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REVIEW ARTICLE

Gynecology

The challenge of FIGO type 3 leiomyomas and infertility: Exploring therapeutic alternatives amidst limited scientific certainties

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Abstract

Uterine leiomyomas (ULs) are non-cancerous tumors composed of smooth muscle cells that develop within the myometrium and represent the most prevalent pathological condition affecting the female genital tract. Despite the volume of available research, many aspects of ULs remain unresolved, making it a "paradoxical disease" where the increase in available scientific literature has not been matched by an increase in solid evidence for clinical management. Fertility stands at the top of the list of clinical issues where the role of ULs is still unclear. The leiomyoma subclassification system, released by the International Federaion of Gynecology and Obstetrics (FIGO) in 2008, introduced a new and more effective way of categorizing uterine fibroids. The aim was to go beyond the traditional classification "subserosal, intramural and submucosal", facilitating a detailed examination of individual ULs impact on the female reproductive system. The "type 3 UL" is a special type of myoma, characterized by its complete myometrial development while encroaching the endometrium. It is a unique "hybrid" between a submucous and an intramural UL, that may exert a detrimental "double hit" mechanism, which is of particular interest in patients wishing pregnancy. To date, no robust evidence is available regarding the management of type 3 ULs. The aim of this narrative review is to provide a comprehensive overview of the physiopathological mechanisms that type 3 UL may exert on fertility, and to present new perspectives that may help us to better understand both the need for and the methods of treating this unique type of fibroid.

KEYWORDS
FIGO classification, hysteroscopy, infertility, leiomyoma, type 3 myoma, uterine fibroid

1 | UTERINE MYOMAS: THE DISEASE OF PARADOX

Myomas or fibroids, commonly known as uterine leiomyomas (ULs), are non-cancerous tumors made up of smooth muscle cells that grow inside the myometrium, representing the most prevalent pathological condition affecting the female reproductive system.[1] While most ULs are asymptomatic, they can lead to pelvic pain, abnormal uterine bleeding, and infertility. Notably, the financial burden associated with UL treatment is substantial, surpassing the

costs associated for ovarian, breast and colorectal cancers in the USA.[2,3]

Due to their prevalence and impact, ULs have been extensively studied, resulting in a plethora of literature on this topic. However, despite the vast amount of research conducted so far, many aspects of ULs remain unresolved, making them "paradoxical diseases", where the growth in available literature has not been matched by an increase in robust evidence for clinical management. This knowledge gap is particularly pronounced when dealing with infertile patients.[4,5] To fully grasp the complexities of this condition, let us retrace our steps and begin the narrative from the start.

The traditional anatomical concept of the uterus, comprising three layers – mucous, muscular, and serous – formed the basis for the initial classification of ULs by early pioneers in gynecology (Figure 1). This categorization of ULs, based on their predominant proximity to one of these anatomical layers, resulted in the classification of submucosal, intramural, and subserosal ULs. Thus, anatomical and supposed clinical relevance formed the basis of this classification system for ULs, with particular attention to proximity to the uterine cavity and potential impact on reproduction. It is important to acknowledge that this classification played a significant role in the past, especially with the advent of two-dimensional ultrasound, as it simplified the clinical approach to ULs. However, over time, it became evident that this topographical view of ULs was oversimplified and did not align with the modern understanding of uterine dynamics and ULs. It was recognized that ULs originate within the myometrium and may subsequently migrate towards the cavity or serosa as they grow, influenced by the propulsive forces exerted by the myometrium. Due to their dynamic nature and considering their potential impact on reproductive outcomes, a more precise classification system that accurately delineates their topography was needed.[6]

In 2011, the Internationa Federation of Gynecology and Obstetrics (FIGO) addressed this need by introducing the "leiomyoma subclassification system", which was further updated in 2018 (Figure 2). This new classification system provided clinicians with a refined tool to more accurately categorize ULs into eight different classes based on their specific location within the uterus.[7,8] The introduction of this classification system enabled researchers to move beyond the traditional "subserosal, intramural and submucous" classification, facilitating a more detailed examination of the effects of individual ULs on the female reproductive system.

Despite the availability of these new tools, the application of the FIGO subclassification system in clinical practice and research has been inadequately implemented. As a consequence, valuable opportunities to generate actionable clinical evidence, which could have a substantial impact on daily clinical practice, may have been missed.[6,9]

2 | FERTILITY AND UTERINE MYOMAS: AN ISSUE TO SHED LIGHT ON

As emphasized by Munro in a recent article,[6] fertility stands at the top of the list of clinical issues where the role of ULs is still unclear. The current body of evidence is insufficient to establish robust conclusions on the impact of ULs on fertility and the effectiveness of treatment on improving reproductive outcomes for women seeking conception.[4,10,11] Several potential mechanisms have been postulated to elucidate the adverse effect of ULs on fertility, including increased uterine peristalsis, neuroendocrine actions of the myoma pseudocapsule, and altered expression of genes involved in endometrial receptivity.[12] These mechanisms may interact in varying

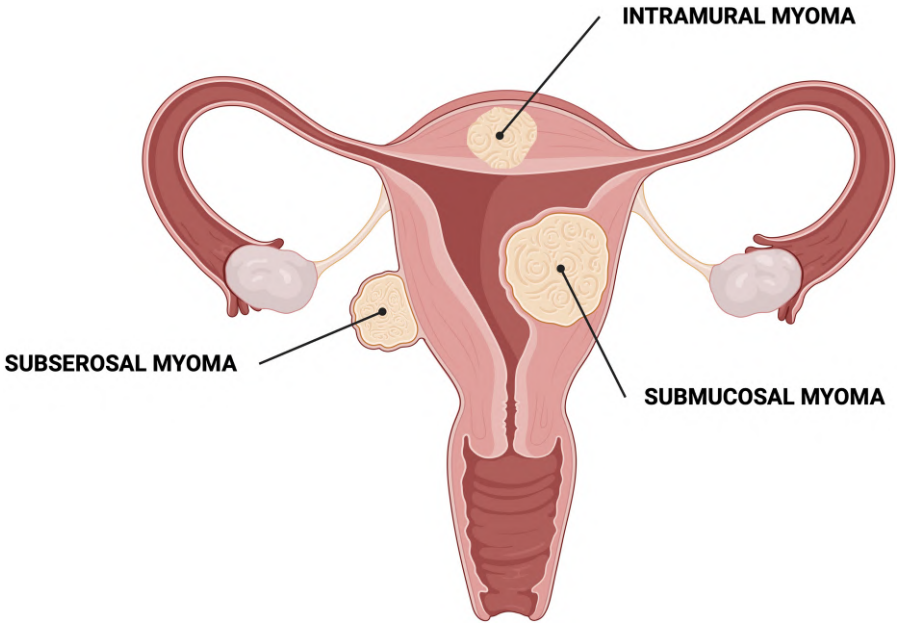

FIGURE 1 Traditional classification of uterine leiomyomas (created with BioRender.com).

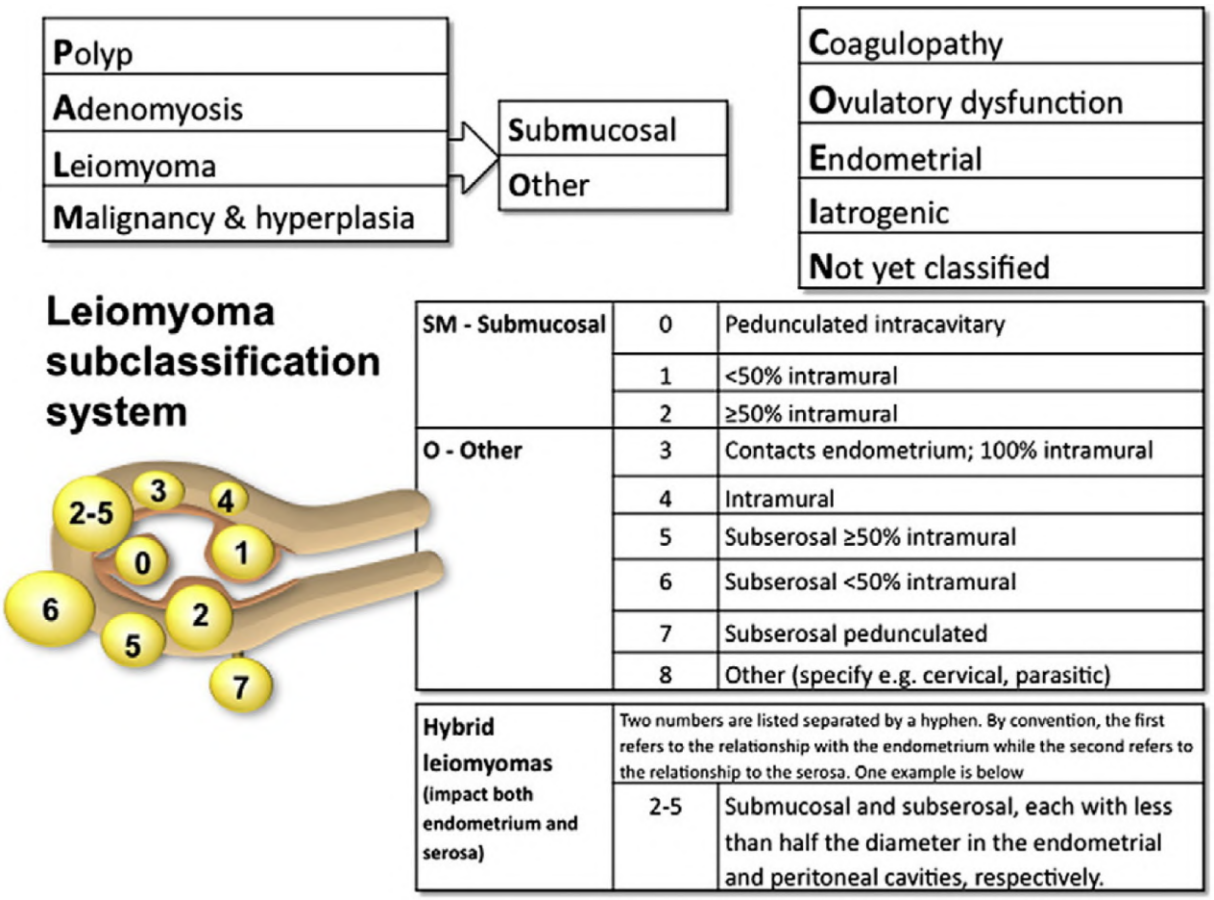

FIGURE 2 FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in non-gravid women of reproductive age.

combinations, influenced by factors such as the volume and location of ULs.[13]

Among the various types of ULs, those that develop within the uterine wall and/or in the uterine cavity are considered to have the highest likelihood of impacting fertility.[11,14] Moreover, larger ULs have the potential to generate a greater quantity of active mediators, while those in close proximity to the uterine cavity can more easily interact with endometrial cells.[12,15] Consequently, the effect of ULs on the endometrium may be global, resulting from a combination of multiple molecular signaling effects and mechanical interference.[16]

3 | THE PECULIAR CASE OF FIGO TYPE 3 MYOMA: THE "HYBRID" MYOMA

The conflicting findings concerning the influence of intramural ULs on fertility imply that certain subtypes of ULs may have a more substantial impact than others.[11,14] In this context, utilizing the FIGO subclassification system for ULs will be essential for revealing fresh knowledge and new insights in this field.[7,8] Among the notable additions brought forth by the FIGO subclassification system for uterine ULs, one of particular interest is the "type 3 UL", characterized by its complete myometrial development while encroaching upon the endometrium.[7] The anatomical features of this category of ULs have sparked significant attention regarding their potential impact on fertility.[11,17] Notably, it stands as a unique "hybrid" between a submucous and an intramural UL, potentially exerting mechanisms similar to both. Analogously to submucous ULs, the FIGO type 3 ULs may alter uterine vascular perfusion, gamete migration, as well as negatively influence the expression of myometrial/endometrial genes involved in regulating endometrial receptivity throughout implantation and embryonic development.[18–22] Furthermore, similarly to intramural ULs, FIGO type 3 ULs may contribute to an increase in myometrial peristalsis, potentially affecting sperm migration and blastocyst implantation, as well as an enlargement and/or deformity of the uterine cavity. In addition, the proximity to the endometrium impairs the junctional zone and facilitates the passage of pleiotropic cytokines into the uterine cavity (Figure 3).[12,23]

4 | FIGO TYPE 3 MYOMA: A SUBMUCOUS ENTITY, DESPITE MISLEADING APPEARANCES

Following the 2018 last update of FIGO subclassification system, the type 3 UL has been reclassified as a submucous fibroid that

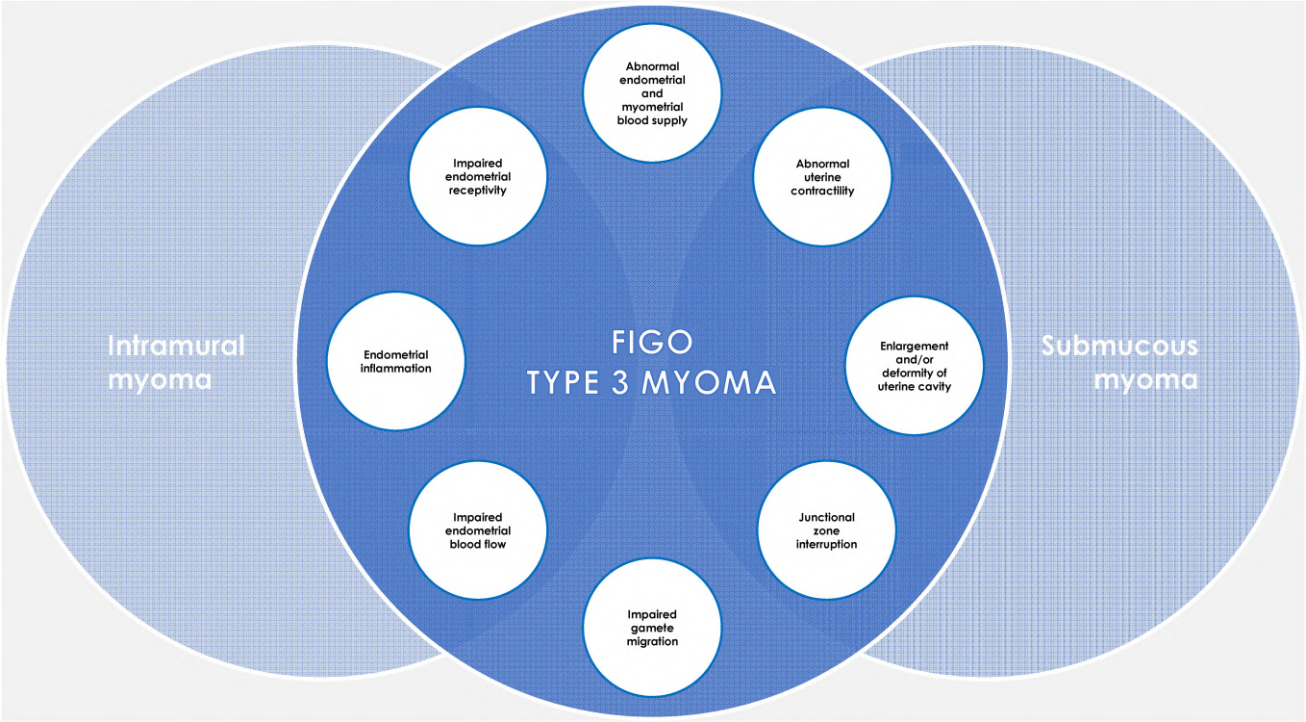

FIGURE 3 Putative detrimental effects on fertility linked to type 3 uterine leiomyoma.

can be "distinguished from type 2 with hysteroscopy using the lowest possible intrauterine pressure necessary to allow visualization" (Figure 4a–e).[8] The reclassification of the type 3 UL as submucous emphasizes the fibroid's dynamic nature, even when the uterine cavity appears unaffected. The position of the UL is determined by vectorial forces related to its size and the pressure exerted on the myometrial fibers. During its growth, the UL displaces rather than invades myometrial fibers, supported by a pseudocapsule.[24] This displacement becomes more evident during pregnancy, where changes in volume, consistency and migration within the uterine wall can be observed.[25] The visibility of the type 3 UL on hysteroscopy with minimal distending media pressure suggests its ability to bulge the cavity contour as a submucosal UL at rest, as the opposing uterine wall is the primary force preventing its development within the cavity. For these reasons, type 3 UL may exert a "double hit" effect on fertility as both a submucous and intramural UL.

Accurate assessment of FIGO type 3 ULs is crucial in this context. Diagnosis typically relies on ultrasound and hysteroscopy, which can determine if the UL is fully surrounded by myometrial fibers or encroaching the endometrial lining without distorting the uterine cavity. However, ultrasound alone cannot evaluate the dynamics of the uterine cavity in vivo, unless hysterosonography is employed. On the other hand, hysteroscopy performed with inadequate distension pressure may cause ULs to move towards the uterine wall, known as the "sinking fibroid" or "ghost fibroid" phenomenon.[26] Therefore, a comprehensive diagnosis of type 3 ULs requires an accurate and integrated evaluation of ultrasound and hysteroscopy, ideally conducted by experienced clinicians.

5 | FIGO TYPE 3 MYOMAS AND INFERTILITY: WHAT DO WE KNOW?

A recent review involving 1020 patients from three studies[27–29] observed significantly poorer in vitro fertilization (IVF) outcomes in women with type 3 ULs compared to controls without ULs (Table 1). Specifically, women with type 3 ULs experienced lower live birth rates (odds ratio [OR] 2.16, 95% confidence interval [CI]: 1.55–3.01), clinical pregnancy rates (OR 2.06, 95% CI: 1.52–2.81), and implantation rates (OR 1.77, 95% CI: 1.35–2.32). On the contrary, no significant impact of ULs on miscarriage rate could be established through data pooling. Interestingly, there was a statistically significant association between an increased number and larger size of ULs and a decline in IVF outcomes.[30] It is important to emphasize that these findings are limited by small sample size and heterogeneity within the study groups. However, the results of the study provide evidence of a negative influence of type 3 ULs, as well as an association between increasing size and number of ULs, and adverse reproductive outcomes.[27–30]

Consistent with the findings of the aforementioned review concerning a potential negative impact of myomas on endometrial receptivity, Governini et al. observed an altered expression of key genes involved in endometrial receptivity in women affected by type 3 ULs. Specifically, the authors reported a differential expression and localization of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) in the endometrium of women with type 3 ULs, as well as a derangement in the expression of key molecules involved in the inflammatory pathway.[22] Notably, the analysis was conducted on a small sample of patients ($n = 18$ per study group) with large ULs (>3 cm) during the proliferative phase

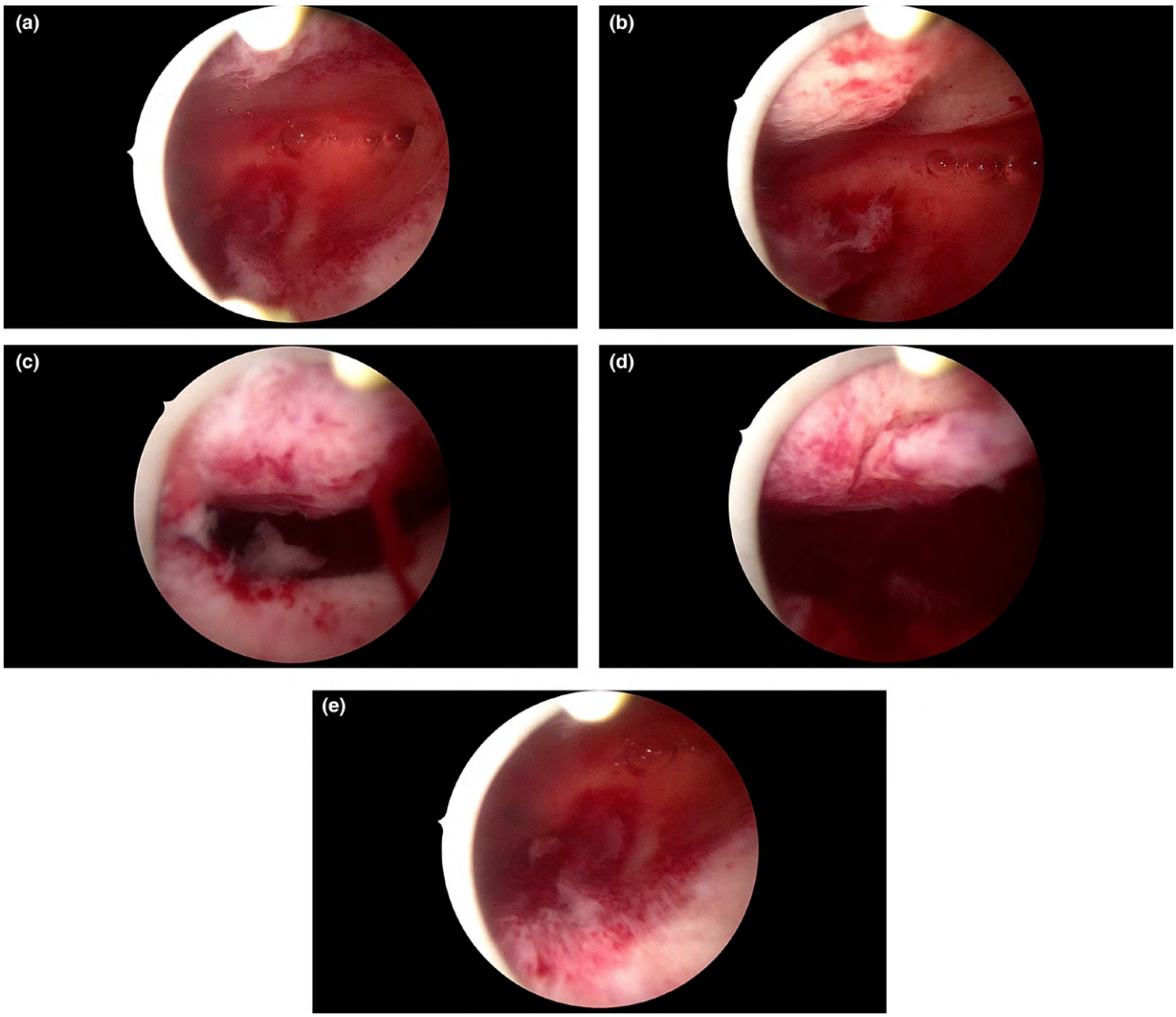

FIGURE 4 (a–e) Hysteroscopic view of a 30 mm type 3 uterine leiomyoma of the anterior wall at different inflow pressures. (a) Maximum pressure, (b, c) progressively reducing inflow pressure and (d, e) progressively augmenting pressure.

TABLE 1 Summary of type 3 ULs impact on reproductive outcomes as reported by Favilli et al.[30]

	Patients (cases - controls)	Live birth rate OR (95% CI)	Clinical pregnancy rate OR (95% CI)	Miscarriage rate OR (95% CI)	Implantation rate OR (95% CI)
Bai et al. (2020)[29]	291 (97; 194)	2.21 (1.19–4.10)	1.98 (1.14–3.44)	0.58 (0.20–1.67)	1.75 (1.11–2.75)
Han et al. (2022)[28]	96 (47; 49)	3.15 (1.28–7.76)	2.52 (0.99–6.42)	0.17 (0.02–1.58)	[Data not available]
Yan et al. (2018)[27]	604 (151; 453)	1.95 (1.26–3.02)	2.03 (1.36–3.04)	0.88 (0.40–1.94)	1.78 (1.27–2.49)
Total	991 (295; 696)	2.16 (1.55–3.01)	2.06 (1.52–2.81)	0.68 (0.37–1.25)	1.77 (1.35–2.32)

Abbreviations: CI, confidence interval; OR, odds ratio; UL, uterine leiomyoma.

of the menstrual cycle, and it was only possible to hypothesize a persistent alteration of the endometrial gene profile during the implantation window. Although further studies are necessary to better elucidate the matter, available evidence appears to support the negative effect of FIGO type 3 ULs on endometrial receptivity, potentially mediated through alterations in gene expression involved in the process.

6 | TYPE 3 MYOMAS IN INFERTILE WOMEN: TO TREAT OR NOT TO TREAT?

A million-dollar question is whether to treat this particular type of UL in order to help infertile women have better reproductive success. A question that stands between the recent evidence on the submucosal nature of this lesion and the absence of clinical studies

that demonstrate the benefits of its treatment. Therefore, good personalized clinical decision making should consider the risks associated to surgical removal and the potential fertility benefits, which may vary from patient to patient.[22,27–29] Certainly, from the perspective of a surgeon, an intriguing question arises regarding the optimal surgical approach for a tumor that was previously classified as intramural but is now considered submucosal.

7 | SURGICAL APPROACH TO TYPE 3 UTERINE FIBROIDS: ANATOMICAL RATIONALE

The primary principle guiding myomectomy procedures should be to preserve as many myometrial fibers as possible. In particular, intracapsular myomectomy, characterized by removal of the UL while preserving the outer layer of muscular fibers referred to as the pseudocapsule, has demonstrated its status as the preferred surgical approach for UL treatment. Additionally, the relevance of the pseudocapsule has also been highlighted, serving as both a natural limit for surgical intervention and potentially aiding in the healing of the myometrium following the procedure.[24]

Myometrial injury during myomectomy, particularly when it involves the opening of the uterine cavity, is a well-known risk factor for uterine rupture during pregnancy.[31] Due to the absence of an established waiting period after surgical treatment,[32–34] these factors become critically important in the management of patients who desire pregnancy. The status of "scarred uterus" may influence clinicians to opt for a cesarean section, which significantly increases the maternal-fetal risks associated with this surgical procedure.[32] As a result, the choice of surgical approach will impact the "time to pregnancy", which holds particular significance, especially for women of advanced reproductive age undergoing assisted reproductive techniques (ARTs).

Considering the anatomical characteristics of type 3 ULs and the existing surgical evidence for treatment, it can be hypothesized that hysteroscopy may currently be the optimal approach for myomectomy in type 3 ULs. The proximity to the endometrium allows for a greater preservation of myometrial fibers compared to laparoscopic, laparotomic, and vaginal approaches.[35]

Hysteroscopic myomectomy, when performed respecting the pseudocapsule, can take advantage of the fibroid's anatomical features. Studies have demonstrated that the distance between the fibroid's edge and the uterine serosa (free myometrial margin) is not a static parameter but increases during myomectomy, starting from the opening of the pseudocapsule.[36] This approach allows the UL to be displaced into the uterine cavity by uterine contractions, minimizing the sacrifice of myometrial fibers. The surgical technique of blunt dissection of fibroconnective bridges anchoring the UL to the pseudocapsule ensures a myometrial-sparing treatment.[37] Cold loop hysteroscopic myomectomy has been shown to be a safe and effective technique, allowing for the enucleation of ULs in a single operation with a low risk of postoperative synechiae (Figure 5a–e).[38–40] Considering that type 2 ULs larger than 30 mm and the number of ULs treated are associated with a high risk of requiring multiple procedures,[41,42] the possibility of performing myomectomy in a multiple-step procedure should be considered for type 3 ULs.

8 | AVAILABLE EVIDENCE ON THE HYSTEROSCOPIC REMOVAL OF TYPE 3 FIBROIDS

Although hysteroscopy appears to be the best option for type 3 ULs, only three studies have evaluated the feasibility of hysteroscopic myomectomy in such cases, yielding conflicting results. Capmas et al. conducted the first retrospective study in 2016, involving 13 women with type 3 ULs who underwent hysteroscopic myomectomy.[43] The mean size of resected myomas was 3.08 cm, and 31% of patients had multiple ULs. The procedure involved incising the endometrium and the first myometrial fibers using a twizzle electrode by a Bettocchi hysteroscope, followed by hysteroscopic myomectomy with a 26 Fr resectoscope for ULs removal. Some patients required multiple procedures, and additional interventions were necessary to achieve a normal uterine cavity for women desiring future pregnancy. In three patients intrauterine synechiae were detected during hysteroscopy follow-up and subsequently treated with hysteroscopic synechiolysis. Notably, no fertility outcomes were reported for the two patients desiring pregnancy. The high occurrence of post-surgical intrauterine synechiae observed in these cases might be attributed to the slicing technique, which does not ensure the integrity of the surrounding myometrial fibers.

In 2022, Han et al. examined the impact of hysteroscopic resection of type 3 ULs on pregnancy outcomes in infertile women undergoing IVF.[28] Hysteroscopic myomectomies were performed under ultrasound guidance using a 26 Fr bipolar hysteroscope equipped with a 30-degree lens. Intravenous infusion of oxytocin was administered to facilitate the bulge of UL in the uterine cavity. A Collins loop was used to detach the myoma from the myometrium, and additional procedures were scheduled for cases with multiple or difficult-to-reach ULs. No surgical complications were reported in 42 patients, and follow-up examinations revealed no residual ULs, abnormal bleeding, or infection. Only two patients reported mild intrauterine adhesions, which were subsequently removed through operative hysteroscopy. However, there was no statistically significant difference in the rates of successful embryo transfer, cumulative pregnancy, and cumulative live birth before and after the procedures.

A recent video case report described a successful hysteroscopic myomectomy using the classic slicing technique while preserving the pseudocapsule in a 35-year-old patient with a 30 mm type 3 UL on the posterior uterine wall and infertility. The patient did not experience any postoperative complications, and follow-up hysteroscopy confirmed an intact endometrium without intrauterine synechiae. The patient subsequently underwent successful IVF.[44]

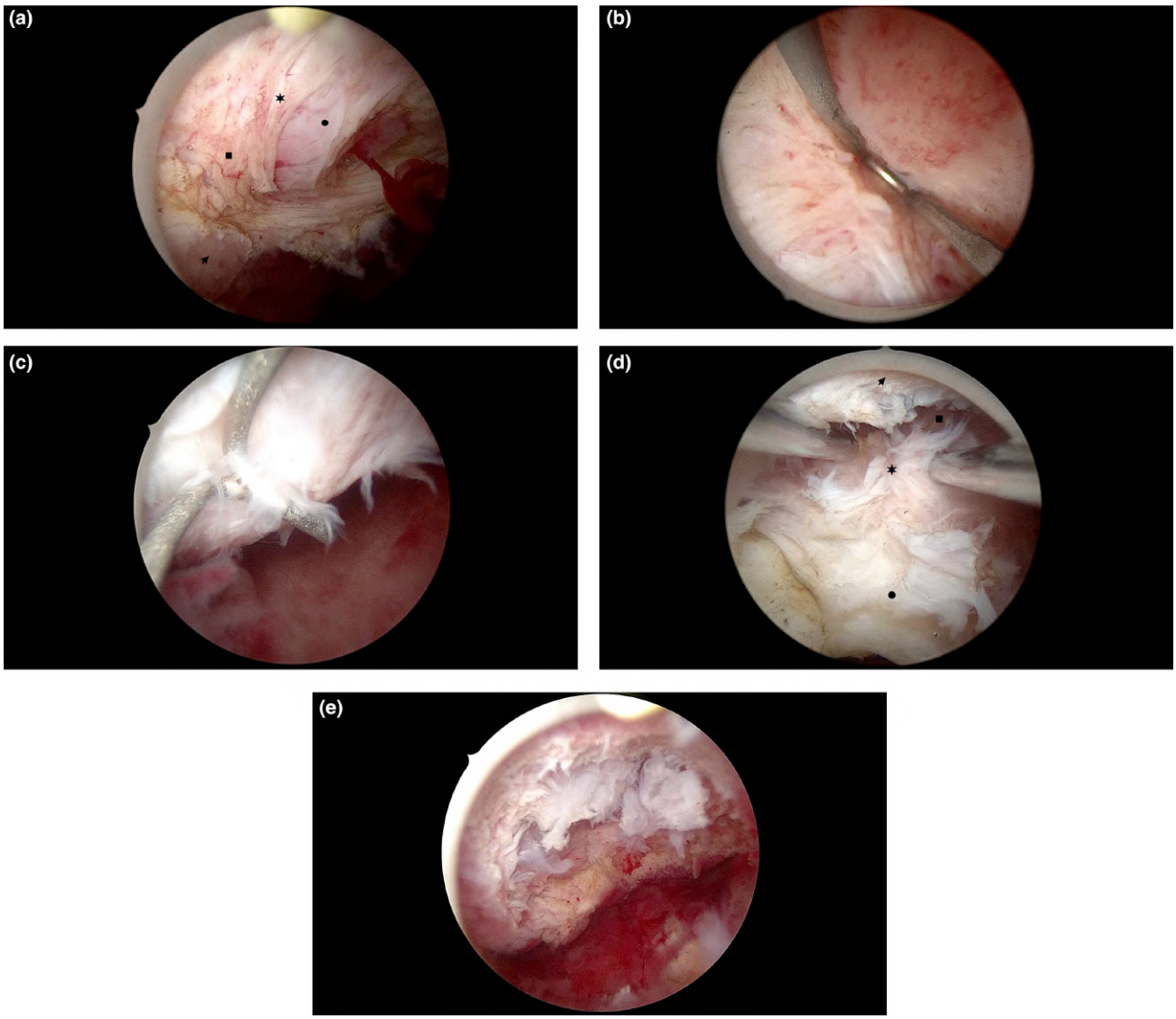

FIGURE 5 (a–e) Hysteroscopic myomectomy by cold loop technique of a 30 mm type 3 uterine leiomyoma of the anterior wall. (a) Slicing of endometrium covering the myoma (dot: myoma; star: pseudocapsule; square: myometrium; arrow: endometrium). (b) Cold loop inserted in the cleavage plane. (c) Blunt dissection of the fibroconnectival bridges anchoring the myoma to the pseudocapsule by the cold loop. (d) Slicing of the intramural component of myoma displaced in the uterine cavity (dot: partially resected intramural component of myoma; star: pseudocapsule with disconnected fibroconnectival bridges; square: myoma fovea; arrow: endometrium). (e) Uterine cavity with the notch of removed myoma.

Unfortunately, the available evidence on the feasibility of hysteroscopic myomectomy for FIGO type 3 ULs is limited. While hysteroscopic treatment appears to be safe and feasible, no definitive recommendations can be made regarding its effectiveness in improving reproductive outcomes.

9 | ABSENCE OF TARGETED MEDICAL THERAPY: ADDRESSING THE GAP

Targeted pharmacological therapy has the potential to revolutionize the treatment of type 3 ULs and ULs in general. In the era of precision medicine, the development of a molecule that specifically targets UL cells could overcome the limitations of surgical treatment and potentially improve reproductive outcomes. Even a reduction in fibroid size could have a positive impact on fertility.[5,12] The dynamic nature of fibroids suggests that their shrinkage, induced by a safe and effective molecule, could lead to a change in their classification according to the FIGO subclassification. For instance, a type 3 UL may transform into a type 4, potentially improving fertility or partially mitigating its detrimental effects (Figure 6). It is important to note that fibroid size also plays a role in reproductive outcomes. Therefore, inducing a reduction in fibroid size could offer a potentially safer and more effective alternative to surgery.[12] A comprehensive assessment of UL location and size is crucial, especially in patients desiring pregnancy. Medical treatment of ULs offers significant advantages, avoiding the need for surgery, which can lead to uterine scarring and

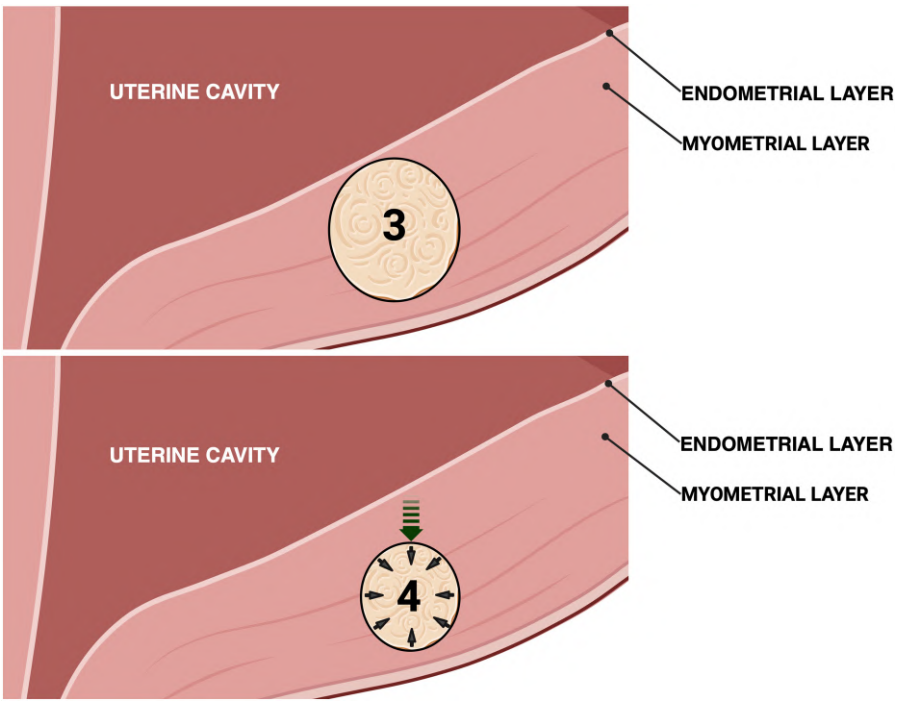

FIGURE 6 Myoma changing in classification from type 3 to type 4 after pharmacological therapy due to myoma volume reduction (green arrow: myometrial margin gain; black arrows: shrinkage effect by pharmacological therapy) (created with BioRender.com).

delayed ART or increase pregnancy complications, and reducing the economic burden associated with ULs, currently estimated at $2 billion annually, while also addressing low patient satisfaction rates.[45]

While various pharmacological and non-pharmacological treatments have been proposed for the symptomatic management of ULs, few have demonstrated effectiveness in reducing their volume. However, these treatments often come with side effects or safety concerns.

9.1 | Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonists (GnRHa) have been widely used as a preoperative treatment before myomectomy to manage anemia in patients with heavy menstrual bleeding, thinning the endometrium, and reducing the size of the uterus and ULs.[46] However, long-term use of GnRHa is associated with significant side effects that are considered difficult to tolerate.[46] It is important to note that the administration of GnRHa before surgery has been linked to prolonged surgical duration and an increased risk of multiple procedures during hysteroscopic myomectomy. These effects are attributed to the changes induced by GnRHa in the structure of the myoma pseudocapsule.[47–49] This aspect is particularly relevant when considering hysteroscopic treatment of FIGO type 3 ULs, which presents challenges for the surgeon. Due to the potential negative impact, GnRHa treatment might be avoided in infertile patients with type 3 ULs scheduled for hysteroscopic surgery and considered only for selected cases where reducing the volume of a UL could lead to an improvement in the uterine cavity.

9.2 | Gonadotropin-releasing hormone antagonists

Despite the modest reductions observed in ULs and uterine volume, oral gonadotropin-releasing hormone (GnRH) antagonists with add-back therapy (ABT) hold great promise for potential impact.[50,51] Dolmans et al.[5] proposed an algorithm suggesting the use of a GnRH antagonist without ABT for 3 months to restore the original shape of the uterine cavity distorted by a UL, considering the type of UL and associated symptoms such as infertility, bleeding, or pelvic pain. For instance, 40 mg/day of relugolix without ABT can reduce UL volume by over 50% after 24 weeks of treatment.[52] The algorithm recommends hysteroscopic myomectomy for type 0, 1, or 2 submucous ULs smaller than 3 cm in cases of infertility, while a GnRH antagonist is advised for 3 months for type 2 submucous ULs larger than 3 cm or multiple intramural ULs with or without adenomyosis. Successful medical treatment should be followed by natural conception or embryo transfer. Surgical myomectomy is only recommended if medical therapy fails to restore the anatomy of the uterine cavity. In cases where the patient's anti-Müllerian hormone (AMH) is reduced or their age necessitates it, oocyte retrieval and vitrification are recommended. Although this algorithm could potentially apply to type 3 fibroids, there is currently no evidence supporting its use. While awaiting the development of new molecules for safe and effective uterine fibroid treatment, well-designed clinical trials are required

to assess the efficacy of existing treatments for type 3 myomas and their impact on reproductive outcomes.

9.3 | Selective progesterone receptor modulators

The introduction of selective progesterone receptor modulators, such as ulipristal acetate, has marked a significant advancement in the treatment of ULs, particularly for patients who desire pregnancy and where surgical intervention is not a cost-effective option. Several studies have reported promising reproductive outcomes following daily administration of 5 mg of ulipristal acetate for 3 months, with one to three cycles of therapy. Spontaneous pregnancies or pregnancies achieved with ART, both with and without subsequent myomectomy – including submucous myomas – have been described.[53,54]

Ulipristal acetate possesses favorable characteristics that make it an ideal candidate for fibroid treatment, without the adverse effects commonly associated with reduced estrogen levels and bone density loss. However, it is worth noting that prior to the review conducted by the European Medicines Agency (EMA), there were reports of severe liver injury in patients with ULs who received ulipristal treatment without undergoing surgery.[12] Currently, the administration of ulipristal acetate 5 mg a day for up 3 months is limited to premenopausal women who are not suitable candidates for surgery or uterine fibroid embolization, or who have experienced unsuccessful surgical interventions. Such patients should be subject to rigorous liver function monitoring.[55]

10 | PUTATIVE ALTERNATIVE SURGICAL TREATMENTS TO HYSTEROSCOPY

10.1 | Uterine artery embolization

Uterine artery embolization (UAE) was initially explored as an alternative technique to standard surgical methods. First described in 1995 by Ravina et al.,[56] UAE performed by an interventional radiologist is a procedure that involves the embolization of the uterine arteries, leading to the devascularization and subsequent involution of leiomyomas.[57] However, in the case of type 3 ULs, due to their close proximity to the uterine cavity, the embolization procedure could have detrimental effects on the endometrium, potentially leading to Asherman's syndrome and irreversibly compromising fertility outcomes.[58] Additionally, UAE appears to be associated with lower birth rates and higher miscarriage rates compared to other treatments.[59] Furthermore, it seems to negatively affect ovarian vascularization, resulting in diminished ovarian function and further impairment of reproductive function. Based on this evidence, the American Society of Reproductive Medicine (ASRM) and the American College of Obstetricians and Gynecologists (ACOG) do not recommend UAE for patients with ULs who also have fertility needs.[60]

10.2 | High-intensity focused ultrasound

High-intensity focused ultrasound (HIFU) treatment delivers rapid heat to target tumor tissue, while minimizing impact on surrounding tissue. The coagulation necrosis induced in the target UL has the potential to reduce UL size, restoring the normal shape of the uterine cavity and physiological myometrial contractions.[61,62]

HIFU has been proposed as a precise therapy for ULs that preserves the surrounding healthy myometrium, protects the endometrium, and maintains favorable conditions for blastocyst implantation, thus potentially improving pregnancy rates. Studies on HIFU treatment for ULs in patients seeking pregnancy have reported few pregnancy complications and a higher rate of vaginal deliveries compared to traditional surgery.[63] The success observed in HIFU studies may be attributed to the preservation of female genital anatomy, shorter recovery times, and faster time to pregnancy.[63] Additionally, HIFU treatment has shown no negative impact on ovarian function, as demonstrated by Liu et al.,[64] with no significant differences in AMH, FSH, INHB, and AFC levels at 6 and 12 months after HIFU compared to pretreatment levels.

While HIFU holds promise as a minimally invasive option for treating FIGO type 3 ULs, further research is necessary to establish its safety and effectiveness in infertile patients and determine its impact on reproductive outcomes.

10.3 | Radiofrequency ablation

Radiofrequency ablation is a minimally invasive procedure that has been used for more than 30 years in the treatment of various organs including kidney, liver, thyroid, and lung.[65–68] In 2012, it was approved by the Food and Drug Administration as a treatment for symptomatic ULs.[69] This technology enables the ablation of ULs by inducing coagulative necrosis using ultrasound-guided laparoscopic or transcervical devices.[70,71] Radiofrequency myolysis (RFM) has shown promising results in reducing symptoms associated with ULs, such as menstrual bleeding and chronic pelvic pain.[72–74]

Several studies have reported favorable pregnancy outcomes in patients who underwent RFM. Polin et al. described 50 pregnancies, with 44 resulting in full-term deliveries, minimal delivery complications, and over half of them being vaginal deliveries. These patients did not experience common complications associated with traditional surgical myomectomy, such as uterine rupture or invasive placentation.[75] However, it should be noted that the reported data only includes patients who successfully conceived after the treatment, making it difficult to draw general conclusions about the effect of RFM on fertility.

RFM offers several advantages over other minimally invasive therapies. A recent systematic review demonstrated a significantly greater reduction in UL volume in patients treated with RFM compared to uterine artery embolization (UAE) and high-intensity focused ultrasound (HIFU).[76] Furthermore, compared to standard

myomectomy, RFM showed lower rates of major surgical morbidity, with no intra- or postoperative complications reported.[77,78]

A recent study by Fasciani et al. followed 61 premenopausal women with 112 symptomatic ULs treated with transvaginal, hysteroscopic or laparoscopic RFM based on the location of the ULs. After 36 months, they observed a reduction in UL volume and diameter of 90.20% and 55.70%, respectively (mean diameter at baseline was 3.86 cm). Among the treated ULs, 11 were classified as type 3 and were treated using vaginal and hysteroscopic approaches (8 and 3 cases, respectively).[71]

The positive surgical outcomes, low complication rates compared to alternative treatments, ease of execution, and successful pregnancies following RFM suggest that it may be a viable method for treating type 3 ULs.[79,80] However, it is important to note that RFM is not applicable to all types of ULs (it is not recommended for FIGO type 7 ULs),[75] and its effectiveness for infertile patients has not been investigated, as women desiring pregnancy have been excluded from all RFM studies.

11 | CONCLUSIONS

The trend of delaying childbirth has led to an increased prevalence of uterine diseases among women participating in assisted reproduction programs. Among these conditions, ULs are the most common and have been associated with potential negative effects on endometrial receptivity.

The FIGO classification system has provided a framework for specifically identifying and studying type 3 ULs, which are characterized as hybrid lesions exhibiting both submucosal and intramural activity under dynamic conditions. The aim of this review was to summarize the current evidence regarding the impact of type 3 ULs on embryonic implantation and explore potential therapeutic strategies based on the limited available data. By highlighting the existing evidence gap, this review emphasizes the need for future studies to delve into the underlying mechanisms of the adverse effects caused by type 3 ULs on endometrial receptivity. In addition, there is a notable lack of cost-effective trials comparing different treatment options aimed at rapidly restoring uterine function. Gathering this new evidence will be of paramount importance in improving outcomes for patients with these challenging conditions.

AUTHOR CONTRIBUTIONS

Acquisition, analysis, and interpretation of data for the work: Alessandro Favilli, Amerigo Vitagliano; Drafting the work: Alessandro Favilli, Amerigo Vitagliano, Andrea Etrusco; Revising the work critically for important intellectual content: Andrea Tinelli, Antonio Simone Laganà, Ivan Mazzon; Final approval of the version to be published: Vito Chiantera, Sandro Gerli and Ettore Cicinelli; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Alessandro Favilli, Amerigo Vitagliano, Miriam Dellino All authors meet the ICMJE criteria for authorship and have read and agreed to the current version of the manuscript.

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The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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