IMPACT: International Journal of Research in Applied, Natural and Social Sciences (IMPACT: IJRANSS)
ISSN(E): 2321-8851; ISSN(P): 2347-4580
Vol. 3, Issue 7, Jul 2015, 117-128

THE INFLUENCE OF PREMENOPAUSAL SIMPLE HYSTERECTOMY ON BONE MASS DENSITY

MOHAMMED G CHABEK[1], THIKRA NAJIM[2], ULFAT MOHAMMAD ALNAKKASH[3] & RAYA OMAR[4]

[1,2]FRCOG, Assistant Professor, Department, of Obs. & Gyn. Al-Kindy College of Medicine, University of Baghdad, Consultant OBG, Elwiyah Maternity Teaching Hospital, Baghdad, Iraq

[3]Specialist in Obs. & Gyn, Al-Elwiya Maternity Teaching Hospital, Iraq

[4] Senior House Officers, Al-Elwiya Maternity Teaching Hospital, Iraq

ABSTRACT

Objective

To evaluate the effect of premenopausal hysterectomy on bone mass in women in their fifties

Setting

Governmental teaching hospital

Study Design

Prospective cross sectional study on 25 healthy women who had premenopausal hysterectomy before the age of 45 & at least 2 years before the study with 40 healthy natural post- menopausal women 45-60 years old. Evaluation of menopausal state was done by serum FSH & serum estradiol, bone mineral density (BMD) of the left proximal femur was determined by dual X-ray absorptiometry in six regions (femoral neck, greater trochanter, intertrochanteric area, wards triangle, shaft and total hip region). Evaluation of bone remodeling was done by measuring serum alkaline phosphatase. The results of both groups were compared.

Results

The study showed slight increment of BMD among cases with hysterectomy than the control group by an amount ranging between 1.9% in the femoral shaft to 4.8% in greater trochanter & wards triangle.

These differences were not statistically significant, even when they were exceptionally significant as the case with BMD of the femoral neck & intertrochanteric areas, they were too small in magnitude to be of clinical relevance.

Conclusion

Hysterectomy had no impact on bone mineralization even after adjusting for duration of menopause.

KEYWORDS: Hysterectomy, Postmenopausal Women, BMD

INTRODUCTION

Hysterectomy is one of the most common gynecologic surgical intervention, although there are large variation in the frequency both among and within nations. In some areas of the United States > 35% of women 60 to 69 years old has undergone hysterectomy [(1)].

In patients of reproductive age, attempts are made to conserve ovarian function to avoid the complications of estrogen deficiency. The future function of ovaries retained after premenopausal hysterectomy has been questioned. It is assumed that the conserved ovaries continue to function, but it has shown that up to 30% of women will have menopausal symptoms within 2 years of hysterectomy [(2)]. Several studies have described increased severity of menopausal symptoms and earlier onset of menopause, attributed to reduce ovarian estrogen production. Furthermore, other studies have indicated an increased risk of coronary heart disease after premenopausal hysterectomy [(1, 2)].

Bone tissue is very sensitive to steroid hormones. Estrogen deprivation as seen at the menopause and after premenopausal oophorectomy causes rapid bone loss. Also, minor disturbances in ovulatory function can influence bone metabolism. A reduction in ovarian function after hysterectomy may therefore cause advanced bone loss, lower bone mass at the age of normal menopause, and increased risk of subsequent osteoporotic fractures [(1)].

The average age of menopause is (50) years, the range is of 45-55 years [(3)], and since the life expectancy in women is now close to 80 years, approximately one third (33%) of life occurs after cessation of reproductive function [(3, 4)].

Menopause could be premature spontaneously or due to surgical removal of both ovaries, radiotherapy, and, chemotherapy [(3, 4)].

The physiological event that leads to menopause is the ovarian exhaustion, with a drop in estradiol production, which, will result in lack of response by the ovary to gonadotrophin stimulation and rise of LH and FSH [(5)].

The precise mechanism of oestrogen action on bone cells are not fully understood, but there is evidence suggesting that it exerts a direct effect as well as indirectly alters local humoral mediators. The main action of oestrogen at the tissue level is a reduction of the rate of bone turn-over by limiting osteoclasts to create new erosion cavities. Furthermore, oestrogen suppresses excessive bone resorption and, thereby, corrects the imbalance at each remodeling site. After menopause, women lose 50% of trabeculae (concellous) bone and 30% of cortical bone mass during her lifetime [(3)].

The dilemma whether to remove or conserve ovaries at the time of hysterectomy has been debated, with varying degrees of passion, for over 100 year [(6)]. Studies suggesting that function in conserved ovaries is compromised following hysterectomy have supported the prophylactic oophorectomy lobby. On the other hand, proponents of conserving ovaries point to the problems of long term compliance with oestrogen replacement therapy to prevent significant risks which could otherwise arise [(7)].

Osteoporosis is defined as a progressive systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, leading to increase in bone fragility and susceptibility to fracture.

Men have a higher BMD than women but from around the fourth decade there is gradual reduction in BMD in both sexes. In women this rate of loss accelerates at the time of the menopause and continous for approximately the next 10-15 years. After that period, the rate of loss is similar to that of men. From population studies, one in four women and

one in twelve men will have at least one osteoporotic fracture by the age of 70 years [7, 8].

In 1994, the World Health Organization (WHO) defined the categories of osteoporosis in white Caucasian females using dual energy X-ray absorptiometry. DXA is now the most commonly used technique for measuring BMD throughout the world and measurements of the lumbar spine PA and lateral, hip, forearm, heel, and total body in adults and children can be obtained, also measurement of total body composition (lean and fat body mass) [9].

Aim of the Study

The aim of the study is to evaluate the effect of premenopausal hysterectomy on bone mass in women in their fifties.

PATIENTS AND METHODS

25 women who have had previous hysterectomy with conservation of both ovaries before the age of 45; and at least 2years before the study & forty healthy post menopausal women aged 45-60 years (control groups) all were recruited to this cross section, case control study which was conducted at Al-Alwyia Maternity Teaching Hospital, Baghdad, for a period of 14 months from December 2011 to February 2013. All participants gave their informed consent.

All women included in this study are healthy, post menopausal women, give no history of hormone replacement therapy or any diseases or medical treatment that influence bone metabolism, no history of endocrine disease, multiple myeloma, Cushing disease, IDDM, hyperthyroidism as both later conditions are characterized by prolonged estrogen deprivation, no history of malabsorption syndromes, no previous history of fracture or bone disease that can change bone metabolism, no history of malignancy, renal disease, liver disease, no history of chronic heparin use, anticonvulsant drugs, glucocorticoid users > 7.5 mg/day for more than 6 months, long time duration of irregular cycles & amenorrhea, the women had not experienced natural menopause before 40 years.

They were subjected to questionnaire to determine the severity of menopausal symptoms, which include somatic symptoms, vasomotor symptoms, memory and concentration, depressed mood, fear , anxiety, sexual behavior, sleep problem, back ache, neck stiffness, parity, duration of breast feeding in months, calcium intake and history of physical exercise were recorded for all participants.

The duration of menopause in both groups, serum FSH and serum estradiol (E_2) were measured, not amenorrhea to avoid differences between those who had undergone hysterectomies and those who had not. Thyroid diseases and parathyroid disease were excluded by measurement of thyroxine, TSH, hematologic and biochemical assays to exclude any renal or hepatic disorders. Serum FSH estimation is done by sandwich method enzyme linked fluorescent assay "ELFA" by mini VIDAS, and serum estradiol (E_2), which is done by competition method of "ELFA" by mini VIDAS, to confirm their menopausal status.

Measurements of serum alkaline phosphatase which is a marker of bone formation, by King-Armstrong method, the principle reaction is between alkaline phosphotase and P-nitrophenyl phosphate (PNPP):

$PNPP + H_2O\ PNP + H_3PO_4$ (*Nitrophenol + Phosphoric acid*)

In our study we measure serum estradiol by picogram/milliliter, and post menopausal value up to 14 pg/ml.

Serum FSH measured in m.IU/ml and postmenopausal value≥ 40m. IU/ml serum alkaline phosphatase measured in I Unit/litter and normal range 30-100 IU/L.

Bone mineral density of the left proximal femur was determined by dural-energy X-ray absorptiometry in six regions:

- Femoral neck, defined as a rectangular band positioned transcervically to avoid the greater trochanter and adjacent pelvic bone.
- The greater trochante, demarked distally by the femoral midline and medially by the femoral neck.
- The intertrochantric region, demarked apically by the femoral midline and medially by the femoral neck.
- Ward's triangle, defined as a square of 1×1 cm with the lowest density within the proximal femurs.
- Shaft.
- Total hip region.

STATISTICAL ANALYSIS

Data were translated into a computerized database structure. An expert statistical advice was sought for. Statistical analyses were computer assisted using SPSS ver 10 (Statistical Package for Social Sciences).

Frequency distribution for selected variables was done first. The statistical significance of difference in mean of an outcome continuous normally distributed variable was assessed by independent samples t-test. P value less than the 0.05 level of significance was considered statistically significant.

The multiple linear regression model provides the following parameters

- P value for the model: In order to generalize the results obtained, the model should be statistically significant.
- (regression coefficient): estimates the expected change in the level of response variable (measured in its units) as a net response to the effect of each independent variable included in the model, after controlling for the remaining independent variables included in the model.
- P value for the calculated regression coefficient: reflects the statistical significance of the calculated β.
- Coefficient of determination (R^2): Measures the percentage of variation in the response variable explained by the combination of independent variables included in the model.

Results

Results presented in this chapter were based on the analysis of 25 female cases with past history of total hysterectomy and complaining of hot flashes (duration of menopausal symptoms ranging between 1-10 years with a mean of 5.3 +/- 2.7 years) and a control group of 40 postmenopausal women (duration of menopause ranging between 1-11 years with a mean of 3.7 +/- 2.6 years).

As shown in table 1, the mean age of cases with hysterectomy, median parity, body mass index & duration of

breast feeding history were not significantly different from the control group.

Table 1: Case-Control Difference in Mean of Selected Independent Variables (Confounders)

	Controls (n=40)	Cases (Hysterectomy) (n=25)	P (t-Test)
Age in Years			0.27[NS]
Range	(45 - 60)	(47 - 58)	
Mean	52	51	
SD	4	3.1	
SE	0.63	0.62	
Parity			0.96[NS]
Range	(0 - 7)	(1 - 8)	
Median	3	3	
Body Mass Index (BMI) in Kg/M2			0.23[NS]
Range	(23.4 - 35.4)	(23.4 - 35.2)	
Mean	27.6	28.5	
SD	3	3	
SE	0.47	0.6	
Duration of Breast Feeding (months)			0.86[NS]
Range	(3 - 37)	(1 - 38)	
Mean	14.3	13.8	
SD	8.8	9.9	
SE	1.43	1.98	

As shown in table 2, the mean serum FSH was significantly higher in the control group (78.1 miu/ml) than cases with hysterectomy (70.7 miu/ml). The mean serum FSH among cases with hysterectomy was lower by 9.5% than its comparable control group. The mean serum Estradiol E2 was slightly lower among the control group (7.2 pg/ml) compared to cases with hysterectomy (7.8 pg/ml), but the difference was statistically insignificant.

Table 2: Case Control Difference in Mean of Serum FSH and Estradiol E2

			Difference from Controls Measured		
	Controls (n=40)	Cases (Hysterectomy) (n=25)	In its Units	As a Percentage of Control Mean	P (t-test)
Serum FSH (miu/ml)					0.03
Range	(55 - 99)	(41 - 90)			
Mean	78.1	70.7	-7.4	-9.5%	
SD	12.4	14.3			
SE	1.96	2.87			
Table 2: Contd.,					
Serum estradiol E2 (pg/ml)					0.52[NS]
Range	(2.3 - 14)	(2.5 - 14)			
Mean	7.2	7.8	0.6	8.3%	
SD	3.9	3.8			

SE	0.61	0.76			

Serum FSH was taken as a surrogate marker that reflects the duration of menopause in both study & control groups (figure 2). It was shown that there is a statistically significant moderately strong positive linear correlation (r=0.32) between serum FSH and duration of menopause in the control group, figure 2.

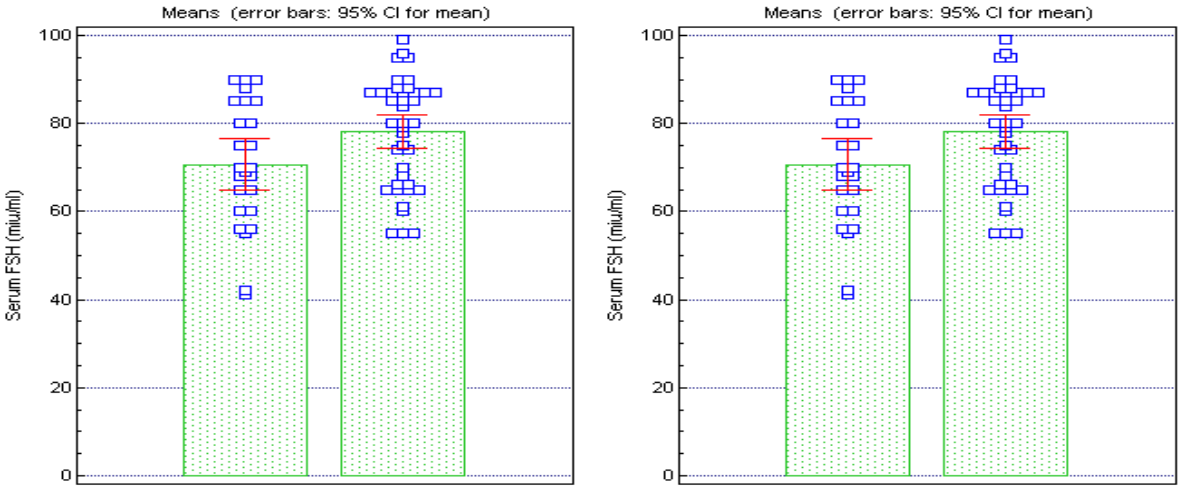

Figure 2: Error bar Chart Showing the Case (Hysterectomy)-Control Difference in Mean (with its 95% Confidence Interval), Left: Serum FSH and Right: Serum Estradiol E2

As shown in table 3 and figure 3, the mean serum Alkaline phosphatase was slightly lower (79.5) among cases than controls (87.2), but the difference was statistically insignificant

Table 3: Case Control Difference in Mean Serum Alkaline Phosphatase

			Difference from Controls Measured		
	Controls (N=40)	Cases (Hysterectomy) (N=25)	in Its Units	As a Percentage of Control Mean	P (T-Test)
Serum Alkaline Phosphatase	IU/L	IU/L			$0.42^{[NS]}$
Range	(32.6 - 153.1)	(30.5 - 170)			
Mean	87.2	79.5	-7.7	-8.8%	
SD	33.9	40.7			
SE	5.36	8.14			

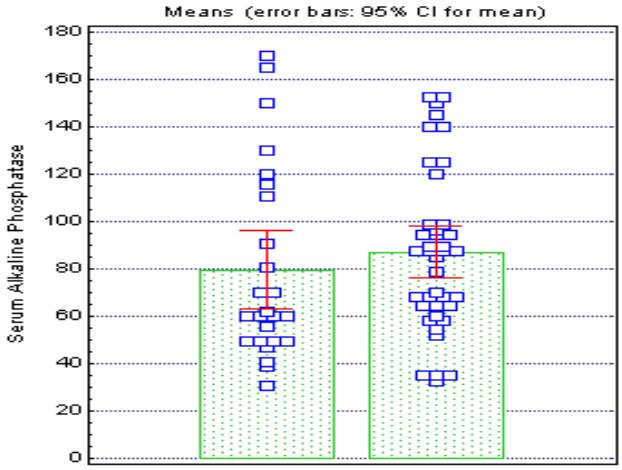

Figure 3: Error bar Chart Showing the Case (Hysterectomy)-Control Difference in Mean (with its 95% Confidence Interval) Serum Alkaline Phosphatase

The bone mineral density (BMD) was measured in 6 different areas of the femur and hip bone. In general the mean BMD was higher among cases with hysterectomy than the control group by An amount ranging between as low as 1.9% in the femoral shaft to as high as 4.8% in the greater Trochanter and Ward's triangle. These differences were statistically insignificant and even when They were exceptionally significant as the case with BMD of the femoral neck and Intertrochantric area they were too small in magnitude to be of clinical relevance, (table 4)

Table 4: Case Control Difference in Mean of Selected Measures of Bone Mineralization Status

			Difference from Controls Measured		
	Controls (N=40)	**Cases (Hysterectomy) (N=25)**	**in Its Units**	**As A Percentage of Control Mean**	**P (T-Test)**
T-Score					**1**[Ns]
Range	(-1.7 to 1.5)	(-1 to 1.3)			
Mean	0.36	0.36	0	0%	
SD	1.04	0.81			
SE	0.165	0.162			
BMD of Femoral Neck (Mg/Cm^2)					0.041
Range	(0.71 - 1.049)	(0.822 - 1.055)			
Mean	0.86	0.9	0.04	4.7%	
SD	0.08	0.06			
SE	0.012	0.012			
BMD of Greater Trochanter (Mg/Cm^2)					0.12[NS]
Range	(0.511 - 0.741)	(0.566 - 0.768)			
Mean	0.63	0.66	0.03	4.8%	
SD	0.07	0.07			

Table 5: Contd.,

SE	0.011	0.014			
BMD of Intertrochantric Area (Mg/Cm^2)					0.004
Range	(0.821 - 1.054)	(0.901 - 1.205)			
Mean	0.97	1.01	0.04	4.1%	
SD	0.06	0.06			
SE	0.009	0.012			
BMD of Wards Triangle (Mg/Cm^2)					$0.1^{[NS]}$
Range	(0.512 - 0.789)	(0.501 - 0.765)			
Mean	0.62	0.65	0.03	4.8%	
SD	0.07	0.06			
SE	0.011	0.013			
BMD of Femoral Shaft (Mg/Cm^2)					$0.49^{[NS]}$
Range	(0.825 - 1.256)	(0.897 - 1.241)			
Mean	1.04	1.06	0.02	1.9%	
SD	0.12	0.11			
SE	0.02	0.021			
BMD of the Total Hip (Mg/Cm^2)					$0.25^{[NS]}$
Range	(0.714 - 1.287)	(0.782 - 1.142)			
Mean	0.86	0.89	0.03	3.5%	
SD	0.12	0.11			
SE	0.018	0.022			

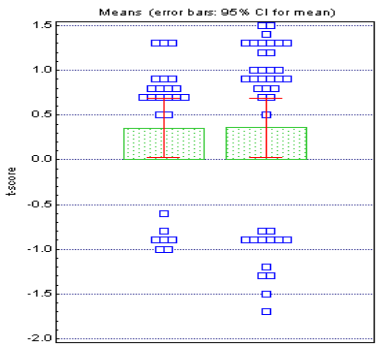

Figure 4: Error bar Chart Showing the Case (Hysterectomy) Control Difference in Mean (with its 95% Confidence Interval) T-Score

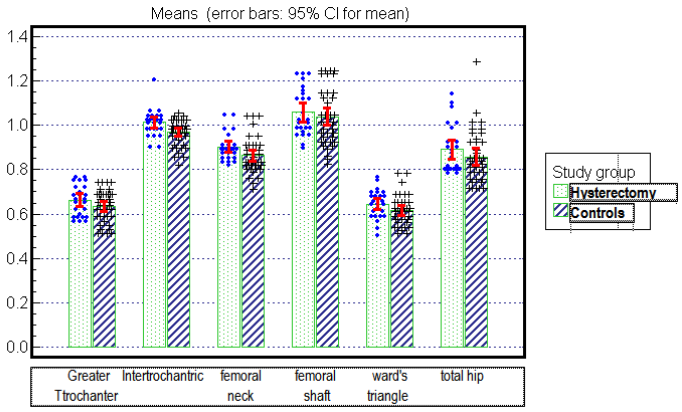

Figure 5: Error bar Chart Showing the Case (Hysterectomy)-Control Difference in Mean (with its 95% Confidence Interval) BMD (Mg/Cm2) in Selected Areas of Femoral and Hip Bone

In figure 5, a multiple linear regression model was used for the duration of menopause as reflected by serum FSH before assessing the effect of hysterectomy on bone mineralization parameters (namely t-score and BMD of Ward's triangle, which is the lowest BMD in the femur bone).

As shown in table 5, after adjusting for serum FSH, hysterectomy was associated with a very small and statistically insignificant increase in t-score (0.03) compared to controls.

Table 5: Multiple Linear Regression Model with T-Score as the Dependent (Response) Variable Showing the Case-Control Difference after Controlling for Duration of Menopause as Reflected by Serum FSH

T-Score	Partial Regression Coefficient	P
Cases with hysterectomy compared to controls	0.03	0.92 *[NS]*
Duration of menopause as reflected by serum FSH (pg/ml)	0.004	0.68 *[NS]*
P (model) = 0.92 *[NS]*		
R^2 = 0.003		

After adjusting for serum FSH, hysterectomy was associated with a very small and statistically insignificant increase in BMD of Ward's triangle (0.02) compared to controls, as shown in table 6.

Table 6: Multiple Linear Regression Model with BMD of Ward's Triangle as the Dependent (Response) Variable Showing the Case-Control Difference after Controlling for Duration of Menopause as Reflected by Serum FSH

BMD of Wards Triangle (Mg/Cm2)	Partial Regression Coefficient	P
Cases with hysterectomy compared to controls	0.02	0.17 *[NS]*
Duration of menopause as reflected by serum FSH (pg/ml)	-0.0006	0.37 *[NS]*
P (model) = 0.17 *[NS]*		
R^2 = 0.06		

DISCUSSIONS

Bone mineralization parameters are known to be affected strongly by ovarian hormones[1]. In this study we want to test the hypothesis that premenopausal hysterectomy might adversely affected ovarian function by inducing early menopause, and reflected by reduced bone mineralization.

In our study, the mean age of natural postmenopausal females is (52 years of age) was not significantly different from the mean age of cases with hysterectomy (51 years of age), and participants above 60 years were not included in the study. The bone minmeralization parameters are known to be affected by the duration of menopause, rapid bone lose occur in all women during the first 3-6 years after menopause[4].

The duration of menopause can be objectively assessed among the control group (by the cessation of menstruation), while the cases group had stopped menstruation since the hysterectomy was done therefore the assessment of menopausal age for this group required to define the duration of their hot flashes as an approximation, although this is a specific symptom, but in fact may not equal to cessation of menstruation. An objective measure for measuring the duration of menopause is therefore needed. In this study serum FSH was taken as a surrogate marker that reflects the duration of menopause in both study groups.

In our study we found that serum FSH was significantly higher among the control group, while mean serum estradiol is slightly lower among the control group compared to the study group, but the difference was not significant statistically. This lower level of FSH among the study group may be partly explained by negative feed back on the hypothalamus, caused by peripheral conversion of androstendion to estrone by extragonadol tissue[1], lead to this lower level of FSH among the study group which is comparable with the result of the study of Watson et. Al. 1993, which show also low level of FSH among the study group[2]. The same result was found by the study done by Ravan, P. et al.[1], 1995 which also found low level of FSH among the study group.

Premenopausal hysterectomy with ovarian conservation is followed by histologic changes in the retained ovaries, there is evidence that the arterial blood supply to the human ovaries is derived mainly from the ovarian and not the uterine arteries, the viens follow the arterial pathways, and are devoid of valves and prone to the development of varicosities, contributing to the stagnation of ovarian venous flow[10]. Histologic study of the ovaries twelve months after hysterectomy showed hyperplasia, the stromal cell density increased by 87%. Ovarian stroma contains collagen, contractile, and interstitial cells, only the latter respond to Luteinizing hormone and human chorionic gonadotropin stimuli and secret androgens, which are the substrate for ovarian estrogen synthesis. No changes were detected in serum estradiol and estrone levels. It is difficult to establish a relationship between the histologic change and the relative stability of the hormonal levels. One possibility is that some developing residual follicles would start producing higher levels of the hormones through a compensatory response[11].

Reduced ovarian function 1 to 15 years after hysterectomy has been reported in two retrospective cross-sectional studies[12]. In another study, however no influence on ovarian function was found 3 to 42 months after hysterectomy[13]. If premenopausal hysterectomy leads to an impairment of ovarian function with reduced ovarian estrogen production and earlier ovarian failure, the operation may result in advanced bone loss and increased risk for subsequent fractures. Two larger studies indicated higher bone mass in the distal forearm and calcaneus in women who had undergone hysterectomy,

compared with women with an intact uterus of similar age and body mass index[14,15].

The result of our study goes with finding of Ravan, P. et al[1], 1995, & Larcos et al[16], 1998.

CONCLUSIONS

Premenopausal hysterectomy had no impact on bone mineralization parameters even after adjusting for the duration of menopause.

RECOMMENDATIONS

- We need large longitudinal study with large sample size to follow up the hysterectomized female and compare them with control group.
- We need to assess the fatty tissue compartment by programming the DXA.

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