

## Systematic Review

# Receptivity-based uterine fibroid surgery: an updated systematic review of the evidence

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## Abstract

**Background:** Analyzing expression patterns of receptivity genes is a minimally invasive diagnostic method to identify the underlying cause of subfertility in women with uterine fibroid with a history of implantation failure or recurrent pregnancy loss. This updated systematic review was designed to determine the molecular and genetic changes in the endometrium of women with fibroid and how myomectomy affect the outcome of spontaneous or assisted conception treatment. We also discussed the extent to which we should consider the effects of fibroids on endometrial receptivity when deciding whether or not to perform myomectomy. **Methods:** A total of 184 articles reached as a result of PubMed research and meeting the selection criteria, were evaluated. Of these, 28 full text articles on uterine leiomyoma and endometrium, leiomyoma and receptivity, fibroid and implantation, myomectomy and implantation, fibroid and genes, fibroid surgery and receptivity, fibroid and uterine peristalsis, fibroid and immune cell were evaluated. **Results:** The endometrium of subfertile women with fibroid appears to have a disease specific pattern according to the type of the fibroid. The response of the endometrium to a fibroid may vary depending on whether the fibroid is close or far from it. Leiomyomas that contribute to subfertility must be near to or in contact with the endometrium, as is the case for Types 0, 1 and 2 leiomyomas. The proximity to the endometrial cavity makes the effect of fibroid on the endometrium more pronounced. While Type 3 fibroid causes subfertility similar to submucosal fibroids, the subfertility-producing effects of Type 4 fibroids have not been clearly clarified. However, the fact that the fibroid is far from the cavity should not mean that it has no effect on the endometrium. The mechanical stress created by a Type 4 fibroid that is not connected to the endometrium may be converted into biological signal and disrupt receptivity. Data on whether myomectomy restores impaired receptivity are mostly based on clinical observations, and studies evaluating endometrial receptivity before and after myomectomy are very few. **Conclusions:** Analysis of receptivity genes in subfertile women with fibroid may assist the clinician in deciding whether or not to perform myomectomy. If it is determined whether fibroids affect receptivity other than their mechanical effects, the indications for myomectomy may expand or narrow.

**Keywords:** fibroid; endometrium; receptivity; gene; myomectomy

## 1. Introduction

The endometrium, which has selectivity and receptivity functions, is a privileged reproductive tissue that hosts the developmental processes of the human embryo. Due to its cyclical nature and high regenerative abilities, primary benign diseases of the endometrium such as polyp and endometriosis are quite common during the reproductive period [1,2]. Moreover many diseases located in other reproductive tissues may adversely affect the receptive functions of the endometrium. Actually reproductive tract lesions

may lead to subfertility according to their anatomical location and the mechanism of disease. However, in addition to their primary effects, some pathologies may negatively affect the receptive functions of the endometrium [1–3]. Despite rare studies claiming the opposite view, it has been reported that the expression of some genes involved in receptivity such as glycodeilin, homeobox, leukemia inhibitor factor, has-miR-504-5p are impaired in the presence of fibroid, endometriosis, adenomyosis, or hydrosalpinx [4–7].



Leiomyomas are highly prevalent benign tumors of the myometrium that can be found in 70 to 80 percent of women by the age of 50 years. It is likely that most leiomyomas are asymptomatic and are not contributing to the woman's symptoms. It is often unclear whether or not the identified leiomyomas have any relationship to the presenting symptom since other causes or contributors to the infertility may exist that are not demonstrable by imaging techniques. It is believed that leiomyomas must be close to or in contact with the endometrium to cause subfertility. FIGO Types 0, 1, 2, and 3 leiomyomas form the groups that best fit this description [1,2]. The larger a fibroid and the closer it is to the endometrium, the more adversely it affects endometrial receptivity [8,9]. Such circumstances facilitate molecular expressions originating in the leiomyomas to diffuse to the adjacent endometrium and then disrupt the process of local hemostasis, embryonic implantation or subsequent growth and development of the fetus [10,11]. To test this hypothesis, it would initially be necessary to analyze molecular expressions that may impact endometrial hemostasis and receptivity to implantation in Types 0, 1 and 2 leiomyomas. The available evidence regarding the impact of what were called intramural leiomyomas is relatively poor and conflicting, a circumstance that contributed to the design of the FIGO subclassification system for leiomyomas—"intramural myomas" are now categorized by their relationship to the endometrium. Consequently, evaluation of molecular expressions in Type 3 and 4 myomas should be performed for comparative analysis. The mechanical stress created by a Type 4 fibroid that is not connected to the cavity can be converted into biological signals which can reach the endometrium and disrupt its receptive functions [12–14]. If it is determined whether fibroids affect receptive function of endometrium, the indications for myomectomy may expand or narrow. In this updated systematic review, we will first discuss the molecular and genetic changes in the endometrium due to the mechanical and non-mechanical effects of uterine fibroids. Next, we will detail how the presence of fibroids and their surgical removal affect the results of spontaneous or assisted conception treatment. Finally, we will discuss the extent to which we should consider the effects of fibroids on endometrial receptivity when deciding whether or not to perform myomectomy.

PubMed was searched for uterine fibroids using the following terms: fibroid, leiomyoma, receptivity gene and molecule, myomectomy and receptivity, fibroid surgery and implantation, fibroid and endometrium, fibroid and decidualization, uterine peristalsis and fibroid, implantation failure and fibroid. A total of eleven authors evaluated the studies for inclusion and exclusion criteria. The references of the selected articles were also checked to see if they were related to fibroids and receptivity. At the first screening, article titles were investigated, and studies with lack of any relevance were excluded. Articles evaluating fibroid

and receptivity, fibroid and endometrium, fibroid surgery and receptivity in human or experimental models were included. In the second screening, the abstracts of the articles whose titles met the inclusion criteria were read. The full texts of the articles with the abstracts matching the selection criteria were accessed and subjected to the third screening. A total of 184 articles meeting the selection criteria were selected, and 28 of them were analyzed extensively for systematic review.

### 1.1 Origin and incidence of fibroids

Fibroids are benign uterine tumors with the highest incidence after endometrial polyps, which occur in approximately three out of ten cases in infertile patients for whom no obvious cause can be found to explain subfertility [15]. They are originating from uterine smooth muscle fibroid stem cells. Although the incidence in women of reproductive age can reach 80%, the incidence of uterine fibroids in infertile women without any clear cause of infertility is estimated to be 1–2.4% [15]. It has been reported that fibroids are monoclonal tumors originating from a single myocyte cell [16]. Although the main reasons for the differentiation of fibroid cells towards stem cell is not known age, ovarian steroids, family history, early menarche, obesity, geographic region, race, diet, caffeine or alcohol consumption, smoking, and soy-based formulas are accepted as the risk factors [17,18]. Elkafas *et al.* [19] reported that vitamin D3 treatment slows down myoma formation by preventing DNA damage in fibroid stem cells. Unlike the well and moderately differentiated fibroid cells that make up the fibroid core, fibroid stem progenitor cells contain very few estrogen receptor (ER) and progesterone receptor (PR) [20–22]. Hence, the initial growth rate of fibroids is determined by fibroid stem cell density rather than circulating estrogen and progesterone [23].

### 1.2 How do fibroids cause subfertility?

Although in a minority, some authors have suggested that the available data are insufficient to establish a causal relationship between uterine fibroids and infertility [15]. Conversely, others have reported that fibroids, especially those located in the submucous area, may increase early pregnancy loss while reducing implantation rates [24]. It is thought that submucous fibroids negatively affect the uterine anatomy and receptive functions of the endometrium and reduce fertility more significantly [9,11,24,25]. On the other hand, the results of studies examining the relationship with intramural fibroids and subfertility are mixed. While some studies have reported that intramural fibroids cause decreased fertility and increased pregnancy loss [9,24,25], other studies have failed to show any relationship between intramural fibroids, subfertility or miscarriage [1,26]. In addition to this classical information about the subfertility-producing effects of fibroids, we would like to briefly mention the FIGO classification system in order to clearly dis-

Discuss the relationship between fibroids and endometrial receptivity.

Fibroids are one of the most important causes of abnormal uterine bleeding in women of reproductive age. In 2011, the International Federation of Gynecology and Obstetrics (FIGO) developed a classification system (called PALM-COEIN or FIGO-AUB System 2) to assist clinicians and researchers in the management of the AUB [27]. This system is the only approved official classification of fibroids and classifies fibroids according to their relationship to the myometrium, endometrium, endometrial cavity, and serosa. Fibroids can be identified with appropriate imaging techniques including ultrasound, especially with intrauterine fluid contrast or MRI. One hypothesis posits that leiomyomas that contribute to infertility must be near to or in contact with the endometrium, as is the case for FIGO Types 0, 1 and 2 leiomyomas. Type 0 is an intracavitary lesion and it is attached to the endometrium via a stalk. Type 1 and Type 2 fibroids are lesions associated with the endometrium, but some of them are intramural localized. Types 0–2 fibroids are known to impair decidualization and implantation by decreasing LIF or HOXA mRNA expression. Rackow *et al.* [8] reported that submucosal fibroids cause a global and significant decrease in receptivity gene expression. Kara *et al.* [28] reported that fibroids decrease implantation rates by diminishing LIF expression. Hesegawa *et al.* [29] showed that LIF mRNA expression was significantly decreased in the presence of submucous fibroids. On the other hand, some type of fibroids indirectly impairs the expression of receptivity genes. Consistent with this, Doherty *et al.* [30] reported that fibroid derived transforming growth factor  $\beta 3$  impairs endometrial receptivity and decidualization by blocking bone morphogenetic protein-mediated HOXA and LIF expression.

According to FIGO classification, total intramural fibroids in contact with the endometrium were defined as Type 3 lesions. Type 4 lesions were defined as completely intramural but not in contact with the endometrium or serosa [27]. As a result of the revision made in FIGO systems in 2018, Type 3 fibroids were included in the category of submucous fibroids due to their contact with the endometrium [31]. For this reason, the effects of Type 3 and Type 4 fibroids leading to subfertility are different from each other. While Type 3 fibroids cause subfertility similar to submucosal fibroids, the subfertility-producing effects of Type 4 fibroids have not been clearly clarified. Governini *et al.* [14] showed that Type 3 leiomyomas change the molecular structure of the endometrium by causing differential expression of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases. They also reported that Type 3 fibroids cause a pathological inflammatory response by increasing the secretion of endometrial COX1, COX2, and VEGF. However, the effects of Type 3 fibroids on receptivity genes and growth factors are not as clear as Types 0–2 fibroids. In a study conducted by our team,

we reported that removal of intramural fibroids that do not compress the endometrial cavity resulted in a significant increase in HOXA10 and 11 mRNA expressions [9].

Type 5–7 subserous fibroids are considered as the mirror image of submucous fibroids. Type 8 fibroids are lesions that are not directly connected to the myometrium and located on the cervix or in round or broad ligaments. Although it has been reported that these types of fibroids are not associated with subfertility, they can sometimes grow intramural and distort the endometrial cavity [9,32].

## 2. Mechanical effects of uterine fibroids

The effects of fibroids that cause subfertility mainly depend on the type of lesions [1]. Occasionally, a fibroid may occupy a large part of the endometrial cavity or cause deformation in the implantation zone, leading to early pregnancy loss. Large fibroids may also obstruct the interstitial segment of the fallopian tubes as well as disrupt the tubal physiology and prevent oocyte pick-up [32,33]. Although the mechanical effects that cause fibroid-mediated subfertility are mostly seen in submucous fibroids, intramural fibroids may also cause mechanical subfertility [9]. In the presence of submucosal fibroid, implantation, clinical pregnancy and live birth rates have decreased, while a nearly three-fold increase in early pregnancy loss has been reported [25]. Fibroids that do not compress the endometrial cavity also decrease implantation and increase miscarriage rates [25]. In good agreement with this, our team showed that intramural fibroids that do not compress the endometrium can also cause subfertility [9].

### 2.1 Myomectomy for mechanical effect elimination

Myomectomy is one of the most common surgical procedures in gynecology practice to eliminate pelvic pain, dysfunctional uterine bleeding, urinary or gastrointestinal symptoms due to fibroids. However, the main problem with the surgery of fibroids is to decide whether to perform or not myomectomy before expectant management or in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) treatment in women of reproductive age. Many experienced surgeons decide whether to perform surgery in otherwise unexplained subfertile women with uterine fibroids based on the location, size and relationship of the fibroid to the endometrium. Some of the authors believe that performing myomectomy does not improve subfertility, since there is no clear and favorable data obtained from RCT that surgical removal of submucous fibroids increases the fertility [34,35]. Some authors citing the data obtained from systematic reviews and observational studies, on the other hand, argued that myomectomy improves the reproductive outcome because submucous fibroids mechanically cause subfertility [24,25].

Opinions on the decision of whether to perform surgery in women with intramural fibroids and otherwise unexplained subfertility are more heterogeneous. The lack

of a single and standard definition of intramural fibroids that is accepted by everyone and the difference in the methods used in the definition are the two main reasons that cause the inconsistency of the results. Some researchers consider all fibroids located on the endometrium and under the serosa to be intramural, regardless of whether they come into contact with the endometrium. In some definitions, the presence of myometrial tissue between the lower border of the fibroid and the endometrium is considered necessary for the diagnosis of intramural fibroids. Although the classification system developed by FIGO was developed to solve the problems in identifying fibroids, many researchers did not use this system [27]. One meta-analysis including studies using different fibroid identification methodologies suggested that intramural fibroids reduce implantation rates [36], while another meta-analysis reported that intramural fibroids did not affect clinical pregnancy rates [37]. There are also studies suggesting that the negative effects of intramural fibroids on fertility outcome are related to the size of the fibroid. It has been reported that fibroid size smaller than 4 cm does not affect ART results, while larger fibroids reduce pregnancy rates [26,38]. Whether or not it is in contact with the endometrium also plays an important role in determining the impact of intramural fibroids on fertility outcome. A recent study by Yan *et al.* [39] reported that patients with Type 3 fibroids larger than 2 cm in contact with the endometrium had significantly lower rates of implantation, clinical pregnancy and live birth compared to healthy controls without fibroid. However, IVF/ICSI results of women with Type 3 fibroids smaller than 2 cm were found to be similar to the control group and did not cause a significant increase in miscarriage rates. In the meta-analysis by Metwally [34], it was reported that intramural myomectomy had no remarkable effect on clinical pregnancy rates. However, the number of myomectomy studies included in this meta-analysis is not sufficient to draw a clear conclusion. Finally, we do not have enough data to comment on whether the failed fertility outcome in patients with FIGO Type 3 fibroids will return to normal after myomectomy.

### 3. Non-mechanical effects of uterine fibroids

When we say non-mechanical subfertility due to fibroid, we mean four things: (i) histomorphological defects in the endometrial architecture prevent the development of a healthy decidualization, (ii) endometrium cannot fully express the cytokines and genes responsible for receptivity, (iii) mechanical stress leads to a biological response in the endometrium by mechanotransduction, (iv) impairment of sperm or embryo transport as a result of abnormal uterine peristaltic activity (Table 1, [7–11,13,14,18,21,23,25,28–31,33,34,36,37,40–55]). Let's detail the effects of removing these non-mechanical effects created by fibroids by myomectomy on the fertility outcome.

#### 3.1 Myomectomy to remove fibroid-related changes in the endometrium

Implantation is a complex but highly organized molecular and genomic interaction between a well-developed embryo and an appropriately primed endometrium [56,57]. In approximately 75% of unsuccessful pregnancies, at least one of the apposition, attachment or invasion stages is impaired [57,58]. For a successful decidual formation, the endometrium should maintain its cyclic and regenerative properties and respond to trophic hormones in a genomic or non-genomic manner. In addition, some immune cells from the bone marrow or systemic circulation must be extravasated to the developing decidua. Macrophages contribute to the formation of the decidua by stimulating the release of LIF and other cytokines [59]. NK cells take a role both in remodeling of uterine vasculature and fetal immune tolerance [60]. It has been reported that while pan-leukocyte density increases in the endometrium adjacent to fibroids, NK cell density decreases [40]. Miura *et al.* [61] reported that macrophage levels were significantly higher in the endometrium of patients with submucous or intramural fibroids compared to subserosal myomas.

Changes that occur in the endometrium due to submucous or intramural fibroids are seen not only in the area overlying the fibroid, but also in the entire endometrium [8,41]. In the presence of fibroids, subtotal or total glandular atrophy, flattening or thinning of the epithelium, as well as fibrosis, hemorrhage or diffuse edema may lead to insufficient decidualization [41,62]. Impaired decidualization may also be due to altered extracellular matrix (ECM) remodeling, as in the myometrium. This evidence is supported by two recent studies. Excessive production of ECM causes the fibroid to harden and enlarge, making it easier to press on the endometrium. A study conducted by Navarro *et al.* [13] showed that the increase in ECM changes the secretion of transforming growth factor  $\beta$  and microRNA through mechanotransduction and negatively affects decidualization through endometrial vascular structures. Governini *et al.* [14] they reported that type 3 fibroids impair decidualization and implantation by causing differential expression of MMP and TIMP and activating inflammatory pathways. Global changes occurring at the cellular level due to fibroid in endometrial architecture prevent a healthy fetomaternal communication, leading to inadequate placentation. Myomectomy can increase fertility rates by normalizing all these fibroid-related endometrial changes. Unfortunately, there is no study examining changes in endometrial morphology and immune cell content before and after myomectomy. Only one study compared the effect of high-intensity focused ultrasound therapy and myomectomy on immune cells. There was a significant decrease in the levels of CD4(+) and CD8(+) T cells and NK cells in blood samples taken 24 hours after myomectomy [63].

**Table 1. Possible mechanisms by which fibroids affect endometrial receptivity.**

Fibroid type	Proposed mechanism of receptivity dysfunction	References
Submucous (Types 0–3)*	<ol style="list-style-type: none"> <li>1. Mechanical interference with sperm transport and embryo implantation.</li> <li>2. Failed glycodeilin synthesis decreases the capacity of spermatozoa to adhere to the zona pellucida.</li> <li>3. Increase in pan-leukocyte density.</li> <li>4. Decrease in uNK cell density.</li> <li>5. Altered extracellular matrix (ECM) remodeling leads to impaired decidualization.</li> <li>6. Subtotal or total glandular atrophy, flattening or thinning of the epithelium, as well as fibrosis, hemorrhage or diffuse edema may lead to insufficient [7–11,13,14,18,21,23,28–31,40–55]</li> <li>7. Increase in ECM changes the secretion of transforming growth factor <math>\beta</math> and microRNA through mechanotransduction and negatively affects decidualization.</li> <li>8. Differential expression of MMPs and TIMPs.</li> <li>9. Fibroid-derived TGF-<math>\beta</math>3 blocks the endometrial BMP-2 receptors and prevent the release of HOXA10 and LIF.</li> <li>10. Global decrease in HOXA10, HOXA11, and BTEB1 mRNA expression.</li> <li>11. Failed LIF mRNA expression.</li> <li>12. Increased endometrial COX1, COX2, and VEGF synthesis.</li> <li>13. Chondrocyte-like modulus and stiffness above 15 kPa affects receptivity by converting mechanical signal to biological signal.</li> <li>14. Activation of RhoA-AKAP13 complex may enable the delivery of biochemical signals to the endometrium (not yet proven at the hypothesis stage).</li> <li>15. Abnormal uterine peristalsis.</li> <li>16. Hypermethylation in CpG21 region of HOXA gene.</li> <li>17. Fibroid stem progenitor cells contain very few estrogen and progesterone receptor.</li> </ol>	
Intramural (Type 4)	<ol style="list-style-type: none"> <li>1. Mechanical interference with sperm transport and embryo implantation.</li> <li>2. Subtotal or total glandular atrophy, flattening or thinning of the epithelium, as well as fibrosis, hemorrhage or diffuse edema: may lead to insufficient [8–11,13,14,18,23,28,29,46–48,50–53,55]</li> <li>3. Impaired glutathione peroxidase 3, placental protein 14 (also called glycodeilin) and aldehyde de-hydrogenase 3 family, member B2 expression.</li> <li>4. Failed HOXA10,11 mRNA expression.</li> <li>5. Failed LIF mRNA expression.</li> <li>6. Chondrocyte-like modulus and stiffness above 15 kPa affects receptivity by converting mechanical signal to biological signal (not yet proven at the hypothesis stage).</li> <li>7. Activation of RhoA-AKAP13 complex may enable the delivery of biochemical signals to the endometrium (not yet proven at the hypothesis stage).</li> <li>8. Abnormal uterine peristalsis.</li> <li>9. Hypermethylation in CpG21 region of HOXA gene.</li> <li>10. Fibroid stem progenitor cells contain very few estrogen and progesterone receptor.</li> </ol>	
Subserous (Types 5–7)	<ol style="list-style-type: none"> <li>1. If these fibroids expand into the myometrium, it may affect receptivity.</li> <li>2. There are no clinical or experimental studies investigating the effects of these types of fibroids on receptivity.</li> </ol>	[9,25,30,33,34,36,37]
Other types (Type 2–5, Type 8)	<ol style="list-style-type: none"> <li>3. Some authors thought that fibroids in this group may affect receptivity by using some of the above mechanisms.</li> <li>4. Despite some clinical observations, we do not have enough scientific data to comment on the effects of fibroids in this group on receptivity.</li> </ol>	

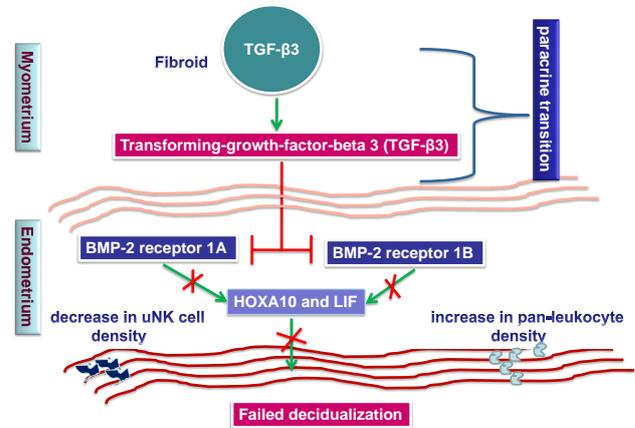
\*: According to the 2018 revision of the FIGO classification, Type 3 fibroids were also included in submucosal fibroids [31].

### 3.2 Myomectomy to prevent *denovo* developing pathway activation

One of the most proposed mechanisms of non-mechanical subfertility is the inability of the endometrium to adequately express receptivity genes or cytokines [42, 64,65]. Although the location, size, number and relationship between the endometrium are important determinants for non-mechanical effects to occur [25], a small and single submucosal or an intramural fibroid that does not have direct contact with the endometrium can also change receptivity [1,38,39]. While some studies reported that intramural myomas larger than 5 cm impair glycodeilin and aldehyde dehydrogenase expressions [7], others reported that intramural myomas that do not compress the endometrium also impair receptivity [9]. Horcajadas *et al.* [42] reported that there was a change in the expression of 69 genes in the presence of intramural fibroids that do not distort the endometrial cavity. Of the 69 genes, 25 were expressed in the implantation window, and only glutathione peroxidase 3, placental protein 14 (also called glycodeilin) and aldehyde de-hydrogenase 3 family, member B2 expression was impaired. Dysregulation of these three genes was more pronounced in patients with intramural fibroid diameter  $\geq 5$  cm.

The question that needs to be answered is by which mechanism fibroids disrupt the receptive functions of the endometrium. Some molecular pathways that are not included in the normal physiology of the uterus may occur in the presence of fibroids and affect endometrium [11]. Although fibroids use the molecules they synthesize primarily for their own growth, these molecules can affect the neighboring myometrium and the endometrium in a paracrine manner. Some molecules, whose secretion increase in the presence of fibroids, reach the endometrium via paracrine pathways and may cause disruption of biosensor functions of endometrium (Fig. 1, Ref. [10,11,30]). Transforming-growth-factor-beta 3 (TGF- $\beta 3$ ) is synthesized by the fibroid cells and transferred to the endometrium and impairs the receptive functions [10,11]. TGF- $\beta 3$  passes into the endometrium and blocks the expression of bone morphogenetic protein 2 (BMP-2) receptor types 1A and 1B [11,30]. BMP-2 is a growth factor secreted from endometrial stromal cells and regulates HOXA and LIF secretion [11,30,43]. Since fibroid-derived TGF- $\beta 3$  will block the endometrial BMP-2 receptors and prevent the release of HOXA10 and LIF, adequate decidualization cannot be achieved and implantation failure occurs [11,30]. Another molecule that negatively affects fertility by increasing synthesis in the presence of fibroids is glycodeilin. In the presence of fibroids, increased glycodeilin in uterine flushing samples also contributes to fibroid-mediated subfertility. Ben-Nagi *et al.* [7] showed lower levels of glycodeilin in uterine flushing samples collected from women with submucous fibroids. It has been reported that impaired sperm-oocyte interaction and decreased capacity of spermatozoa to

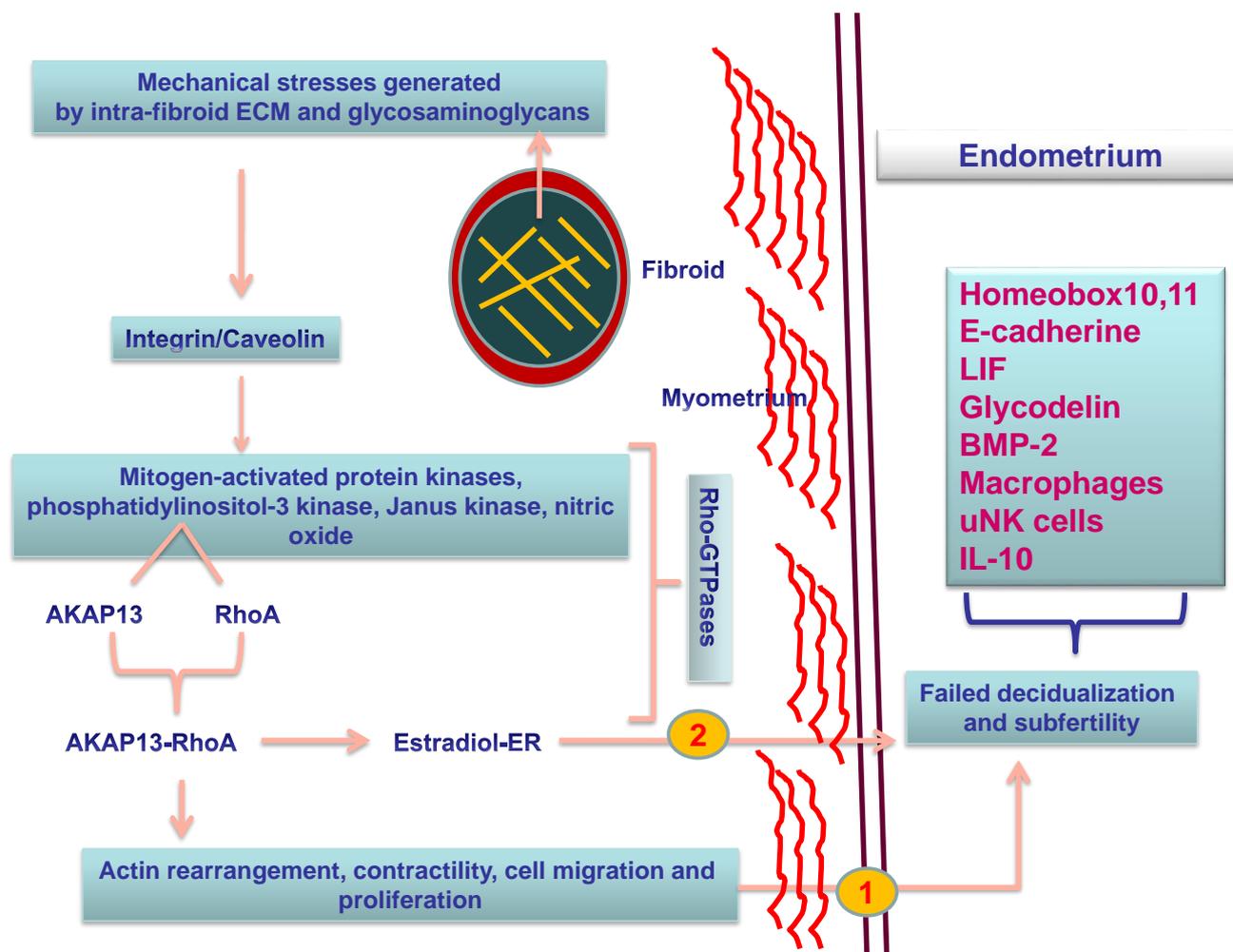
adhere to the zona pellucida in women with impaired glycodeilin synthesis [7,44]. In the light of these findings, it would not be wrong to state that the production and release of the TGF- $\beta 3$ , BMP-2, HOXA, LIF, and glycodeilin are disrupted by fibroids and myomectomy can restore *denovo* developing pathway activations [7,9,11,30].



**Fig. 1. Schematic representation of the fibroid-derived TGF- $\beta 3$  pathway that disrupts decidualization and causes subfertility.** TGF- $\beta 3$ , whose synthesis and secretion increases in the presence of fibroids, passes into the endometrium in a paracrine manner and blocks BMP-2 receptor types 1A and 1B. Blockage of BMP-2 receptors leads to cessation of HOXA10 and LIF production, impaired decidualization and subsequently implantation failure (Adapted from [10,11,30]).

### 3.3 Myomectomy to prevent biological signal generation due to fibroid

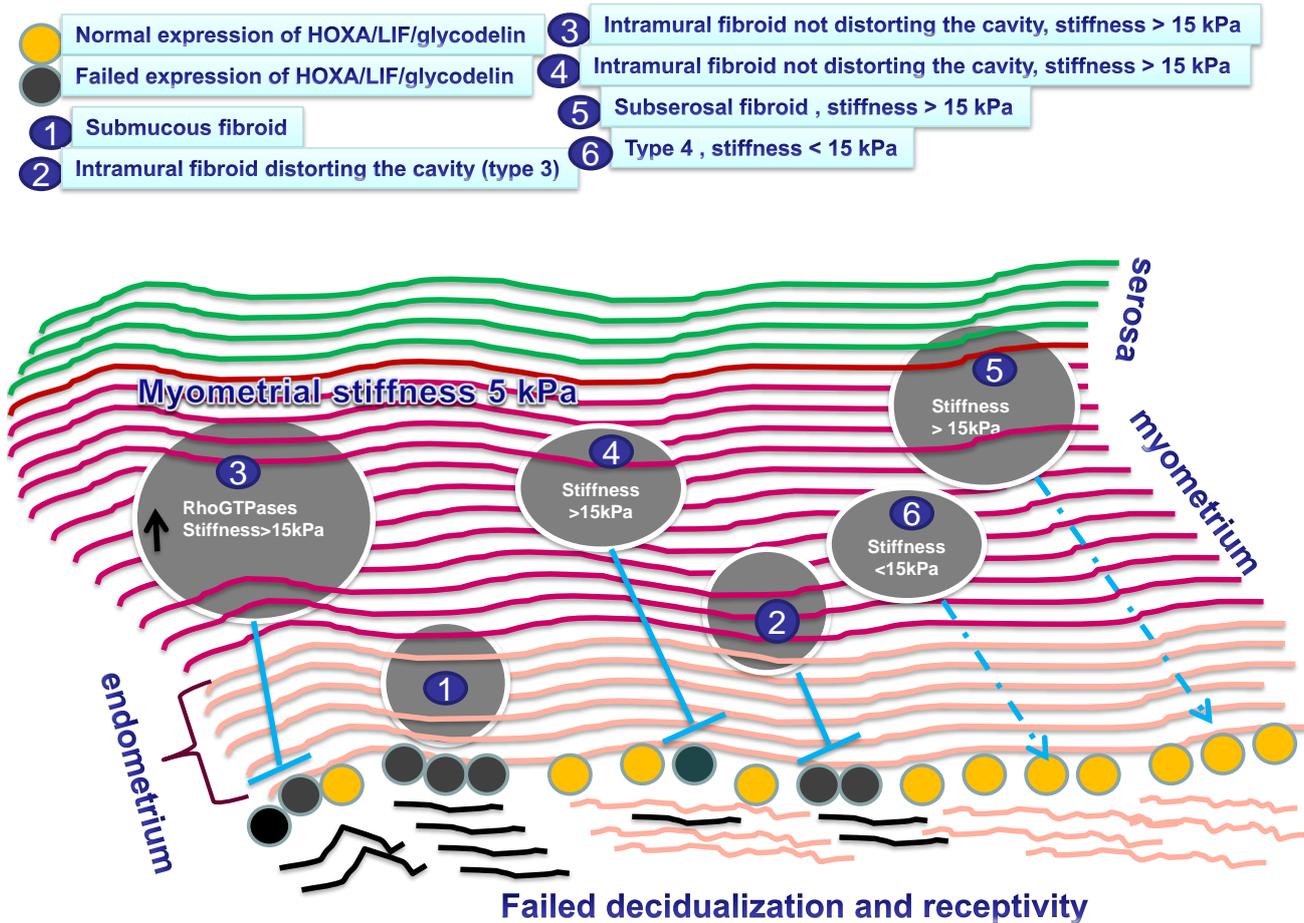
Little is known about the pathologic response of endometrium cells to fibroid, in particular whether altered mechanical stress might lead to a change in the gene expression pattern of endometrium. The significant increase in stress response gene expression in fibroid cells is important evidence that fibroid-related mechanical stress may play a role in the up- and/or down-regulation of genes in the endometrium [45]. The conversion of mechanical stress to a biological signal via mechanotransducers [12]. Although the mechanotransduction between the fibroids and endometrium has not been clearly demonstrated, mitogen activated protein kinases, phosphatidylinositol-3 kinase, Janus kinase, and Rho family small GTPases are key regulators of this pathway [46,47]. A-kinase anchoring protein 13 (AKAP13) regulates protein kinases necessary for actin filament to perform its functions. RhoA is involved in the cellular response to mechanical stress and is the target molecule of AKAP13. As shown in Fig. 2 (Ref. [46–48]), the RhoA-AKAP13 complex binds to filamines and communicates with caveolins, allowing the mechanical signal to propagate to the endometrium [46–48]. The stiffness and



**Fig. 2. Schematic representation of the conversion of fibroid-generated mechanical signal into biological signal via mechanotransducers such as caveolin and integrin.** AKAP13-RhoA complex stimulates stress-activated kinases, triggering cell migration and proliferation as well as contraction of actin fibers. It is not clear how the biological signals pass to the endometrium. Damage to the endo-myometrial interface due to myofilament contraction and cell migration may provide signal transmission (1). The second possible way of transmission may be via the estrogen receptor (ER). The AKAP13-RhoA complex can potentiate ligand-dependent ER activation, allowing biological signals to pass to the endometrium (2). Rho-GTPases is a molecule that has a critical role in providing the necessary energy during mechanotransduction (Adapted from [46–48]).

modulus of fibroids play an important role in the formation of biological signals by mechanotransduction. Although the myometrium is a tissue with an elastic modulus, fibroids have a cartilage-like modulus due to their dense matrix content. Although the stiffness of the myometrium is about 5 kPa, the stiffness of the fibroid is about three times greater than that of the myometrium [46–48]. Since the stiffness of myoma depends on the density of the extracellular matrix a fibroid with a small but large amount of ECM may have a higher value for stiffness than a large fibroid with a small amount of ECM. For this reason, the signals generated by an intramural myoma that does not compress the cavity but with a stiffness above 15 kPa can easily reach the endometrium and impair receptivity (Fig. 3, Ref. [46–48]).

Expression of receptivity genes may be impaired by fibroid-mediated biological signals [8,9]. In a previous study, we found a significant increase in receptivity genes after myomectomy of intramural fibroids. However, we failed to show a significant increase in HOXA10 mRNA in patients who underwent myomectomy for submucous fibroids [9]. Another important molecule related to endometrial receptivity affected by fibroid-related biological signals is LIF. It is a pleotropic cytokine that is involved in wound healing after menstrual bleeding by regulating cell growth and differentiation [8,9,29]. A study conducted in women with submucous fibroids, a significant decrease was found in LIF expression [29]. These findings may be evidence that the type of fibroids may not be crucial for mechanotransduction, as both submucous and intramural fi-



**Fig. 3. Schematic representation of how fibroids generate biological signals according to their location and stiffness.** Since the stiffness of fibroid depends on the density of the extracellular matrix, the main factor determining the stiffness is not the size but the matrix content. A fibroid with a small but large amount of ECM may have a higher value for stiffness than a large fibroid with a small amount of ECM. For this reason, the signal generated by an intramural myoma that does not compress the cavity but with stiffness above 15 kPa can easily reach the endometrium and impair receptivity. Since submucous or intramural fibroids compressing the cavity are in direct contact with the endometrium, they may impair receptivity regardless of the stiffness. A subserosal or an intramural fibroid that does not compress the cavity must reach sufficient modulus and stiffness to affect receptivity (Adapted from [46–48]).

fibroids affect endometrial receptivity by generating biological signals. Finally, although the expression of some receptivity markers is decreased in the presence of uterine fibroids, some remain unchanged, suggesting that the impact of submucous or intramural fibroids on receptivity is realized in a gene-specific manner. However, surgical removal of fibroids does not always restore receptivity to normal. This suggests that other unknown factors may contribute to subfertility in patients who do not have any finding other than fibroid the cause of subfertility (Table 1).

### 3.4 Myomectomy to prevent abnormal uterine peristalsis

Physiological uterine peristalsis, which varies according to the phase of the cycle, provides sperm transport, embryo implantation and discharge of menstrual blood [66,67]. Abnormal uterine peristalsis due to fibroid is also considered to be the cause of non-mechanical subfertility.

Biomechanical stress signals produced by uterine fibroids disrupt the functions of ion channels and cause involuntary contraction of myocytes independent of the phase of the cycle [47,49]. Mechanical signals reach the internal cytoskeleton through transmembrane receptors lead to involuntary contractions [49,68,69]. High-frequency or low-frequency peristalsis in the presence of fibroids may adversely affect fertility [50]. In cine MRI measurement performed in the mid-luteal phase in women diagnosed with intramural fibroid, Yoshino *et al.* [51] detected abnormal uterine peristalsis in approximately half of the patients. While they did not detect pregnancy in the presence of high-frequency peristalsis ( $\geq 2$  times/3 min), approximately one-third of the patients with low frequency peristalsis (0 or 1 time/3 min) became pregnant. Only one study reported that peristalsis returned to normal in 14 of 15 women with intramural fibroid with high-frequency uterine peristalsis and 6

cases became pregnant after myomectomy [51]. Detecting changes in uterine peristalsis after myomectomy will help us to determine the relationship between fibroid and abnormal subendometrial contractions.

#### 4. Discussion

Uterine fibroids present a somewhat unique challenge. Those women without symptoms don't require health care providers, but others present with one or a combination of infertility, recurrent pregnancy loss (RPL), abnormal uterine bleeding, and pressure symptoms, the latter when the mass of the fibroid or fibroids expands to a volume sufficient to place pressure on surrounding structures. Myomectomy is necessary to eliminate infertility, recurrent pregnancy loss, abnormal uterine bleeding, and pressure symptoms. In the light of new data obtained from receptivity-based studies performed so far, it may be possible to expand or narrow the indications for fibroid surgery. Since it may adversely affect endometrial receptivity with its unique molecular mechanisms, when making a surgical decision, not only the type of the fibroid, but also its possible effects on receptivity should be taken into account. Molecular tests for receptivity in subfertile women with intramural fibroids that do not compress the endometrium may guide the surgeon on how to behave. The goals of this type of investigative strategy include guidance regarding the appropriate management of leiomyomas when identified in conjunction with infertility, or RPL. Important to clinicians is the methodology for determining such a relationship; is imaging an appropriate screen? Alternatively, should endometrial sampling and analysis of relevant molecular markers be the arbitrator determining the impact of Type 3 or Type 4 leiomyoma on infertility, or RPL thereby guiding decisions regarding procedural interventions. So, it seems clear that evaluation of the differential impact of leiomyomas on endometrial markers associated with endometrial receptivity or hemostasis is important for clinicians and patients alike.

Contribution of receptivity studies to patients who have difficulty in making myomectomy decision varies according to the location of the fibroid. Since subserosal fibroids do not have a negative effect on the receptivity, their surgical removal does not improve the fertility outcome [24,25,70]. Detection of changes in receptivity in subfertile patients with subserosal fibroids may give surgeons an idea about whether to perform myomectomy. However, there are no receptivity-based studies investigating the effects of subserosal fibroids on endometrium. Based on the data obtained from current receptivity studies, myomectomy is not recommended for subserosal fibroids to restore receptivity. Submucosal fibroids lead to a decrease in both implantation and clinical pregnancy rates compared to those without fibroids. Surgical removal of the submucosal fibroid restores impaired fertility and provides pregnancy rates similar to healthy controls [70,71]. Since submucosal fibroids are in direct contact with the endometrium, they significantly re-

duce the expression of receptivity genes [8,9,29]. Fibroids in this location may cause hypermethylation of receptivity genes and lead to subfertility [52]. Many authors believe that DNA methylation is reversible and can be modified by lifestyle factors and some treatment modalities [72]. Therefore, removal of submucosal fibroids can restore impaired receptivity. The increase in fertility outcome after hysteroscopic myomectomy is evidence of restoration of impaired receptivity. However, we could not detect a significant increase in the expression of receptivity genes after myomectomy of submucous fibroids [9].

The clinical pregnancy and live birth rates of women with intramural fibroids larger than 2 cm and in contact with the endometrium before IVF/ICSI were found to be significantly lower than women without fibroids. If intramural fibroids do not have a connection with the endometrium, it is considered that the chance of adversely affecting fertility is reduced. However, depending on the modulus and stiffness of the fibroid core, an intramural fibroid unrelated to the endometrium may negatively affect receptivity [69]. Actually, intramural fibroids larger than 4 cm may adversely affect fertility even if they do not compress the endometrium. Although removal of intramural fibroids provides some improvement in the fertility outcome, myomectomy does not lead to a significant increase in clinical pregnancy and live birth rates [25,70,71]. However, the number of studies on intramural fibroids is limited and their quality is low. In addition to meta-analysis accepting that intramural fibroids negatively affect fertility [36], there is also a meta-analysis reporting that both the presence of intramural fibroids and their surgical removal have no effect on the results of assisted conception treatment [34]. However, the authors claimed that myomectomy did not increase pregnancy rates based on the results of only one study in the meta-analysis [34]. Therefore, data on whether myomectomy restores impaired fertility in women with intramural fibroids is unclear [24,25,34,36]. At this point, receptivity studies have shed light on some vague issues. After studies reporting that intramural fibroids negatively affect endometrial receptivity, it has been suggested that myomectomy may increase fertility outcomes [9,53]. Makker *et al.* [53] reported a significant decrease in HOXA10 expression in the presence of intramural fibroids. Since aberrant methylation alters the expression of HOXA gene in the presence of myoma, the decrease in HOXA gene expression may have developed secondary to increased methylation in the target gene. In the endometrium of women with submucosal or intramural fibroids HOXA gene is highly methylated. Methylation of homeobox gene is associated with decreased fertility and implantation failure. Kulp *et al.* [54] showed that HOXA10 expression decreased in the presence of intramural fibroids and they attributed this decrease to hypermethylation of its promoter region. Sagi-Dain *et al.* [55] reported that intramural fibroids not distorting the endometrium may lead to spontaneous miscarriage in oocyte donation cycles

probably by disrupting endometrial receptivity. In the study conducted by our team, we noted that surgical removal of intramural fibroids led to an increase in the expression of HOXA10 and 11 mRNA [9]. These four studies are critical in showing that endometrial receptivity is impaired in the presence of intramural fibroids. Conversely, study by Horcujadas *et al.* [42] showed that intramural fibroids not affecting the endometrium change the expression of genes unrelated to implantation. Only one study showed that the expression of receptivity genes increased after removal of intramural fibroids [9]. In other studies, the authors suggested that failed receptivity may improve after myomectomy of intramural fibroids. However, these thoughts were based only on clinical observations and researchers did not evaluate the endometrial receptivity in post-myomectomy period [24,25].

Considering the results of the studies so far, we do not have sufficient data to evaluate the endometrial receptivity and make a decision for myomectomy in women who do not have a reason to explain subfertility other than fibroid. A conclusive cause–effect relationship between uterine fibroids and endometrial receptivity requires further investigation. Fibroids that distort the uterine cavity, irrespective whether they are submucous or intramural, may adversely affect receptivity. Although the fibroids are located far from the endometrium, it is possible that the mechanical signals reach the endometrium and become a biological stimulus and affect receptivity [45,69]. Detection of hypermethylation in the CpG21 region of the HOXA gene in the presence of intramural or submucosal fibroids is an important finding suggesting that fibroids affect the expression of receptivity genes regardless of their location [54]. We can briefly summarize what we can do with the data we have as follows. In subfertile women presenting with fibroid the type, size, and number of fibroids should be determined and classified according to FIGO. The relationship of the fibroid to the endometrium should be particularly noted. In addition to conventional myomectomy indications, the detection of failed expression of receptivity genes may help the surgeon in making the myomectomy decision. In subserous fibroids without significant intramural component, myomectomy is not appropriate to increase fertility. However, in subfertile women with Type 3 or Type 4 fibroid where a clear decision for myomectomy cannot be made, a decision can be strengthened by receptivity tests. In Type 3 fibroids that are in contact with the endometrium, myomectomy may improve fertility outcome. However, in women with Type 4 fibroids who have sonographically or hysteroscopically confirmed that there is no contact with the endometrium, receptivity can be evaluated and a surgical decision should be made accordingly. Consequently, comprehensive studies that allow clinicians to determine which fibroids contribute to infertility or recurrent pregnancy loss are very much needed.

## Author contributions

OC—design, hypothesis and writing of the article; OK, AY, AE, NC, FT, NG, RO, MDO, BD, CU—data collection for systematic analysis, data interpretation, assistance with design and hypothesis, checking and approval of final manuscript.

## Ethics approval and consent to participate

Not applicable.

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## Conflict of interest

The authors declare no conflict of interest.

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