

Paper Title - Conservative Management Of Fibroid In Infertile Women Yield Similar Result As Myomectomy With Proper Patient Selection

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Abstract

Introduction

Uterine fibroids (leiomyomas or myomas) arising from smooth muscle cells, are the most common benign tumors among women of reproductive age. Leiomyomas are usually asymptomatic but almost one-fourth of these patients have symptoms, infertility and complications in pregnancy. Treatment options for myoma in infertile women include medical therapy, myomectomy, uterine artery embolization, myolysis, high intensity focused ultrasound.

Objective- To demonstrate the effect of the various treatment modalities in infertile women and outcome of pregnancy

Material and method - 327 infertile women with uterine fibroid, enrolled over a period of 62 months (January 2014 to February 2020) conducted at Calcutta Fertility Mission in the present study.They had all undergone transvaginal ultrasonography (TVUS) and were individualised to be treated either by medications or uterine artery embolization or by myomectomy.The clinical pregnancy rate and live birth rate following treatment were statistically analysed.

Result –Clinical pregnancy rates(CPR) in primary infertility cases after treatment with Tranexamic acid,Ulipristal acetate,myomectomy,uterine fibroid embolization(UFE) were 34.15%,29.69%,35%,37.5% respectively and the same in women with secondary infertility and fibroid were 32.97%,50%,40% and 42.11% respectively.Live birth rate (LBR) in women with primary infertility after treatment with Tranexamic acid,Ulipristal acetate,myomectomy,UFE were 21.95%, 17.19%, 30%, 25% and the same in those with secondary infertility were 23.08%,30%, 26.67%,26.32% respectively. None of the treatment modalities were found to be statistically significant when these parameters were analysed.

Conclusion – Medical treatment in uterine fibroid with infertility has similar outcome as myomectomy in achieving pregnancy, in judiciously selected patient cohort.

Keywords- uterine fibroid, infertility, myomectomy, medical treatment, embolization,pregnancy

I.INTRODUCTION

Uterine leiomyoma are one of the most common benign tumours in women of reproductive age, prevalence being 20-40%.[1] Leiomyomas are largely asymptomatic. Approximately 25% of these patients have symptoms such as abnormal uterine bleeding, pelvic heaviness, urinary retention symptoms, infertility and complications in pregnancy.[2] Uterine fibroids have been observed to create an unsuitable environment for conception as well as continuation of pregnancy. The very presence of it may cause hindrance in pregnancy by distortion of the normal uterine anatomy or by implantation failure. Many underlying mechanisms have been suggested for increase in myometrial contractility like excess of cytokines, growth factors, neurotensin, neuropeptides, enkephalin and oxytocin modulators in the fibroid capsule. [3]

Uterine leiomyoma may be described as intramural, submucosal or subserosal. So far infertility is concerned the subserous group has least implication in pregnancy; submucous group has highest chance of poor pregnancy and intramural group of fibroids may or may not affect fertility potential depending on position, size, vascularity etc.It has been long debated regarding treatment of fibroid in infertile women especially whether a woman requires surgical treatment, but the opinion largely indicates that if fertility is hampered due to its presence or else better to avoid if not. [4]

II. MATERIAL AND METHOD

Almost 400 women who visited our clinic for infertility treatment from January 2014- February 2020 were diagnosed to have had uterine fibroids. They were treated adequately and 327 of them were included in the present study as the rest lost follow-up.

These patients were not a part of a big cohort. They had complaints of menorrhagia and dysmenorrhea; few had increased frequency of micturition due to pressure by the fibroid and were treated with Tranexamic acid, Ulipristal Acetate (UPA) or Gonadotrophin (GnRH) analogue or had undergone myomectomy or Uterine fibroid embolization (UFE). Patients were explained about the procedures and complications regarding conception and pregnancy post-procedure.

A.Planning of management of fibroid in infertile women

The initial assessment should be how far a leiomyoma is responsible for infertility. In our clinic few things are considered- 1. Position and size of the fibroid, 2.length of the uterine cavity, 3.Tubal patency, 4. Uterine cavity invaded by the fibroid. [5] Subserosal fibroids usually need not be treated when patient is asymptomatic and her only complaint is infertility. In presence of submucosal fibroid or pedunculated submucosal fibroid intruding the cavity, women suffer from infertility or recurrent pregnancy loss, and need to be treated.The symptoms usually improve and the conception rates following such treatment are quite rewarding. In cases of failed medical management or women with huge fibroids or the ones with pressure symptoms, myomectomy becomes the treatment of choice. Non-surgical techniques, such as Uterine Artery Embolization (UAE), more specifically termed as selective uterine fibroid embolization (UFE) has emerged as an accepted procedure by many clinicians now-a-days.[6]

B.Medical management and its outcome

Selection of patients

- Intramural or submucosal fibroid if less than 5cm in diameter
- Symptomatic patients presenting with AUB/ primary or secondary infertility

In these patients with complaints of AUB and infertility tranexamic acid (500mg – oral) or Ulipristal acetate (UPA) (5mg- oral) or mifepristone(25mg – oral) were prescribed for a duration of 90 days.

C.Myomectomy

Myomectomy is a uterine- preserving surgical treatment for women with symptomatic fibroids. It is done by open myomectomy (OM) or by minimally invasive techniques such as hysteroscopy and laparoscopic myomectomy (LM). LM is a less invasive method with minimal complications, and it has been established in recent years

Selection of patients

- Intramural / Submucosal fibroid > 5cm diameter
- Large fibroid (>10cm diameter) causing pressure symptoms
- Large fibroid interfering with the procedure of oocyte retrieval in IVF programm

Myomectomy performed as a treatment of menorrhagia have seen to yield equivocal outcome when conception rates are considered.

D.Uterine fibroid embolization

UFE is a unique accepted quasi-surgical treatment for symptomatic uterine fibroids but its safety in women desiring future childbearing is still pondered over.

Selection of patients

In couples who tried for pregnancy for at least 1 year with or without ovulation induction (primary infertility)

- Any woman with uterine fibroid distorting the cavity
- Largest fibroid size <10cm ; intramural or submucosal type
- Multiple small to medium fibroids (<5cm), scattered in the uterine

wall

Procedure

UFE was performed using bilateral femoral artery catheterisation under local anaesthesia and conscious sedation using previously described techniques in an interventional catheterisation laboratory. The procedure was followed as has been elaborated in previous literature.[6]

E. Fibroid with co-morbidities

Infertile women presenting with menorrhagia or dysmenorrhea are often seen to have uterine fibroids associated with endometriosis or adenomyosis. They are usually diagnosed by laparoscopy or now-a-days with high resolution ultrasonography. Non-invasive diagnosis of endometriosis is largely accepted now. This shows good number of association of fibroids with endometriosis and adenomyosis in hyperestrogenic women, especially women with polycystic ovarian ovarian disease (PCOD). In our patients with Stage I or II endometriosis dienogest (2mg) was prescribed for 90days and then followed up.

III. RESULTS

A. Statistical Methods

Categorical variables will be expressed as Number of patients and percentage of patients and compared across the 2 groups Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate.The statistical software SPSS version 20 will be used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it will be considered as significant.

Table 1 – Age of patients

AGE	Frequency	Percent
25-30	93	28.4
31-35	161	49.2
36-40	73	22.3
Total	327	100.0

Table 2-Clinical Pregnancy Rate in women with fibroid after treatment

INFERTILITY			MODE OF TREATMENT				Total	p Value	Significance
			TRANEXAMIC ACID	UPA	MYOMECTOMY	UFE			
PRIMARY INFERTILITY	CLINICAL PREGNANCY RATE	NO	54(65.85)	45(70.31)	13(65)	10(62.5)	122(67.03)	0.908	Not Significant
		YES	28(34.15)	19(29.69)	7(35)	6(37.5)	60(32.97)		
	Total	82(100)	64(100)	20(100)	16(100)	182(100)			
SECONDARY INFERTILITY	CLINICAL PREGNANCY RATE	NO	61(67.03)	10(50)	9(60)	11(57.89)	91(62.76)	0.504	Not Significant
		YES	30(32.97)	10(50)	6(40)	8(42.11)	54(37.24)		
	Total	91(100)	20(100)	15(100)	19(100)	145(100)			
Total	CLINICAL PREGNANCY RATE	NO	115(66.47)	55(65.48)	22(62.86)	21(60)	213(65.14)	0.890	Not Significant
		YES	58(33.53)	29(34.52)	13(37.14)	14(40)	114(34.86)		
	Total	173(100)	84(100)	35(100)	35(100)	327(100)			

Pearson's Chi Square test for Independence of Attributes

Table 3 – Live Birth Rate in women after treatment of fibroid

INFERTILITY			MODE OF TREATMENT				Total	p Value	Significance
			TRANEXAMIC ACID	UPA	MYOMECTOMY	UFE			
PRIMARY INFERTILITY	LIVE BIRTH RATE	NO	64(78.05)	53(82.81)	14(70)	12(75)	143(78.57)	0.639	Not Significant
		YES	18(21.95)	11(17.19)	6(30)	4(25)	39(21.43)		
	Total	82(100)	64(100)	20(100)	16(100)	182(100)			
SECONDARY INFERTILITY	LIVE BIRTH RATE	NO	70(76.92)	14(70)	11(73.33)	14(73.68)	109(75.17)	0.922	Not Significant
		YES	21(23.08)	6(30)	4(26.67)	5(26.32)	36(24.83)		
	Total	91(100)	20(100)	15(100)	19(100)	145(100)			
Total	LIVE BIRTH RATE	NO	134(77.46)	67(79.76)	25(71.43)	26(74.29)	252(77.06)	0.767	Not Significant
		YES	39(22.54)	17(20.24)	10(28.57)	9(25.71)	75(22.94)		
	Total	173(100)	84(100)	35(100)	35(100)	327(100)			

Pearson's Chi Square test for Independence of Attributes

IV. DISCUSSION

Treatment of uterine fibroid in infertile women must be individualized. A great proportion of women are diagnosed with fibroids when seeking medical care for infertility or for other complaints or when performing imaging studies for other indications. These women must be counselled on the characteristics of the disease, especially those who are asymptomatic. Fibroid size and volume, by themselves, must not be considered an indication for surgical intervention and asymptomatic women at times may need nothing more than regular monitoring. Large fibroids, however,

require treatment, especially if the size or position is a cause of infertility. There is no consensus, especially in asymptomatic patients, on whether patients with large ones should always receive surgical treatment.[7] However rapidly growing fibroids deserve attention due to the risk of leiomyosarcoma.

In symptomatic women with fibroids, pelvic pain, not associated with menstruation is a rare entity and should prompt a search for other associated diseases. It has been stated that pelvic pain and dyspareunia doubled in severity in women with leiomyomas ; however, since the leiomyomas were

diagnosed by transvaginal ultrasound (TVUS), the presence of concurrent adenomyosis could not be entirely ruled out. [8] Though expert guided TVUS have been documented to diagnose adenomyosis still the combination of TVUS and MRI offers the highest sensitivity. [9] Uterine fibroids and endometriosis may be associated with each other as both these are steroid hormone-dependent and they act similarly under the influence of estrogen. Women with uterine fibroids were symptomatic, reported to have endometriosis more often than those without fibroids. There is a hypothesis that a hyperestrogenic state might have a role in the development of fibroids, endometriosis or adenomyosis and related to increased subfertility independently or associated with each other. [10][11]

A. Medical management

Antifibrinolytics are the non-hormonal alternatives used for treatment of uterine fibroids. The efficacy of tranexamic acid (TXA) in controlling fibroid-related bleeding is controversial and it has been related to cause necrosis and infarction. [12] Although there is a lack of high quality evidence, non-hormonal treatments are commonly used for symptomatic patients during an acute episode of uterine bleeding. In our study TXA has been prescribed to 173 symptomatic infertile women with uterine fibroids and 58 (33.53%) of them responded to the treatment and had subsequent pregnancies.

A meta-analysis of studies assessing the association of COCs to uterine fibroid growth has demonstrated a 17% reduction in the risk of growth in current users, although there has been significant heterogeneity among included trials. [13] COC have also been seen to improve menstrual blood loss and hematocrit improvement, but no significant change in the volume of the tumors. [14]

Oral and injectable progestogens like depot medroxyprogesterone acetate (MPA), lynestrenol, dienogest, norethisterone have been documented time and again by many authors as some pharmacological agents used to treat uterine fibroids. [15]

Treating fibroids with progestogens may be effective in some cases, but such treatment has been associated with histopathological changes that may be mistaken for leiomyosarcoma or smooth-muscle tumors of unknown malignant potential. [16] The LNG-IUS was introduced as a contraceptive device, but it was recognized later as an effective treatment for AUB, decreasing its intensity by almost 86% and reduction in uterine volume in group of women with fibroids. [17]

According to Cochrane review, daily administration of mifepristone 5 mg and 10 mg has shown reduced heavy menstrual bleeding and improved fibroid-specific quality of life but no reduction in fibroid volume. Although long-term use, however, is still controversial till endometrial safety is documented. In

our study we had included patients on mifepristone but had lost follow up on them. [18]

GnRH-analogues are one the most widely used medications to improve symptoms and reduce the fibroid size by almost 45% in 6 months, but side effects and a maximum length of safe use limit their clinical application according to ACOG. Strategies involving long-term use of GnRH-a with add-back therapy may be offered to patients with good responses to avoid a surgical intervention. Significant adverse effects, such as hot flashes, insomnia, mood disorders, sensation of vaginal dryness, headaches and loss of bone mineral density (BMD) have also been documented. These agents have also been used pre-operatively and have been seen to decrease the size of fibroid, reduced intra-operative blood loss, but difficult enucleation of fibroids, loss of cleavage planes and higher risk of recurrence due to the reduction of previously small fibroids into surgically undetectable ones, need to be considered. [19][20]

According to De Gasperis-Brigante C et al., selective progesterone receptor modulator (SPRM) such as ulipristal acetate (UPA) can be used in fibroid with infertility. 47 patients had spontaneous conception post-UPA treatment, 31 (66%) women had live birth and 13 of them had miscarriage at early weeks [21]. In our study about 34.52% women had conception after treatment with UPA. [Table 2] No recurrence of fibroids has also been documented by few [22]. Both PEARL trials led to the approval of ulipristal in the European Union as a pre-operative treatment of moderate to severe symptoms associated with uterine fibroid. [23,24] Although there is no much evidence of increased risk for birth defects or spontaneous abortions after UPA exposure during implantation and early embryogenesis, a possible epigenetic effect cannot be ruled out due to report of one child diagnosed with Beckwith-Wiedemann syndrome (BWS). [25] In our study there was 20.24% live birth rate after UPA treatment and no congenital defects were detected in the neonates. [Table 3]

B. Myomectomy

Myomectomy has been the standard approach in patients desiring a future pregnancy, especially with submucosal and intramural fibroids [26,27]. Laparoscopic myomectomy is a preferred procedure for fibroids less than 5 cm diameter, though larger fibroids are excised in similar way. Removal of large fibroids by open or laparoscopy myomectomy, repair of uterus by multilayered suture or successful single-layered laparoscopic suturing and higher laparo-conversion rates, associated intraoperative, postoperative complications and recurrence risk, have been discussed in detail in previous literature. The risk of surgical complications from myomectomy may outweigh the fertility benefit for these women [28-31] A Cochrane review including four studies with 442 patients also suggest that there is limited evidence to determine the role of myomectomy for infertility in women with fibroids. [32]. Moreover, previous

literature have mentioned high adhesion rate on second-look laparoscopy with highest incidence with posterior uterine incision. [33]

The fact that the cumulative probability of conception after myomectomy was lesser suggests the hypothesis that adhesions are responsible for lower postoperative fertility. [34] Almost 50%-60% patients had been reported to conceive after laparoscopic myomectomy and about 34%-44% had viable pregnancies [35]. In our study 37.14% women had conceived within 6 months of myomectomy and 28.57% had uneventful live births. [Table 2, Table 3]

C. Uterine fibroid embolization

UFE has the advantage of embolizing all fibroids in a single procedure and pregnancy after UFE appears to be safe, with low morbidity but the complications like pelvic infections, tissue ischaemia, diminished ovarian reserve or premature ovarian failure, radiation injury, postembolization syndrome, pulmonary embolism, contrast allergy, nephropathy etc., according to Society of Interventional Radiology have been noted after UFE in some women [36]. In our study it has been shown that CPR after UFE is about 40% and LBR is 25.71%. [Table 2, Table 3]

Medical management of leiomyoma should always be considered when counselling women on the potential strategies for addressing infertility due to fibroid or other fibroid-related complaints. Many women will prefer long-term medication use over some form of invasive treatment. Previous literature also supports the efficacy of many agents for symptomatic control and a trial of medical treatment in selected cohort of patients may obviate the need for surgery.

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Conflict of Interest

There is no conflict of interest among the authors involved in this study.

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