Invest101:1379-1384.
17. Taylor HS, Igarashi P, Olive DL, Arici A (1999) Sex Steroids Mediate HOXA11 Expression in the Human Peri-Implantation Endometrium1. J Clin Endocrinol Metab 84:1129-1135.
18. Rackow BW, Taylor HS (2010) Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity. Fertil Steril 93: 2027-2034.
19. Cakmak H, Taylor HS (2011) Implantation failure: molecular mechanisms and clinical treatment. Hum Reprod Update 17: 242-253.
20. Makker A, Goel MM, Nigam D, Bhatia V, Mahdi AA, et al. (2017) Endometrial Expression of Homeobox Genes and Cell Adhesion Molecules in Infertile Women With Intramural Fibroids During Window of Implantation. Reprod Sci. 24: 435-444.
21. Doherty LF, Taylor HS (2015) Leiomyoma-derived transforming growth factor-β impairs bone morphogenetic protein-2-mediated endometrial receptivity. Fertil Steril 103: 845-852.
22. Pier B, Crellin C, Katre A, Conner MG, Novak L, et al. (2020) Large, Non-Cavity Distorting Intramural Leiomyomas Decrease Leukemia Inhibitory Factor in the Secretory Phase Endometrium. Reprod Sci. 27: 569-574.
23. Roșu GA, Ionescu C, Călin F, Dimitriu M, Pleș L, et al. (2021) Prognostic value of the location of submucosal uterine leiomyomas in infertility. Exp Ther Med 22:1482.
24. Sinclair DC, Mastroyannis A, Taylor HS (2011) Leiomyoma Simultaneously Impair Endometrial BMP-2-Mediated Decidualization and Anticoagulant Expression through Secretion of TGF-β3. J Clin Endocrinol Metab 96: 412-421.
25. Novin MG, Moini A, Niknezhad S, Najafi T, Ghaffari Novin M (2018) Immunohistochemical Localization of Endothelial Nitric Oxide Synthase in Endometrial Tissues of Women With Uterine Myomas. Int J Womens Health Reprod Sci 6: 263-268.
26. Ng EHY, Ho PC (2002) Doppler ultrasound examination of uterine arteries on the day of oocyte retrieval in patients with uterine fibroids undergoing IVF. Hum Reprod 17:765-770.
27. Wang T, Zhang X, Obijuru L, Laser J, Aris V, et al. (2007) A micro□ RNA signature associated with race, tumor size, and target gene activity in human uterine leiomyomas. Genes Chromosomes Cancer 46: 336-347.
28. Marsh EE, Steinberg ML, Parker JB, Wu J, Chakravarti D, et al. (2016) Decreased expression of microRNA-29 family in leiomyoma contributes to increased major fibrillar collagen production. Fertil Steril 106:766-772.
29. Chuang TD, Khorram O (2016) Mechanisms underlying aberrant expression of miR-29c in uterine leiomyoma. Fertil Steril 105: 236-245.e1.

30. Chuang TD, Panda H, Luo X, Chegini N (2012) miR-200c is aberrantly expressed in leiomyomas in an ethnic-dependent manner and targets ZEBs, VEGFA, TIMP2, and FBLN5. Endocr Relat Cancer 19: 541-556.

31. Kim YJ, Kim YY, Shin JH, Kim H, Ku SY, et al. (2018) Variation in MicroRNA Expression Profile of Uterine Leiomyoma with Endometrial Cavity Distortion and Endometrial Cavity Non-Distortion. Int J Mol Sci. 19: 2524.

32. Eldar-Geva T, Meagher S, Healy DL, MacLachlan V, Breheny S, et al. (1998) Effect of intramural, subserosal, and submucosal uterine fibroids on the outcome of assisted reproductive technology treatment. Fertil Steril 70: 687-691.

33. Klatsky PC, Tran ND, Caughey AB, Fujimoto VY (2008) Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. Am J Obstet Gynecol198: 357-366.

34. Oliveira FG, Abdelmassih VG, Diamond MP, Dozortsev D, Melo NR, et al. (2004) Impact of subserosal and intramural uterine fibroids that do not distort the endometrial cavity on the outcome of in vitro fertilization–intracytoplasmic sperm injection. Fertil Steril 81: 582-587.

35. Pritts EA, Parker WH, Olive DL (2009) Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 91: 1215-1223.

36. Somigliana E, De Benedictis S, Vercellini P, Nicolosi AE, Benaglia L, et al. (2011) Fibroids not encroaching the endometrial cavity and IVF success rate: a prospective study. Hum Reprod 26: 834-839.

37. Freytag D, Günther V, Maass N, Alkatout I (2021) Uterine Fibroids and Infertility. Diagnostics 11:1455.

38. Hart R, Khalaf Y, Yeong CT, Seed P, Taylor A, et al. (2001) A prospective controlled study of the effect of intramural uterine fibroids on the outcome of assisted conception. Hum Reprod 16: 2411-2417.

39. Bulletti C, De Ziegler D, Levi Setti P, Cicinelli E, Polli V, et al. (2004) Myomas, Pregnancy Outcome, and In Vitro Fertilization. Ann N Y Acad Sci 1034: 84-92.

40. Klatsky PC, Lane DE, Ryan IP, Fujimoto VY (2007) The effect of fibroids without cavity involvement on ART outcomes independent of ovarian age. Hum Reprod 22: 521-526.

41. Bozdag G, Esinler I, Boynukalin K, Aksu T, Gunalp S, et al. (2009) Single intramural leiomyoma with normal hysteroscopic findings does not affect ICSI–embryo transfer outcome. Reprod Biomed Online 19: 276-280.

42. Yan L, Ding L, Li C, Wang Y, Tang R, et al. (2014) Effect of fibroids not distorting the endometrial cavity on the outcome of in vitro fertilization treatment: a retrospective cohort study. Fertil Steril 101: 716-721.

43. Christopoulos G, Vlismas A, Salim R, Islam R, Trew G, et al. (2017) Fibroids that do not distort the uterine cavity and IVF success rates: an observational study using extensive matching criteria. BJOG Int J Obstet Gynaecol 124: 615-621.

44. Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A (2010) The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Reprod 25: 418-429.

45. Rikhraj K, Tan J, Taskin O, Albert AY, Yong P, et al. (2020) The Impact of Noncavity-Distorting Intramural Fibroids on Live Birth Rate in In Vitro Fertilization Cycles: A Systematic Review and Meta-Analysis. J Womens Health 29: 210-219.

46. Erden M, Uyanik E, Polat M, Ozbek IY, Yarali H, et al. (2023) The effect of ≤6 cm sized noncavity-distorting intramural fibroids on in vitro fertilization outcomes: a systematic review and meta-analysis. Fertil Steril 119: 996-1007.

47. Pritts TL, Ogden M, Parker W, Ratcliffe J,et al. (2024) Intramural Leiomyomas and Fertility: A Systematic Review and Meta-Analysis. Obstet Gynecol 144:171-179.

48. Favilli A, Etrusco A, Chiantera V, Laganà AS, Cicinelli E, et al. (2023) Impact of FIGO type 3 uterine fibroids on in vitro fertilization outcomes: A systematic review and meta□analysis. Int J Gynecol Obstet 163: 528-539.

49. Casini ML, Rossi F, Agostini R, Unfer V (2006) Effects of the position of fibroids on fertility. Gynecol Endocrinol 22:106-109.

50. Vimercati A, Scioscia M, Lorusso F, Laera AF, Lamanna G, et al. (2007) Do uterine fibroids affect IVF outcomes? Reprod Biomed Online 15: 686-691.

51. Penzias A, Bendikson K, Butts S, Coutifaris C, Falcone T, et al. (2017) Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline. Fertil Steril 108: 416-425.

52. Motan T, Cockwell H, Elliott J, Antaki R (2024) Guideline No. 446: Hysteroscopic Surgery in Fertility Therapy. J Obstet Gynaecol Can 46:102400.

53. Metwally M, Raybould G, Cheong YC, Horne AW (2020) Surgical treatment of fibroids for subfertility. Cochrane Gynaecology and Fertility Group, editor. Cochrane Database Syst Rev 1: CD003857.