A Retrospective Analysis On The Risk Factors For Uterine Fibroid – A Pilot Study

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Abstract: Uterine fibroids (UF) or myomas are the most common benign female tumors of the reproductive organs affecting 70% to 80% of women during their lifetime. More risk factors are associated with a higher probability of uterine fibroid formation and development. WHO-IPCS defines Endocrine Distrupting Chemical (EDC) as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." This was a retrospective study for the analysis of risk factors associated with uterine fibroid along with analysis of various EDCs utilization pattern which were done through a semi-structured questionnaire. This study had arrived strong relation with various risk factors of UF. Among the risk factors, vitamin D deficiency (95%), exposure to EDCs (85%) and obesity (81.7%) showe more association than others. The identification of risk factors associated with UF may help to prevent its occurrence, which could improve the general health of female population.

***Keywords* – Uterine Fibroid, risk factors, EDC, association, prevention.**

I. INTRODUCTION

1.1 Uterine fibroid (UF)

Uterine fibroids (UF) or myomas are the most common benign female tumors of the reproductive organs. Although benign, uterine fibroids are associated with significant morbidity and quality of life impairment; they are the primary indication for hysterectomy, and a major source of gynecologic and reproductive dysfunction, ranging from menorrhagia and pelvic pain to infertility, recurrent miscarriage, and preterm labor. UFs affect 70% to 80% of women during their lifetime [1].

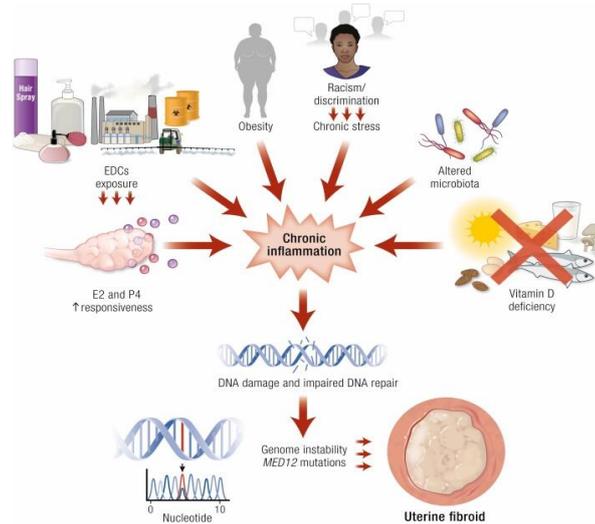## 1.2 Risk factors associated with UF

Figure 1. Various risk factors of UF

There are wide range of risk factors associated in the development of UF. More risk factors are associated with a higher probability of uterine fibroid formation and development. The most important and frequently reported risk factor for uterine fibroids is race. Other risk factors include older age, premenopausal state, non-parity, family history of UFs, hypertension, food additives, and frequent consumption of soybean milk. Other important risk factors include obesity, vitamin D deficiency, excessive vitamin E levels, altered reproductive tract microbiome, exposure to endocrine-disrupting chemicals, and various early life adverse environmental exposures [2]. Tobacco smoking and alcohol abuse can also contribute to the formation of UFs.

1.2.1 Age
Increasing age is a significant risk factor for uterine fibroids, especially among women at the premenopausal stage and those ≥ 40 years of age [2], which could be explained by the increasing patient age, endogenous estrogen accumulation, changes in the immune system, and continuous exposure to environmental risk factors [3].

1.2.2 Obesity
Several studies have found obesity as a significant risk factor for uterine fibroids development [2], which has been attributed to the metabolic functions of adipose tissues. Adipose tissues produce and release various cytokines and growth factors involved in regulating diverse physiological and pathological processes, including immunity and inflammation [2]. Obesity and particularly excess visceral fat may be complemented with the reduced production of the sex hormone–binding globulin (SHBG), which binds circulating hormones, disrupting the hormonal activity toward sensitive tissues, and thereby influencing the delicate hormonal balance in the body [2]. Each kilogram of excessive body weight is correlated with an increased risk of uterine fibroids development [2].

1.2.3 Non-parity
Nulliparous women are more commonly affected by uterine fibroids than multiparous women. Each subsequent child may lower the risk of this pathology [2].

1.2.4 Hypertension
There is a direct correlation between arterial hypertension and uterine fibroids. Women suffering from hypertension are 5 times more likely to develop uterine fibroids [2].

1.2.5 Frequent consumption of soy products
It is well-acknowledged that uterine leiomyoma is an estrogen-dependent tumor. Milk or soybean-rich diet is rich in estrogen-like nutrients, which may be associated with the development of uterine leiomyoma [3].

1.2.6 Vitamin D deficiency

Vitamin D is a group of steroid compounds with a powerful impact on many parts of the human body [4]. Nowadays, hypovitaminosis D is believed to be a major risk factor in the development of UFs. In many studies vitamin D appears to be a powerful factor against UFs, resulting in inhibition of tumor cell division and a significant reduction in its size [4]. Vitamin D has an antifibrotic effect on uterine myoma via the reduction of transforming growth factor-beta3 (TGFβ3) and extracellular matrix protein expression. It has also been reported that vitamin D inhibits uterine myoma cell growth through the downregulation of proliferating cell nuclear antigen and cyclin-dependent kinase 1 and the inhibition of COMT expression and activity. Additionally, it has been revealed that vitamin D regulates the expression and activity of matrix metalloproteinases, enzymes that play a role in extracellular matrix remodeling. Moreover, vitamin D presents potent antiestrogenic and antiprogesterone activities through reducing the expression of the estrogen and progesterone receptors. Other possible explanations as to how vitamin D decreases the growth of uterine myomas is its inhibition of wnt/β-catenin pathway activation and the role of vitamin D in DNA repair networks [5].

1.2.7 Genetic mutations

Among these, somatic mutations in the *Xq13* gene encoding the RNA Polymerase II (Pol II) mediator subunit MED12 are the most prevalent, occurring in 45–90% cases of uterine fibroids depending upon patient ethnicity. A proportionally smaller fraction of uterine fibroids has been attributed to genetic alterations leading to the overexpression of *HMGA2*, disruption of the *COL4A5-COL4A6* locus, and biallelic loss of *FH* encoding the tricarboxylic acid (TCA) cycle enzyme fumarate hydratase [2]. Several additional findings suggest that *MED12* mutations are true drivers of fibrotic transformation.

1.2.8 Endocrine Distrupting Chemicals (EDCs)

Additionally, a large body of evidence shows that exposure to some chemical substances, including endocrine disrupting chemicals (EDCs), can harm female reproductive health. The World Health Organization's International Program on Chemical Safety defines an endocrine disruptor as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." It represents "a global threat that needs to be resolved". There are thousands of EDCs in the environment, and people are widely exposed to them in their daily lives [6]. As UFs are hormone-dependent tumors, they are potentially promoted by exposure to hormone-active environmental agents such as EDCs. Also, as the chemical structure of most of EDCs mimics sex gonadal hormones and has the ability to bind to endocrine receptors interfering with hormonal signals, reproductive system represents the most vulnerable endocrine axis to EDCs actions [7]. Exposure to EDCs has been associated with impaired fertility, uterine fibroids, endometriosis, polycystic ovarian syndrome, pregnancy complications, breast cancer, endometrium cancer, ovarian cancer, and early onset menopause, among others [8]. Many other EDCs, including parabens, environmental phenols, alternate plasticizers, organophosphate esters, tributyltin, and phthalates, have been associated with uterine fibroids outcomes and their related processes. Phthalates have received increasing attention as they are tightly linked to uterine fibroid prevalence and severity [2]. The development and growth of fibroids are mainly characterized by abnormal cell proliferation, inhibited apoptosis, DNA instability, excessive deposition of ECM, and other critical biological pathways. Delineating the effects of EDC exposure and the underlying mechanisms by which they, or other environmental exposures, promote MSC progression to UFs, including the role of epigenetic alterations and acquisition of mutations in genes such as MED12, will be key to the development of new interventions to prevent and treat this important disease of women. EDC binding to nuclear receptors can alter hormonal functions by mimicking naturally occurring hormones in the body, blocking the endogenous hormone from binding or interfering with the production or regulation of hormones and/or their receptors [1].

Table 1. Various EDCs and their sources

Name of EDCs	Sources
Bisphenol A (BPA)	water bottles, canned foods and beverages, bottle tops
Per- and polyfluoroalkyl substances (PFAS) or forever chemicals	waterproof fabric such as nylon, yoga pants, carpets, shampoo, feminine hygiene products, mobile phone screens, wall paint, furniture, adhesives, food packaging, heat-resistant non-stick cooking surfaces such as teflon, in most cosmetics and personal care products, including lipstick, eye liner, mascara, foundation, concealer, lip balm, blush, and nail polish[9]
Phthalates	some food packaging, cosmetics that may contain phthalates include nail polish, hair spray, aftershave lotion, cleanser, and shampoo, fragrances, medical device tubing
Phytoestrogens	Soy foods
Polybrominated diphenyl ethers (PBDE)	furniture foam and carpet, flame retardants used in black plastic electronic devices, black plastic cooking utensils
Triclosan	personal care products like liquid body wash, soaps, detergents, toothpaste and surgical cleaning treatments

II. MATERIALS AND METHODS

2.1 Ethical consideration

The study had obtained IEC clearance (IEC No. GSMC-CH-3466/ME-2/018/2022) and got registered in CTRI (CTRI No. CTRI/2023/12/060682).

2.2 Study design and setting

This study was a retrospective pilot study conducted at special OPD for infertility in Arignar Anna Government Hospital of Indian Medicine and Homoeopathy, Chennai for a period of 6 months.

2.3 Sampling techniques and Sample size

60 participants were selected by purposive sampling method. Among them, 20 participants were again enlisted for a survey for analysis of various EDCs utilization.

2.3.1 Inclusion criteria
- Age: 25-60 years
- Patients with known complaints of uterine fibroid
- Patients with known USG findings
- Wide users of cosmetics, plastic and non-stick utensils

2.3.2 Exclusion criteria
- Patients who are not willing to give consent for study
- Patients with other uterine diseases except uterine fibroid
- Menopausal women
- Pregnant and lactating women

2.4 Study enrollment

The enrollment of patients was based on inclusion and exclusion criteria. The patients were informed about the study and consent was obtained from all the patients.

2.5 Study procedure

Retrospective analysis of risk factors associated with uterine fibroid along with analysis of various EDCs utilization pattern were done through a semi-structured questionnaire.

2.6 Data collection

A Semi-structured questionnaire (Tamil and English) was designed to collect related information and determine the risk factors for uterine fibroid based on the relevant literature. The questionnaires were filled by the participants when they were first enrolled. The questionnaire had two parts. The contents of first part of questionnaire included general demographical characteristics, such as name, age, height, weight, basic personal information, such as marital and reproductive history; present diseases; case history and family history; and living habits including tobacco chewing and diet. Part two addressed various EDCs utilization pattern of the study population.

"Frequent tobacco chewing" was defined as the average of 4 times of chewing every week and "frequent physical exercise" was as at least 4 times every week. "Frequent soybean consumption" was referred to at least 4 times every week [3]. The questionnaire was filled according to the own judgment of the participants on the average within the recent year.

2.7 Statistical analysis

Data obtained from the study participants were recorded and documented. The collected data were analyzed using MS -Excel and the analyzed data were presented by using tables and figures.

III.   Result

3.1 Demographic details of study population

Table 2. Demographic details

Age group (years)	No. of participants (n=60)	Percentage (%)
25-35	13	21.7
36-45	38	63.3
46-55	9	15
Total	60	100

3.2 Various risk factors association in UF

Table 3. Various risk factors association in UF

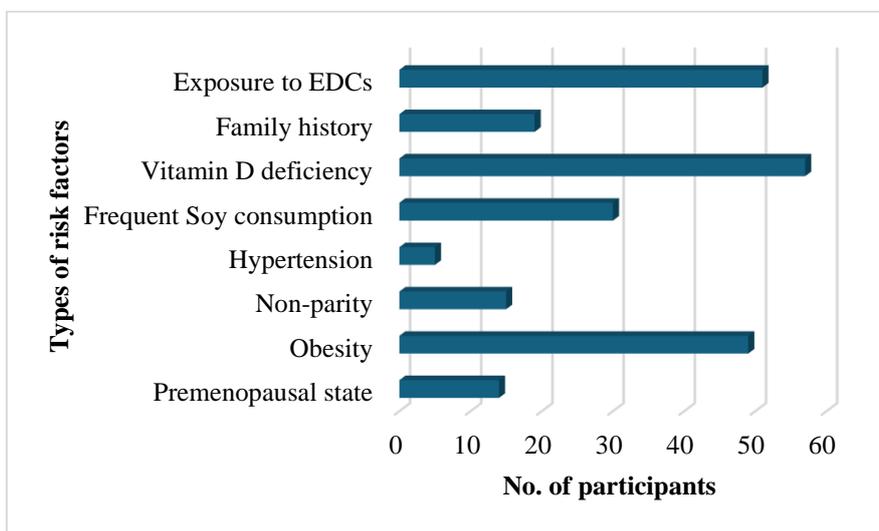| S. No.	Risk factors	No. of cases (n=60)	Percentage (%)
1	Premenopausal state	14	23.3
2	Obesity	49	81.7
3	Non-parity	15	25
4	Hypertension	5	8.3
5	Frequent Soy consumption	30	50
6	Vitamin-D deficiency	57	95
7	Family history	19	31.7
8	Exposure to EDCs	51	85

Figure 2. Various risk factors association in UF

3.3 Analysis of various EDCs utilization pattern
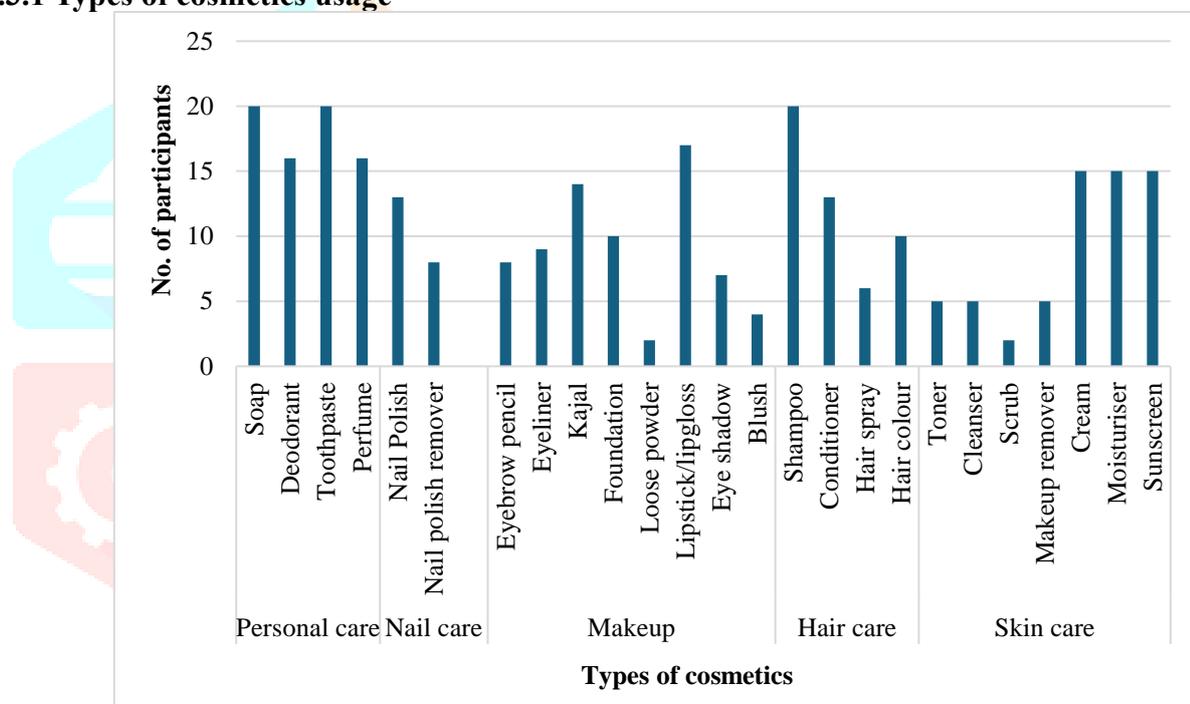
3.3.1 Types of cosmetics usage

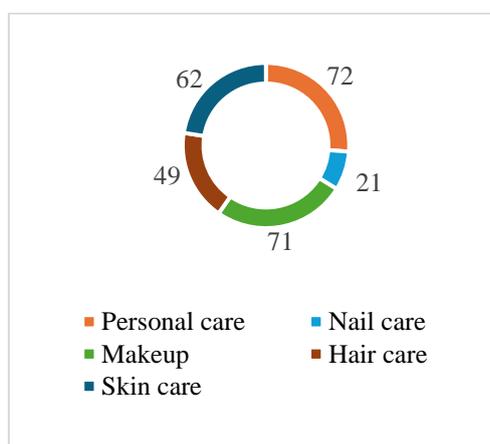Figure 3. Types of cosmetics usage

Figure 4. Categorical representation of cosmetics

3.3.2 Cosmetics utilization behaviour

Table 4. Usage of cosmetics in a day

No. of cosmetics used per day	No. of participants used (n=20)
≤ 2	2 (10%)
3–5	4 (20%)
6–10	11 (55%)
>10	3 (15%)

Table 5. Frequency of cosmetics utilization in a day

Frequency of cosmetics utilization per day (No. of times/day)	No. of participants used (n=20)
1	9 (45%)
2	5 (25%)
3	4 (20%)
≥4	2 (10%)

Table 6. Duration of use of cosmetics

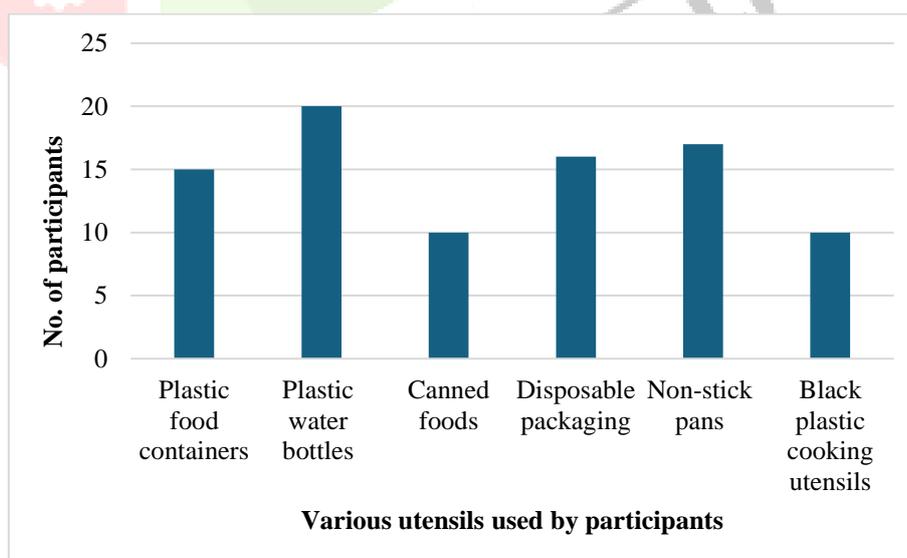| Duration of cosmetics use	No. of participants used (n=20)
≤6 months	0
6–12 months	2 (10%)
≥2years	5 (25%)
≥5years	13 (65%)

3.3.3 Types of utensils usage

Figure 5. Types of utensils usage

3.3.4 Distribution of various associated EDCs in UF
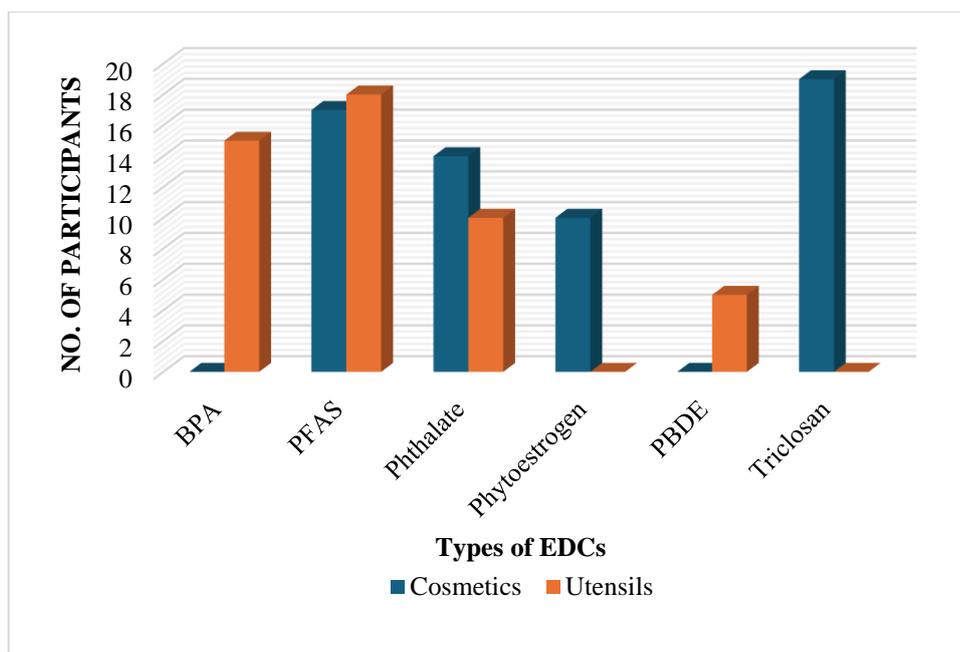

Figure 6. Distribution of various associated EDCs in UF

IV. DISCUSSION

Uterine fibroids are benign monoclonal neoplasms of the myometrium, representing the most common tumors in women [2]. There were many studies establishing various risk factors associated with UF with their underlying mechanisms. Also, there were studies conducted partially for certain risk factors. But, this study had included maximum number of risk factors associated with UF mentioned in literatures for analysis and arrived strong relation between them. Among the risk factors, vitamin D deficiency (95%), exposure to EDCs (85%) and obesity (81.7%) attained strong assocation. Frequent soy consumption (50%), family history (31.7%), non-parity (25%) and premenopausal stage (23.3%) showed moderate association whereas Hypertension (8.3%) showed weak assocaition. Among EDCs, triclosan, PFAS, phthalates and BPA had strong association with UF in day-to-day utilization.

V. CONCLUSION

Due to changing lifestyle and food habits, we are rushing into the world of hormone imbalance. Diseases due to hormonal issues are increasing day-by-day. Uterine Fibroid is one such problem which needs present attention. The identification of risk factors associated with UF may help to prevent its occurrence, which could improve the general health of female population. This data could provide new insight into understanding on the prevention of Uterine Fibroid. Also, "chemicals of emerging concern" which are Endocrine Disrupting Chemicals (EDCs) are now a major public health hazard associated in this concern. Therefore, effective reduction of EDC exposure should be the individual's choice achieved by individual behavior changes to avoid risk of any potential health effects.

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