Intramural myomas more than 3–4 centimeters should be surgically removed before in vitro fertilization

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Disclaimer: Authors for "fertile battles" are chosen to represent the full breadth of opinions. Individual authors, even within one side of the debate, do not necessarily agree with all viewpoints expressed.

PRO: Intramural myomas more than 3–4 cm should be surgically removed before in vitro fertilization

Pro 1: Marie-Madeleine Dolmans, M.D., Ph.D.

Not all myomas are the same

Relevance of uterine fibroids and infertility. Myomas can cause infertility depending on their size and site (1, 2). The International Federation of Gynecology and Obstetrics (FIGO) classification takes into account the degree of intramural extension and distortion of the uterine cavity (3). There are numerous mechanisms (Fig. 1) linking uterine fibroids and infertility (2): uterine cavity distortion (myoma types 0, 1, 2, 2–5); impaired endometrial and myometrial blood supply; greater uterine contractility; hormonal, paracrine, and molecular modifications; defective endometrial receptivity and gene expression, role of transforming growth factor beta-3 (TGF-β3) and HOXA-10; and a thicker capsule.

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Con 1: Malcolm G. Munro, M.D.

Intramural Leiomyomas and Endometrial Receptivity: Is Now the Time to Consider Type 3 Leiomyoma?

Endometrial receptivity and the impact of leiomyomas on implantation. The implantation process results from the coordinated and synchronous development of the embryo and the endometrium leading up to the window of receptivity (70). Among the endometrial expressions that are associated with successful implantation are the homeobox (Hox) genes

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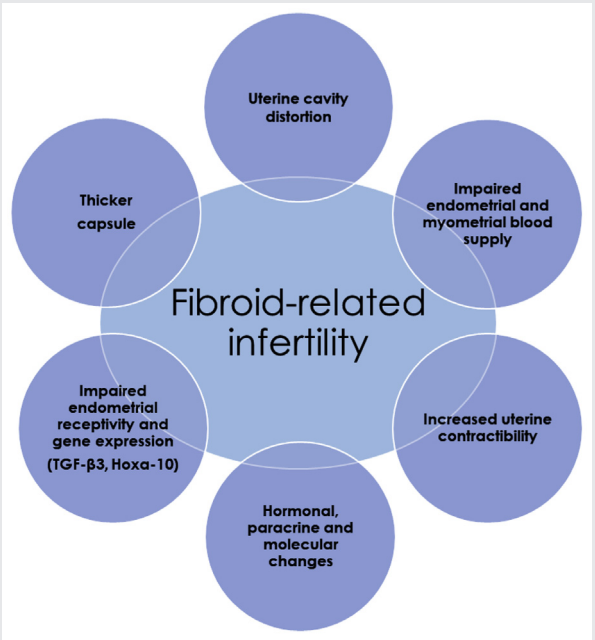
FIGURE 1



Mechanisms linking uterine fibroids and infertility. (Adapted from Donnez and Dolmans [2].)

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Uterine cavity distortion. The first mechanism is clearly discernible and has been widely documented (4). Because this Fertile Battle is focusing on intramural myomas, we will investigate intramural myoma-related infertility (2, 5).

Impaired endometrial and myometrial blood supply. The presence of myomas close to the uterine cavity (type 3) impedes endometrial blood flow (6, 7). Indeed, studies using magnetic resonance imaging have reported diminished blood flow in fibroids and their surrounding myometrium (6). Transvaginal ultrasound (7) has shown that uterine fibroids possess lower resistance and uterine artery pulsatility indices.

A prospective study by Nieuwenhuis et al. (8) demonstrated that blood supply alterations interfere with myoma growth because volume is typically greater in highly vascularized fibroids.

Greater uterine contractility. Intramural fibroids may alter uterine peristalsis and, hence, blastocyst implantation (9–11). Decreased contractility in response to progesterone could favor embryo implantation (12, 13), but if the proximity of intramural myomas impacts uterine peristalsis, it may cause defective blastocyst implantation.

Hormonal, paracrine, and molecular modifications. Fibroids can affect the expression of genes needed for implantation, like glycodelin and bone morphogenetic protein (BMP) receptor type 2 (14). Myomas may also be responsible for

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(71), of which HoxA-10 and HoxA-11 appear to be the most important (72, 73) possibly via their role in activating or repressing target genes such as β3-integrin and Emx2 (2). Women with a deficient endometrial expression of HoxA-10 and HoxA-11 experience reduced implantation rates (73, 74).

A spectrum of growth factors such as heparin-binding epidermal growth factor, a member of the TGF-β family that, under the influence of progesterone, induces secretion of BMP-2, a protein that seems critical to normal decidualization, are also important (75–77). Low endometrial levels of BMP-2 are associated with reduced levels of HoxA-10 and LIF (78). Therefore, one may ask, how might leiomyomas affect these critical physiological processes?

How do leiomyomas impair endometrial receptivity?. A potential mechanism by which leiomyomas may influence receptivity is via TGF-β3-induced downregulation of BMP-2 receptors and resulting endometrial BMP-2 resistance, thereby altering relevant molecular expressions, including HoxA-10. Indeed, available evidence has demonstrated reduced endometrial HoxA-10 expression in women with submucous leiomyomas, a finding that appears to affect the endometrium globally, not just the endometrium overlying the fibroid (79) (Fig. 2).

Compared with women without submucous leiomyomas, there are other altered molecular endometrial expressions in those with submucous tumors. The normal luteal phase increase in LIF appears to be "blunted" (80), a finding associated with unexplained infertility and recurrent abortion (81). Additionally, endometrial interleukin-2 levels are reduced (80), and there are demonstrable differences in relevant inflammatory markers such as macrophages, monocyte chemotactic protein (MCP-1), and PGF2α (10).

Collectively, these data suggest that the TGF-β3 secreted by submucous leiomyomas initiates a global endometrial signaling mechanism that results in reduced expression of factors such as HoxA-10 and LIF, thereby altering decidualization resulting in reduced implantation success (78, 82). In addition, it could be postulated that this endometrial manifestation occurs when a leiomyoma is in contact with, or in proximity to, the endometrium regardless of whether or not the endometrial cavity is physically distorted.

Issues with studies on "intramural myomas". The role of the "intramural leiomyoma" in the genesis of infertility has been unclear for a variety of reasons. While there is evidence from some studies suggesting that intramural leiomyomas are associated with increased rates of reduced fecundity and early pregnancy loss (4, 23, 40, 43, 46, 47, 83–84), other investigators have failed to support this hypothesis (20, 45, 85–90). Studies on genetic and molecular expressions are also inconsistent, with some showing reduced luteal phase expressions of HoxA-10, LIF, and E-cadherin in women

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declining levels of cytokines crucial to implantation, such as leukemia inhibitory factor (LIF) and cell adhesion molecules. Furthermore, the decreased expression of cell adhesion molecule E-cadherin has been reported in the endometrium of subjects with non-cavity-distorting intramural fibroids. Uterine myomas have a considerable influence on both function and gene expression in the endometrium, hampering endometrial receptivity (14).

Defective endometrial receptivity and gene expression: role of TGF-β3 and HOXA-10. In 2015, Rackow and Taylor (15) reported that the endometrial messenger ribonucleic acid expression of HOXA-10 (critical to regulating endometrial receptivity) was consistently lower in the presence of submucosal myomas. HOXA messenger ribonucleic acid and stromal protein expression were also affected in the intramural group compared with controls. In an editorial, Taylor (16) proposed that larger fibroids produce greater quantities of TGF-β3, allowing those closest to the uterine cavity to release more TGF-β into endometrial cells, thereby altering BMP-2 and HOXA-10 expression. The amounts of TGF-β reaching the

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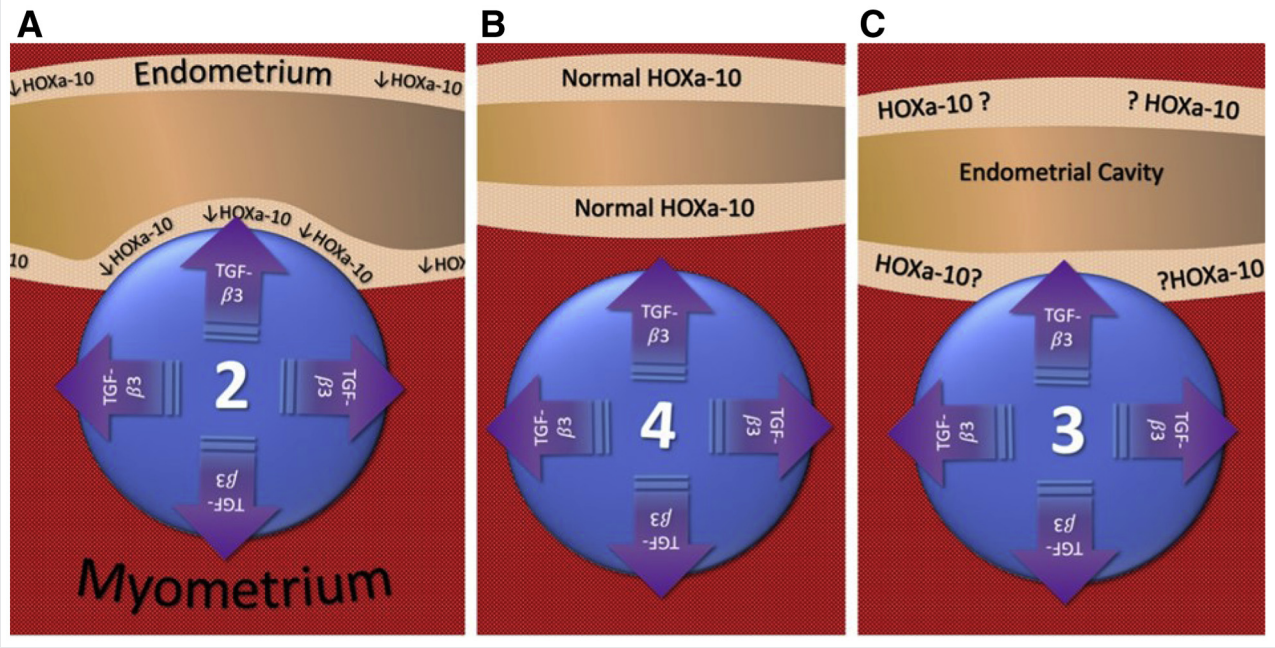
with intramural leiomyomas (91, 92), while others suggesting no alterations in relevant endometrial gene expressions (93, 94).

By some definitions, intramural leiomyomas require that there exists myometrium interposed between the border of the leiomyoma and the endometrium. In contrast, others include tumors that abut the endometrium, even if they do not distort the endometrial cavity. Distinguishing between these two entities is not always readily achieved. There is little doubt that the accuracy of leiomyoma phenotyping varies depending on the imaging or endoscopic techniques used—ultrasound, sonohysterography, hysteroscopy, or magnetic resonance imaging.

Other confounders may impact analysis of studies evaluating the relationship between "intramural myomas" and endometrial receptivity, including tumor volume, leiomyoma number, genetic heterogeneity, the cycle day for sampling, and even the thickness of the myometrium between the leiomyoma and the endometrium, if present. For example, one set of investigators demonstrated that

FIGURE 2



Impact of submucous leiomyomas on endometrial HoxA-10 messenger ribonucleic acid expression. (Munro)
(A)Investigators from Yale University found that submucous leiomyomas (e.g., FIGO type 2) were associated with reductions in HOXa-10 expression both over the leiomyoma and throughout the endometrial cavity.
(B) On the other hand, the HoxA-10 expression in women with intramural myomas (FIGO type 4) was similar to that of women without any leiomyomas. (Adapted from Rackow et al., with permission (10).)
(C) What is not known, to date, is the impact on endometrial HOXa-10 and other relevant expressions of leiomyomas that are "intramural" but in contact with the endometrium (FIGO type 3).
FIGO = International Federation of Gynecology and Obstetrics.

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uterine cavity vary by the square of the distance from the cavity ($1/x^2$, where x is the distance between the endometrium and the fibroid) (16).

Thicker capsule. The capsule surrounding fibroids is made up of compressed myometrium and contains nerves and neuroendocrine fibers, which may affect muscle contractility (17).

Impact of non-cavity-distorting uterine fibroids. While the need to treat submucosal fibroids is generally acknowledged (4), the debate around non-cavity-distorting uterine fibroids continues (1, 2). In a recent review (2), all series published to date were discussed, including two important meta-analyses that are reported here (18, 19).

Data from Yan et al. (18) strongly indicated that type 3 fibroids have a negative impact on clinical pregnancy and live birth rates, especially if their individual diameter exceeds 2 cm. Rikhraj et al. (19) reviewed 15 quantitative studies out of 139 identified records. They concluded that patients with non-cavity-distorting intramural fibroids undergoing in vitro fertilization (IVF) have a 44% lower chance of a live birth and 32% lower odds of a clinical pregnancy than unaffected women.

In conclusion, all published studies and meta-analyses reviewed by Donnez and Dolmans (2) concur that non-cavity-distorting intramural myomas do indeed have a deleterious impact on IVF outcomes. Two factors have emerged as key: fibroid size (the larger, the more TGF-β3 secretion) and proximity to the uterine cavity. In other words, a type 3 myoma of 2 cm or more will have a detrimental effect close to the endometrial lining. If a fibroid is intramural but not in contact with the underlying endometrium (types 4 and 5), 3 cm is usually considered the cutoff (2). A number of investigators recommend surgical removal of intramural fibroids (16), but we should perhaps be asking ourselves another crucial question (1, 2). If the negative impact of myomas is linked to size and proximity to the uterine cavity, why not try a medical approach to reduce their size and force them further into the myometrium?

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while intramural tumors with a mean diameter of 4 cm or less did not impact pregnancy rates after embryo transfer, larger leiomyomas were associated with reduced pregnancy rates (89). These findings are in accord with those reported by others (4, 87, 95).

FIGO type 3 or 4?. The FIGO system was designed to recognize and distinguish between two basic categories of "intramural" leiomyomas—those that are surrounded by myometrium (type 4) and those that have contact with the endometrium without distortion of the endometrial cavity (type 3 fibroid) (3, 96). This distinction was made to help investigators and clinicians distinguish between two entities that were previously conflated under the intramural label.

Given the evidence that contact with the endometrium is associated with impaired decidualization, it could be hypothesized that FIGO type 3 leiomyomas may have a very different impact on endometrial receptivity than type 4 tumors. Indeed, there is early evidence that this may be the case. Recent evidence from Italy identified alterations in matrix metalloproteinases in women with type 3 leiomyomas compared with controls that may reflect reduced endometrial receptivity (97). Two retrospective comparative studies from China are supportive (Table 2). In both, which collectively comprised almost 250 women and approximately 650 controls, there were highly significant reductions in implantation/chemical pregnancy, clinical pregnancy, and live birth rates in those with type 3 leiomyomas (18, 98). Unfortunately, and to date, there are no published prospective studies evaluating similar outcomes.

Where do we go from here?. Whereas these preliminary data are consistent with the hypothesis that type 3 leiomyomas may indeed be the intramural tumors with the most significant impact on endometrial receptivity, they are not confirmatory. As a result, it seems necessary to produce more studies that evaluate the effect of type 3 tumors on relevant endometrial molecular expressions compared with other types and further assess these leiomyomas' impact on the

TABLE 1

Reproductive outcome in patients with small intramural myoma vs. controls.

Author	Pregn. Rate M > < C	Clin. Pregn rate M > < C	LBR M > < C	Abortion M > < C
Check et al. 2002	42.6> <52.4	34.4><47.5	22.9> <37.7	33.3> <20.7
Hart et al. 2001	23.3> <34.1	15.1 > < 28.3	-	-
Khalaff et al.2006	23.6> <32.9	18.8> <28.5	14.8> <24	-
Behbehani et al. 2018	-	32> < 47	25.5> <37.8	15.8 > < 14.4
Lei Yan et al. 2018	29.1> <51.4	27.8> <43.9	21.2> <34.4	23.8> <22.1
Sunkara et al. 2010		15% reduction	21 % reduction	Non significant 24% increase

Note: C = controls; LBR = live birth rate; M = myoma.

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Pro 2: Wenjia Zhang, M.D., and Keith Isaacson, M.D.

Type 3 uterine myomas should be removed hysteroscopically before embryo transfer to maximize clinical pregnancy rates

Submucosal (types 0–2) fibroids distorting the endometrial cavity can impact pregnancy and assisted reproductive technology (ART) outcomes (20, 21). A 2009 systematic review demonstrated that the presence of fibroids decreased fertility overall, with the largest impact seen in the submucosal group with a 70% reduction in clinical pregnancy rates. In the intramural group, a reduction in both live birth (RR, 0.70) and clinical pregnancy (relative risk [RR], 0.81) rates was seen (4). Women who underwent hysteroscopic resection of submucosal fibroids had improved clinical pregnancy rates compared with those who did not undergo hysteroscopic

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spectrum of fertility and pregnancy outcomes. If the molecular and clinical data are supportive, the performance of well-designed studies evaluating the effect of therapy would be justified.

Con 2: Elizabeth A. Stewart, M.D.

Minimizing Bias and Harm from Treating Intramural Fibroids for Fertility

I believe that because our knowledge regarding intramural fibroids and fertility is limited and subject to biases, we should be open to a range of options including uterine artery embolization (UAE) and magnetic resonance-guided focused ultrasound (MRgFUS) rather than reflexively choosing surgery. There is biologic heterogeneity among fibroids, most clearly in driver mutations, and there are correlations between mutation status and clinical characteristics (99–102). Thus, it is likely that only a subset of fibroids impair fertility. In the United States, particularly, many are biased to remove all fibroids before fertility treatment because surgery is typically covered by insurance, whereas fertility care is often not.

We also cite the evidence that while all fibroids impair fertility, only surgical treatment of submucosal fibroids improves pregnancy and live birth rates (4, 103). Is it because submucosal fibroids are biologically different or because the

TABLE 2

In vitro fertilization and embryo transfer outcomes in women with FIGO type 3 leiomyomas.

							Pregnancy outcomes (%)							
							Biochemical		Clinical		Miscarriage		Live Birth	
Author	Year	Embryos Fresh/frozen	Group	N	Embryos transferred per cycle	SD	Rate	*P*	Rate	*P*	Rate	*P*	Rate	*P*
Bai et al.	2019	Fresh	Control	194	2.0	0.6	24.6	.015	38.1	.014	20.3	.309	30.4	.011
			Type 3	97	2.0	0.5	15.7		23.7		30.4		16.5	
Yan et al.	2018	Frozen	Control	453	1.7	0.9	51.4	<.001	43.9	.010	22.1	.839	34.4	.002
			Type 3	151	1.6	1.0	29.1		27.8		23.8		21.2	

Note: Shown are data from Yan et al. (18) and Bai et al. (98), who retrospectively evaluated the results of embryo transfer in women with and without FIGO type 3 leiomyomas. FIGO = International Federation of Gynecology and Obstetrics; SD = standard deviation.

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myomectomy (4). Recommendations for myomectomy are less clear for asymptomatic women with infertility who have intramural fibroids that do not distort the endometrial lining (types 3–4) (4, 22, 23). We strongly believe that women with type 3 myomas (intramural abutting the endometrial cavity) ranging from 2 to 4 cm in diameter should have these fibroids removed hysteroscopically in patients with recurrent implantation failure and unexplained infertility. Our opinion is supported by science and logic presented in the following.

Normal myometrial activity and intramural fibroids. Uterine peristalsis is initiated by the inner myometrium and changes throughout the menstrual cycle in a hormonally mediated manner (24, 25). During the estrogen-dominant follicular phase, there is a progressive increase in uterine contractility peaking in the preovulatory period (25–28). In the periovulatory period, the predominant uterine peristalsis propagates from the cervix to the fundus, which can facilitate fertilization by assisting sperm transportation (25, 28–30). After ovulation, the progesterone-dominant luteal phase shows relative uterine quiescence to facilitate fundal implantation. If no pregnancy occurs, the early follicular phase demonstrates an antegrade wave from the fundus to the cervix, emptying uterine contents and establishing hemostasis (25, 31).

Both submucosal and intramural fibroids cause abnormal uterine peristalsis (9, 11, 32). In a large retrospective cohort in 2018, Yan et al. (18) sought to explore the impact of type 3 intramural fibroids on ART success given the small numbers of women with type 3 intramural fibroids in their 2014 cohort. A total of 453 control subjects without fibroids were matched with 151 women with type 3 intramural fibroids undergoing IVF-intracytoplasmic sperm injection, 23 of whom had more than one of fibroids such as multiple intramural or subserosal fibroids. There was a decrease in the fibroid vs. control group regarding the implantation, clinical pregnancy, and live birth rates (22.7% vs. 34.4%, $P=.001$; 27.8% vs. 43.9%, $P=.003$; and 21.2% vs. 34.4%, $P=.013$, respectively) (18). Using the receiver operating characteristic curves, the investigators noted that a size greater than 2.0 cm for type 3 fibroids was associated with a trend in lower birth rates.

Myomectomy: laparotomic, laparoscopic, and hysteroscopic. Given that the data overwhelmingly supports removing type 3 myomas to enhance embryo implantation, the only question is the best method of removal with the options being laparotomic, laparoscopic, and hysteroscopic. It has been well documented that laparoscopic surgery, vs. laparotomy, is associated with a faster recovery and lower risk of blood loss and infection and has no

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harm of hysteroscopic surgery is less than other myomectomies? We do not know.

As surgeons, we also have a familiarity bias in favor of surgical therapies (104). I saw this when I hosted resident journal club for an article titled "Loss of ovarian reserve after uterine artery embolization: a randomized comparison with hysterectomy," and the consensus was that women lost ovarian reserve after UAE (105). Even after reviewing the data figures that showed there was no significant difference in ovarian reserve between the two groups, some of the trainees persisted in believing there was. Similarly, many believe that pain after UAE is worse than that after surgery despite good RCTs demonstrating the opposite (106, 107).

The risks of surgical myomectomy are substantial and well known but are also minimized because of familiarity bias. Many of us would label transfusion as an inevitable part of treating fibroids due to heavy menstrual bleeding and anemia. Nonetheless, the risk of transfusion is significantly reduced (OR, 0.07) with UAE compared with surgery (108, 109). In addition, for women actively seeking pregnancy, surgical risks include the risk of serosal or intrauterine adhesions, commitment to future cesarean section and its attendant risks, and delay of pregnancy pursuit. Thus, taking advantage of nonsurgical fibroid interventions is an attractive alternative.

Uterine artery embolization is a widely used uterine-sparing intervention with substantial evidence from RCTs of symptomatic relief following treatment (108, 110). Nonetheless, there is limited information specifically about reproductive outcomes after UAE (108). Concern about UAE and fertility center on two major factors: live birth rate and preservation of ovarian reserve. Systematic reviews have shown better reproductive outcomes after myomectomy than UAE, yet over half of women undergoing UAE have live births (111). This is especially remarkable because gynecologists likely differentially refer better fertility candidates to myomectomy. While underpowered, the recent FEMME RCT showed similar pregnancy and live birth rates in a group of women whose mean age was in their early 40s (112, 113).

Regarding ovarian function, studies comparing markers of ovarian reserve between surgery and UAE (105) and MRgFUS and UAE (114) showed no difference between groups in ovarian reserve for up to 36 months following treatment. Moreover, the precipitation of menopause after UAE treatment seemed to be confined only to women aged ≥ 45 years (115).

Finally, both the risks of a subsequent cesarean section and risks of multiple myomectomies tend to be minimized and favor consideration of an alternative such as UAE and MRgFUS. Much work has focused on preventing cesarean de-

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higher risk of uterine dehiscence in pregnancy. It has also been demonstrated that removal of the entire myoma and not a fraction of the myoma is associated with the best long-term outcomes (33).

We believe that the preferred method of myomectomy for type 3 myomas between 2 and 4 cm is hysteroscopic and not laparoscopic for the following reasons:

- Fibroids are monoclonal and are derived from a single cell. They displace normal myometrium and do not invade normal myometrium. When a type 2 or 3 myoma is removed hysteroscopically using a bipolar loop electrode, the surgery is contained within the pseudocapsule, and no normal myometrium is damaged. When this same procedure is performed laparoscopically, the normal myometrium is cut to reach the myoma. This damaged myometrium requires difficult suturing when repaired in multiple layers. There is higher blood loss and longer operating room time associated with the laparoscopic method. Likewise, the recommendation for pregnancy after operation is 3–6 months following a laparoscopic approach and 6–8 weeks following a hysteroscopic approach.
- Because the normal myometrium is interrupted with a laparoscopic approach, most patients will undergo a cesarean section for delivery to minimize the risk of dehiscence during labor. This is not the recommendation after a hysteroscopic resection. There are no case reports in the recent literature describing uterine dehiscence after a hysteroscopic myomectomy.
- There is very little scar tissue formed with a hysteroscopic myomectomy if the opposing endometrium is not traumatized. There are often intrapelvic adhesions after a laparoscopic myomectomy that can lead to pain and infertility.

Hysteroscopic type 3 myomectomies can be safely accomplished with a bipolar resectoscope and transabdominal ultrasound guidance. Tissue shavers with side opening blades are not designed for this type of dissection. Because there are no abdominal incisions with the hysteroscopic approach, the patient can return to normal activities in 24 hours as opposed to the typical 2–4 weeks with a laparoscopic approach.

Conclusion. Removal of intramural myomas should be considered in women with infertility seeking ART. The size and location of intramural fibroids likely contribute to the success of ART, and special consideration should be given to counseling women regarding myomectomy for type 3 fibroids with a size of 2 cm or larger. Hysteroscopic myomectomy using a bipolar resectoscope is the preferred approach for type 3 myomectomies and, thus, should be considered as a first-line therapy.

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livery, and although the evidence is sparse, several surgeons recommend a cesarean section after laparoscopic and open myomectomy (116, 117). In contrast, most practitioners allow vaginal delivery after nonsurgical approaches (118).

Because of the high risk of formation of new fibroids, the primary treatment of fibroids does not end fibroid care. Because parity is strongly protective for the risk of new fibroids (119), for the woman actively pursuing pregnancy, the risk is less than that of the woman desiring optimized future fertility. The secondary fibroid treatment brings on an additional risk that is seldom acknowledged (120). Restructuring the paradigm of fibroid care to think of a "uterine fibroid life" as has been eloquently advocated for in endometriosis by Chapron et al. (121) has value for uterine fibroids. The introduction of oral gonadotropin-releasing hormone antagonists formulations for long-term therapy will benefit this group who can aim for one definitive intervention prepregnancy (122, 123).

Con 3: Mathilde Bourdon, M.D., Ph.D., and Pietro Santulli, M.D., Ph.D.

The Contraindications and Complications of Surgery Before IVF

Fibroids are highly prevalent in young women, and they are frequently, although not always, associated with symptoms (heavy or prolonged menstrual bleeding, bulk and painful symptoms). The data regarding the impact of fibroids on fertility are inconsistent, and those who do conceive may be

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Pro 3: Stephan Gordts, M.D.

Surgery Is Mandatory: Place of Minilaparotomy/Laparotomy

More than 150 years after the reported successful abdominal myomectomy in 1845 by brothers Washington and John Atlee (34), we are still discussing the advantages of myomectomy and its impact on reproductive performance. Myomas affect 20%–40% of reproductive-aged women (35, 36), and has age of childbearing is postponed, we will be facing an increased incidence in women seeking fertility treatment.

Impact on fertility. The impact in women with otherwise unexplained infertility is well known (35, 37, 38). In a series of 72 patients, the live birth rate before myomectomy was 31% compared with 75% after myomectomy with a decreased pregnancy loss from 69% to 25 % (39). In a cohort of seven studies (20, 40–45), evaluating the results after IVF, a significant decrease in pregnancy rates was reported in patients with a distorted uterine cavity (9% vs. 29.5% without distortion). In several studies, the negative impact of small intramural myomas $<$ 5 cm without distortion of the uterine cavity (18, 23, 46–48) on pregnancy, implantation, and ongoing pregnancy rates vs. controls is described (Table 1). Khalaf et al. (47) reported a reduction of the cumulative ongoing live birth rate of 47%. The prospective controlled study by Casini et al. (49) showed the importance of the localization of the myoma in relation to the junctional zone, in which importance in implantation and deep placentation is well known (50, 51). This is reflected in the significant impact of intramural non-cavity-distorting myomas on placental histopathology (52). The importance of uterine dysperistalsis in the presence of intramural myomas in achieving pregnancies and normalization after surgery was clearly demonstrated by Yoshino et al. (11, 53).

Laparoscopy vs. (mini-)laparotomy. Four randomized controlled trials (RCTs) compared laparotomy vs. laparoscopy; the latter is clearly associated with less postoperative pain, shorter hospitalization, less morbidity, and less blood loss (54–56). No difference in recurrence rates existed between a laparoscopic approach and laparotomy (57).

CON: Intramural myomas more than 3–4 cm should not be surgically removed before in vitro fertilization *(continued)*

at increased risk of a range of pregnancy-related adverse events (124). Such variability in the clinical manifestations of fibroids, including a majority of asymptomatic patients, may be related to the fact that fibroids are a heterogeneous condition with huge differences among affected women in terms of the number, dimensions, and location of the lesions and the concomitant presence of conditions that can interfere with fertility (125). Uterine and endometrial sparing surgical interventions are therapeutic options available to women with severe fibroid-associated symptoms who are planning on becoming pregnant. Myomectomy is the standard option for removing intramural fibroids, and it typically involves laparotomic or laparoscopic approaches, with or without robot assistance. Minimally invasive surgical procedures (laparoscopic and robotic) are generally preferred over abdominal myomectomy, with the latter generally being reserved for large fibroids (>9–10 cm in diameter) (105). Previous studies have concluded that, compared with open surgery, laparoscopic myomectomy is associated with a faster postoperative recovery, reduced operative blood loss, diminished postoperative pain, fewer overall complications, and a reduction in postoperative adhesions (58, 126, 127). Thus, when surgery is required, laparoscopic myomectomy appears to be a better option than open surgery, when feasible (128). However, in case of a desire to become pregnant, reverting to myomectomy for the management of intramural myoma exposes both the affected women and the clinicians to specific drawbacks and risks.

First of all, the suitability of a surgical approach for intramural myomas in the setting of infertility is currently a matter of debate. Indeed, the effect of intramural fibroids on fertility remains controversial. On the one hand, there is evidence that fibroids may reduce both natural fertility (125) and ART-induced chances of live birth (129, 130); on the other hand, it is uncertain whether myomectomy improves the postoperative clinical pregnancy rate in case of intramural fibroids (130). The substantial heterogeneity of the disease itself and the existence of several confounding factors, such as age, associated diseases, and fertility factors, may explain such inconsistency. Thus, for women with heavy bleeding, as well as bulk and painful symptoms, surgery is generally indicated irrespective of the fertility status. By contrast for women with only infertility, the potential—albeit nonvalidated—benefit in terms of pregnancy chances should be carefully balanced with the surgical risks. Second, although the risk depends on the number, size, and position of the intramural fibroids, laparoscopic myomectomy exposes women to a nearly 10% rate of surgical complications (131). The main intraoperative complications include excessive blood loss, myometrial hematoma (1.3%–29.2%), blood transfusion (0.1%–1.3%), and conversion to laparotomy (0.3%–2.7%), which are mainly related to excessive bleeding (128, 132). Severe complications include a rare case report of conversion to hysterectomy due to severe blood loss (131). Third, myomectomy is a well-known operation associated

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Dubuisson et al. (58) stated that laparoscopic myomectomy offers the possibility of a minimally invasive approach for subserosal or intramural myoma < 9 cm when there are only two or three of them. In a prospective series of 426 women scheduled for laparoscopic myomectomy, the conversion rate to laparotomy was 11.3 % (59). The factors increasing the risk for conversion were size of the myoma > 5 cm, intramural and/or anterior location, and preoperative use of gonadotropin-releasing hormone agonist. Gonadotropin-releasing hormone agonist may increase difficulties in the identification and dissection of the cleavage plane between myoma and surrounding myometrium (60). The advantages of a minimally invasive approach by laparoscopy must be balanced against the experience of the surgeon and the severity of the uterine pathology.

At laparotomy, exteriorization of the uterus avoids blood loss entering the abdominal cavity, an important factor in the prevention of adhesion formation. Tactile sensation is helpful in the localization of the myomas allowing the removal of several myomas through the same incision. Laparotomy is preferable if multiple incisions for removal of myomas are requested. Avoiding extensive coagulation and good approximation of the deep layers are mandatory in avoiding the risks of uterine rupture. The attributable risk of uterine rupture is 0.5% (58). Less trained gynecologists have a two times higher risk of uterine rupture by a laparoscopic approach compared with laparotomy (61). Reaching the same accuracy in the closure of the uterine defects by the microsurgical approach at laparotomy requires a high degree of laparoscopic expertise.

The lower reported postoperative adhesion formation rate after laparoscopy compared with laparotomy (51.1% vs. 89.6%) (62–64) must be interpreted carefully because bias in the selection of patients, by referring the more complex pathology to laparotomy, cannot be excluded. Not the way of access but expertise with reduction of operating time (65–66) and the meticulous use of the principles of microsurgery are the key players in the prevention of adhesion formation.

Obstetrical outcome. The increased risks of abruptio placentae (odds ratio [OR], 3.87; 95% confidence interval [CI], 1.63–9.17), first trimester bleeding (OR, 1.82; 95% CI, 1.05–3.20), dysfunctional labor (OR, 1.85; 95% CI, 1.26–2.72), and breech presentation (OR, 3.98; 95% CI, 3.07–5.16) (62, 67–69) must be considered in the final decision for myomectomy.

Conclusion. Several data are reporting the negative impact of myoma on reproduction and obstetric outcome with an amelioration after myomectomy. Decision for a laparoscopic approach must be balanced between the uterine pathology and the experience of the surgeon. There is much more to

CON: Intramural myomas more than 3–4 cm should not be surgically removed before in vitro fertilization *(continued)*

with the formation of both intrauterine and intra-abdominal de novo adhesions that can reduce fertility (131–134). Although laparoscopy is thought to provide a safer access route with less induction of adhesions than laparotomy, it has been shown that even with laparoscopy, a considerable percentage of patients develop adhesions after myomectomy (1). The incidence of adhesions after laparoscopic myomectomy is high and varies between 23% and 88% (132). Neither the surgeon's experience nor the use of laparoscopy can fully prevent adhesion formation. Adhesions can be associated with severe complications such as bowel obstruction, chronic pelvic pain, complications in subsequent operations, and impaired future fertility (132). Fourth, long-term complications include the risk of uterine rupture in subsequent pregnancies. While published series indicate that the risk of uterine rupture is low after laparoscopic myomectomy, several cases have nonetheless been reported (135). Uterine rupture during pregnancy/labor appears to be mainly related to a weakened myometrium, especially after devascularization with cautery and/or myometrial tissue injury or after defective suturing and/or poor tissue approximation (128, 134). Appropriate counseling for patients contemplating pregnancy is important, and although not corroborated by strong evidence, an adequate expectant interval of 12 weeks to 12 months after myomectomy can be recommended (136). However, postponing conception to achieve optimal uterine healing after myomectomy exposes women to age-related fertility decline. Fifth, a significant reproach regarding myomectomy is that the remaining uterus will still contain diseased areas and be liable to sooner or later suffer from recurrences (137). It is widely known that, after myomectomy, the rate of recurrence of myomas can reach almost 60% after an interval of 4–5 years. In addition, the rate of reoperation after myomectomy varies from 4.3% to 18.8% with a maximum follow-up of 5 years (137). This risk of reoperation can approach 30% with longer follow-up (138, 139). Consequently, the risk of pelvic adhesions is significantly increased after a repeat myomectomy, thereby increasing the risk of potential detrimental impacts on reproductive outcomes (15). Sixth, the presence of uterine leiomyomas during pregnancy increases the likelihood of adverse pregnancy outcomes (140). Several observational studies have reported an association between leiomyomas and preterm birth, hospitalization for threatened preterm birth, preterm premature rupture of membranes, intrauterine growth retardation, preeclampsia, and cesarean delivery (67, 141). A French cohort study has shown that women with a leiomyomatous uterus are at risk of preterm birth and that this risk persists after myomectomy (142). To date, there is no evidence in the literature of obstetrical risk reversibility after myomectomy. Seventh, the current literature, on the basis of several previously published studies, reports an incidence of concomitant fibroids and endometriosis/adenomyosis ranging from 20% to 40% (1, 143–147). Considering the potential of endometriosis/adenomyosis to

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gain for patients and surgeons by a well-performed myomectomy through laparotomy than by a difficult laparoscopy and an inappropriate suturing.

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affect fertility, the coexistence of these uterine disorders would interfere and possibly worsen the chances of conception (143). Indeed, overlooking the coexistence of endometriosis/adenomyosis in women with leiomyoma undergoing surgery may lead to suboptimal treatment of both fertility and persistent pelvic pain (121). As women can have both of these conditions at the time of surgery (148), it is important that physicians are aware of the possibility of this association and that they evaluate the presence of concomitant endometriosis/adenomyosis through an appropriate clinical and imaging preoperative workup before fibroids surgery in an effort to avoid unnecessary and interactive surgeries and to provide the best treatment plan (121). Eighth, finally, fibroid morcellation during laparoscopic surgery has been associated with rare but serious complications. The overall probability of direct power morcellator injury of internal organs (bowel, bladder, kidneys, vascular system, etc.) is low and has been reported to be between 0.06% and 0.12% (128). Although rare, such injuries should be considered to be severe complications, as highlighted in a previous study that reported six (11%) deaths among 55 registered morcellator-related complications (149). In addition, specimen removal using power morcellation exposes women to the risk of inadvertent peritoneal tissue spread with a variety of consequences according to the nature of the tissue disseminated. In case of undiagnosed cancer, power morcellation, which increases the risk of spreading cancer throughout the abdominopelvic cavity, exposes patients to a major adverse impact on their survival. The US Food and Drug Administration consequently recommends limiting the use of power morcellation in the surgical treatment of uterine leiomyomas (150). In addition, the use of a morcellator is associated with possible grafting of benign fibroid fragments, thereby leading to an increased risk of developing parasitic myomas (1.2% after myomectomy) (151) or adenomyoma (152, 153).

In conclusion, surgery in patients with intramural fibroids presenting with infertility, especially in the absence of associated heavy bleeding or bulk and painful symptoms, should be considered to be a risky procedure, not only because of the limited evidence of the efficacy of myomectomy on reproductive outcomes but also because of the potential for several surgery-related complications. When surgery is the preferred option, because fertility declines with the women's age and in the light of the risk of reoperation, postoperative adhesions, and a delayed conception to achieve optimal uterine healing, fertility preservation should be considered on a case-by-case basis (154, 155).

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