



Assessment of Environmental Factors in Occurrence of Uterine Fibroids among North Indian Women Aged between 35- 49yrs

Abhijeet Bisht^{a*}, Abhijit Murthy^b, Akansha Gaur^c, Arpit Anand^d, Ruchi Narula^e, Shagun Dubey^f, Satyam Khanna^g

^{a,b,c,d,e,f,g}Research Scholars, Biological Upliftment Academic foundation.

^eManaging Trustee, Cteck Educational Consultants.

^gDirector, and Research Head Rass Biosolution Pvt. Ltd.

^eEmail: ruchi@rass-biosolution.com

^gEmail: sk@rass-biosolution.com

Abstract

Uterine fibroids have always been the prime medical issue for females, especially the ones travelling in their reproductive age (20-35), with some studies reporting 20-80% of women developing fibroids by the age of 50 also. Apart from being of reproductive age there are other risk factors to be familiar with, which includes race, obesity, heredity and hypertension. Fewer than 25% of patients with fibroids have symptoms but those experiencing them have to compromise with the quality of life. Despite of extensive research actual cause of these tumors remains unrevealed, that restrains for an effective pharmaceutical approach. According to latest research environment alone or in interaction with genetic factors influence the formation and growth of uterine fibroids. An awareness of such factors can lead to more advance non-invasive treatment for such deep uterus monsters.

* Corresponding author.

Keywords: leiomyoma; myometrium; stem cells; developmental reprogramming; Red Degeneration; diethylstilbestrol; bisphenol A; antitumorogenic agent; dietary glycemic index; polycyclic aromatic hydrocarbons.

1. Introduction

Reproduction phase of women is accompanied by various gynecological disorders, that seriously affects the quality of life .One most frequent among them is a genetically or hormonally induced and regulated tumor known by different names such as as leiomyoma's, myoma, leimyomata, fibromyoma or uterine fibroids. These are clonal neoplasm of uterus that have both smooth muscle and fibroblast components, in addition to substantial amount of fibrous extracellular matrix that contribute to pathogenic process. The discovery of these lesions lays back to Hippocratic period in 460-375 B.C, when they were called "uterine stone", later, in Christian period it was called "scleromas" by Galen. The term fibroid was coined and introduced in 1860 by Rokitansky and in the 1863 by Klob, while word "myoma" was given by a German pathologist named Virchow in 1854 [1].

They are extremely heterogeneous in their pathophysiology, size, location and clinical symptomatology. One of the most surprising fact about such myomas is that black women have a higher risk of encountering these fibroids earlier in life with more severe symptoms than their white counterparts, clinically they account for one-third to half of all hysterectomies in US, recently some authors have reported a statistically significant inverse correlation between serum 25-(OH) Vitamin D levels and fibroid prevalence in black subjects [2]. The pathogenesis of fibroids seems to involve a positive feedback loop between extracellular matrix production and cell proliferation, and vitamin D might act to block the positive feedback . It is also seen that women after the age of 30 are more likely to develop symptoms may be due to time-related hormonal changes or an enhanced symptomatology from already existing fibroids. Exact biology behind there occurrence is still unknown, but there are several distinct pathways involved in leiomyomata formation. Human uterus can increase its capacity from 500- to 1000-fold and increase its weight more than 20-fold during pregnancy and then retains its original size. This remodeling of uterus indicates the presence of adult stem/progenitor cells that reside in myometrial compartments [3]. We suspect that several pathological conditions, such as endometrial cancer, adenomyosis, and leiomyoma, can be attributed to dysregulation of these stem cells. Recent studies also suggest the involvement of epigenetic mechanisms such as DNA methylation and micro-RNA and histone modification in leiomyomas [4]. The cellular origin of uterine leiomyomas remains undefined but it is believed that the transformation of a single tissue-specific stem cell within the myometrium can be an important factor. Stem cells derived from leiomyoma tissues are known to carry MED12 mutations, This finding suggests that at least one genetic hit initially transforms a myometrial stem cell that subsequently interacts with the surrounding myometrial tissue to give rise to a leiomyoma tumor [3]. Step towards such findings also have developed the idea that Genetic factors likely influence fimbroid development and growth; approximately 40% of uterine leiomyoma have chromosomal abnormalities detectable by conventional cytogenetic analysis like several mutations, such as germ line mutations causing fumarate hydratase deficiency, have been associated with leiomyoma formation ,also aberrations involving the short arm of chromosome 6 or the long arm of chromosome 12. Two members of the high-mobility group (HMG) protein gene family, HMGIC and HMGIY,

are found to be frequently rearranged in tumors and it has been suggested that these genes are directly involved in the aberrant growth control observed in tumors[5]. Recurrent somatic mutations in MED12 was also identified as most frequently altered gene in leiomyoma's. A striking feature of uterine fibroids is their dependency on the ovarian Steroids estrogen and progesterone and their ligands. These hormones initiates the growth of these uterine fibroids. Estrogen/progesterone treatment of mature myometrial cells induces expression of WNT11 and WNT16, which remained constitutively elevated in leiomyoma tissues and also targets nuclear translocation of β -catenin and induced transcriptional activity of its heterodimeric partner T-cell factor and their target gene AXIN2, leading to the proliferation of these cells. This effect could be blocked by a WNT antagonist. Several growth factors, such as vascular endothelial growth factor (VEGF), EGF, heparin binding epidermal growth factor (HB-EGF), PDGF, IGF, TGF- α , TGF- β , acidic fibroblast growth factor (aFGF), and basic fibroblast growth factor (bFGF), and their respective receptors have been demonstrated to play a role in leiomyoma growth [6].

Depending on their position fibroids can be of four types : intramural, subserosal, sub mucosal and pedunculated. A woman may have one or all of these types of fibroids. Some fibroid tumors don't produce any symptoms at all, while others can be severely symptomatic. It is common for a woman to have multiple fibroid tumors also. INTRAMURAL fibroids are the most common type of tumors that develop within uterine wall and extend from there and can cause bulk of symptoms, which include excessive menstrual bleeding that may cause prolonged menstrual cycles and clot passing, and pelvic pain that is caused by the additional pressure placed on surrounding organs by the growth of the fibroid. If developed in the cervical region it can prevent the entry of the sperm into the uterus [7].

Developing on outer uterine wall SUBSEROSAL tumors exerts additional pressure on surrounding organs . Symptoms of subserosal fibroid tumors usually do not include abnormal or excessive menstrual bleeding or interfere with a women's typical menstrual flow. These fibroid tumors instead cause pelvic pain and pressure. Depending on the severity and the location of the fibroids other complications can accompany this pain and pressure [7].

The least common and most complicated is the SUBMUCOSAL fibroids that develop just under the lining of the uterine cavity. Large submucosal fibroid tumors may increase the size of the uterus cavity, and can block the fallopian tubes preventing ovum release and sperm from entering which can cause complications with fertility. Myomas greater than 5 cm in size, or located near the Ostia of the fallopian tubes, are more likely to cause fertility problems. Other associated symptoms with submucosal fibroids include very heavy, excessive menstrual bleeding and prolonged menstruation. These symptoms can also cause the passing of clots, and frequent soiling which can take its toll on your everyday lifestyle. Untreated, prolonged or excessive bleeding can cause more complicated problems such as anemia and/or fatigue, which could potentially lead to a future need for blood transfusions [7].

PEDUNCULATED uterine fibroids occur when a fibroid tumor grows on a stalk, resulting in pedunculated submucosal or subserosal fibroids. These fibroids can grow into the uterus and also can grow on the outside of the uterine wall. Symptoms associated with pedunculated fibroid tumors include pain and pressure as the

fibroids can sometimes twist on the stalk. Some fibroid tumors don't produce any symptoms at all, while others can be severely symptomatic [7].

Certain general symptoms include pain in legs that is due to fibroids press on nerves that extend to the pelvis and legs, pressure on bladder that can cause frequent urination, urinary incontinence or urine retention, pressure on bowel that leads to constipation and/or bloating. The constipation may be exacerbated by iron supplements taken for the anemia caused by excessive bleeding, lower back pain, Infertility, recurrent miscarriage or premature labor during pregnancy. Growth of fibroids during pregnancy complicates the condition mainly due to the flux of steroid hormones. Normally the myomas are not removed during pregnancy due to the increased risk of hemorrhage. It is possible that between weeks 12-22 the blood supply to the fibroid may stop causing it to turn red and die, this is called "Red Degeneration", which is accompanied by intense abdominal pains and contractions that becomes a cause of premature labor or even miscarriage [8]. An important fact has come into light that women with fibroids are not more prone to fibrocystic changes in the breast, a totally unrelated condition and they are not more prone to develop any other benign or cancerous conditions.

Fibroids are an enormous healthcare problem because they are the primary reason given for surgery in 199,000 hysterectomies and 30,000 myomectomies performed yearly in the US .The medical treatments readily available for fibroids can range from mild to severe, leaving women of childbearing age unable to have children [9].

Currently there are limited therapies and no prevention strategies available, this paper clarifies the natural history of uterine fibroids involving environmental and lifestyle influence on endocrine function and other epidemiological factors.

It is likely that factors in the environment acting alone or in interaction with genetic factors influence the formation and growth of uterine fibroids. Medical studies have shown that diet, smoking and various types of contraception affect the risk of developing fibroids. There has also been research into chemicals which women are exposed to and whether these chemicals can cause fibroids to form and grow. Another possibility is that current environmental factors may cause genes which have been dormant in previous generations to exert their influence. Scientists and doctors are concerned about chemicals such as pesticides or toxins which have an estrogen-like affect.

1.a Synthetic chemicals

A number of studies have evaluated exposure to environmental endocrine disruptors, such as diethylstilbestrol (mixed), phenols (null), dioxin (protective), and polychlorinated biphenyls (increased) . The danger of estrogen-like chemicals already has been well-documented with DES, or diethylstilbestrol, a drug that was prescribed to millions of women at risk of miscarriages from 1940 through 1971. Daughters and granddaughters of the pregnant women who took the potent estrogenic drug had an increased risk of endometriosis, uterine fibroids and rare reproductive cancers. Also the intake of xenoestrogens, or environmental chemicals that possess estrogenic activity fuels fibroid growth, such as bisphenol A in water bottles and canned foods [10].

1.b Dairy/ diet

Research has suggested a relationship may exist between diet and the growth of uterine fibroids. More than a decade ago, a study by Chiaffarino and colleagues published in *Obstetrics & Gynecology* reported that uterine fibroids were associated with the consumption of ham and beef. The study indicated that a high intake of green vegetables has a protective effect against fibroids “Italian women with fibroids have been observed to consume more red meat and ham, and alcohol consumption has been linked to increased likelihood of fibroids in Japanese women [11]. In the study, published in the January 2010 issue of the *American Journal of Epidemiology*, researchers followed more than 22,000 premenopausal black women from the US Black Women’s Health Study over a 10-year period. Results based on dietary intake were used to assess whether intake of dairy foods such as low-fat and whole milk, cheese, yogurt, and ice cream—and some dairy components such as calcium, vitamin D, and butyric acid—may reduce risk of uterine fibroids. The findings indicated a lower risk of uterine fibroids associated with higher dairy consumption. The perceived protective effect of dairy, according to the researchers, may lie in the ability of calcium to reduce fat-induced cell proliferation and in butyric acid (present in milk fat), which is considered a potent antitumorigenic agent that may inhibit cell proliferation and angiogenesis [12]. That can be an expected reason for black women to suffer more, which consumes less dairy products (and thus have lower mean intakes of calcium, magnesium, and phosphorus) than whites. Eating foods with a high dietary glycemic index (GI), a measurement of the effects of carbohydrates on blood glucose levels, or high glycemic load (GL), a ranking of carbohydrate content of various foods based on their GI, is thought to potentially promote tumor growth by increasing endogenous concentrations of insulin like growth factor 1 (IGF-1). Examples of high GI and GL foods include instant white rice, white bread, rice cakes, French fries, donuts, and scones. In vitro studies have shown that uterine fibroid cells proliferate in the presence of IGF-1. Other studies have found a positive association between high GL and other hormone-responsive tumors, such as ovarian and endometrial cancer. Radin and colleagues have mentioned in a study published in the May 2010 issue of the *American Journal of Clinical Nutrition* that a high GI and GL diet may encourage uterine fibroid growth, they concluded that high dietary GI (but not GL) may be associated with increased uterine fibroid risk overall, and high GL was associated with increased risk in women younger than 35 [13].

Soybeans are a rich source of phytoestrogens, specifically isoflavones, that may have an “antiestrogen” effect in the body by competing with estrogen for receptor binding, thereby possibly decreasing the availability of estrogen or altering estrogen biosynthesis. In the January issue of *Experimental and Molecular Medicine*, Di and colleagues reported that high serum concentrations of genistein (an isoflavone abundant in soybeans) downregulate several signaling pathway genes involved in uterine fibroid growth, suggesting that high doses of this isoflavone have an inhibitory effect on uterine fibroids and therefore a potential to be used as a therapeutic agent in their treatment [13] but Converse to this, in May 2009 issue of the *British Journal of Nutrition*, Nagata and colleagues said they observed no statistically significant association between soy isoflavones and uterine fibroids in 285 premenopausal Japanese women [13].

In the January 2011 issue of *Fertility and Sterility*, Sharan and colleagues reported that vitamin D inhibits the growth of cells involved in uterine fibroid growth, suggesting that low serum vitamin D levels may be a risk factor for their development. In the December 2011 issue of the *American Journal of Clinical Nutrition*, relation between dietary intake of fruits, vegetables, and carotenoids, and fibroid risk was discussed. It was observed that there is a reduced risk of uterine fibroids among women with greater intake of fruit and retinol, preformed

vitamin A from animal sources such as whole milk and eggs as well as reducing the intake of growth hormones present in foods such as conventionally raised, nonorganic beef reduces the risk. Foods such as white bread, cookies, cakes, and pasta increase insulin, which changes the way estrogen is metabolized, creating compounds that are more likely to cause cellular inflammation and fibroid symptoms, including enhanced growth of existing fibroids[14]. women with fibroids should increase their intake of cruciferous vegetables such as cabbage, broccoli, and kale. This group of vegetables, in particular, contains indole-3-carbinol, according to research which may prevent estrogen-driven tumors due to its effect on estrogen metabolism [15].

chemicals like caffeine and alcohol also put stress on the liver, making it work less effectively at metabolizing estrogen in the body. Specific food groups and nutrients can also help women manage fibroids by encouraging weight loss, because estrogen is also produced in peripheral fat in the form of estrone, which in higher doses such as in overweight women, affect fibroid growth and cause them to be more symptomatic. The dietary component towards the treatment of fibroids can add to the traditional therapies to treat this condition [16].

1.c Herbal products

There are various herbal products as well that can help reduce the risk of fibroids like:

VITEX- helps to normalize hormonal production and ovulation through its effects on the pituitary gland

DANDELION- is a very good nutritive herb with high levels of vitamins and minerals and improves liver function, helping to metabolize hormones.

WITCH HAZEL- is a good astringent herb to help with excessive uterine bleeding

WILD YAM-a good antispasmodic (Pain reliever)

CRAMP BARK- is used for relieving cramps, including muscle spasms, menstrual cramps, and cramps during pregnancy and also used as a kidney stimulant for urinary conditions that involve pain or spasms.

BLACK HAW- is used for relieving cramps after pregnancy and for treating miscarriage

Method 1 : complications of leiomyomas during caesarian section: a case report.

We analyzed 20 women (aged between 30-40 years) that were in their 12-15 weeks of pregnancy.

The study was conducted in Kanpur dehat (suburbs of Kanpur), and 6 were screened among them that were recommended c- section by their gynecologists. Inconsistent increase in their abdomen size was reported as discussed by their gynecologist and sonography reports revealed large intramural, subserosal or pedunculated fibroids (ranging between 10.5-13 cm) on the anterior wall of the maternal uterus encroaching upon the cervix, along with their fetus.

The patients were examined and were admitted due to pain reported in the above data . Detailed sonographic

images of the fetus at 20 weeks of gestational period showed no evidence of any major structural abnormalities but later on the size of these myomas was seen to increase progressively.

Table 1: complications of leiomyomas during caesarian section: a case report .

Case No.	Age	WEIGHT	DURATION OF PREGNANCY	POSITION OF FIBROID	SIZE OF FIBROID	FAMILY HISTORY	SYMPTOMATI C/ NON SYMPTOMA	Hb READING
1.	32 yr.	70 kg.	12 week	Intramural Fibroid	12 cm	Present in mother	Pain due to red degeneration	10.2g/dl
2.	30 yr.	75 kg.	13.5 weeks	pedunculat ed fibroid	11.3 cm	Effected sister	Bleeding during initial stage of pregnancy	9.5 g/dl
3.	35 yr.	80 kg.	15.3 weeks	Intramural, near cervix	10.8 cm	No report	Pain due to fibroid degeneration	10.5 g/dl
4.	29 yr.	84 kg.	14 weeks	Subserosal , encroachin g cervix	11.5 cm	Present	Pain due to red degeneration	10.9 g/dl
5.	33 yr.	79 kg.	12.5 weeks	Intramural, blocking birth canal	13 cm	Not present	Hypertension, retarded fetal growth	10.2 g/dl
6.	36 yr.	88 kg.	15 weeks	Subserosal, in the lower uterus	12.4 cm	No report	Pain, enlarged uterus	9.9 g/dl

Their last ultrasonography reports as discussed by the gynecologist showed fibroids reaching unto 25-30 cm. Myomectomy was preformed after delivery.

The babies were healthy and the patients were discharged after 7-8 days [16] .

Method- b

Surgical removal of uterus is the only choice for fibroids : case study

Table 2: Surgical removal of uterus is the only choice for fibroids: case study

Case no.	Age	Position of fibroid	Size of myomas	Hb reading	Other symptoms	No. of miscarriages
1.	44 yr.	Submucosal, in endometrium	4.5 kg	9.8 g/dl	Long and heavy bleeding	4
2.	42 yr.	sub mucosal	3.4 kg	9.2 g/dl	Prolonged bleeding	3
3.	48 yr.	pedunculated	3.3 kg	8.8 g/dl	Abnormal vaginal bleeding	4
4.	45 yr.	Subserosal	2.4 kg	8.3 g/dl	Heavy prolonged bleeding	3
5.	42 yr.	intramural	4.5 kg.	8.2 g/dl	Abnormal vaginal bleeding	3

8 cases(near the age of menopause , 40-48) were reported in the gynecology department of city hospital in Kanpur Nagar. The patients reported problem of heavy and prolonged bleeding.

There clinical reports, as discussed by their doctor also indicated the history of mass per abdomen and miscarriages. The best way to get rid of fibroid complications in most of the cases (5) was to remove the uterus along with the fibroids(total hysterectomy) [17].

Method-3

Laparoscopic Myomectomy for Multiple Submucous Myomas: case report

A study was carried out on 5 women (aged between 28- 35 yr.) with multiple submucous fibroids that were all above 5 cm.

Clinical diagnosis of the patients revealed their uterine mass above 16 weeks. As discussed by their gynecologist, they also have a history of abnormal uterine bleeding due to which their hemoglobin level was

also at risk level (between 5.5-7 g.%).

Ultrasonography reports indicated enlarged uterus with multiple echoes in endometrial lining. The safe measure to avoid them from perforation and fluid overload that can occur during normal hysterectomy, laparoscopic myomectomy was suggested [18].

Table 3: Laparoscopic Myomectomy for Multiple Submucous Myomas: case report

Case no.	Age	Type of fibroid	Size of fibroid	Uterine mass	Hb reading	symptoms	No. of fibroids removed
1.	30 yr.	Multiple submucous	All above 7 cm	20 weeks	6.7 gm.%	Abnormal uterine bleeding	58
2.	33 yr.	Multiple submucous	All above 6 cm	16 weeks	5.7 gm.%	Heavy and prolonged bleeding	54
3.	28 yr.	Multiple submucous	All above 5.9 cm	18.5 weeks	6.9 gm.%	Abnormal vaginal and uterine bleeding	60
4.	29 yr.	Multiple submucous	All above 5 cm	21 weeks	6.8 gm.%	Uterine cramps and heavy bleeding	65
5.	32 yr.	Multiple submucous	All above 6.6 cm	22 weeks	5.9 gm.%	menorrhagia	58

Method-4

Unusual presentation of rare uterine leiomyosarcoma: case study

Uterine leiomyosarcoma is a rare form of uterine cancer that occurs mainly in women after menopause . 4 women aged between 40- 50 years were screened from urban areas of Kanpur nagar.

Their clinical reports as discussed by the gynecologist showed pelvic mass growth, and uterine size increased upto 20 weeks, also they complained about symptoms including lower abdominal pain, pelvic pressure etc. Increased rate of CA-125 level (normal- : 0-35 ng/ml) also indicated the malignant tumor[19].

Table 4: Unusual presentation of rare uterine leiomyosarcoma: case study

Case no.	Age	Symptoms	Stage
1.	46 yr.	Lower abdominal pain, mass arising from pelvis, uterus enlarged to 17 weeks, increased CA-125 level	1
2.	48 yr.	Mass arising from pelvis, pelvic pressure, uterus enlarged to 20 weeks , inc. CA-125 level.	1
3.	49 yr.	Pelvic mass, swelling , weight loss, post menstrual bleeding	2
4.	46 yr.	Pelvic mass, lower abdominal pain, uterus enlarged to 16 weeks	2

3. Conclusion

Constant regular menstrual cycles have played a role in the formation of uterine fibroids as well as other gynecological diseases. Fibroids are constantly being remodelled as certain genes are turned on and others are turned off each month as a result of the changing hormonal levels of estrogen and progesterone during the normal menstrual cycle. One theory states that having, on average, 13 menstrual cycles every year for up to 40 years gives room for many mistakes to take place within the tissues of the uterus. Thus, genetic or environmental factors plus having regular menstrual periods may be the initial problem and uterine fibroids are the resulting endpoint of the tissue damage which occurs because of these factors, also modern women have less pregnancies which may lead to an increase in fibroids that grow and are diagnosed. Because the only approach towards successful treatment was surgical strategies including myomectomy or hysterectomy, also new techniques are on the fast way towards treatment but it is believed that etiological clues in factors including dietary, stress, and environmental influences will enhance the work.

References

- [1]. M. S. Siddegowda, Jasneet Kaur Sandhu, Sundaram Shivakumar. "Clinico pathological correlation of morphological lesions in hysterectomy specimens- A 3- year study in a medical college hospital." J.Evid .Based Med .Healthc, 2016.
- [2]. Baird, Donna Daya, Hill, Michael C.b, Schectman, Joel M.c, Hollis, Bruce W.d. "Vitamin D and the

- Risk of Uterine Fibroids.” *International society for environmental epidemiology*, vol. 24, pp.447-453, May 2013.
- [3]. Masanori Ono, Serdar E. Bulun, and Tetsuo Maruyama, “Tissue-Specific Stem Cells in the Myometrium and Tumor-Initiating Cells in Leiomyoma.” *Biology Of Reproduction*, Nov. 2014
- [4]. Qiwei Yang, Aymara Mas, Michael P.Diamond, Ayman Al-Hendy, “The Mechanism and Function of Epigenetics in Uterine Leiomyoma Development.” *Reproductive sciences*, April 2015.
- [5]. Aymara Mas, Irene Cervello, Ana Fernandez-Alvarez, Amparo Faus, Ana Diaz, Octavio Bergues, Marta Casado and Carlos Simon, “Overexpression of the truncated form of High Mobility Group A proteins (HMGA2) in human myometrial cells induces leiomyoma-like tissue formation.” *MHR Basic science of reproductive medicine*, Dec. 2014
- [6]. Pasquapina Ciarmela, Md. Soriful Islam, Fernando M. Reis, Peter C. Gray, Enrrico Bloise, Felice Petraglia, Wylie Vale and Mario Castellucci. “Growth factors and myometrium: biological effects in uterine fibroid and possible clinical implications.” *Human Reproduction Update*, vol.17, pp. 772–790, 2011.
- [7]. Robert . I. Faulkner, “Red degeneration of uterine myomas.” *American Journal Of Obstetrics and Gynecology*, vol 53
- [8]. Forney JP, Buschbaum HJ, “Classifying staging and treating uterine sarcomas.” *Contemporary Ob Gyn* ,1981.
- [9]. Preda, Cristina; Ungureanu, Maria Christina; Vulpoi, Carmen, “Endocrine Disruptors IN The Environment And Their Impact On Human Health.” *Environmental Engineering & Management Journal*, vol.11, Sep. 2012.
- [10]. Chiaffarino et al. “Diet and uterine myomas”, *Obstetrics & Gynecology*. 94(3): 395-398, 1999.
- [11]. H. Davoodi, S. Esmaili, A.M. Mortazavian, “Effects of Milk and Milk Products Consumption on Cancer,” *Food Science and Food Safety*, vol. 12, April 2013.
- [12]. Megan Tempest, “Uterine Fibroids and Nutrition,” *Today’s Dietitian*, vol. 14, May 2012.
- [13]. “Protective Factors: Fibroid Risk Reduction,” *Vitamin insider*, April 2016.
- [14]. August McLaughlin, “Seven Foods That May Shrink Fibroids.” *Livestrong.com*, diet and nutrition. April 2015
- [15]. Wise, et al. “A prospective study of dairy intake and risk of uterine leiomyomata”, *American Journal of Epidemiology*. 171(2): 221-232, 2010
- [16]. Rajiv Mahendru , Parneet Kaur Sekhon, Geetinder Gaba and Shweta Yadav, “At times, myomectomy is mandatory to effect delivery,” *Annals of Surgical Innovation and Research*, vol.5, 2011.
- [17]. Hetal Vyas,TNN , “Uterine fibroids becoming health hazard in women,” Jul 2012.
- [18]. Rakesh Sinha et al, “Laprosopic Myomectomy for multiple submucous myomas” *Bombay Endoscopic Academy and center for minimal Invasive Surgery*, Beams Hospital, Mumbai ,India .
- [19]. Venkata Sujatha Vellanki, Meghana Rao, Chinna Babu Sunkavalli, Rao N Chinamotu, and Shailaja Kaja, “A rare case of uterine leiomyosarcoma: a case report,” *J Med Case Reports*. Vol. 4, pp. 222, 2010.