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Fibroids and Subfertility: A Systematic Review of Latest Evidence from international Societies

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ABSTRACT

Uterine fibroids (leiomyomas) are benign tumors of the uterus, commonly present among women of reproductive age, affecting fertility outcomes. This systematic review aims to gather the current evidence regarding the association between fibroids and subfertility. Additionally, this review aims to analyze national recommendations to conclude the best uterine fibroid treatment, while highlighting the optimal method of enhancing pregnancy rates. A thorough literature search was conducted to retrieve standard of practice guidelines across PubMed, Google Scholar, and MEDLINE databases. Further guidelines were also searched through relevant websites of obstetrics and gynecology associations. Hence, seven international clinical guidelines were retrieved. The findings state that fibroids can affect fertility through several mechanisms, such as modification of the uterine environment, and distortion of fallopian tubes and uterine cavity, leading to potential implantation and placentation failure. In addition, various fibroid management approaches, including medical treatments like surgical and minimally invasive interventions in women desiring future fertility, are investigated. Latest studies suggest that the amount, size, and location of fibroids impact fertility outcomes. All guidelines recommend that during the selection of a treatment method, personalized patient requirements like the preference for childbirth in the future should be taken into consideration. The number, size, and location of fibroids are critical elements to take into consideration. Globally, fibroid management with inexplicable infertility in women has limited empirical and standardized guidelines. Therefore, further research is crucial to understand the fundamental mechanisms and to establish effective management strategies for women with fibroids facing subfertility.

INTRODUCTION

Uterine myomas (leiomyomata, fibroids) are known to be the most common type of reproductive tract tumors, showing a cumulative incidence rate of 70% among women of reproductive age (Baird *et al.*, 2003; Cramer & Patel, 1990). Due to fibroids, a woman's quality of life is impacted along with fertility and obstetrical results. They are developed through the fibroblasts of myometrium and the cells of smooth muscle, categorized as submucosal, intramural, or sub-serosal, reliant on their position (Michos *et al.*, 2023). The stimulation of estrogen has a positive association with the development of fibroids, resulting in fibroid reduction as menopause initiates (Goerke *et al.*, 2014; Toprak *et al.*, 2019).

Usually, leiomyomas are one the main issue that arises in women of reproductive age, which can pose detrimental effects on fertility outcomes or exhibit symptoms like bleeding, pressure, abnormal uterine bleeding, or pelvic pain (Drayer & Catherino, 2015; Khaund & Lumsden, 2008). Uterine myomas, also known as benign monoclonal tumors, are typically common among women of African lineage (Khaund & Lumsden, 2008; Mahdi, 2019). At an early age, African descent women usually give birth with a substantially adverse burden of myoma as compared to Caucasian women with symptomatic myomas (Peddada *et al.*, 2008).

Throughout the years, several research groups and

societies either national or international, have led studies to investigate the link between leiomyomas and fertility, with contradictory outcomes concerning the influence on fertility (Khaund & Lumsden, 2008; Mukhopadhaya *et al.*, 2007; Pritts, 2001). Uterine fibroid management is highly debated among women with subfertility, with different recommendations for non-surgical procedures like, medical intervention and observation, and surgical procedures like, myomectomy. Furthermore, concerns have been raised regarding the probability of success and intervention protocols with the application of assisted reproductive technologies (ART), like in-vitro fertilization (IVF) in cases of leiomyomas. There is a critical need for a comprehensive systematic review evaluating the current evidence on fibroids and subfertility, keeping in consideration the complexity of the problem and the constant modifications of clinical guidelines. Hence, this review aims to investigate the effects of fibroids on fertility outcomes, while assessing and presenting findings established on recent international guidelines.

MATERIALS AND METHODS

This systematic review is executed based on the methodology permitting the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements (Moher *et al.*, 2009).

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Inclusion Criteria

Guidelines were included if they met the following criteria: (1) Clinical guidelines associated with uterine fibroids with fertility, subfertility, assessing fertility outcomes and treatment strategies (2) Guidelines published/authorized by one or more nationally or internationally recognized medical associations linked to obstetrics/gynecology or interventional radiology, who classify as quality improvement guidelines or practice standards (3) Recent studies published in the last few years, ranging from 2012 to 2024 (4) Guidelines available in English.

Exclusion Criteria

Guidelines were excluded if: (1) Guidelines were non-current and outdated (2) Guidelines related to non-uterine fibroids (3) Not available in English.

Search Strategy

Several electronic databases including PubMed, MEDLINE and Google Scholar were searched from 2012 to 2024 for relevant clinical guidelines regarding uterine fibroid treatments, reporting its clinical fertility outcomes which meets the inclusion criteria. To further search guidelines undiscovered through search strategy, the included guidelines' reference lists were searched manually. Guidelines were specifically limited to the availability in English language. Varying on the database, different combinations of MeSH terms were employed. The search

terms included “Fibroids”, “Fertility”, “Guidelines”, “Leiomyomas”, “Infertility”, “Uterine Fibroids”.

Data Extraction and Management

Screening of the abstracts and titles were performed by two reviewers. The titles and abstracts of the screened clinical guidelines were reviewed to ensure compliance with inclusion criteria. Data extraction was performed employing the general data extraction methods comprising study attributes such as title, publication year, treatment approaches, and outcome measures.

Quality Assessment

In this review, the GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation) was employed to evaluate the quality of guidelines (Brignardello-Petersen & Guyatt, 2024).

RESULTS AND DISCUSSIONS

Initially, 44 studies were overall identified and screened through comprehensive database searches. After implementing the inclusion and exclusion criteria, 7 articles were chosen for a thorough analysis, which included clinical guidelines available from 2012 to 2024. Figure 1 shows the identified databases and screened studies included in this systematic review, meeting the inclusion and exclusion criteria. The PRISMA flow diagram was created using PRISMA2020 (Haddaway *et al.*, 2022).

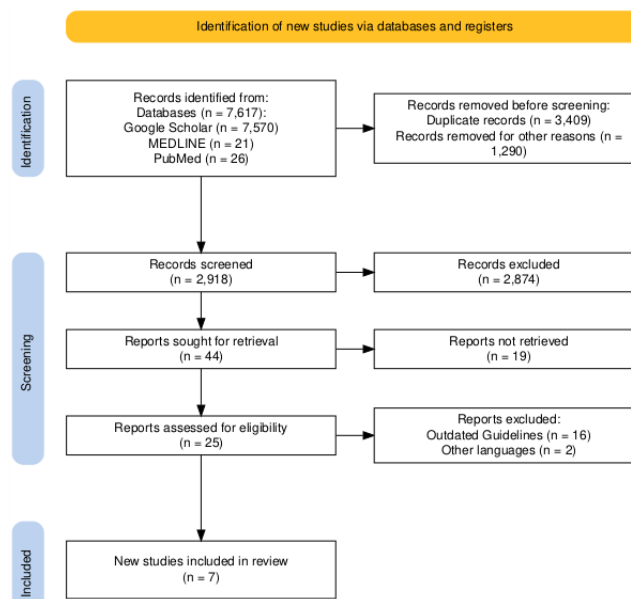


Figure 1: PRISMA Flow Diagram detailing the process of study selection

This review follows the guidelines from the British Fibroid Society (BFS) (Trust, 2021), European Medical Journal of Reproductive Medicine (EMJ) (Mahdi, 2019), Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG) (Australia, 2020), the American Society for Reproductive Medicine (ASRM) (Penzias *et al.*, 2017), Society of Obstetricians and Gynecologists of Canada (SOGC) (Vilos *et al.*, 2015),

the French College of Gynecologists and Obstetricians (CNGOF) (Marret *et al.*, 2012), and American Association of Gynecologic Laparoscopists (AAGL) (Laparoscopists, 2012). All the guidelines support the statement that the effect of fibroids on fertility is associated to the endometrial cavity alteration and the fibroids position in the uterus. However, the type of treatments such as surgical treatments including, minimally invasive

gynecologic surgeries (MIGS), myomectomy, Magnetic Resonance-guided Focused Ultrasound (MRgFUS), and Uterine Artery Embolization (UAE) or medical treatments needed is dependent upon the particular boards.

Leiomyomas on Fertility Outcomes

Due to uterine leiomyomas, clear anatomic disruption of the normal uterine cavity can occur. The endometrial

cavity can be affected specifically by submucosal leiomyomas, potentially influencing embryo development and implantation. However, leiomyomas can occur in other positions like, in sub-serosal site or in myometrium (Donnez & Jadoul, 2002). Leiomyomas can augment into large masses before the occurrence of symptoms such as, pelvic pain or pressure although, it may plausibly disturb pregnancy management and fertility (Penzias *et al.*, 2017). Figure 2 shows the postulated mechanisms of fibroids.

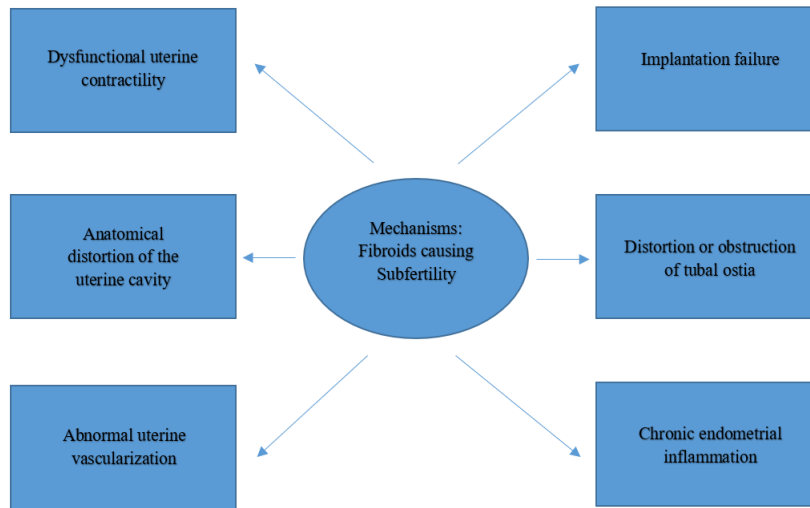


Figure 2: Postulated mechanisms through which fibroids results in subfertility

This figure shows the postulated theories of mechanisms that can result in fibroids causing subfertility (Khaund & Lumsden, 2008).

Although, there are several fibroid categories (Lasmar *et al.*, 2005; Stamatellos & Bontis, 2007), the International Federation of Gynecology and Obstetrics (FIGO) targeted a comprehensive categorization, suggesting the division of leiomyomas into eight types, 0 to 8 (Munro

et al., 2011). Figure 3 shows the FIGO Classification System for Uterine Leiomyoma. In accordance with this classification system, reliant on the percentage of protruding fibroid from the endometrial cavity sub-mucosal myomas are subcategorized into 0, 1, and 2. Moreover, the intramural myoma are subcategorized into 3, 4, and 5 whereas, the sub-serosal myomas are subcategorized into 6, 7, and 8.



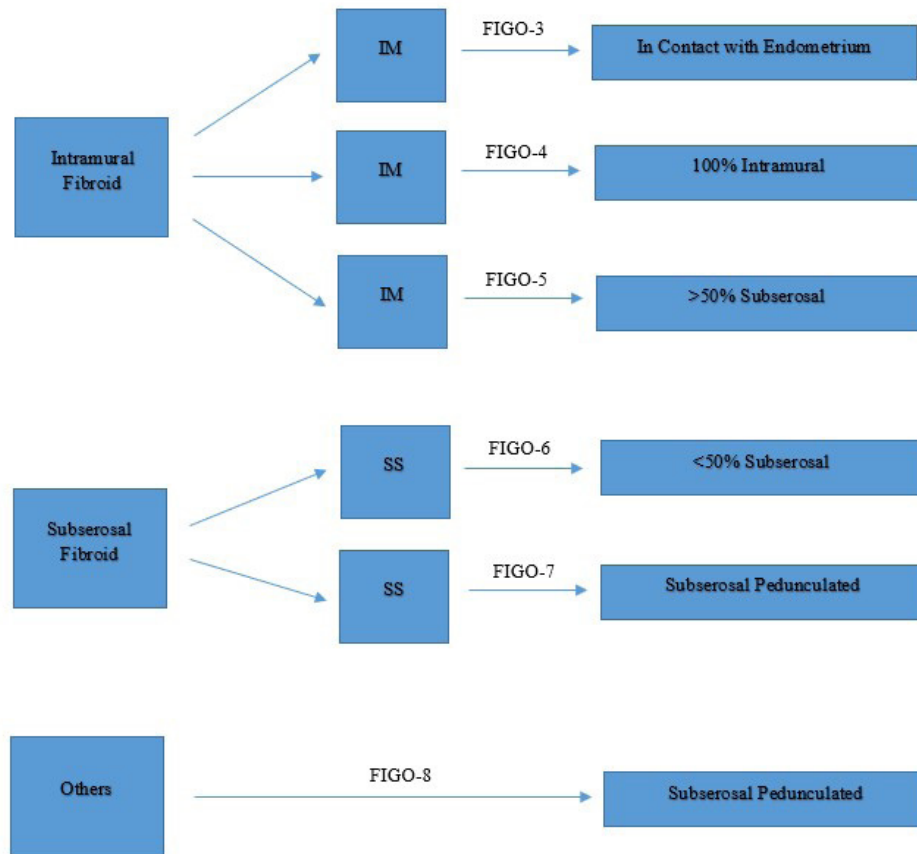


Figure 3: FIGO Revised Classification System 2023 for Uterine Leiomyoma

This model summarizes the FIGO classification system for uterine leiomyoma (fibroids) based on its location (Munro *et al.*, 2011). This classification system was established for clinical and research purposes (Gomez *et al.*, 2021), however, in clinical application, there is substantial deviation in agreement (Laughlin-Tommaso *et al.*, 2017).

Medical Management in Fibroids

For the clinical management of fibroids, the recommendations of the guidelines promote gonadotropin-releasing hormone (GnRH) analogues as a pre-operative intervention and suggest careful application regarding ulipristal acetate (UPA). Table 1 shows the summary of the interventions associated with medical management of fibroids according to various international societies. If the other treatments are unsuccessful, BFS permits restricted use of UPA for intermittent intervention of moderate to severe symptoms of fibroids due to the risk of severe liver injury (Trust, 2021). On the other hand, the ASRM does not approve UPA in the United States for the treatment of fibroids, especially in infertile women, due to its significant adverse effects (Penzias *et al.*, 2017). The EMJ notes that UPA can reduce fibroid size by inducing apoptosis in leiomyoma cells, but its use is limited to three months, with effects lasting up to six months (Mahdi, 2019). According to RANZCOG, usage of UPA is restricted in

infertile women with leiomyomas due to the associated risk of substantial adverse effects (Australia, 2020). In contrast, GnRH analogues are widely suggested by the ASRM, RANZCOG, CNGOF, BFS, and AAGL as pre-operative therapies to reduce uterine volume and manage anemia, facilitating less invasive surgeries (Australia, 2020; Laparoscopists, 2012; Marret *et al.*, 2012; Penzias *et al.*, 2017; Trust, 2021). However, the EMJ does not discuss GnRH analogs in their guidelines (Mahdi, 2019). Similarly, CNGOF and AAGL do not discuss UPA in their guidelines (Laparoscopists, 2012; Marret *et al.*, 2012). Although, SOGC has discussed both UPA and GnRH analogues, there is no role of their medical management as a stand-alone treatment (Vilos *et al.*, 2015).

Surgical Management of Fibroids to Improve Fertility

Myomectomy, a surgical procedure to remove uterine fibroids, is considered an option for improving pregnancy rates in certain cases, though recommendations vary across medical guidelines (Casini *et al.*, 2006). Table 2 shows the summary of the interventions associated with surgical management of fibroids in enhancing fertility outcomes according to various international societies. The BFS suggests hysteroscopic resection for submucosal fibroids and open abdominal or laparoscopic surgery for intramural and sub-serosal fibroids (Trust, 2021). EMJ suggests hysteroscopic or laparoscopic

Table 1: Summary of the Medical Management of Fibroids.

Medical Management	BFS	EMJ	RANZCOG	ASRM	SOGC	CNGOF	AAGL
UPA	Restricted use granted for intermittent treatment of moderate or severe symptoms	Used for its fibroid size-reduction effect	Not recommended due to the risk of adverse effects	Not approved for treatment in the USA	No medical management as a stand-alone treatment	Not Discussed	Not Discussed
GnRH analogues	Used as a pre-operative management (Hemoglobin optimization)	Not discussed	Used as a pre-operative treatment for anemia or volume reduction of fibroid	Used as a pre-operative treatment for fibroid volume reduction	No medical management as a stand-alone treatment	Used as a pre-operative treatment	Used as a pre-operative treatment for anemia

myomectomy for submucosal fibroids and hysteroscopic myomectomy for fibroids situated in the FIGO 0 and FIGO-1 cavity (Mahdi, 2019). ASRM recommends myomectomy for women with distorted cavity fibroids (intramural with submucosal components or submucosal fibroids). However, it is generally advised against the procedure for non-cavity distorting fibroids in women experiencing no symptoms (Penzias *et al.*, 2017). On the other hand, in cases where severe distortion of pelvic architecture complicates oocyte retrieval, myomectomy may still be considered. RANZCOG supports the use of hysteroscopic myomectomy to enhance fertility outcomes, particularly for submucosal fibroids, though it acknowledges the need for further research (Australia, 2020). Studies suggest that up to 50% of women suffering

from infertility associated with fibroids become pregnant following myomectomy, with the most significant improvement observed in women with submucosal fibroids (Jeldu *et al.*, 2021). Although, SOGC suggests myomectomy as an effective treatment option for enhancing fertility, further investigation is stated (Vilos *et al.*, 2015). Moreover, CNGOF recommends hysteroscopic myomectomy in sub-mucosal fibroids ranging less than 4 cm. Whereas, laparoscopic myomectomy is recommended for symptomatic fibroids, taking in consideration its amount and size for enhancing fertility (Marret *et al.*, 2012). AAGL recommends abdominal myomectomy when hysteroscopic myomectomy may widely damage the endometrial surface or in the presence of 3 or more sub-mucous fibroids (Laparoscopists, 2012).

Table 2: Summary of the Surgical Management of Fibroids to Improve Fertility.

	Surgical Management
Societies	Myomectomy (Hysteroscopic/Laparoscopic/Abdominal)
BFS	Myomectomy enhances 50% of fertility in women with fibroid-associated infertility Hysteroscopic suggested for sub-mucosal fibroids (<5cm and >50% intramural) Open abdominal or laparoscopic suggested for intramural and sub-serosal fibroids
EMJ	Myomectomy enhances 50% of fertility in women with fibroid-associated infertility Hysteroscopic or laparoscopic suggested for submucosal fibroids Hysteroscopic suggested for fibroids situated in the FIGO 0-1 cavity
RANZCOG	Hysteroscopic may enhance fertility in sub-mucosal fibroids Myomectomy may be suggested for women undergoing ART with sub-mucosal fibroids
ASRM	Hysteroscopic, laparoscopic or open may enhance fertility in asymptomatic women with cavity-distorted fibroids Not suggested in infertile, asymptomatic women with non-cavity distorted fibroids
SOGC	Myomectomy suggested for enhancing fertility
CNGOF	Hysteroscopic suggested for sub-mucosal fibroids (<4 cm) Laparoscopic suggested for symptomatic fibroids
AAGL	Abdominal suggested for 3 or more sub-mucosal fibroids or when hysteroscopic may extensively damage endometrial surface

Minimal Invasive Surgical Options

In context to preservation of fertility, MRgFUS and UAE are both under scrutiny. Table 3 shows the summary of the minimally invasive surgical interventions associated with medical management of fibroids to improve fertility outcomes according to various international societies. BFS and SOGC does not discuss MRgFUS in its guidelines in context to fertility. EMJ recognizes the potential of MRgFUS in treating infertility but concurs that additional studies are necessary to substantiate its effectiveness and safety (Mahdi, 2019). ASRM notes that currently, there is lacking evidence to suggest MRgFUS for patients aiming to maintain future fertility, emphasizing the need for further research (Penzias *et al.*, 2017). RANZCOG advises MRgFUS, alongside other interventions like, radiofrequency ablation (RFA) and myolysis must be utilized only within approved clinical trials (Australia, 2020). Similarly, according to CNGOF and AAGL, MRgFUS must only be utilized within approved clinical trials (Laparoscopists, 2012; Marret *et al.*, 2012). Regarding UAE, BFS acknowledges a growing number of pregnancies following the procedure but asserts that there is still inadequate data to endorse its safety for women with leiomyomas, desiring preservation of their fertility (Trust, 2021). The ASRM considers UAE unsuitable for patients desiring pregnancy in the future as a result of augmented risks associated with pregnancy

and possible ovarian reserve declines (Penzias *et al.*, 2017). RANZCOG supports this stance, recommending that UAE be limited to clinical trials when applied to fibroids in women with infertility (Australia, 2020). EMJ reports that UAE is associated with lower pregnancy rates and longer conception times in women under 35 compared to myomectomy, making it a less favorable option for those seeking to preserve fertility. Additionally, CNGOF and AAGL state UAE as an inadvisable intervention for women desiring future pregnancies (Laparoscopists, 2012; Marret *et al.*, 2012). Whereas, SOGC may recommend UAE only in selective women due to increased pregnancy-associated risks (Vilos *et al.*, 2015). According to BFS, RFA is not suitable for treating all types of fibroids (Trust, 2021). EMJ, ASRM and SOGC does not discuss both RFA and myolysis in context to fertility. CNGOF states that further research is essential for RFA and myolysis (Marret *et al.*, 2012). AAGL does not recommend RFA for women wanting future pregnancies (Laparoscopists, 2012). Moreover, it does not discuss myolysis. Overall, there is a consensus that all of the minimally invasive surgical procedures require further investigation and should currently be considered primarily within the framework of clinical trials. In line with this cautious approach, uterine-sparing, minimal invasive procedures are being explored as substitutes to myomectomy.

Table 3: Summary of the Minimal Invasive Surgical Procedures.

Minimally Invasive Surgical Procedures	BFS	EMJ	RANZCOG	ASRM	SOGC	CNGOF	AAGL
MRgFUS	Not Discussed	Promising role in treatment of infertility	Recommended only in approved clinical trials	Further studies required	Efficacy in fertility not discussed	Recommended only in approved clinical trials	Recommended only in approved clinical trials
UAE	Insufficient data as a safe method for women desiring future fertility with fibroids	Not recommended as it has a low fertility rate and lengthy conception duration (<35 age)	Recommended only in approved clinical trials	Not recommended for women desiring future fertility due to potential risks	May be recommended for selective women	Not recommended	Not recommended for women desiring future pregnancy
RFA	Not appropriate for all types of fibroids	Not Discussed	Recommended only in approved clinical trials	Not Discussed	Efficacy in fertility not discussed	Further research required	Not recommended for women desiring future pregnancy

Myolysis	Not Discussed	Not Discussed	Recommended only in approved clinical trials	Not Discussed	Efficacy in fertility not discussed	Further research required	Not Discussed
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Quality Assessment Findings

The quality assessment findings show that myomectomy is strongly recommended and supported by high-quality evidence from cohort, observational studies and systematic reviews for the treatment for fibroid-related infertility (Grade 1A or A). Whereas, UAE is conditionally suggested for women suffering from large-sized fibroids, unable to treatment from surgery (Grade 2B or B). Furthermore, the expert opinion

recommends that myomectomy and UAE as effective interventions in accordance with most of the guidelines. No recommendations for the treatment of small-sized asymptomatic fibroids are suggested unless fertility is impacted. Table 3 and 4 summarizes quality assessment findings using the GRADE system, applicable to fibroids and their treatment in infertility according to various international guidelines.

Table 4: GRADE System for Fibroids and Infertility Treatment.

Evidence Type	BFS	EMJ	RANZCOG	ASRM	SOGC	CNGOF	AAGL
RCTs	High quality; Myomectomy improves fertility (Grade 1A)	High quality; Myomectomy for submucosal fibroids (Grade A)	High quality; Myomectomy for fertility (Grade A)	High quality; Myomectomy effective (Grade 1A)	High quality; Myomectomy improves fertility (Grade 1A)	High quality; Myomectomy is the gold standard (Grade 1A)	High quality; Myomectomy recommended (Grade 1A)
Cohort Studies	Moderate quality; Support for myomectomy (Grade 2B)	Moderate quality; Support for myomectomy (Grade B)	Moderate quality; Myomectomy for fertility (Grade B)	Moderate quality; Supports myomectomy (Grade 2B)	Moderate quality; Supports myomectomy (Grade 2B)	Moderate quality; Benefits of surgery (Grade 2B)	Moderate quality; Benefits of surgery (Grade 2B)
Case-control Studies	Moderate quality; Benefits of surgery (Grade 2B)	Low quality; Case-control evidence (Grade C)	Low quality; Limited evidence (Grade 3C)	Low quality; Limited data (Grade 3C)	Low quality; Case-control evidence (Grade 3C)	Low quality; Limited evidence (Grade 3C)	Low quality; Limited evidence (Grade 3C)
Systematic Reviews	High quality; Strong evidence for myomectomy (Grade 1A)	High quality; Supports myomectomy (Grade A)	High quality; Strong evidence for myomectomy (Grade 1A)	High quality; Supports myomectomy (Grade 1A)	High quality; Favor myomectomy (Grade 1A)	High quality; Strong evidence for myomectomy (Grade 1A)	High quality; UAE and myomectomy (Grade 1A)
Expert opinion	Moderate quality; Agreement on myomectomy (Grade 2A)	Moderate quality; Supports surgery (Grade B)	Moderate quality; Supports surgery (Grade 2A)	Moderate quality; Supports surgery (Grade 2A)	Moderate quality; Supports surgery (Grade 2A)	Moderate quality; Supports surgery (Grade 2A)	Moderate quality; Supports surgery (Grade 2A)

Table 5: Recommendations of Fibroid-treatments Across Various Guidelines.

Evidence Type	BFS	EMJ	RANZCOG	ASRM	SOGC	CNGOF	AAGL
Strong recommendation	Grade 1A; Myomectomy for fibroid-associated infertility	Grade A; Myomectomy for submucosal fibroids	Grade A; Myomectomy for fertility	Grade 1A; Myomectomy for infertility	Grade 1A; Myomectomy is standard treatment	Grade 1A; Myomectomy is the optimal standard	Grade 1A; Recommends myomectomy
Weak recommendation	Grade 2B; UAE for large fibroids	Grade B; UAE for large fibroids	Grade B; UAE for large fibroids	Grade 2B; UAE for larger fibroids	Grade 2B; UAE for large fibroids	Grade 2B; UAE for large fibroids	Grade 2B; UAE as fertility-sparing treatment
No recommendation	Grade B; No treatment for asymptomatic small fibroids	Grade C; No treatment for small fibroids without symptoms	Grade 3C; No treatment for asymptomatic fibroids	Grade 3C; No treatment for small fibroids	Grade 3C; No treatment for small fibroids	Grade 3C; No treatment for asymptomatic fibroids	Grade 3C; No treatment for small fibroids

CONCLUSION

This systematic review reports an agreement over significant guidelines concerning the effect of fibroids on fertility, emphasizing the negative impacts of submucosal fibroids that can modify the normal uterus lining. According to the reviewed guidelines, specifically of ASRM and RANZCOG, the results demonstrate that sub-serosal fibroids do not have negative fertility effects, whereas fertility is negatively affected through intramural fibroids impacting the cavity of the uterus. Furthermore, myomas can substantially diminish the rates of conception and clinical fertility, regardless of their position. The main discussion revolves around improving the potential of conception among infertile women with fibroids and the adequacy of its surgery management. To enhance both the chances of IVF and spontaneous pregnancy, the surgical treatment must be personalized to attain an ideal uterine cavity. The surgeon must decide the type of surgical intervention; either a minimally invasive procedure or myomectomy is required, keeping in consideration the site and size of the fibroid. Even though the fibroid position may be closely associated with clinical results, the effect of the amount and size of fibroids on fertility stays uncertain. Current minimal invasive procedures consisting of MRgFUS, myolysis, RFA, and UAE are potentially effective treatments. However, further research regarding these procedures is required for comprehensive assessment. Due to a lack of empirical evidence, recent guidelines except ASRM, do not endorse these procedures for

application other than in clinical trials. The high frequency of leiomyomas and their prospective detrimental effects on fertility highlight the establishment of empirical-based procedures and further research is critical.

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