Reproductive History and Menopause: An Analysis on Influence of Hysterectomy, Parity, and Miscarriage on Menopausal Outcomes

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ABSTRACT

Background: Menopause marks the transition from a woman's fertile to infertile reproductive status, typically occurring between ages 45 and 55. Early menopause, which happens before age 45, is linked to various risk factors, including medical interventions, genetics, family history, autoimmune conditions, lifestyle choices, and environmental influences. Both early and premature menopause are associated with long-term health risks such as early mortality, cardiovascular disease, neurological disorders, osteoporosis, psychosexual dysfunction, and mood disorders. This research aims to evaluate the impact of reproductive factors on menopause.

Methodology: A 6-month ambidirectional, cross-sectional study collected data from 200 female volunteers in various Ahmedabad societies, using specific inclusion and exclusion criteria. Data was stored and tabulated in MS Excel, and statistical analysis was performed with GraphPad Prism 8.0.1. Chi-square (X^2) tests were used to determine statistically significant differences, with a significance level set at $P < 0.05$.

Result: The mean age of women was found to be 51.51 ± 7.77 years. Out of 200 volunteers, 116 (58%) had natural menopause while 84 (42%) had early menopause. No statistical significance was found for hysterectomy, hormonal treatment, miscarriage, or parity between both groups.

Conclusion: Research on reproductive factors and their impact on women's quality of life during menopause provides valuable insights. The study identified various postmenopausal complications in women, highlighting the need for education about these issues, their causes, and appropriate treatments.

Keywords: Early menopause, Normal menopause, menopausal symptoms, stress, quality of life.

1. INTRODUCTION

1.1 Introduction to menstruation

The monthly cycle, albeit a continuum, is typically addressed as starting on the principal day of the menses and finishing on the last day before the following menses. The typical length of the period is 28 days, with a scope of 25-32 days. The best changeability in cycle length happens soon after the beginning of menarche and before menopause (1).

1.2. Menopause

The meaning of menopause, a year of amenorrhea (with next to no different clarifications), means the finish of a lady's regenerative limit (2). The routineness and length of the period change across a lady's regenerative life expectancy, however, the age at which normal menopause happens is by and large somewhere in the range of 45 and 55 years for ladies around the world.

Regular menopause is considered to have happened following 12 continuous months without a feminine cycle for which there could be no other clear physiological or neurotic reason and without clinical intercession (3). While the crucial course of menopause is connected straightforwardly to ovarian maturing, all parts of the hypothalamic-pituitary-ovarian-uterine hub are changed with time. Sequential and ovarian maturing are 2 entwined, simultaneous cycles that impact the speed of the interaction and its span (4).

1.3. Types of menopauses: natural, surgical, chemotherapy, or radiation therapy

There are different types of menopause such as perimenopause, menopause, post menopause

a. Perimenopause- is called menopausal transition, the most common effect of perimenopause is a drop in estrogen levels especially in 2 years after actual menopause. Can also called ‘around menopause’

b. Menopause- is a natural life event, it officially marks the end of female reproduction menopause is a condition where a female stops menstruating

c. Post menopause- the time after menopause has occurred.

Natural menopause is defined as the absence of menstruation for 12 months without medical intervention, typically occurring between ages 47 and 53, though this varies by ethnicity (5, 6). Menopause before 40 is termed premature, while menopause between 40 and 45 is considered early (7). Genetic factors influence its timing, and reproductive factors like menarche, parity, and contraceptive use also play a role (8).

Surgical menopause, caused by hysterectomy or bilateral oophorectomy, may affect estrogen levels, potentially increasing cardiovascular disease (CVD) risk, especially if surgery occurs before age 46 (9, 10). However, studies like SWAN suggest no significant differences in CVD risk between women who undergo surgical

menopause and those who experience natural menopause (11). Early removal of ovaries can lead to premature hormone cessation, increasing the risk of dementia and cognitive decline (12).

Chemotherapy or radiation therapy, commonly used to treat breast cancer, often causes chemotherapy-induced amenorrhea (CIA) or premature menopause, particularly affecting younger patients (13). These women may experience significant psychological and physical challenges (14). While low-dose vaginal estrogen has not been shown to increase breast cancer recurrence, its safety is still under investigation (15). Women undergoing cancer treatments need access to evidence-based information on managing menopausal symptoms (16).

1.4. Factors influencing age of onset of menopause. / Risk factors and causes for early menopause.

1.4.1. Reproductive factors

Rapid expenditure of primordial follicles is thought to be caused by frequent ovulation with an early menarche, regular menstrual cycles, and the absence of pregnancy. Therefore, precluding ovulatory cycles may offer protection against primary ovarian insufficiency (POI) and early menopause (17).

1.4.1.1 Age at menarche

Women who experience menarche before age 11 have a higher risk of early menopause and premature menopause compared to those who begin menstruation at age 13, as shown in studies from InterLACE and the UK Biobank (18). Although earlier menarche is linked to earlier menopause, factors such as genetics, prenatal conditions, and childhood variables complicate the establishment of a clear linear relationship between the two (8).

1.4.1.2 Parity

Nulliparity is associated with a higher risk of early menopause and POI, while multiparity is linked to later menopause. Women with early menarche and nulliparity have an even greater risk of early menopause and POI (18). Infertility and subfertility may confound the relationship between parity and menopause (19, 20), as studies show that lower parity does not necessarily lead to earlier menopause, despite declining birth rates in affluent nations (21).

1.4.1.3 Mannerism of menstrual cycle

The Nurses' Health Study II (NHS II) study found that women aged 18 to 22 with shorter menstrual cycles (less than 25 days) had a higher risk of early menopause, with lower Anti-Mullerian hormone (AMH) levels potentially indicating ovarian aging, though results may be influenced by conditions like polycystic ovarian syndrome and oral contraceptive use (22). Dysregulation of the stress response is suggested as a possible underlying mechanism (21).

1.4.2 Early life factors

1.4.2.1 Low Birth/Early Childhood Weight

There is conflicting evidence about the impact of birth weight on menopausal age. Nine out of eleven studies included in a 2018 systematic review found no significant correlation between age at natural menopause and low birth weight (23). Additionally, there were no noteworthy correlations found in twin studies between the age at menopause and birth weight (24). Nonetheless, a 2020 prospective study involving 1,001 women between the ages of 39 and 49 found that women with lower birth weights were twice as likely to go through a natural menopause or undergo an early menopausal transition (25). There is evidence linking low body weight from infancy to an early menopausal age (23, 25, 26).

1.4.2.2 Parenting/Childhood Experience

Age at natural menopause was coupled with childhood intelligence, and lower cognitive scores in childhood were linked to an earlier age at menopause (26-28). According to the Avon Longitudinal Study of parents and children, victims of sexual abuse had an earlier age at menopause. This finding suggests that early-life violence may have an impact on reproductive aging (29, 30). An earlier age at natural menopause was linked to poor parenting, which was characterized by low levels of caring from mothers and fathers and high levels of overprotection. A reduced reproductive lifespan of fewer than 33 years was linked, in particular, to paternal overprotection (relative risk ratio: 1.09; 95% CI: 1.01–1.18) (31).

1.4.2.3 Breastfeeding duration

In the NHS II cohort, longer breastfeeding durations of 7 to 12 months (multi-adjusted HR: 0.72; 95% CI: 0.62, 0.83) or 13 to 18 months (multi-adjusted HR: 0.80; 95% CI: 0.66, 0.97) were linked to a lower risk of early menopause compared with less than 1 month of exclusive breastfeeding (32).

1.5 Rationale and Objectives

This study aims to evaluate and compare the quality of life in women experiencing early versus normal menopause, focusing on the impact of risk factors, causes, and complications. Over 80% of women report physical and psychological symptoms during menopause, which can significantly affect their quality of life. The objectives include identifying the risk factors and etiology behind early and normal menopause, assessing complications, and measuring health-related quality of life in these women.

2. METHODOLOGY

2.1 Study Criteria

The following inclusion and exclusion criteria were considered when screening volunteers for the study.

2.1.1 Inclusion Criteria:

Volunteers were included based on the following:

(i) Age between 30-75 years, (ii) Currently in the perimenopause, menopause, or post-menopause phase, (iii) May or may not have undergone hormone replacement therapy (HRT) or surgery, (iv) May or may not have a history of endocrine issues, (v) May or may not have cardiovascular co-morbidities.

2.1.2 Exclusion Criteria:

Volunteers were excluded based on the following:

(i) Psychiatric conditions (e.g., schizophrenia, epilepsy, Alzheimer's) or cognitive impairments, (ii) Congenital disorders, (iii) Those who experienced late menopause.

2.2 Method of study

The data from 200 female volunteers were collected randomly per inclusion and exclusion criteria. The study was conducted over 6 months. The women approached were from different societies across Ahmedabad. We briefly explained the purpose of the study to those who met the inclusion criteria. All women were informed that the participation is voluntary and signed acceptance of women to participate in the study was obtained through an informed consent form. Data collection was carried out by interviewing the women using questionnaires. Time consumed for each interview ranged from 15-20 minutes with each woman. The volunteers were then divided into two groups based on their age of menopause namely, early menopause (till 45 years of age) and normal menopause (age above 45 years). The questions related to the gynecological history such as miscarriages, age of menses and menopause, hysterectomy, and hormonal treatments were asked. Then the parameters were compared.

2.3 Procedure of Study:

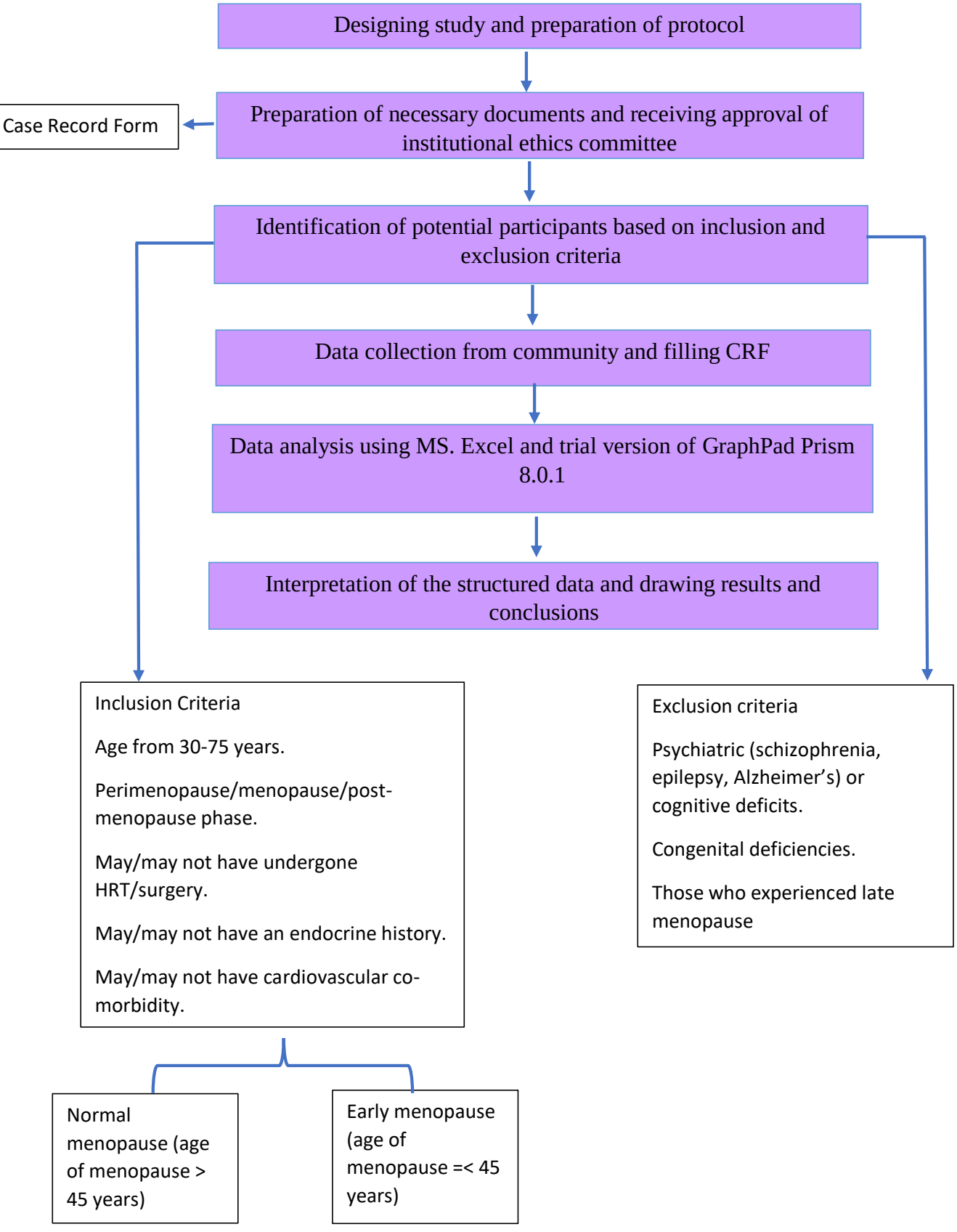

Figure 1: Flowchart of Methodology

3. Statistical Analysis Plan

Data was collected, stored, and tabulated in MS. Excel and was analyzed using the trial version of GraphPad Prism 8.0.1 for statistical analysis. Descriptive statistics was used to calculate 37 percentages, frequencies, Mean, and standard deviations. The chi-square (X^2) test was used to estimate the statistically significant differences. A

significant P-value will be considered when P is less than 0.05 and it will be considered highly significant when the P-value is less than or equal to 0.01. The confidence interval is kept at 95%.

4. RESULTS

4.1 Hysterectomy

Tables (1) and (2) represent the data of hysterectomy in both groups. 17.24% of women in the normal age group, whereas 27.38% of women in the early menopause group have undergone a hysterectomy. There was no statistically significant difference observed. The same has been depicted in fig.2 and fig.3.

Table 1: Prevalence of hysterectomy in both groups

Hysterectomy	Normal menopause (N=116)		Early menopause (N=84)		X^2	p-value
	No.	%	No.	%		
Yes	20	17.24	23	27.38	2.968	0.08
No	96	82.75	61	72.61		

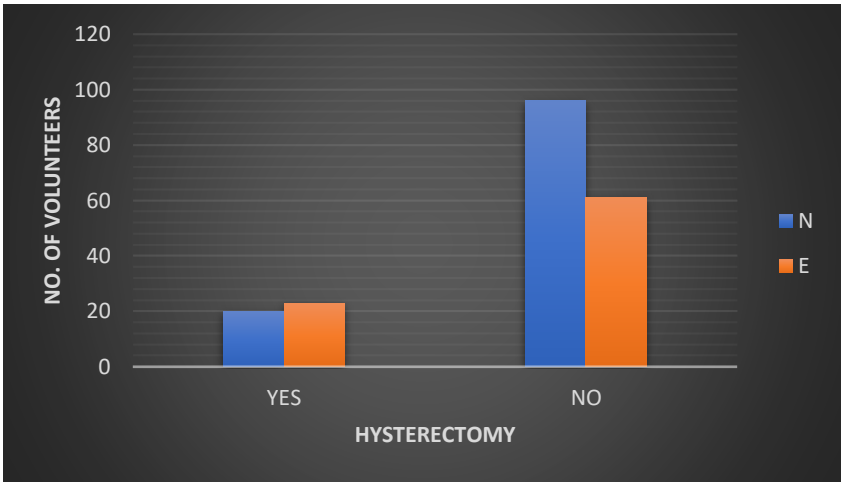

Figure 2 Prevalence of hysterectomy

The figure shows the number of volunteers who underwent hysterectomy and those who did not in the respective groups.

9.48% of women in the normal age group have undergone a hysterectomy due to fibroid, 6.9% due to heavy, painful bleeding, and 0.86% due to other reasons. 10.71% of women have undergone a hysterectomy due to fibroids in the early age group, 9.52% due to heavy, painful bleeding, and 5.95% due to other reasons. A statistically significant difference in the frequency of women undergoing hysterectomy between both groups was not observed.

Table 2: Reason for Hysterectomy

Reason for hysterectomy	Normal menopause (N=116)		Early menopause (N=84)		X^2	p-value
	No.	%	No.	%		
Fibroid	11	9.48	9	10.71	2.778	0.2494
Heavy, painful bleeding	8	6.9	8	9.52		
Other	1	0.86	5	5.95		

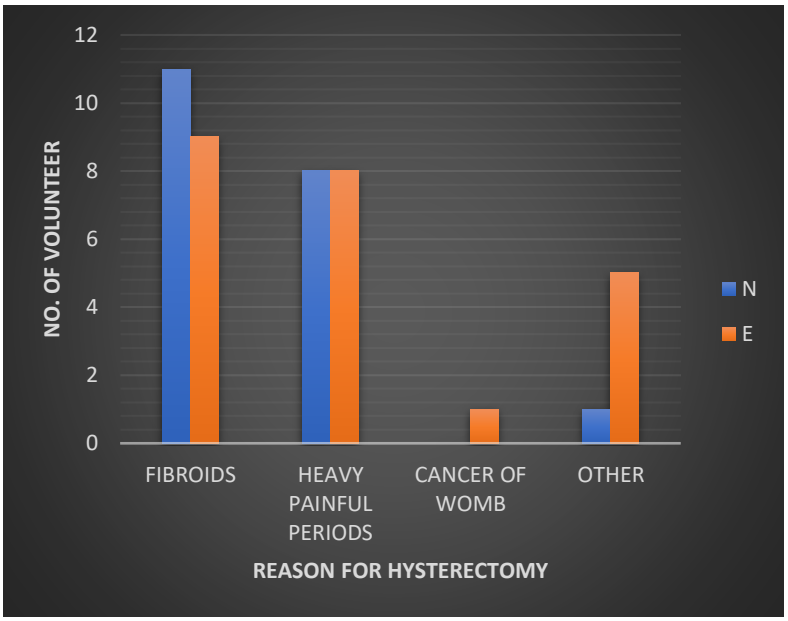

Figure 3 Reason of hysterectomy

The figure represents the reasons for hysterectomy in both groups.

4.2 Hormonal Treatment

As depicted in Tables (3), (4), and (5), 26.72% of women in the normal menopausal age pool have taken hormonal treatment, whereas 34.52% of women in the early menopausal age pool have taken hormonal treatment. No statistically significant difference was observed between the two groups. Fig.4, 5, and 6 represent information about hormonal treatment.

Table 3: Prevalence of hormonal treatment in both groups

Hormonal treatment (past)			Normal menopause (N=116)		Early menopause (N=84)		X^2	p-value
			No.	%	No.	%		
Yes	31	26.72	29	34.52	1.411		0.23	
No	85	73.27	55	65.47				

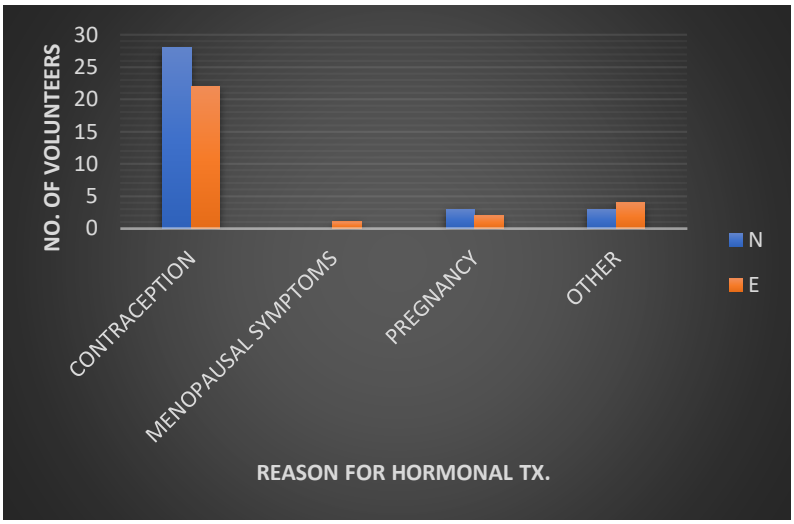

Figure 4 Prevalence of hormonal treatment

The figure suggests the number of volunteers taking hormonal treatment in both groups.

90.32% of women in the normal menopause age group had taken it for contraception, 9.68% took it to get pregnant, and 9.68% for other reasons. Among the early menopause age group, 75.86% of women received hormonal treatments for contraception, 6.9% to get pregnant, and 5.95% for other reasons. A statistically significant difference in the frequency of women receiving treatments for whatever reason was not observed between both groups.

Table 4: Reason for hormonal treatment and relation with age at menopause.

Reason of HRT	Normal menopause (N=116)		Early menopause (N=84)		X^2	p-value
	No.	%	No.	%		
Contraception	28	90.32	22	75.86	1.030	0.5976
To get pregnant	3	9.68	2	6.9		
Other	3	9.68	5	5.95		

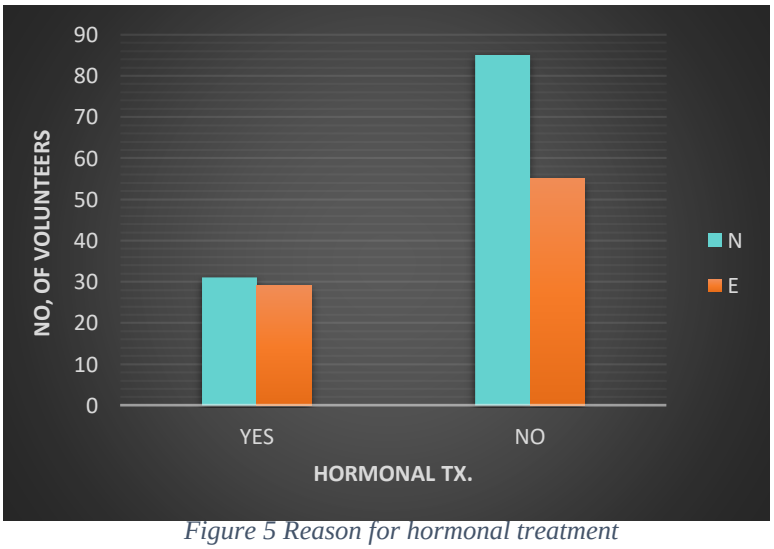

Figure 5 Reason for hormonal treatment

This figure depicts the number of volunteers taking the hormonal treatment for different reasons.

In the normal menopause age group, 7.76% of women were taking Mirena, 16.38% took tablets, 1.72% had taken hormone-impregnated coil and 1.72% had other types of treatment. Whereas in the early group, Mirena was taken by 4.76%, 27.38% took tablets, 1.19% had hormone-impregnated coil, and the remaining 1.19 % had other types of treatment. No statistically significant difference was observed between the two groups.

Table 5: Type of hormonal treatment with respect to age at menopause

Hormonal type	Normal menopause (N=116)		Early menopause (N=84)		X^2	p-value
	No.	%	No.	%		
Mirena	9	7.76	4	4.76	2.830	0.4186
Tablet	19	16.38	23	27.38		
Hormone impregnated coil	2	1.72	1	1.19		
Other	2	1.72	1	1.19		

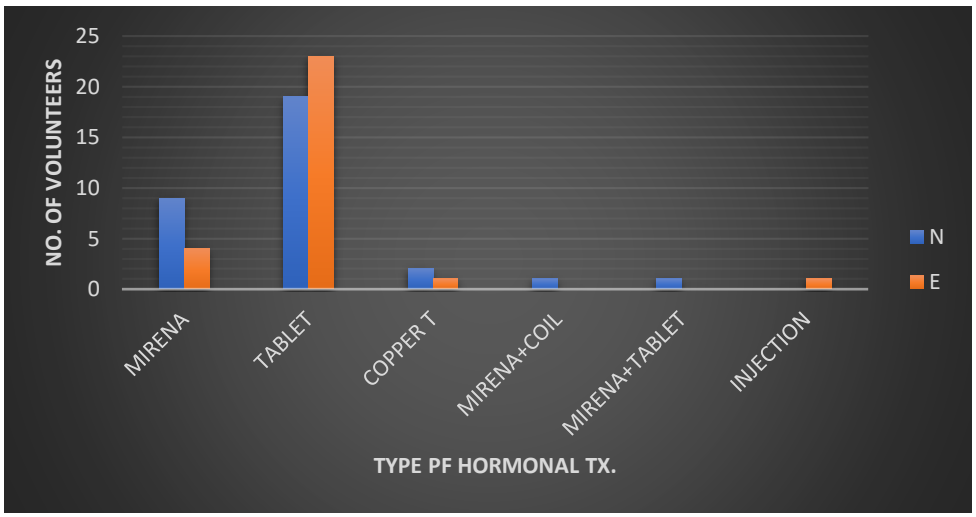

Figure 6 Types of hormonal treatment

This figure shows what hormonal treatment is taken by the volunteers in each group.

4.3 Etiology

Table (6) and figure 7 shows the difference in etiology between the two groups. Out of 116 women in the normal menopause age group, 84.48% of women were observed to have spontaneous, 14.66% had surgical, and 0.86% had menopause due to other reasons. Among the 84 women in the early group, spontaneous menopause was experienced by 70.24%, 28.57% experienced surgical, and 1.19 % experienced it due to other reasons. No statistically significant difference was observed between the two groups.

Table 6: Cause of menopause

Etiology	Normal menopause (N=116)		Early menopause (N=84)		X^2	p-value
	No.	%	No.	%		
Spontaneous	98	84.48	59	70.20	5.914	0.052
Surgical	17	14.66	24	28.57		
Others	1	0.86	1	1.19		

4.4 Miscarriage

As shown in Table (7) and Figure 8, 67.24% of women had no miscarriages, 24.14% had 1 miscarriage, 6.9% had 2 miscarriages, and 1.72% had more than two miscarriages in the normal menopause age group. In the early menopause age group, 64.29% had no miscarriages, 25% had 1 miscarriage, 8.33% had two miscarriages, and the remaining 2.38% had more than two miscarriages. There was no statistical difference seen between the groups.

Table 7: Number of miscarriages in both groups.

Miscarriage	Normal menopause (N=116)		Early menopause (N=84)		X^2	p-value
	No.	%	No.	%		
0	76	65.52	50	59.52	0.4880	0.9215
1	28	24.14	21	25		
2	8	6.9	7	8.33		
>2	2	1.72	2	2.38		

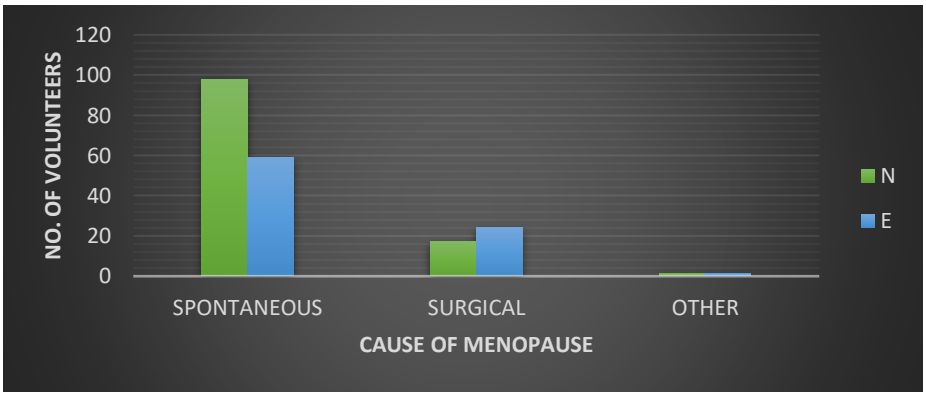

Figure 7 Cause of Menopause

The figure shows what was the cause of menopause in both groups.

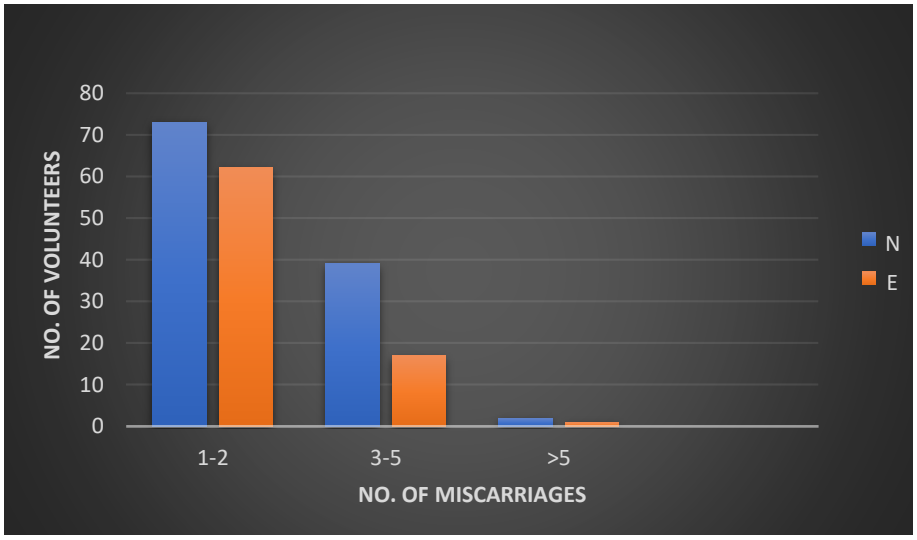

Figure 8 No. of Miscarriages

The figure shows the number of volunteers who had experienced miscarriages in both groups.

4.5 Parity

As demonstrated in Table (8) and Figure 9, 73.80% of women had one or two pregnancies, 20.23% of women had three to five pregnancies, and 1.19% of women had greater than five pregnancies in early menopause pool. In normal menopause category, 62.93% of women had one or two pregnancies, 33.63% had three to five pregnancies, and 1.74% had greater than 5 pregnancies.

Table 8: Effect of Parity on age of menopause

Parity	Normal menopause (N=116)		Early menopause (N=84)		X^2	p-value
	No.	%	No.	%		
1-2	73	62.93	62	73.80	4.038	0.1328
3-5	39	33.62	17	20.23		
>5	2	1.72	1	1.19		

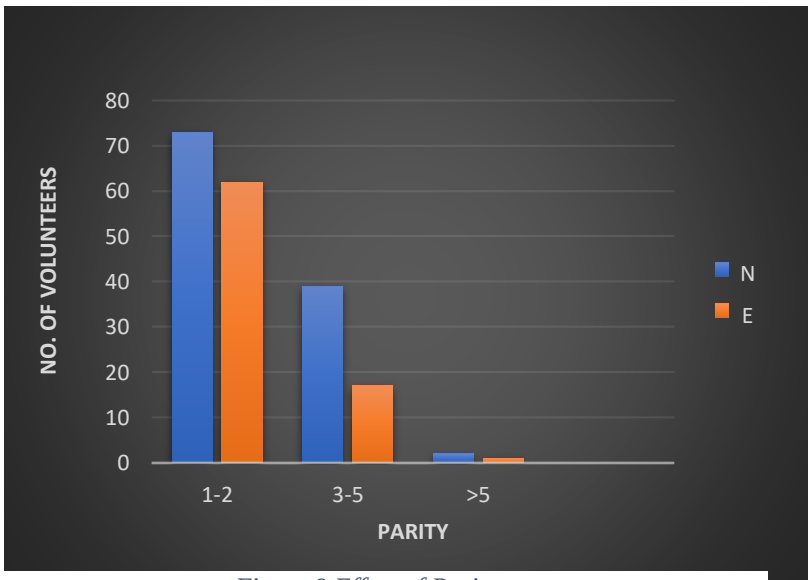

Figure 9 Effect of Parity

The figure represent what's the effect of parity on the age of menopause in both groups.

5. DISCUSSION

5.1 Etiology of menopause

Although the cause of early menopause cannot be established with certainty, most of the times early menopause has been surgically induced. The results of our investigation did not reveal any statistically significant distinction between early menopause and normal menopause in terms of surgical menopause induction although the percentage prevalence is more in early menopause.

5.2 Gynaecological factors

Hormonal treatments can potentially influence the age at which a person experiences menopause. Some medications and therapies may either accelerate or delay the onset of menopause, depending on the specific treatment and individual factors. It is essential to consult with healthcare professionals for personalized guidance on hormonal treatments and their potential impact on menopause.

Also our result does not indicate any significant difference in prevalence of hysterectomy between the two groups. No such definite evidence was found that can conclude hysterectomy was the cause of early menopause in most of the women who experience menopause at early stage of life.

6. CONCLUSION AND FUTURE ASPECTS

In conclusion, the research and studies on menopausal symptoms and their impact on women's quality of life provide valuable insights into this significant phase of a woman's life. While early menopause is often associated with surgical interventions such as hysterectomy, our study did not find statistically significant evidence linking surgical menopause to early menopause compared to normal menopause, despite a higher prevalence of surgical interventions in early menopause cases. Hormonal treatments may also influence the timing of menopause, though no significant difference in the prevalence of hysterectomy was observed between the two groups. Thus, the exact causes of early menopause remain unclear, and more research is needed to establish a definitive link between surgical or hormonal factors and early menopause. Understanding these factors can help healthcare professionals and support systems better tailor interventions and support strategies to improve women's well-being during this transition. By addressing menopausal symptoms, promoting healthy lifestyle habits, managing stress, and considering individualized care based on genetic and reproductive factors, we can enhance the quality of life for women going through menopause.

Further work can be done to understand the post-menopausal complication and their impact on quality of life. Further research is needed to delve deeper into the complexities of menopausal symptoms and related factors to develop more targeted and effective approaches to support women during this phase. By continuing to explore and address these issues, we can strive to provide comprehensive care and empower women to navigate menopause with grace and resilience.

7. List of Abbreviations

AMH	Anti-Mullerian hormone
CI	Confidence interval
CIA	Chemotherapy-induced amenorrhea
CRF	Case Record Form
CVD	Cardiovascular disease
HR	Heart Rate
HRT	Hormonal replacement therapy
InterLACE	International collaboration on the Life course Approach to reproductive health and Chronic disease Events
NHS	Nurses' Health Study
POI	Primary ovarian insufficiency
SWAN	Study of Women's Health Across the Nation

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12. Ethical considerations

12.1 Ethical Approval

This observational study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki. Approval was obtained from the Institutional Ethics Committee at L.M. College of Pharmacy, with approval number LMIEC/2023-24/04. Informed consent was obtained from all participants before data collection, with information provided about the study's purpose, procedures, and any potential risks. Participants were informed of their right to withdraw from the study at any time without penalty. To protect participants'

privacy, all collected data were anonymized and stored securely on password-protected devices, accessible only to authorized research personnel. The study design minimized risks by ensuring that observations did not interfere with participants' daily activities and that any sensitive topics were approached with care. Data will be used solely for research purposes and will not be shared with unauthorized individuals. Any ethical misconduct identified during the study will be reported in accordance with institutional policies.

12.2 Conflict of Interest

The authors declare no conflict of interest.