**UTERINE FIBROIDS: ANY SIGNIFICANT ASSOCIATION WITH THE AGE, MENARCHE AGE, MENSTRUAL AGE, OR PARITY OF THE SUBJECTS?**

**ABSTRACT**

**Background**

Uterine fibroid is the commonest gynaeclogical tumor and is responsible for much of the morbidity and mortality among women. Parity and various age parameters (age at menarche, actual age and menstrual age) have been postulated to have influence on the development of fibroids. Some works have been done on some of these variables, while there is little or no work documented with regards to others. The objective of this study is to check for association between parity as well as various age variables with uterine fibroids among premenopausal women.

**Methodology:** This is a prospective analytical study carried out on premenopausal women referred for transabdominal ultrasound (TAUS) and hysterosalpingography (HSG) on account of infertility. They were recruited consecutively over a period of six months. Institutional ethical clearance and subjects’ consent were obtained appropriately. Both the TAUS and HSG were performed the same day but HSG was performed after TAUS. The data was analysed with Statistical package for Social Sciences version 23. Simple descriptive statistics, independent sample t-test for difference in means and Fisher’s exact test for association were carried out. In all the tests for significance, p-values ≤0.05 were considered statistically significant.

**Result:** A total of 200 subjects were recruited out of which 108 knew their age at menarche while 92 had forgotten theirs. Fibroids were found more frequently among those of older age, older menstrual age, late onset of menarche as well as those with low parity. With regards to all of these variables, independent sample test showed no statistically significant difference in means between subjects with fibroids and those without. Fisher’s exact test found no significant association between the presence of fibroids and those variables.

**Conclusion:** Though fibroids were found more frequently among those of older age, older menstrual age, late onset of menarche as well as those with low parity, no significant association was found between the presence of fibroids and those variables.

**Key words:** uterine fibroids, menstrual age, menarche, parity, ultrasound

**Explanation of terms**

**Actual age:** Time interval from the time of birth to the last birth day, taken as age in years as at last birth day.

**Menarche age:** Actual age at which the first menses (first menstrual period) occurred.

**Menstrual age:** The number of years the women has had menses. It is also the interval in years between the first menstrual period and the last menstrual period. This is calculated as actual age minus menarche age.

**Parity**: The number of times a woman has conceived and the pregnancy carried to the age of survival if delivered, whether the pregnancy eventually ended in still birth, preterm delivery or full term delivery or not.

**INTRODUCTION**

Uterine fibroid (UF) or leiomyoma is a benign tumor of the uterus. Since the uterus is a reproductive organ normally only found in the female, the disease condition is only seen among females. It arises from the smooth muscles (the myometrium) and the connective tissues of the uterus1. Some somewhat related aetiopathogenetic pathways have been propounded for the development of fibroids. These include estrogen-mediated stimulation2-4, mediation by high levels of estrogens and progestogens in the uterus5-8, and mitotic activities in the uterus which reach peak at the luteal phase of the menstrual cycle8-9**.**

With reference to gynaecologic neoplasms or to tumors of the female pelvis or benign tumors of premenopausal women, different authorities reported fibroids as being the commonest and as such, leading to considerable morbidity and mortality among women1,10,11. This makes it important to enquire into the predisposing factors.

Uterine fibroids may be asymptomatic, especially at the early stage. Dahnert noted 70-75% of the cases of fibroids to be asymptomatic1. When symptomatic, uterine fibroids may present as abnormal uterine bleeding (especially as heavy and prolonged menses)1,12, feeling of mass in the abdomen, abdominal bloating, pelvic pain, infertility, miscarriage and increased urinary frequency13,14**.**

It has been noted that the number of fibroids as well as their sizes and locations, influence the nature and the severity of the symptoms15. For instance; according to Saghir et al.16, multiple fibroids predispose to miscarriage more than single fibroid, while Udobi et al.17, reported a single large submucosal fibroid causing bilateral cornual obstruction and hence infertility. Similarly, multiple fibroids located near the cornual regions bilaterally may cause cornual obstruction and infertility. Some other authors have reported positive relationship between fibroids and infertility 18,19.

It has also been reported that severe intrauterine adhesions which may complicate myomectomy (fibroid surgery), may cause bilateral tubal obstruction and infertility20,21. Other authors have reported further that submucosal fibroid or intrauterine adhesions following myomectomy may interfere with implantation and lead to early spontaneous abortion1,22,23, thereby reducing the chance of parity among such individuals.

While many factors have been reported to constitute risk for fibroid formation, some others have been noted to be protective. The reported risk factors include; age, age at menarche and race4,19,24-27. But, parity and use of oral or injectable hormonal contraceptives are said to have preventive effect againstit18,27.

With regards to the actual age; Dahnert, reported fibroids to be rare before the age of 18 years and among the postmenopausal women, but commoner among those aged more than 30 years1, while Saghir et al.16 reported that 46% of patients with fibroids in their study were within the age range of 40-49 years. Similarly, a study in USA reported the incidence of leiomyomas at the age of 35 years for African-Americans and Caucasians to be 60% and 40% respectively and noted that at the age of 50 years it increased to 80% and 70% respectively28.

With reference to the age at menarche, the available literature reported the incidence of uterine fibroids to be higher in subjects with earlier onset of menarche than those with later onset29-33. While some noted the early onset to be as early as at age of 10 years or less34, others considered age of below 12 years as the early onset16. Some authors further noted the differences between various menarche ages of; less than 11 years, 11 years, 12-13 years, 14 years, and 15 years or above30. Siregar et al.34 found fibroids to be 2.5 times in those with menarche age of 10 years or less than in those above 10 years, while Edwards et al.30 reported negative association between one year increase in menarche age and the incidence of fibroid. The trend has been attributed to the earlier exposure to estrogen and other sex hormones5-8.

The occurrence of fibroids at younger age among blacks as noted by some authors have been attributed to the occurrence of menarche at earlier age among blacks than whites33,35. However, Edwards et al.30 found no significant association between age at menarche and race.

With regards to menstrual age, despite the relative availability of studies on the relationship of the two age variables (actual age and the age at menarche) with fibroid, our search showed no study in the available literature on the relationship between fibroids and menstrual age. This finding underscores the need for a study like ours.

Concerning parity: many authors reported a negative association between parity and the incidence of fibroids. They reported that increase in parity caused a decrease in the incidence of fibroids11,29,30,33,36. Some authors have specifically noted parity, as distinct from the total number of conceptions, to be the variable with this protective effect; and that abortion and miscarriages do not have protective effect against fibroids33,37,38.

Various radiological modalities can be used to assess the uterus for fibroids. These include ultrasound [transabdominal, transvaginal, sonohysterography (SHG)], hysterosalpingography (HSG), magnetic resonance imaging (MRI), and computed tomography (CT). Both CT and MRI are very costly in our environment, and, while MRI is in addition, very rare in our environment; CT in addition uses ionizing radiation. Similar to CT, HSG makes use of ionizing radiation.

Though histology is considered the gold standard for diagnosis of fibroids, ultrasound is the modality primarily deployed for this purpose because of its numerous advantages which include high sensitivity, specificity and positive predictive value relative to histology 39-41.

Ultrasound, in addition, does not use ionizing radiation and is relatively cheap. Transabdominal ultrasound, though commonly adjudged less sensitive than TVS and SHG, has appreciable sensitivity and specificity in the detection of fibroids39,41,42. It is cheaper and more readily available in our environment. It is also less sophisticated and has higher patient compliance. It is with the above considerations that ultrasound through the transabdominal approach was used in our study.

This study is aimed at determining the association of fibroids detected by transabdominal ultrasound with actual age, age at menarche, menstrual age and parity of the subjects among premenopausal women with infertility in our environment.

**METHODOLOGY**

This prospective analytical study was carried out at University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla, Enugu state, Nigeria, and Hansa Clinics (a radiology center located in Enugu). Prior to the study, ethical clearance was obtained from the University of Nigeria Hospital Research Ethics Committee. Informed consent was obtained from each subject prior to enrolment for the study.

The participants were females referred for transabdominal ultrasound (TAUS) and hysterosalpingography (HSG) on account of infertility and who volunteered for the study. They were recruited concurrently over a period of six months. The TAUS was performed on the same day with HSG but before the HSG. Aloka SSD-550 manufactured by Aloka, Japan 1995 was used for the ultrasound. The machine has a curvilinear probe of 3.5-5.0MHz frequency, B-mode as well as colour Doppler facilities.

The data was analysed with Statistical package for Social Sciences version 23; IBM Corp. (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp; 2015). Simple descriptive statistics was used in the analysis of measures of central tendencies and dispersion. In addition, presence of fibroid (a bivariate categorical variable) was paired with the following continuous numerical variables (actual age, age at menarche, menstrual age, and parity) and subjected to independent sample t-test for difference in means. The continuous numerical variables were further grouped (grouped actual age, grouped age at menarche, grouped menstrual age, and grouped parity) and tested for association with fibroids using Fisher’s exact test. In all the tests for significance, p-values ≤0.05 were considered statistically significant. Results were displayed in tables and bar charts. Missing data were excluded from the analyses of the variable(s) or subgroup(s) concerned.

**RESULTS**

Two hundred participants were recruited for the study. Out of these, 108 were sure of their age at menarche, and 92 subjects could not remember theirs. The later were excluded from all the analysis involving the menarche age. They were also excluded from the menstrual age analysis since this variable depends on the menarche age.

The age range of the study population was 20-49 years, menarche age range was 9-19 years, and menstrual age range was 5-35 years. Uterine fibroids were detected in 39 of the 200 (19.5% of the study population). The subpopulation with uterine fibroids had age range of 25-49 years,menarche age range of 13-17 years, menstrual age range of 10-33years; and mean age of 34.62 ± 6.15 years, mean menarche age of 14.39 ±1.29 years and mean menstrual age of 19.33 ± 6.28 years.

As seen in table 1, seven subjects were aged 24 years or less. This constituted 3.5% of the total population. No fibroid was found among subjects in this age group.

Subjects aged 25-29 years were 50 (25.0% of the entire population). The number of subjects with fibroids in this group were 11; this constituted 22.0% of the patients in the age group.

 **Table 1: frequency of various subgroups**

|  |  |  |  |
| --- | --- | --- | --- |
| **Subgroup****ranges** | **No of subjects**  | **No of subjects with fibroids** | **Percentage of subjects with fibroids** |
| **Actual****age range**20-2425-2930-3435-3940-4445-49**Total** |   7 50 60 55 24 4**200** |    0 11 5 13 9 1 **39** |   0.022.0 8.323.6 37.525.0 |
| **Menarche age range**  9-1213-16≥17Total |  7 96 5108 | 017 118 |  0.0 17.7 20.0 |
| **Menstrual age range**5-1415-24≥25Total |  27 63 18108 |  310 518 | 11.115.927.8 |

 

 **Fig.1: Frequency of parity**

Subjects aged 30-34 years were 60 in number (30.0% of the total population). Five of the subjects in this age group had fibroids, accounting for 8.3% of the patients in this age group.

There were 55 subjects (27.5% of the entire population) aged 35-39 years. Thirteen of those in this age group (23.6%) had fibroids. The number of subjects within 40-44 years age group was 24 which was 12.0% of the entire population. Fibroids were detected in 9(37.5%) persons in this group. The number of subjects in 45-49 year age group was 4 (2.0% of the entire population). Fibroids were detected in 1 person in this group; accounting for 25% of patients aged 45-49 years.

From table 1, out of the 57 aged 20-29 years, 11(19.3%) had fibroids, while out of the 115 aged 30-39 years, 18(15.7%) had fibroids and out of the 28 that were aged 40-49 years,10(35.7%) had fibroids. Therefore fibroids occurred most frequently among those aged 40-49 years in this study.

Among the 108 that could recall their age at menarche, 18 had uterine fibroids (see table 1). The menarche age of 7 (6.5% of them) was 9-12 years, among whom none had fibroids. Those with menarche age of 13-16 years were 96 in number, constituting 88.9% of those with known menarche age. Seventeen subjects had fibroids in this subgroup constituting 17.7% of them. Those with menarche age of ≥ 17 years were 5 in number, constituting 4.6% of those with known menarche age. One subject (20%) had fibroids in this subgroup.

With regards to the menstrual age, the menstrual age of 27 subjects was 5-14 years, representing 25% of those with known menstrual age. Three of them had fibroids. This represented 11.1% of those with known menstrual age of 5-14 years.

The menstrual age of 63 subjects was 15-24 years, representing 58.3% of those with known menstrual age. Ten of them had fibroids, accounting for 15.9% of those with known menstrual age of 15-24 years.

The menstrual age of 18 subjects was ≥25 years, representing 16.7% of those with known menstrual age. Five of them had fibroids, representing 27.8% of those with known menstrual age of ≥25 years.

It can also be seen in fig. 1, that there were 132 null nulliparous subjects (those with parity of zero) in the study. This was 66.0% of the entire population. Fibroids was detected in 30 persons in this group; accounting for 22.7% of the nulliparous subjects. The number of those with parity of 0-1 was 165 which was 82.5% of the entire population. Fibroids was detected in 35 persons in this group; which is 21.2% of subjects with parity of 0-1. Subjects with parity of 1-4 (see fig.1) were 64 in number, which was 32% of the entire population. Fibroids were detected in 9 persons in this group accounting for 4.1% of subjects with parity of 1-4.

The number of those with parity of 2-4 was 31 which was 15.5% of the entire population. Fibroids was detected in 4 persons in this group; accounting for 12.9% of subjects with parity of 2-4. The number of those with parity of 5 or more was 4 (see fig.1), which was 2.0% of the entire population. Fibroids was not detected in this group. Of the entire study population, 19.5% had fibroids; while those with parity of 0-1 accounted for 17.5%, those with parity of ≥2 accounted for 2%.

Independent sample tests with equal variances assumed (table 2.) showed no statistically significant difference in means between the women with fibroids and those without, with regards to their: actual age, age at menarche, menstrual age, or parity.

Fisher’s exact test for association (table 3) similarly showed no significant association between fibroids and the following grouped variables: actual age, age at menarche, menstrual age and parity.

 **Table 2:** **Independent samples t-test**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables Fibroids vs:** | **Mean difference** | **P value** | **Significance** |
| Actual age  | 1.858 | 0.061 | Not significant |
| Menarche age | 0.256 | 0.511 | Not significant |
| Menstrual age | 0.811 | 0.587 | Not significant |
| Parity  | -0.334 | 0.152 | Not significant |

**Table 3:** **Fisher’s exact test for association**

|  |  |  |  |
| --- | --- | --- | --- |
| **Fibroids vs:** | **Fisher’s exact value** | **P-value** | **Significance** |
| Grouped actual age (˂30, 30-40, ˃40) | 1.712 | 0.456 | Not significant |
| Grouped menarche age (9-12, 13-16, ≥17) | 0.215 | 0.677 | Not significant |
| Grouped menstrual age (5-14, 15-24, ≥25) | 3.014 | 0.397 | Not significant |
| Grouped Parity (0-1, 2-4, ≥5) | 1.386 | 0.448 | Not significant |

**DISCUSSION**

Our study did not find uterine fibroids among those aged ≤24 years. This is in concordance with the view that fibroids is rare before the age of 18 years, as noted by Dahnert1. On the other hand, finding of no fibroid among subjects aged ≤24 years in our study population made up of Blacks, does not suggest a higher incidence of fibroids among the younger age in Blacks than in Whites as opined by some authors33,35. However, our study population is made up of subjects with infertility. The time interval between attainment of the age of marriage, marital processes and consummation, and the diagnosis of infertility in these subjects, would add to the age of the subjects prior to the diagnosis of fibroids using ultrasound.

Besides, in our environment, it is a common experience that even when faced with the challenge of infertility, the subjects would take some time to seek for other options of solving the problem, including traditional medication and religious rituals (and this may last for some years), before seeking for conventional medical consultation and ultrasonography. All these may have accounted to failure to detect fibroids in those aged ≤24 years in our study population possibly because by the time of ultrasound consultation, a lot of the subjects would have passed the age of 24 years.

In our study, using interval of 5 years, fibroids were found more frequently among those aged 40-44 years followed by the other age groups in this order; 45-49 years, 35-39 years, 25-29 years, 30-34 years. Though this interval age grouping did not show consistent rise of frequency of fibroids with age; broadly, it can be seen that 13.7% of the subjects aged 20-34 years in our study had fibroids, while fibroids is found in 27.7% of those aged 35-49 years (see table 1). This is in agreement with the finding that fibroids tend to be more frequent in the older age group among premenopausal women28. Using the interval of 10 years, the finding of fibroids most frequently among those aged 40-49 years in this study is in keeping with that of Saghir et al.16 who found that among the age ranges, most of the patients with fibroids in their study were within 40-49 years.

The finding of fibroids more frequent among subjects with menarche age ≥16 years, followed by those of 13-15 years, and none among those of ≤12 years in our study is at variance with the report by some other authors who found the incidence of fibroids to be higher among those with early onset of menarche29-33. The reason for this variation is not obvious. However, it is likely that our result may have been affected by the fewness of the patients that were sure of their menarche age. Hence, a study in our environment involving a larger population of women who are certain of their menarche age, may be more elucidatory.

Though our study population were predominantly Blacks, the finding that of the 108 that were sure of their menarche age, 96 (94.4%) were within 13-16 years, does not support the observation that menarche occurs at lower age among Blacks than Whites33,35. It rather tends to agree with the report of Edwards et al.30 who found no significant association between age at menarche and race.

In our study, the finding of fibroids more frequently among those with menstrual age range ≥25 years, followed by 15-24 years, and least among the 5-14 years; suggests that the incidence of fibroids decreases with decreasing menstrual age and increases with increasing menstrual age among premenopausal women in our environment. Our literature search did not show any work relating uterine fibroid with menstrual age. However, some authors have opined that fibroid stimulation is mediated by oestrogen and that the longer the period of oestrogen exposure, the more the likelihood of fibroid formation2-4. Our findings is in keeping with this view because menstrual age is the number of years which the uterus is exposed to oestrogen stimulation and this starts from the onset of menarche.

From the finding on actual age, the age at menarche and the menstrual age; our results suggest that the frequency of fibroids increases with increasing menstrual age but does not necessarily increase with the actual age nor decrease with increasing age at menarche.

The increase in the frequency of fibroids at lower parity levels seen in our study is in keeping with the reports by other authors that increase in parity decreased the incidence of fibroids11,29,30,33,36. However it has been noted by some authors that fibroids can predispose to infertility17-19 and spontaneous abortion1,22,23. Since infertility and / or abortion can result in nulliparity or low parity, and our study population is a group of women with infertility; it is possible that the finding of fibroids more frequently among the nulliparous or those with low parity in our study population, may be due to the compounding effect of infertility. That is, fibroids may as well be the cause of nulliparity or low parity in this group of people, instead of nulliparity or low parity being the cause of fibroid formation.

The findings of no statistically significant difference in means between the two groups of women (those with fibroids and those without) with regards to their actual age, menarche age and menstrual age or parity, using the independent sample t-test, showed that though the frequency of fibroids may differ among these various variables, such differences are not to a statistically significant level. Consequently, the absence of significant association between fibroids and these variables does not support these variables as significant predisposing factors to fibroids. These two findings tend to rather support other options like the compounding effect mentioned above. Though some of the earlier researches reported some of these factors as predisposing to fibroids, most of those conclusions were largely derived from frequencies and incidences and not backed up with tests for significance, as done in our present study.

**CONCLUSION**

In a population of premenopausal women with infertility, our study found fibroids more frequently among those of older age as well as those with higher menstrual age than the younger. It also found fibroids more frequent among those with late onset of menarche as well as those with low parity. However, independent sample test did not show statistically significant difference in means between subjects with fibroids and subjects without fibroids with regards to any of these variables neither did Fisher’s exact test find significant association between the presence of fibroids and those variables.

**RECOMMENDATION**

Our study population consisted of premenopausal women with infertility. The number of the subjects with fibroids were few. The fewness of the fibroids may have affected the results obtained. There is paucity of literature on studies of association between fibroids and actual age, menarche age, menstrual age or parity in our environment. Independent sample tests and Fisher’s exact tests similar to ours and involving larger population of women with and without infertility as well as involving premenopausal and postmenopausal women are recommended and will help to bridge the gaps in this study vis-a-vis the findings in other studies done in other climes. It is hoped that such studies will overcome the limitations encountered in our study and throw more light on the main differences among women with fibroids and those without fibroids with regards to these variables.

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