



Intramural fibroid and fertility—to operate or not

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Abstract: Small intramural fibroids in subfertile women pose a clinical challenge. Based on the FIGO classification, types 3 and 4 are intramural fibroids. There are many reasons why intramural fibroids causes infertility but the only measurable cause is uterine peristalsis. It is not known why some patients with intramural fibroids have increased uterine peristalsis. However, studies have shown that increased uterine peristalsis in patients with intramural fibroids have poorer pregnancy outcome. Studies have also shown that intramural fibroid that affects the junctional zone (JZ) have increased frequency of abnormal uterine peristalsis. Due to this reason, we propose that type 4 fibroid should be further classified into type 4a and type 4b. Type 4a fibroid disrupts the JZ and type 4b does not. There appears to be sufficient evidence that intramural fibroid affects fertility but the evidence that myomectomy in such patients will improve pregnancy outcome is not strong. Alternatives to myomectomy in these patients are to shrink the fibroid or decrease the uterine peristalsis using medication. Methods to shrink these intramural fibroids include ulipristal acetate, gonadotrophin releasing hormone (GnRH) agonist, uterine artery embolization (UAE) and high intensity focused ultrasound (HIFU). Atosiban can be used to suppress uterine peristalsis. These methods are discussed. We recommend that future research should be directed at development of an effective and cheap method of measuring uterine peristalsis. Until measurement of uterine peristalsis is easily available, it is difficult to recommend routine myomectomy in subfertile patients with small intramural fibroid and non-invasive methods such as HIFU appears to be a more attractive method to shrink these fibroids to improve fertility, but this need to be assessed in clinical studies.

Keywords: Intramural fibroids; myomectomy; fertility; peristalsis; ulipristal acetate (UPA); atosiban; gonadotrophin releasing hormone agonist (GnRH_a); uterine artery embolization (UAE); high intensity focused ultrasound (HIFU)

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Introduction

Uterine fibroid also called leiomyoma is the commonest monoclonal tumour in women. 70–80% of women will develop fibroid by the age of 50 (1). Thirty percent of infertile patients have fibroids. Fibroids may be the sole cause of infertility in 2–3% of women (2). Current literature calls for removal of submucous fibroid and possibly cavity distorting intramural fibroids to optimize pregnancy

outcome (3). However, removal of non-cavity distorting (NCD) intramural fibroids is still controversial. This review is aimed at looking at the current literature on this type of fibroids. We aim to answer the following questions:

- I. What are the classifications of fibroids?
- II. What is the pathophysiology that causes subfertility in patients with intramural fibroids?
- III. Does intramural fibroid cause infertility?
- IV. Does myomectomy improve pregnancy rates?

- V. Are there alternatives to myomectomy in these patients?

Classification of fibroids

Traditionally fibroids are classified by its location in the uterus. They are classified as cervical, submucous (SM), subserosal (SS) and intramural (IM) fibroids (4,5).

Based on the International Federation of Gynaecology and Obstetrics (FIGO) systems, fibroids are classified into several types (6). Based on this FIGO classification, Type 0 and 1 are SM fibroids. Type 2 although >50% is IM has been classified as SM as well. Type 3 is an IM fibroid and it is distinguished from type 2 by doing a hysteroscope with the lowest possible intrauterine pressure necessary to allow visualization. There should not be any bulge into the endometrial cavity. Type 4 is the classical IM fibroid. Type 5 even though >50% is IM is often classified as SS. Types 6 and 7 are SS fibroids.

Based on this FIGO classification, an IM fibroid should be only type 3 and 4. The average thickness of the myometrium at the body of the uterus ranges from 1.5 to 3 cm (7,8). Even though a fibroid can expand the thickness of the myometrium and remain type 3 and 4, there is a high chance that a fibroid >3 cm may have SM or SS component. We believe that most published literature on IM fibroids may have included type 5 fibroids and some even would have included type 2 fibroids because the SM component was not clearly seen on ultrasound and/or hysteroscopy.

Pathophysiology

Studies show that uterine fibroid causes endometrial vascular disorders and inflammation resulting a non-conductive environment for embryo implantation and thus leading to infertility (9,10). The way IM fibroid causes difficulty in conceiving has been discussed extensively in the paper by Pier and Bates (11). The following discussion on the pathophysiology of IM fibroid causing subfertility is extracted from this paper.

Implantation

Implantation is a complex process. Several factors such as HOXA-10, glycodelin, leukemia inhibitory factor and glutathione peroxidase 3 are involved in this process.

HOXA-10 is responsible for cellular differentiation while glycodelin is responsible in promoting angiogenesis,

suppressing natural killer cells (NKc) and inhibiting the binding of the spermatozoa to the zone pellucida. Normally, both factors reduce during follicular phase and increase during implantation. With the presence of IM fibroids, both HOXA-10 and glycodelin were reduced during implantation (12-19). Although studies which showed a reduction trends in HOXA-10 is not conclusive but this reduction causing inability of the embryo to implant is confirmed in animal model (12-15). So, we hypothesis that the reduction of both factors is responsible in embryo implantation failure causing infertility.

JZ

In women of reproductive age, magnetic resonance imaging (MRI) has shown three distinct layers in the myometrium. The innermost layer that immediately abuts the endometrium is labelled the JZ (20). This zone may affect fertility by two different mechanisms. Firstly, the origin of myometrial peristalsis in the JZ (21). Disruption of this zone by fibroids may lead to increased peristalsis (22). This will be discussed in the next section. Secondly, IM fibroids may cause thickening or disruption of the JZ leading to poor reproductive outcome (22).

The changes in the thickness of the JZ can be due to the changes in the expression of oestrogen, progesterone, the respective receptors and aromatase (23-25). Besides, we noticed that the amount of NKc and macrophage cells in the uterine influence the fertility potential. Study demonstrated that the NKc were significantly reduced while the macrophage cells were significantly increased in the endometrium closer to the fibroid compared to other area, the amount of both cells were significantly reduced regardless of the area when compared to the fibroid-free patient (26).

Since JZ plays an important role in implantation and its disruption may lead to implantation failure, we propose that type 4 fibroid can be further classified into type 4a and 4b as shown in *Figure 1*. 4a are fibroids that disrupt the JZ but does not reach the endometrium and type 4b are fibroids that do not disrupt the JZ.

Uterine myometrial peristalsis

There are 2 types of uterine contractions. The first is focal and sporadic bulging of the myometrium first described by Togashi *et al.* (24). The second is the rhythmic and subtle stripping movement in the subendometrial myometrium

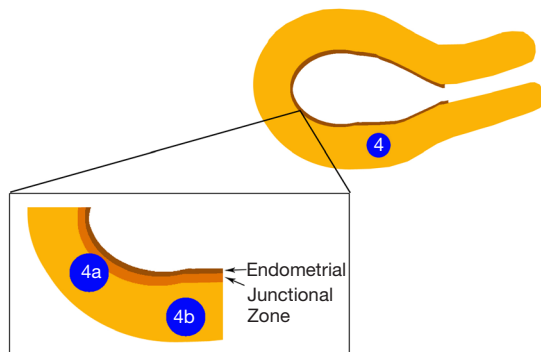


Figure 1 Based on FIGO classification, type 4 fibroid is a classical intramural fibroid. We postulate type 4 fibroid into type 4a and type 4b. Type 4a is fibroid which disrupts the junctional zone but has not reach the endometrium lining while type 4b is fibroid which does not disrupt the junctional zone.

known as uterine peristalsis (UP) captured by cine mode magnetic resonance imaging (cMRI) (25).

From menstruation to the mid-ovulatory phase of the menstrual cycle, the uterus contracts from the cervix to the fundus with increasing frequency. Post-ovulation, the contraction frequency decreases to relatively quiet during implantation. In the luteal phase, the direction of peristalsis is reversed (26). Based on the studies, UP is increased in patients with IM and SM fibroids during the mid-luteal phase and decreased during the peri-ovulatory phase compared to the healthy controls (27,28).

The relationship between infertility and abnormal UP among patients with IM fibroids was explored by Yoshino *et al.* (29). Ninety-five infertile patients with only IM fibroids underwent cMRI during the implantation period (luteal phase days 5–9) and were further categorized into two groups (low and high uterine peristaltic frequency). Low uterine peristaltic frequency was categorized as having <2 peristalsis in 3 mins while high frequency was categorized as having ≥ 2 movements within 3 mins. To avoid bias, the authors recruited patients with same numbers and diameter of fibroid but half of them had cavity-encroaching fibroids. They offered infertility treatment like natural cycle, ovulation induction by hormonal therapy and intrauterine insemination in an increasing manner depends on the severity of the infertility. Results showed 34% of pregnancy rate in the low-frequency group while 0% in the high-frequency group within 2 years post-treatment. This demonstrates that abnormal UP is a likely cause of infertility. However, why some IM and even SM fibroids

cause high frequency peristalsis while other doesn't is not known.

Since UP is at the JZ, disruption of this zone by fibroid may further increase UP (18). So, one can postulate that type 3 and type 4a fibroids may have more UP than type 4b fibroids leading to more subfertility. This needs to be further evaluated by clinical studies. There are several methods of measuring UP namely intrauterine pressure measurement, transvaginal ultrasound and cMRI. Each method has its own advantages and disadvantages (30). Measuring UP accurately and inexpensively will assist in determining which patients with IM fibroid will benefit from treatment.

Fibroid pseudocapsule

Leiomyoma is covered by a thin layer which can be identified easily during myomectomy, known as fibroid pseudocapsule (PC). This layer contains bundle of smooth muscle cells and neurotransmitters. Besides, it is highly vascular to supply blood to the myoma and allows neovascularization to occur (31). This statement is proven in studies showing an upregulation of endogelin and CD34 (marker of neovascularization) in the PC compared to the fibroid and surrounding myometrium (32,33).

Thickness of the PC varies with the type and location of the fibroid which may alter the expression of modulators. It is significantly thicker in SM than IM fibroids while significantly thicker in IM than SS fibroids. The thickness also increases as the fibroid approaches to the cervix resulting an increase in the expression of enkephalin and oxytocin which will alter the UP and affect fertility (34). The altered UP may also be contributed by the high levels of neurotensin, neuropeptide tyrosine, and protein gene product 9.5 present in the IM fibroid PC (35). The presence of PC and the associated cytokines, growth factors and hormones may be responsible for the abnormal UP which may result in pregnancy complications like premature uterine contraction resulting in preterm delivery in women with large IM fibroids (36).

Although these neurotransmitters produced by PCs induce UP, they are important in promoting inflammation and proper wound healing. So, it is mandatory to perform intracapsular myomectomy without excising the PC to reduce intraoperative blood loss, enhance better uterine healing and correct musculature anatomical restoring to preserve the uterine functionality for reproductive purpose (37–39).

Steroid hormones

Uterine fibroid does not present in pre-puberty and rarely post-menopausal with low incidence in multiparity and late menarche (40). This implies that fibroid development depends on the hormonal status. Ovarian steroids, oestrogen (E2) and progesterone (P4) are responsible for the formation and growth of the fibroid (41). Fibroid tissues have a higher concentration of aromatase, E2, oestrogen receptors α and β , and progesterone receptors (PR) compared to the surrounding healthy myometrium (41,42).

Fibroids are known as E2-dependent tumour since E2 is the primary growth promoter of fibroids (43,44). High level of E2 decreases the tumour suppressor protein (p53) in the fibroid cells and regulates its growth factors and signalling pathways, stimulating cellular proliferation and fibroid growth (45). Besides, E2 is important in maintaining the progesterone receptor (PR-A and PR-B) level to induce the PR ligands action and subsequently mediate the P4 actions (43,45).

Previous studies have shown that the growth of fibroid is solely dependent on E2 and inhibited by P4 (46). However, recent studies concluded that P4 plays an equally important role as E2 in fibroid growth and maintenance (47,48). With the presence of E2, PRs will be expressed more in the fibroid cells to allow the binding of P4 to PRs. Once P4 binds to PR, the growth factors levels will be regulated to increase the expression of cell proliferation regulatory genes (*PCNA*, *EGF*, *TGF- β 3*) and inhibits IGF-1 expression in the fibroid cells. Besides, P4 will stimulate the signalling pathways by increasing the proliferating cell nuclear antigen (causing proliferation) and anti-apoptotic B-cell lymphoma protein 2 while decreasing the cleaved caspase 3 (causing anti-apoptosis) (43,45). As a result, the fibroid cells will continue to proliferate without apoptosis (41,43).

Ishikawa *et al.* have studied on the types of hormone that is responsible for the fibroid growth and maintenance (44). They found that the fibroid which was treated with E2+P4 was significantly larger whereas fibroid treated with E2 or P4 alone was significantly reduced in volume. This showed that both E2 and P4 are mandatory for fibroid growth and maintenance, the absence of either one will not stimulate cellular proliferation. They also found high PR expression in any groups treated with E2, demonstrating the essential of E2 in PR upregulation.

Besides promoting fibroid growth, E2 and P4 are involved in uterine peristalsis. A study has demonstrated a significant higher peristalsis rate in E2 perfusion but

lower in P4 perfusion (49). This is because the endometrial oxytocin and oxytocin receptor which are responsible UP are up-regulated by E2 (30). High E2 level stimulates the JZ and subsequently induces rapid uterine contraction whereas P4 antagonizes the effect of E2 and suppresses the uterine contractility.

In short, hormonal factors are involved in fibroid development. Medications which suppress E2 such as GnRH agonists, selective oestrogen receptor modulators and aromatase inhibitors and medications which suppress P4 like PR modulators will be beneficial in fibroid treatment.

The summary of the causes of IM fibroids affect fertility are well described in *Figure 2*.

Does intramural (non cavity distorting) fibroids cause infertility?

SM fibroids (type 1 and 2 fibroids) are proven to affect fertility and hysteroscopic resection-helps to improve the reproductive outcomes. SS fibroids (type 5, 6, 7 fibroids) do not affect fertility, as they do not protrude into the endometrial cavity (3). However, the effect of NCD IM fibroids such as type 3 and 4 fibroids on fertility remains controversial with studies yielding conflicting results.

Here, we will review on 10 retrospective studies and 5 prospective studies which show the impact of NCD IM fibroids on fertility outcomes. The participants of these studies consisted of women who were undergoing assisted reproductive treatment (ART) (IVF and ICSI) as they were believed to be more sensitive to study on the implantation process (50,51). The outcomes were determined based on the pregnancy rate (PR), clinical pregnancy rate (cPR), live birth rate (LBR), delivery rate (DR), implantation rate (IR) and miscarriage rate (MR).

Intramural fibroids reduce fertility outcomes

Few studies have suggested that NCD IM and SS fibroids cause significant adverse effects on the pregnancy outcomes (8,52-55).

Yan *et al.* reported significant reduction of cPR, biochemical pregnancy rate (bPR) and LBR among women with Type 3 fibroid compared to healthy controls (cPR =27.8% *vs.* 43.9%; bPR =29.1% *vs.* 51.4%; LBR =21.2% *vs.* 34.4%) (52). A single IM NCD fibroid with diameter <7 cm caused significant lower cPR and LBR compared to the control group (cPR =25.8% *vs.* 39.9%; LBR =17.7% *vs.*

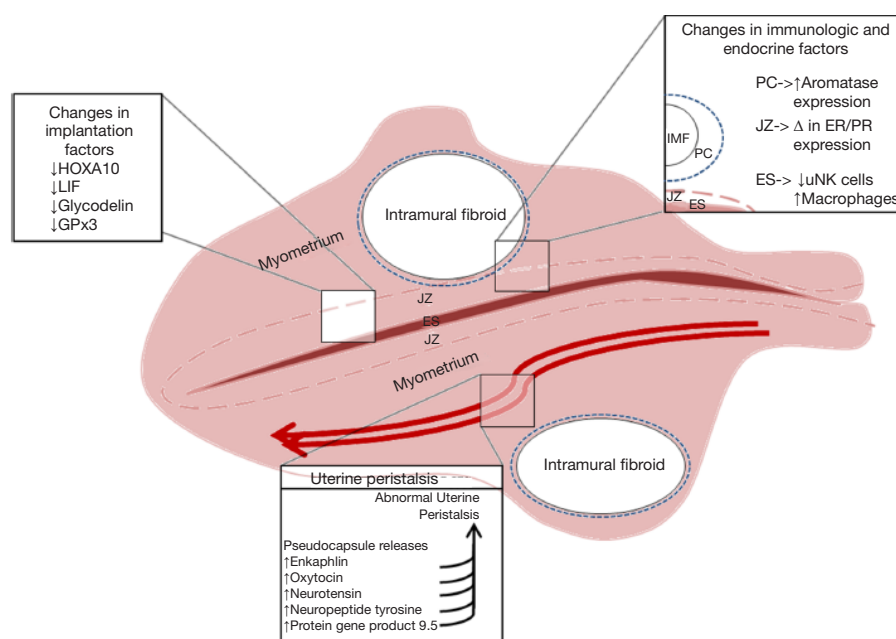


Figure 2 Potential causes of decreased fertility and pregnancy loss in patients with IM fibroids. Note: Reprinted from Fertil Res Pract 2015;1:12. Under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).

30.9% respectively) (53). In Khalaf *et al.*'s study, the group with small IM fibroids demonstrated a significant reduction of cPR, ongoing PR (oPR) and LBR than the control group (cPR =23.6% *vs.* 32.9%; oPR =18.8% *vs.* 28.5%; LBR =14.8% *vs.* 24% respectively) (8). After adjusting the confounding variables, they found significant reduction of the oPR by 40% and LBR by 45% per cycle. Besides, Eldar-Geva *et al.* reported reduced PR in the SM (10%) and IM fibroids (16.4%) compared to SS fibroids (34.1%) and control (30.1%) (54). Although the cPR and oPR were significantly reduced in fibroid with diameter 22 mm in Hart *et al.*'s study, the results were not generalized as the women in the fibroids group were 2 years older than the control group (55).

Besides poor PR, the IR and MR were also affected by these fibroids (6,8,52-59). Yan *et al.* reported a significant reduction of IR in type 3 fibroids compared to the control group, 22.7% *vs.* 34.4% (52). However, there were no significant changes in the MR between both groups. Guven *et al.* also stated single NCD IM fibroid with diameter <7 cm caused significantly lower IR and non-significantly higher MR (53). In the study conducted by Surrey *et al.*, the IR was significantly reduced among women <40 years old with fibroids compared to the age-matched control group, 21.4% *vs.* 33.3% respectively (57). However, no significant

difference was found when comparing women >40 years old with fibroids and the age-matched control group, 17.5% *vs.* 11.6% respectively. Eldar-Geva *et al.* and Hart *et al.* also demonstrated significant reduction of IR among women with fibroids compared to the control group (54,55). A few studies reported insignificant increment of MR and reduction of the IR among women with fibroid compared to the control group (8,58,59). Somigliana *et al.* reported a higher IR in women with fibroids but it was due to the higher number of transferred embryos in women with fibroids (6).

Similar fertility outcome between study and control groups

In contrast to the above-mentioned studies, several studies demonstrated similar fertility outcomes in patients with and without fibroids indicating that the presence of NCD fibroids does not adversely affect the pregnancy outcomes (7,50,56,58-63). Vimercati *et al.* reported no significant differences in cPR, IM and MR between cavity distorting *vs.* NCD fibroids (56). Klatsky *et al.* also reported no statistical difference in cPR, IR and MR between patient with and without fibroids (cPR =47% *vs.* 54%, IR =36% *vs.* 38% and MR =15% *vs.* 9%) (61). Despite insignificantly lower PR in the IM and SS fibroid groups, Yarali *et al.* reported similar

readings of cPR, IR, MR and multiple PR between groups of IM, SS and without fibroid (50). These results ran along with the study conducted by Oliveira *et al.* (7). Bozdag *et al.* reported comparable results of the bPR, cPR and IR between women with single IM fibroid and without fibroids (bPR =43% *vs.* 42%; cPR =36% *vs.* 38%; IR =20% *vs.* 19% respectively) (58).

No significant difference was found in the cPR, bPR, DR and MR when comparing women with fibroids with diameter <6 cm and women without fibroid (60,62). By comparing fibroids with diameter <4cm *vs.* control group, the cPR and IR were similar (7). Two prospective studies reported non-significant difference in the pregnancy outcomes between IM fibroids <5 cm with the control group except lower trend of LBR and DR, higher trend of MR in the fibroid groups (6,59). Aboulghar *et al.* reported non-significant differences of cPR between women with fibroids, with previous myomectomy and without fibroids (63). They also found that the PR in fibroids <5 mm away from the endometrial lining was lower but not significant when compared to fibroids >5 mm away from the endometrium lining.

Does size of IM fibroids affect fertility?

Several studies further analysed the effect of the fibroid size on the fertility outcomes (7,52,56,60). Yan *et al.* set the cutoff value of the fibroid diameter at 2 cm (type 3 fibroid) (52). The results showed a significant reduction of cPR, LBR, bPR and IR in fibroid diameter >2 cm compared to the control group. On the other hand, an earlier study conducted by the same authors showed NCD fibroids >2.85 cm had significant negative impact on the LBR and DR but insignificantly higher MR compared to the control group (60).

Christopoulos *et al.* reported multiple fibroids or NCD fibroids >3 cm lowered the cPR and LBR significantly (64). Vimercati *et al.* reported fibroids >4 cm have adverse impact in the pregnancy outcomes since they require more ART cycles (56). This statement was supported by another study conducted by Oliveira *et al.* where IM fibroids >4 cm lowered the cPR and IR more than the IM <4 cm, SS fibroids and the control groups (7).

Correlation between the number and location of fibroids with the fertility outcomes

Yan *et al.* reported absence of significant differences of cPR and DR on the number of fibroids as compared to the

control group (60). They also found that single and multiple fibroids have the similar outcomes. No correlation was found between the number and location of the IM fibroids on the IVF-ICSI outcomes (6,7,50,59,61). Few studies reported absence of correlation between the size of the fibroids with cPR (6,50,58,61). Furthermore, Surrey *et al.* demonstrated no correlation between the total mean fibroid diameter or volume and the implantation among women with fibroids regardless of their age (57).

Review articles

There are two meta-analyses reporting on the effect of intramural fibroids on fertility. Sunkara *et al.* and Wang *et al.* reported statistically significant reduction of LBR and cPR (65,66). However, Sunkara *et al.* found no significant reduction in IM and no significant increase in MR among the study and control groups. Wang *et al.* demonstrated a significant reduction of IM and significant increase MR. Although Sunkara *et al.* have applied various strategy to increase the sensitivity and generality of their results, several limitations were difficult to be controlled (65). For example, different diagnostic tools were applied to confirm the normality of the uterine cavity, different inclusion and exclusion criteria as well as different mean size and number of the fibroids across the studies. On the other hand, Wang *et al.* was unable to match the age of the participants, number and mean size of the fibroids across the studies (66).

In summary, small IM fibroids (type 3 and 4) probably affect fertility and decrease PR and LBR in patients undergoing ART. It is difficult to decide which patients with small IM fibroids will benefit from surgical or non-surgical intervention.

Does removal of intramural fibroids (myomectomy) improve pregnancy rates?

Myomectomy improves pregnancy

Bulletti *et al.* reported higher PR and LBR post-laparoscopic myomectomy compared to non-surgical group (LBR =42% *vs.* 11% respectively) (67). They concluded that surgical removal of large and multiple fibroids resulted in better outcomes but there were also positive results for women with smaller fibroids. Campo *et al.* also reported significant improvement in the pregnancy outcomes post-myomectomy among women with SS or IM fibroids without undergoing ART (68). The DR was improved from 38.5% pre-surgery

to 86.2% post-surgery while MR was reduced from 61.5% to 13.8% respectively. These improvements were resulted from the removal of the plausible cause of impaired fertility such as altered UP and blood supply.

Yoshino *et al.* identified patients with IM fibroid who have increased frequency of UP by cMRI (discussed earlier in the UP section under pathophysiology) (69). They then performed myomectomy on all these patients. MRI was done post-myomectomy to determine the reduction of UP and PR was evaluated following 8 months of ART. As a result, 14 of 15 patients had normalized UP, 6 of them achieved pregnancy. The authors also suggested that cMRI might play a role in selecting patient who is required for surgery.

Myomectomy according to fibroid size / diameter

In the earlier discussion, we have seen that not all studies with IM fibroids decrease fertility potential. As such the size of fibroid/s may be important in determining which fibroid/s may benefit from myomectomy (70). Yan *et al.* suggested that resection of type 3 fibroids with diameter >2 cm may improve fertility while Benecke *et al.* concluded that surgery will be beneficial for patients with history of unsuccessful pregnancy with IM fibroids >2 cm without other infertility factors (52,71). Kolankaya *et al.* reported that most surgeons recommend surgery for fibroids >7 cm or women with multiple failed IVF cycles (72). Vimercati *et al.* supported pre-IVF myomectomy for fibroids >4 cm (56). Bulletti *et al.* demonstrated higher success rate and DR among patients with IM fibroids >5 cm and underwent laparoscopic myomectomy prior to IVF (73). The PR was 33% and DR was 25% in the myomectomy group while 15% and 12% in the control group with no significant difference in the MR.

Myomectomy according to fibroid location

The fibroid location is important in determining the necessity of myomectomy. Casini *et al.* reported that the PR post-myomectomy was higher in all types of fibroids compared to non-surgical group (74). When there is a SM component of the fibroid, myomectomy showed a statistically significant improvement in PR. This was not seen in patients with IM and SS-IM fibroids but there was an overall higher trend of PR among these women who underwent myomectomy compared to those with fibroid left in situ. Besides, myomectomy can reduce MR in most

of the fibroids and improve the chances of fertilization to achieve better pregnancy outcomes.

Myomectomy is not advisable

Myomectomy is associated with surgical morbidities (53,56,59,64). There are three studies which do not advocate myomectomy as a routine treatment for infertile women with fibroids. Aboulghar *et al.* demonstrated no significant difference in the cPR between the groups of surgical, non-surgical and infertile women without fibroids (36% *vs.* 29% *vs.* 36% respectively) (63). They also found no statistically significant in the cPR regardless of the distance between the fibroid and the endometrial lining except a trend of higher cPR when fibroids were at >5 mm away from the endometrial lining. Cochrane review also found no improvement in the fertility outcome post-myomectomy regardless of the fibroid location (75). Belina *et al.* against myomectomy in women with IM fibroids regardless of the size (76). They encouraged women to weigh the benefits of the surgery against the risks.

Some authors recommend surgery only for cases like repeated IVF treatment failure, fibroid related obstetrical complications and recurrent miscarriage (6,62). A review study concluded that there is no significant difference in the fertility outcomes between surgical and non-surgical groups (77). Although IM fibroids reduced fertility and increased MR, myomectomy did not significantly increase the cPR. They concluded that removal of intracavitary fibroid is beneficial, but removal of NCD IM fibroids does not significantly increase the cPR and LBR. Although NCD IM fibroids significantly decreased the LBR and cPR, it does not mean that removal of such fibroids will restore the LBR to the expected rate among women without fibroids (65).

Alternative to myomectomy (non-surgical methods)

Since myomectomy may be considered a big procedure for small fibroids and its benefit is still controversial, is it possible to consider non-surgical methods to improve fertility in such patients? Here we will look at some alternatives to myomectomy namely ulipristal acetate (UPA), gonadotrophin releasing hormone agonist (GnRHa), atosiban, uterine artery embolization (UAE) and high intensity focussed ultrasound (HIFU).

UPA

UPA is a selective progesterone receptor modulator (SPRM) which is a synthetic steroid that have agonistic and antagonistic effects on the PR (43,78,79). Since its structure is like P4, they will compete at the PR binding site. However, UPA has higher selectivity for PR than P4, so it is more potent to modulate the PR activity (41,43). This unique selectivity makes SPRM superior to GnRHa as it maintains the circulating E2 level within the mid-follicular phase range thereby avoiding the side effects of hypoestrogenism which are commonly reported in GnRHa treatment (43,78-82).

SPRM specifically acts on the pituitary gland, fibroid and endometrium (78,80). By acting on the hypothalamic-pituitary-ovarian axis, UPA reduces the secretion of luteinizing hormone (LH) and follicular-stimulating hormone (FSH) to induce amenorrhea and inhibit ovulation. Alongside with its action at the PR on the endometrium, menorrhagia can be controlled. In the fibroid cells, UPA acts as P4 antagonist to inhibit cellular proliferation and induce cellular apoptosis. Neovascularization can also be inhibited by reducing the angiogenic growth factors. To shrink fibroid, UPA increases matrix metalloproteinases and decreases tissue inhibitor thereby reduces the collagen deposition in the fibroid extracellular matrix (43,80,81).

Five case reports focused on the fertility outcome post-UPA without surgical treatment (41,81,83-85). Among these, 2 case reports demonstrated spontaneous pregnancy while the remaining 3 reported successful ART post-UPA. Besides proving a significant reduction of the fibroid size, they also showed sustained effect in maintaining the fibroid volume for up to 6 months after treatment cessation. UPA helps to increase the distance between the fibroid and the endometrium lining, subsequently restore the uterine anatomy to allow embryo implantation without interfering the endometrial receptivity (41,83). UPA is superior to myomectomy in terms of lower risks and complications with shorter waiting period to conceive. The optimal waiting period for conception post-myomectomy was 9.8 months and majority of the pregnancies occur within 2 years to allow wound healing and better uterine perfusion. This long waiting period is insecure especially for advanced-age infertile patients. With UPA, patients can conceive immediately post-treatment (41,85). All these case reports are based on patients with type 2 or 3 fibroids. Whether this can be extrapolated to benefit type 4 NCD fibroids is yet to be confirmed in studies.

As UPA selectively acts on the PRs, the unopposed E2 stimulation causes endometrial overgrowing and thickening. This endometrial modification is known as PR modulator associated endometrial changes (PAEC) (43,78,80,86). It is a benign and reassuring condition as it is reversible after treatment cessation. It usually resolves within 6 months post-treatment where the endometrium thickness and quality will be restored for blastocyst implantation (81,87-89).

UPA has been reported to cause serious liver injury in a few patients (78). Few recommendations on prescribing UPA have been released by the Pharmacovigilance Risk Assessment Committee to maintain its safety profile.

Gonadotrophin releasing hormone agonist (GnRHa)

Gonadotrophin releasing hormone (GnRH) is a native peptide which regulates the production of FSH and LH to stimulate the ovaries to produce sex steroid hormone like 17 β -estradiol and P4 (90).

GnRHa acts directly on the pituitary gland by binding to the GnRH receptors (91). Initially, it will increase the release of gonadotropins causing a surge of FSH and LH. After 1-3 weeks, the GnRH receptors will be desensitized and downregulates the hypothalamic-pituitary-ovarian axis, causing a reduction in E2 and P4 thus causing a reduction in fibroid growth (92). GnRHa also acts on the GnRH receptors expressed by the fibroids to reduce cellular proliferation (91). Besides decreasing the expression of several growth factors, it also reduces the expression of the nuclear factor of activated T cells 5 which acts as a hyperosmolarity gene (90,91). During this process, the water will diffuse out from the fibroid cells causing shrinkage of the fibroid.

Few studies have been conducted to study the effect of GnRHa on fibroid volume reduction. They have proven a significant reduction of the fibroid volume during the treatment period (93-95). One of the review articles stated that five studies reported 30-60% reduction of the fibroid size (96-99). Friedman *et al.* demonstrated a 6-month treatment of 3.75 mg leuprolide acetate caused 36% reduction of uterine volume at 12 weeks while 45% at 24 weeks of treatment (100). Since there are lack of studies to determine the effect of GnRHa on fertility, we postulate that the significant reduction of fibroid volume by GnRHa may reduce the impact of cavity encroaching fibroid and subsequently improve implantation. In the study conducted by Kessel *et al.*, 3 out of 5 infertile women with fibroids successfully conceived, 2 of them conceived without surgical

intervention (95).

Atosiban

Atosiban is a combined oxytocin and vasopressin V1a receptor antagonist. As an oxytocin receptor antagonist, atosiban competes with oxytocin at the oxytocin receptors in the endometrial cells to decrease endometrial contraction and prevent embryo expulsion during the implantation phase (101,102). By reducing the oxytocin effect, it will inhibit the oxytocin-induced prostaglandin production and increase the endometrial blood supply (101-105). As a vasopressin V1A antagonist, atosiban relaxes the uterine arteries and decreases the systolic blood pressure to improve blood perfusion to the endometrium and myometrium (101-103). These antagonistic effects on the oxytocin and vasopressin receptors improve uterine receptivity and embryo implantation.

Atosiban is uterine specific which has immediate and profound effect on the uterine activity (103,106,107). Since UP is one of the suspected causes of infertility in patients with IM fibroid, atosiban may be used to improve PR in such patients.

However, all studies done with atosiban recruited patients with repeated implantation failures. Four studies have proven significant increase in the cPR, LBR and IR and significant decrease in MR in atosiban group compared to the placebo group (101,102,105,106). Two case reports have demonstrated positive pregnancy outcomes after receiving atosiban (103,107). These studies have also shown a significant reduction of uterine contractions post-atosiban (103,105,107). However, double-blinded RCT showed non-significant changes in the LBR post-atosiban to women with repeated implantation failure including women with fibroids (104). Whether atosiban will improve PR in patients with NCD IM fibroid is yet to be determined in studies.

UAE

UAE is performed by injecting small embolic particles into both uterine arteries to occlude the target vessel. This will induce ischemia leading to necrosis of the fibroid cells (108). While obstructing the blood supply to the fibroids, the vascularity of the whole endometrium and myometrium will be affected during UAE (109,110). UAE is believed to affect embryonic implantation and difficulties in maintaining gestation leading to increased miscarriages. The risk of amenorrhoea and ovarian failure after UAE in

young women is low. However, there is a worry of poor oocyte quality and poor response to ovarian stimulation in patients who have undergone UAE (111-113). Two patients <40 years old who underwent IVF post-UAE showed low response to ovarian stimulation (114). Four patients desiring pregnancy became amenorrheic post-UAE and another patient underwent unsuccessful IVF treatment (115). Several cases of intrauterine adhesions, endometrial atrophy and fistula between the uterine cavity and the embolized myoma post-UAE were described in the literature (115-117). >1/3 of 127 patients were found to have intracavity tissue necrosis 3-9 months post-UAE (118). This alarming finding could help to explain the high MR in post-UAE women.

Therefore, UAE is listed as a relative contraindication for women desiring future fertility by the American College of Obstetrics and Gynaecology, the Society of Interventional Radiology and the Royal College of Obstetrics and Gynecology (119-121). However, there are several studies reporting pregnancies after UAE. Karisen *et al.* reviewed articles and concluded that 50% of the women achieved pregnancy post-UAE, which is lower than post-myomectomy (78%) (122). MR appears to be higher post-UAE (60%) than post-myomectomy (20%).

As the benefits of UAE on fertility remains debatable and a low level of evidence to suggest better pregnancy outcomes post-UAE, some authors advice UAE should not be the 1st choice for women with fibroids and have future pregnancy plans (108,122,123).

HIFU

HIFU is also known as focused ultrasound surgery. It is an organ sparing, non-invasive, thermal ablative procedure. It uses an extracorporeal transducer to focus the high-intensity ultrasonic beams to the targeted myoma to thermally ablate the tumours without introducing needles or probes into the tumour (124,125). There are two types of HIFU treatment namely Magnetic Resonance Imaging focused ultrasound surgery (MRgFUS) and Ultrasound guided high intensity focused ultrasound (USgHIFU). HIFU treatment is limited to ablation within the pseudomembrane. Therefore, there is minimal damage to the surrounding normal myometrium without obvious damage to the elastic and collagen fibers in the normal uterine muscle, resulting in less scar tissue formation and less risk of collagen fiber hyperplasia. Theoretically, this would reduce the pregnancy risks in women who have undergone HIFU treatment for uterine

fibroids, as compared to myomectomy. Previous studies have found that, compared with laparoscopic myomectomy, HIFU has the advantages of fewer complications, faster recovery, less patient discomfort, and lower treatment-associated risk (126,127). Clinical studies also confirmed that HIFU avoids ovarian function impairment and adverse reaction, thus preserve the ability to conceive (128-132).

Li *et al.* found that the volume of the uterine fibroids decreased, and the symptoms of uterine fibroids improve significantly post-HIFU treatment (133). The PR post-HIFU reached 69.3% (despite not considering male infertility), which is similar to the PR (62.2–68%) post-myomectomy (134-136). Almost 74% of women conceived within one-year post-HIFU treatment. The spontaneous PR post-HIFU was 95.4%, which is slightly higher than that of post-myomectomy (64.6–88.6%) (134,137). Although the spontaneous abortion rate (14.9%) post-HIFU is similar to that of post-myomectomy (13–24%), this rate is still significantly lower than in pregnancy with untreated fibroids (20–46.7%) (138,139).

Discussion

NCD IM fibroid with infertility poses a difficult clinical challenge. There appears to be enough evidence that NCD IM fibroid affects fertility. Type 3 fibroids may have a higher risk of poor pregnancy outcome compared to type 4 fibroids (52). Since disruption of the JZ appears to be an important cause of subfertility, type 4a fibroids may have a poorer outcome than type 4b fibroids. This will be difficult to prove in clinical studies because it is difficult to visualize the JZ and the changes in its thickness during the menstrual cycle on transvaginal ultrasound.

There are many possible causes why IM fibroids affect fertility. The only measurable cause appears to be increased UP. Unfortunately, not all patients with IM fibroids have increased UP. Currently there is no good and inexpensive method of measuring UP. cMRI seems to be an accurate method but it is expensive (30). Transvaginal ultrasound method is a cheaper modality but it is still very user dependent. A better method needs to be devised to measure UP easily and effectively.

With vitrification, pregnancy after frozen embryo transfer is improving (140). As such, it has been suggested that myomectomy should not be the first line treatment in patients with small IM fibroids. In patients with many frozen embryos, the strategy could be to consider surgical or non-surgical intervention only in patients who have a

failed embryo transfer.

Myomectomy may appear to be a big procedure to perform in patients with small IM fibroid/s. Non-surgical modalities described above may be another option. While UPA seems encouraging, this may be an option to reduce the size of fibroids especially the type 3 and 4a fibroids. The shrinkage may move the fibroid away from the endometrial lining and the JZ thus improving IR. However, this needs to be balanced with the risk of liver complications. GnRHa may have similar effect as UPA although this has not been researched in clinical studies. In patients with increased UP, atosiban may be given but this option has not been explored in clinical studies as well. UAE may not be a good option for small IM fibroids because of the complications discussed above. HIFU is an attractive option to shrink these small IM fibroids because it is a non-invasive technique with very few side effects. Its use in small fibroids has not been explored in clinical studies.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://gpm.amegroups.com/article/view/10.21037/gpm.2019.11.01/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

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