

## ORIGINAL ARTICLE

## Normograms of Ovarian Volume, Uterine Size and Endometrial Thickness in Urban Midlife Malaysia Women

<sup>1</sup>Adeeb N, <sup>1</sup>Nur-Azurah AG, <sup>1</sup>Ong FB, <sup>1</sup>Seri SS, <sup>2</sup>Shamsuddin K, <sup>3</sup>Noor-Aini MY

<sup>1</sup> Department of Obstetrics & Gynaecology, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Kuala Lumpur

<sup>2</sup> Department of Community Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Kuala Lumpur

<sup>3</sup> Department of Nutrition and Dietetic, Faculty of Allied Sciences, Universiti Kebangsaan Malaysia, 53000 Kuala Lumpur

### ABSTRAK

Kanser ovari dan uterus merangkumi 5.0% dan 3.6% keseluruhan kes kanser wanita Malaysia. Kanser ovari (OC) merupakan ketumbuhan ginekologi pembawa maut yang utama kerana tiada terdapat gejala di peringkat awal sehingga kanser telah merebak. Ultrasonografi membenarkan pengesanan awal memberi peluang bagi pakar perubatan menyediakan rawatan dan kaunseling untuk wanita tersebut. Sebagai teras untuk saringan selektif, satu kajian telah dijalankan merangkumi 517 wanita bandar berusia 45+ tahun bebas penyakit, bukan pengguna HRT dan masih mempunyai uterus. Normogram ovari, uterus dan endometrium yang diperolehi daripada pemeriksaan ultrasound garisdasar dibentang. Sampel kajian terdiri daripada 58% dan 42% wanita pra dan pos-menopaus dengan umur purata  $51.27 \pm 5.35$  tahun. Lebih dua pertiga terdiri dari kaum Cina, diikuti oleh Melayu dan India. Kajian menunjukkan saiz purata jasad uterus dan ukuran endometrium (ET) adalah  $7.21 \pm 1.67 \times 4.36 \pm 1.30$  cm and  $6.36 \pm 3.73$  mm masing-masing. Saiz uterus wanita pre-menopaus lebih besar berbanding pos-menopaus ( $p < 0.0005$ ) dan atrofi uterus berlaku berikutan umur dan menopaus. Ukuran ET juga lebih tebal pada wanita pre berbanding pos-menopaus ( $p < 0.0005$ ), semakin tipis mengikut usia. Wanita pada awal pos-menopaus menunjukkan ET  $< 5$  mm, mencapai 2 mm pada wanita berusia  $> 70$  tahun. Dengan demikian, tetapan normal klinikal kesemua wanita pos-menopaus tanpa mengira kaum ditetapkan pada ET  $< 5$  mm. Hampir seperlima wanita (18.9%) didapati mempunyai fibroid uterus, sebanyak sesuku (25.0%) semasa pre berbanding 10% pos-menopaus ( $p < 0.0005$ ). Purata isipadu ovari (OV) kanan dan kiri masing-masing adalah  $5.48 \pm 7.85$  cm<sup>3</sup> and  $5.80 \pm 16.78$  cm<sup>3</sup>. Terdapat pengurangan OV mengikut usia dan menopaus, daripada 7 cm<sup>3</sup> pada usia 45-49 tahun kepada  $< 1.5$  cm<sup>3</sup> pada 70 tahun, menghasilkan tetapan normal klinikal wanita Malaysia pre dan pos-menopaus pada OV  $< 7.5$  cm<sup>3</sup> and  $< 3.5$  cm<sup>3</sup>. Sista ovari tidak ada bahaya dijumpa pada 2.9% dengan saiz purata  $65.14 \pm 88.22$  cm<sup>3</sup>. Sebagai kesimpulan, normogram ET dan OV harus disediakan bagi populasi Malaysia untuk memudahkan saringan kanser ginekologi.

**Kata kunci:** perimenopaus, ukuran endometrium, saiz uterus, isipadu ovari

**Address for correspondence and reprint request:** Professor Nafisah Adeeb, Dept of Obstetrics & Gynaecology, Medical Faculty, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur. Email: [naadeeb@mail.hukm.ukm.my](mailto:naadeeb@mail.hukm.ukm.my)

## ABSTRACTS

Cancers of the ovary and corpus uteri afflict 5% and 3.6% Malaysian women respectively. Ovarian cancer (OC) remained the deadliest gynaecological malignancy in perimenopausal women mainly due to the lack of symptoms until the disease had spread. Ultrasonography could provide a preliminary screening allowing the clinician to tailor subsequent management and counselling for these women. To support the basis for selective screening, a study on 517 urban disease free women aged 45 years and above, uterus-intact, non-users of HRT was undertaken. This study presented normograms of ovary, uterus and endometrium derived from entry ultrasound assessment. The sample comprised of 58.0% premenopausal and 42.0% postmenopausal women with an average age of  $51.27 \pm 5.35$  years old. Over two thirds were Chinese followed by Malays and Indians. The findings indicated that the average uterine size and endometrial thickness (ET) was  $7.21 \pm 1.67 \times 4.36 \pm 1.30$  cm and  $6.36 \pm 3.73$  mm respectively. Premenopausal women had larger uterus compared to those postmenopausal ( $p < 0.0005$ ) and atrophy of the uterus with age and menopause was demonstrable regardless of ethnicity. Likewise, mean ET in the premenopausal was thicker than the postmenopausal ( $p < 0.0005$ ), showing a gradual decrease with age. Early postmenopausal women demonstrated ET of  $< 5$  mm, eventually reaching 2 mm in women  $> 70$  years old. From these findings, a cut-off of  $< 5.0$  mm was considered clinically acceptable in normal postmenopausal regardless of ethnicity. Nearly one fifth (18.9%) had uterine fibroids, a quarter (25%) in premenopausal women as compared to 10% postmenopausal ( $p < 0.0005$ ). The mean right and left ovarian volume (OV) was  $5.48 \pm 7.85$  cm<sup>3</sup> and  $5.80 \pm 16.78$  cm<sup>3</sup> respectively. There was a gradual decline in OV with age and menopause from about 7 cm<sup>3</sup> at age 45-49 years to less than 1.5 cm<sup>3</sup> at 70 years giving a clinical norm OV of  $< 7.5$  cm<sup>3</sup> and  $< 3.5$  cm<sup>3</sup> respectively in pre and postmenopausal Malaysian women. Benign ovarian cysts seen in 2.9% had a mean size of  $65.14 \pm 88.22$  cm<sup>3</sup>. In conclusion, ET and OV normograms should be made available for the Malaysian population to facilitate screening for gynaecological malignancies.

*Keywords:* perimenopause, endometrial measurement, uterine size, ovarian volume

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## INTRODUCTION

In healthy life expectancy studies, women can expect to spend more years of their lives with functional limitation than men, both in developed and developing countries. With increasing gender difference in life expectancy, data at hand is insufficient to assess the extent of disability of older women in developing countries. In developed countries, studies showed that the prevalence of disability is less than 5% at 60-64 years, less than 10% at 70-74% and above 20% after 85 years. With more women reaching beyond 80

years of life, there is concern on the quality of their extended lives in the 21<sup>st</sup> century [United Nations Statistic Division 2000].

With the majority of women between 45 to 60 years being apparently well, it is opportune to counsel them at this juncture to undergo a general medical audit to detect and correct any underlying disease early. Currently in Malaysia, this subgroup (female) above 45 years comprised 10% of the population or about 1.25 million [Dept of Statistics 2002]. The perimenopause presented a challenge to the clinical practitioner as it offered opportunities for identification of risk factors for future

diseases, indicators for the early presence of established disease with subsequent enhancement of life quality and care for women in the later years [Lobo 2004].

Women between the ages of 40-59 have a 1 in 11 chance of developing some type of invasive cancers. In comparison, women from ages 1-39 have a 1 in 51 chance of being diagnosed with cancer [Givens and Ling 2003]. The most frequent cancers in Malaysian women were cancers of the breast, cervix, colon, ovary, leukaemias and lung. Cancers of ovary and corpus uteri, respectively made up 5% and 3.6% of all cancer cases [Looi et al 2004].

Endometrial cancer (EC) accounted for 3.8% of all cancers in women worldwide. EC is one of the commonest malignancies seen in 1-25% of women with unexpected postmenopausal bleeding, and caused fewer deaths compared to cancer of other reproductive organs. Almost 90% of women above 50 years old had abnormal bleeding as the commonest presenting symptom [Goldstein et al 2002; Parkin 1998]. Prior to 1982, diagnostic evaluation was routinely by diagnostic dilatation and curettage. Nowadays, transvaginal sonography is becoming an increasingly popular tool for endometrial assessment with similar false positive rates as endometrial sampling in cancer detection. During ultrasonography, the image of the endometrium showing thickened and heterogeneous areas was a predictive factor for endometrial malignancy [Gull et al 2003].

The overall five year survival rate was 70-80% in western countries, ranging from 90% for stage 1 patients to 20% for stage 4. The incidence rate rose steadily 5 to 10 years before menopause, peaked at 65-70 years and thereafter declined [Parkin 1998]. The menopausal transition or perimenopause was distinguished as a period of elevated serum estrogen and low levels of progesterone whereby a possible "window of risks" existed for development of EC. Studies have shown that prolonged inter-menstrual period, common in peri-

menopause lead to sustained  $E_2$  and irregular progesterone levels [Hale et al 2002].

Ovarian cancer (OC) remained the deadliest of all gynaecological malignancies. In the United Kingdom, it accounted for nearly 6% of all deaths from cancer in females causing more deaths in women than for all other gynaecological malignancies combined. In United States, OC affected 1 in 56 women and caused 14,500 deaths annually. It was the fourth leading cause of cancer death in perimenopausal women, mainly due to the lack of symptoms in affected patients until the disease had spread. With the lack of early symptoms, 65-75% of cases presented at an advanced stage of the disease [Lacey et al 2002; DePriest & DeSimone 2003]. The overall five year relative survival rate was 28%, but the five year survival rate for stages III and IV combined was a dismal 10%. A five year survival rate greater than 90% may be achieved in a small minority when the disease was confined to the ovary at diagnosis [Austoker 1994].

Sonographic detection of abnormal postmenopausal ovarian volume or demonstration of deviation from the norm could assist the clinician in diagnosing early ovarian neoplasia. Currently, pelvic ultrasonography visualise and characterise adnexal masses with greater sensitivity and specificity than clinical palpation alone. Transvaginal sonography was recommended as the principal technique for final assessment of whether a subject should be referred for surgical investigations [DePriest et al 1997; Collins et al 1998].

To support the basis of selective screening, a study on disease free urban midlife women, non-users of HRT with intact uterus aged 45 years old and above was undertaken to provide normograms of ovarian volume, uterine size and endometrial thickness. The findings would hopefully provide health indices relevant to the local community.

## MATERIALS AND METHODS

Data for this study was obtained from entry assessment of subjects who participated in a lifestyle intervention program. Briefly, healthy women aged 45 years and above with intact uterus, non HRT users were recruited from November 1999 to October 2002 via flyers distributed to the residential areas around the hospital including subjects from other areas who responded after being informed by friends.

After an initial screening of 745 women by telephone, 522 subjects were accepted into the study. Exclusion criteria included pregnancy, immigrants, those on treatment for hypertension, diabetes mellitus, hyperlipidaemia and chronic illnesses. Those with secondary causes of osteoporosis such as a thyroid/endocrine condition e.g. Cushing's disease, hyperthyroidism, hyperparathyroidism, malabsorption, hypogonadism, and prolonged immobilisation were also excluded. Five women were later excluded for surgically induced menopause leaving only 517 subjects. The study protocol was approved by the hospital ethics committee as part of a Masters of O&G study thesis [Nur Azurah 2003].

All subjects gave a written informed consent before participation in the study. Recruits were interviewed for medical history and examined by a designated physician. Height and weight were measured to the nearest 0.1 unit with a balance beam weighing machine and stadiometer [Health-O-Meter, USA]. Information acquired by questionnaires included personal characteristics and lifestyle. All activities were carried out in the general gynaecology clinic by trained personnel.

Pelvic ultrasound was performed transvaginally (TVS) by qualified sonographers using a 5.0 MHz transvaginal probe [Toshiba-Tosbe SSH140A, Tokyo, Japan]. Measurements of endometrium, uterus and ovaries were taken. Uterus and ovaries were measured along the major and minor axes in the transverse and

longitudinal planes. Images and thickness of the endometrium were measured along with endometrial heterogeneity as a predictive factor for endometrial malignancy.

The prolate ellipsoid formula (width  $\times$  height  $\times$  thickness  $\times$  0.523) was used to calculate the ovarian volume (OV) and/or cyst. TVS results were deemed abnormal/positive if premenopausal OV was  $>20\text{cm}^3$ ; postmenopausal OV  $>10\text{cm}^3$  respectively and cyst volume  $>10\text{cm}^3$ . The presence of structures such as solid area or papillary projection extending into the cavity of a cystic ovarian tumour of any size; or any mixed (solid/cystic) component within a cystic ovarian tumour suggesting malignancy was noted.

Only unambiguous ultrasound measurements were taken into consideration. Data were analysed using SPSS for Windows version 11.0 software. Continuous variables were expressed as mean and standard deviation, and compared by the Student's *t* test. Categorical data were compared using the Chi-squared test and relationships with Pearson correlation where appropriate. The differences were considered significant if  $p < 0.05$ .

## RESULTS

### *Subject characteristics*

The study sample comprised of 300 (58.0%) premenopausal and 217 (42.0%) postmenopausal women, similarly distributed between the major ethnic groups [Table 1]. Over two thirds were Chinese followed by Malays and Indians, reflecting an urban distribution as opposed to the general population whereby Malays were the major ethnic entity. The average age of participants was  $51.27 \pm 5.35$  years old.

The mean and median age of menopause was  $49.97 \pm 2.90$  years and 50.00 years respectively with no significant difference between the ethnic groups. The postmenopausal group, aged  $55.53 \pm 5.27$

years was 7.4 years older than the premenopausal group, 48.14±2.67 years (p<0.0005). Malays were the youngest, followed by Chinese, Indians and others with respective mean age of 50.14±4.33, 51.51±5.53, 54.47±7.83 and 57.00±10.53, a significant difference (p=0.039).

The average and median age of menarche was 13.57±1.73 and 13.00 years old. Indians reached menarche at 12.55±1.62 years; earlier than Malays, Chinese and others with a respective mean of 13.36±1.32, 13.72±1.87 and 13.20±0.84 years (p<0.005). All other reproductive and demographic characteristics were not significantly different between ethnic groups or menopausal status.

The mean height, weight and the body mass index (BMI) of the sample population was 1.55±0.05cm, 59.41±9.50kg and 24.64±3.89kg/m<sup>2</sup> respectively. The premenopausal group was similar in weight, height and BMI to the post-menopausal group. Malays were the heaviest, 62.39±10.00kg with significantly higher BMI, 26.15±4.30kg/m<sup>2</sup>, compared to the others (both p<0.0005). Weight and BMI of Chinese, Indians and other races were 58.30±9.14kg, 58.03±7.75kg and 57.20±9.76; 24.08±3.60kg/m<sup>2</sup>, 23.98±2.83 kg/m<sup>2</sup> and 23.61±2.40kg/m<sup>2</sup> respectively. Overall, 56.3% had BMI between 18.5 to <25 kg/m<sup>2</sup>, 32% were overweight and 8.6% obese.

*Uterine size*

The average uterine size for the sample population was 7.21±1.67 x 4.36±1.30 cm. Premenopausal women had significantly larger uterus compared to postmenopausal women (p<0.0005). There was no significant difference in uterine measurements between the three major ethnic groups and atrophy of the uterus with menopause was demonstrated regardless of ethnicity [Table 2].

Nearly a fifth (18.9%) of the sample population had fibromyoma, most being detected from ultrasonography as intramural and posterior. A quarter (25%)

of premenopausal women had uterine fibroids compared to 10% postmenopausal which was statistically significant (p<0.0005). There was no significant difference observed in the size of the fibroids and prevalence within the three ethnic groups [Table 3].

Table 1 : Sociodemographics variables

	N=517	N (%) or mean ± sd
<b>Ethnic distribution</b>		
Malay		143 (27.7)
Chinese		347 (67.1)
Indian		22 (4.3)
Others		5 (1.0)
<b>Sociodemographics</b>		
Age (yrs)		51.27±5.35
Age of menarche (yrs)		13.57±1.73
Menopausal age (yrs)		49.97±2.90
Income (RM)		3311±3141
<b>Education<sup>§</sup></b>		
No formal schooling		21 (4.1)
Primary level		113 (21.9)
Secondary level		278 (53.8)
College/tertiary level		104 (20.1)
<b>Marital status<sup>§</sup></b>		
Married		401 (77.6)
Widowed		47 (9.1)
Never married/divorced		68 (13.2)
<b>Reproductive history</b>		
Post-menopausal		217 (42.0)
Breastfed (n=449)		299 (66.6)
Ever user of OCP		197 (38.1)
Parity (n=450)		3.28±1.38
Regular menses (before age 35 yrs)		456 (88.2)
Days of menstrual cycle		27.93±2.95
Breastfeeding duration (month)		11.14±24.60
OCP duration (month)		19.29±42.83
<b>Lifestyle</b>		
Never smoke		501 (96.9)
Never drink alcohol		466 (90.1)
<b>Anthropometry</b>		
Weight (kg)		59.41±9.50
Height (m)		1.55±0.05
Body mass index (kg/m <sup>2</sup> )		24.64±3.89

<sup>§</sup> one subject did not report these variables

Table 2 : Uterine measurements by menopausal status and ethnicity

Uterine measurements	All women	Malays	Chinese	Indians	Others
			(cm, mean±sd)		
<b>All</b>	N=417	N=90	N=308	N=14	N=5
Uterine length	7.21±1.67	7.37±1.49	7.17±1.73	7.28±1.68	6.60±1.23
Uterine width	4.36±1.30	4.47±1.18	4.34±1.35	4.29±1.08	3.80±1.09
<b>Premenopause*</b>	N=236	N=56	N=169	N=8	N=3
Uterine length	8.08±1.30	8.09±1.18	8.10±1.32	7.95±1.78	7.27±1.16
Uterine width	4.99±1.09	5.02±1.02	4.99±1.12	4.76±1.07	4.50±0.70
<b>Postmenopause</b>	N=181	N=34	N=139	N=6	N=2
Uterine length	6.08±1.39	6.18±1.15	6.05±1.47	6.38±1.11	5.60±0.14
Uterine width	3.54±1.08	3.55±0.77	3.54±1.16	3.65±0.77	2.75±0.35

\*p&lt;0.0005 (menopausal status)

Table 3 : Prevalence and size of fibromyoma by menopausal status and ethnicity

N	All women	Malays	Chinese	Indians	Others
	417	90	308	14	5
Prevalence			% (n)		
<b>Fibromyoma present</b>	18.9 (79)	15.5 (13)	19.8 (61)	28.6 (4)	20.0 (1)
Premenopause*	75.9 (60)	76.9 (10)	73.8 (45)	100.0 (4)	100.0 (5)
Postmenopause	24.1 (19)	23.1 (3)	26.2 (16)	-	-
<b>Fibroid measurements</b>			(cm, mean±sd)		
Lengthwise	3.17±1.31	3.07±1.15	3.23±1.39	2.75±0.55	2.50
Width	3.48±1.42	3.63±1.50	3.49±1.46	3.00±0.51	2.60
<b>Premenopause</b>					
Lengthwise	3.29±1.28	3.48±0.90	3.32±1.40	2.75±0.55	2.50
Width	3.57±1.43	4.13±1.27	3.51±1.51	3.00±0.51	2.60
<b>Postmenopause</b>					
Lengthwise	2.78±1.39	1.70±0.79	2.99±1.40	-	-
Width	3.21±1.40	1.97±0.95	3.44±1.37	-	-

\*p&lt;0.0005 (menopausal status)

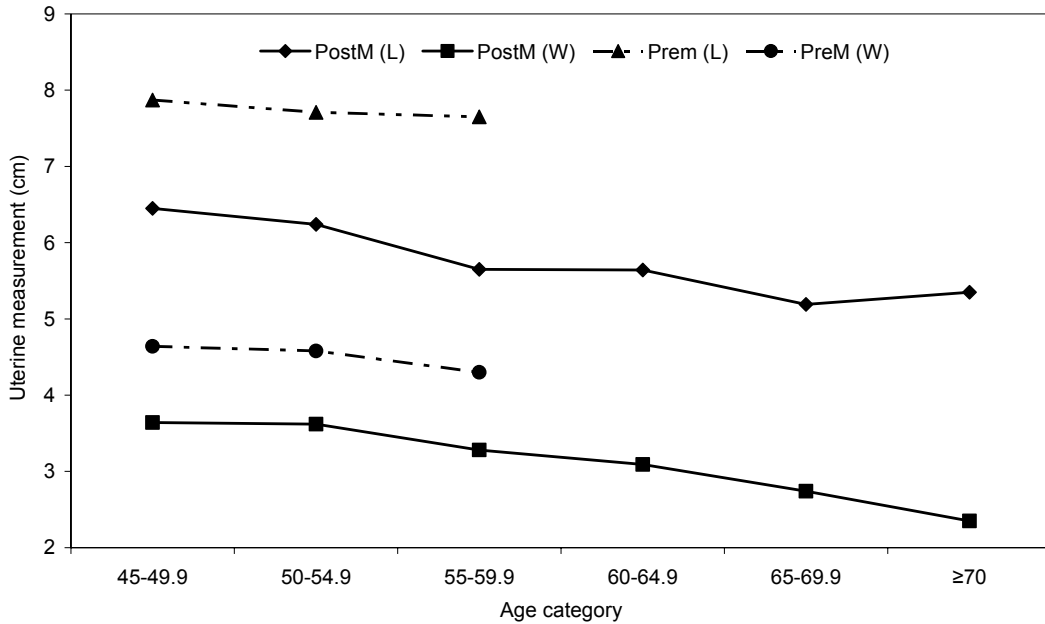
A normogram drawn of pre and postmenopausal women free of fibroids showed a gradual decrease in uterine measurements with age. Postmenopausal women demonstrated much smaller uterine measurements than premenopausal women [Figure 1]. Length and width of the uterus was positively correlated to weight, height, BMI, education and income but negatively correlated to current age, age of menarche or being postmenopausal. The main predictors of uterine length (adjusted  $R^2=0.380$ ,  $p<0.0005$ ) from multiple regression analysis were current age ( $\beta=0.140$ ,  $p<0.009$ ), menopausal status

( $\beta=0.496$ ,  $p<0.0005$ ) and income ( $\beta=0.081$ ,  $p<0.043$ ). Uterine width also showed similar associations.

The occurrence of fibroids was negatively correlated to current age, age of menarche, and postmenopausal state but the only significant predictor was menopausal state ( $\beta=0.189$ ,  $p<0.043$ ;  $R^2=0.033$ ,  $p<0.0005$ ).

#### Endometrial thickness (ET)

Mean ET for the sample was  $6.36\pm 3.73$ mm [Table 4]. Premenopausal ET was significantly thicker than the post-



**Figure 1:** Uterine size (normogram) in pre and postmenopausal women by age. The two upper lines represent uterine length while the two lower lines were the uterine widths. Only uterine measurements from women without fibroids were included in plotting the normogram. Solid and dotted lines denote mean values in postmeno-pausal and premenopausal women res- pectively. There were a total of 176 pre-menopausal subjects divided into age category 45-49.9 (129), 50-54.9 (43) and 55-59.9 (4). Number of postmenopausal subjects in each age category was 45-49.9 (14), 50-54.9 (60), 55-59.9 (50), 60-64.9 (24), 65-69.9 (12) and ≥70 (2) for a total of 122. Number in parentheses denoted the number of subjects in each age category.

menopausal group ( $p < 0.0005$ ). Indian women had a comparatively thicker ET than other ethnic groups but this is not statistically significant.

ET showed decreasing thickness with age in pre and postmenopausal women. Early postmenopausal women demonstrated ET of less than 5mm, eventually reaching 2mm in women of more than 70 years old. From these findings, a cut-off of less than 5.0mm was considered as clinically acceptable for normal postmenopausal ET regardless of ethnicity [Figure 2]. Utilising this cut off (less than 5mm) for postmenopausal women at 55 years old and above, 16.3% of postmenopausal women required further investigation although none of the subjects showed endometrial cancer (EC) on

endometrial sampling.

ET was positively correlated to weight, height, education and income but was negatively correlated to current age, age of menarche and being postmenopausal. Multiple linear regression analysis showed the significant predictors to be menopausal status ( $\beta=0.373$ ,  $p < 0.0005$ ) and current age ( $\beta=0.213$ ,  $p < 0.0005$ ) with adjusted  $R^2=0.290$  ( $p < 0.0005$ ).

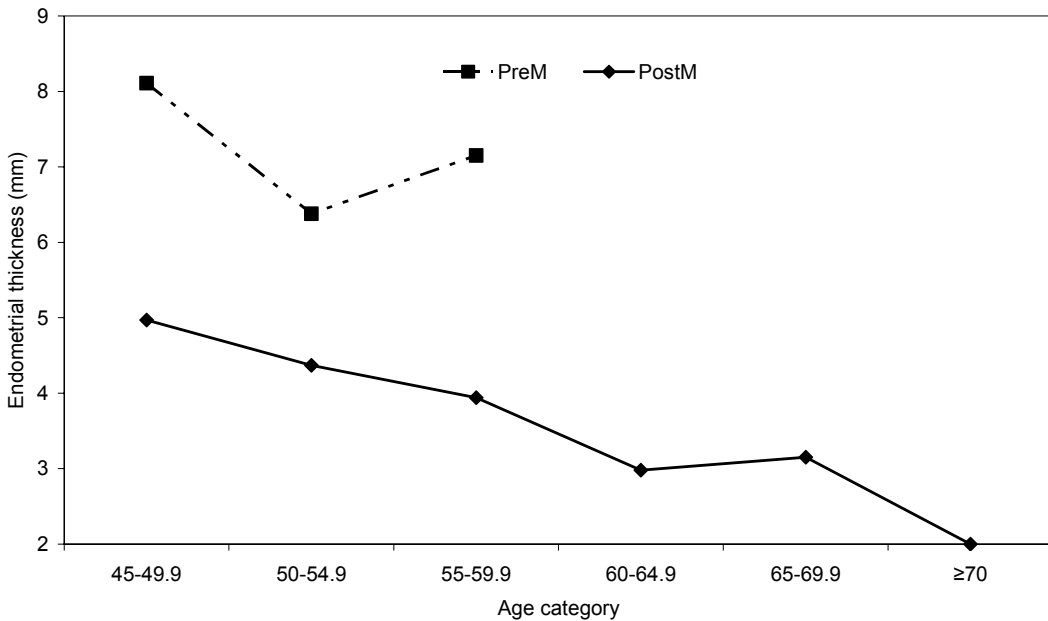
#### Ovarian volume (OV)

The average right and left ovarian volume (OV) was  $5.48 \pm 7.85 \text{cm}^3$  and  $5.80 \pm 16.78 \text{cm}^3$ , being not statistically different [Table 5]. A significant difference in right ovarian volume (ROV) was observed between the three main ethnic

Table 4: Endometrial thickness by menopausal status and ethnicity

Endometrial thickness	All N=417	Malays N=90	Chinese N=308	Indians N=14	Others N=5
	(mm, mean±sd)				
All women	6.36±3.73	6.78±3.80	6.17±3.70	7.58±4.14	6.52±3.16
Premenopause*	8.05±3.59	8.00±3.69	7.97±3.58	9.81±3.61	8.70±1.01
Postmenopause	4.14±2.60	4.78±3.11	3.98±2.46	4.60±2.78	3.25±1.48

\*p<0.0005 (menopausal status)



**Figure 2:** Endometrial thickness (normogram) of pre and postmenopausal women by age. Solid and dotted lines represent mean values in postmenopausal and premeno-pausal women respectively (Figure 2). There were a total of 176 premenopausal subjects divided into age category 45-49.9 (129), 50-54.9 (43) and 55-59.9 (4). Number of postmenopausal subjects in each age category was 45-49.9 (14), 50-54.9 (60), 55-59.9 (50), 60-64.9 (24), 65-69.9 (12) and ≥70 (2) for a total of 122. Number in parentheses denoted the number of subjects in each age category.

groups ( $p < 0.005$ ). Premenopausal Indian women had larger ROV compared to Malays and Chinese due to the presence of ovarian cyst with mean LOV being similar. In postmenopausal women, ROV and LOV were similar between the ethnic groups. Postmenopausal ROV was significantly smaller than the premenopausal ( $p < 0.0005$ ) but LOV was not

statistically different.

Ovarian cysts were seen in 12 women i.e. 2.9% of sample with a mean size of  $65.14 \pm 88.22 \text{ cm}^3$  [Table 6]. Cysts were slightly larger in postmenopausal women than in premenopausal although the premenopausal had a higher prevalence. The size and prevalence of asymptomatic ovarian tumour was not significantly



Table 5 : Ovarian volume by menopausal status and ethnicity

Ovarian volume	All women	Malays	Chinese (cm <sup>3</sup> , mean±sd)	Indians	Others
<b>All women</b>	N=409	N=89	N=302	N=13	N=5
RO volume*	5.48±7.85	5.51±7.44	5.17±5.90	12.97±27.36	3.68±3.18
LO volume	5.80±16.78	5.04±5.38	6.07±19.33	5.84±5.92	3.79±3.21
<b>Premenopause</b>	N=236	N=56	N=169	N=8	N=3
RO volume <sup>#</sup> <sup>§</sup>	7.19±9.18	7.08±8.75	6.68±6.07	19.26±34.12	5.37±3.05
LO volume	6.64±10.07	6.66±6.21	6.60±11.28	7.721±6.99	5.29±3.64
<b>Postmenopause</b>	N=173	N=34	N=137	N=6	N=2
RO volume	3.14±4.66	2.85±2.98	3.26±5.09	2.91±1.75	1.14±0.64
LO volume	4.65±23.02	2.35±1.37	5.37±26.40	2.84±1.19	1.53±0.46

\*p<0.005 (ethnicity)

<sup>#</sup>p<0.002 (ethnicity)

<sup>§</sup>p<0.0005 (menopausal status)

Table 6 : Ovarian cyst prevalence, dimensions and volume by menopausal status and ethnicity ]

N	All women 409	Malays 89	Chinese 297	Indians 13
Prevalence	% (n)			
<b>All</b>	2.9 (12)	2.2 (2)	3.0 (9)	7.7 (1)
Premenopause	58.3 (7)	50.0 (1)	55.6 (5)	100.0 (1)
Postmenopause	41.7 (5)	50.0 (1)	44.4 (4)	-
Ovarian cyst volume	(cm <sup>3</sup> , mean±sd)			
<b>All</b>	65.14±88.22	31.38±33.28	66.97±99.74	116.24
Premenopause	62.35±56.51	54.92	53.05±62.78	116.24
Postmenopause	69.06±128.76	7.84	84.37±143.33	-

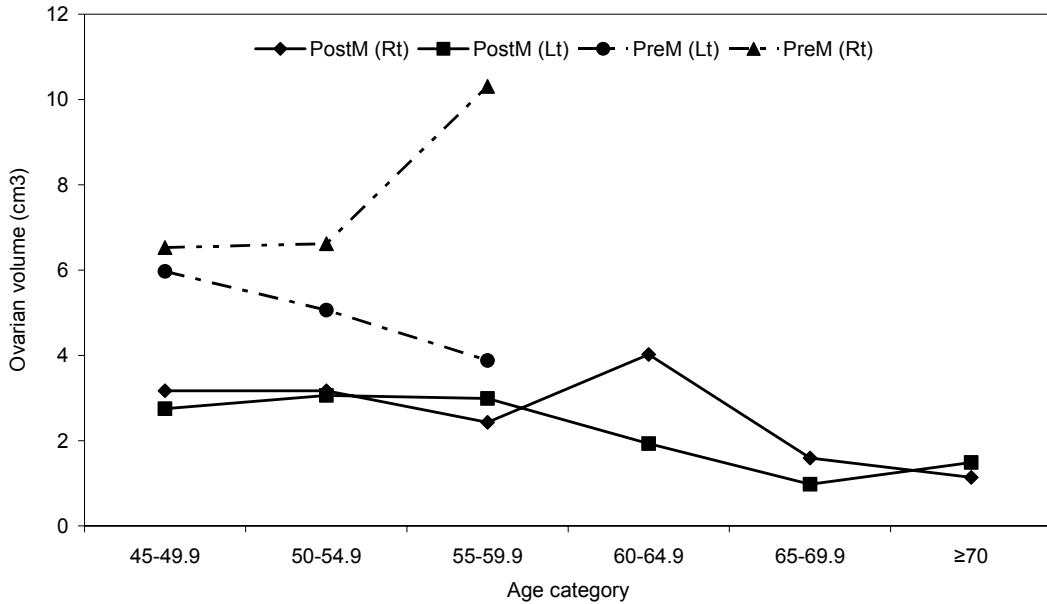
different between premenopausal and postmenopausal women with no differences observed between the ethnic groups in this small number [Table 6].

A normogram plotted using measurement from women who were cyst-free, showed a gradual decline in pre-menopausal OV from about 7cm<sup>3</sup> at age 45-49 years to less than 4cm<sup>3</sup> at age 55-59 years. ROV was comparatively larger in older premenopausal (>50 years) compared to younger (≤50 years) pre-menopausal women. Among post-menopausal women, OV declined from over 3cm<sup>3</sup> at age 50-54 to less than 1.5cm<sup>3</sup> at 70 years old. After 60 years of age, both ROV and LOV remained consistent at less than 3cm<sup>3</sup> [Figure 3].

Since there was no statistical difference in volume between the right and left ovary,

correlation was reported for the largest ovary. OV was positively correlated to weight and negatively correlated to current age, age of menarche, days of menstrual cycle and being postmenopausal. The only predictor of ROV from multiple linear regression analysis was menopausal status (β=0.255, p<0.0005) with adjusted R<sup>2</sup>=0.063 (p<0.0005). Unlike ROV, the significant predictors for LOV were age of menarche (β=0.152, p<0.004) and number of days in the menstrual cycle (β=0.107, p<0.040) with adjusted R<sup>2</sup>=0.029 (p=0.002). Ovarian cyst volume showed positive correlation to age of menarche and age of 1<sup>st</sup> childbirth with the age of 1<sup>st</sup> childbirth (β=0.578, p=0.030) as the only predictor with adjusted R<sup>2</sup>=0.620 (p=0.014) in the final model.

From this study, a clinically normal OV of



**Figure 3:** Ovarian volume (normogram) of pre and postmenopausal women by age. Solid and dotted lines represent mean values in postmenopausal and pre-menopausal women respectively. Premenopausal subjects (229) were divided into age category 45-49.9 (167), 50-54.9 (57) and 55-59.9 (5). Postmenopausal women (168) were distributed into age category 45-49.9 (14), 50-54.9 (66), 55-59.9 (52), 60-64.9 (24), 65-69.9 (10) and ≥70 (2). Number in parentheses denote the number of subjects in each age category.

<7.5cm<sup>3</sup> and <3.5cm<sup>3</sup> respectively for pre and postmenopausal Malaysian women aged 45 and above was unquestionably demonstrated. Ovarian tumour was suspected when ovaries were larger in size than the clinical norm by two standard deviations i.e. over 20cm<sup>3</sup> for premenopause and 10cm<sup>3</sup> for postmenopausal women. Utilising this cut-off index, 3.0% and 3.4% premenopausal and postmenopausal women respectively would require follow ups. Older postmenopausal women aged 55 years old and above showed a higher incidence of deviation from norm, i.e. 4.5%. Any enlargement in the ovaries in the postmenopause was considered ominous requiring vigilant monitoring. Follow ups showed that except for a larger volume, no subject had the presence of structures associated with malignancies.

## DISCUSSION

### *Uterine size and uterine leiomyomata*

Uterine size of women in this study was comparable to other reported studies [Merz et al 1996]. The size of uterus was influenced by the presence of uterine fibroids which prevailed in 25 to 77% women of various populations [Stewart 2001]. In a study of 95,061 premenopausal nurses, the age-standardised rates of ultrasound or hysterectomy confirmed diagnoses of uterine fibroids per 1000 women years were 8.9 among white women, 30.6 among black women, 11.0 among Hispanics and 8.0 among Asians with peak incidence ranging from 40-44 years [Marshall et al 1997]. In comparison, 19% of all women in this study had asymptomatic fibroids, more common in

premenopausal (25%) compared to the postmenopausal (10%). This was higher than the 4.9% prevalence reported for 164 women who attended an urban menopause clinic in Malaysia [Damodaran et al 2000]. In comparison, the reported prevalence in Thai women was 45% in the premenopausal and 6.3% in postmenopausal [Jirapinyo et al 1998].

Despite the prevalence, very little is known about this condition as few studies had been carried out probably due to its benign nature with few clearly established risk factors for fibroids [Baird 2004]. A significant positive association was seen between its incidence with age, race, body mass index, years since last term birth, history of infertility and current alcohol consumption. Significant inverse association was seen between age at menarche, age at first term birth, age at first oral contraceptive use and never being married [Marshall et al 1997]. In concordance, this study found that fibroids were negatively correlated to current age, age of menarche, and postmenopausal state with the only significant predictor being menopause.

### **Endometrial cancer (EC)**

As this study recruited only disease-free, non-users of HRT with intact uterus, none presented with EC but postmenopausal endometrium thickness cut-off of 5mm was proposed based on the normogram, similar to the consensus made by the Society of Radiologists in Ultrasound Consensus Conference Statement on Postmenopausal bleeding, the recommended cut-off point to rule out malignancy in symptomatic postmenopausal women [Goldstein et al 2002] as thin endometrium was found almost never to harbour carcinoma [Gull et al 2003].

In a meta-analysis, when postmenopausal women with EC presented with vaginal bleeding, the median ET was found to be 3.7 times thicker than those unaffected. The detection rate was 96%

with a 50% false positive rate which in the authors' opinion, still required invasive diagnostic testing in order not to miss 4% of EC [Tabor et al 2002]. Not much was known about EC in Malaysia except it being among the ten commonest malignancies [Lim 2002].

Known factors that affected the endometrium were obesity, reproductive characteristics, certain medical conditions and cigarette smoking which may be explained partly by their effect on estrogen and progesterone [Hale et al 2002]. In this study, ET was positively correlated to weight, height, education and income. ET was negatively correlated to current age, age of menarche and being postmenopausal. Multiple linear regression analysis showed the significant predictors to be menopausal status and current age. The relationship between ET and variables such as obesity and smoking was not observed as most of our subjects did not smoke (>97%) and few were grossly overweight.

### **Ovarian cancer (OC)**

Results from this study showed a decline of OV with age in premenopausal and postmenopausal women not receiving HRT. The sizes of ovaries concurred with those from other studies [Opperman et al 2003; Pavlik et al 2000] and consequently similar clinical cut-off values were considered applicable to our population. Zalel et al [1996] showed an increased OV of more than two standard deviations from norm for each postmenopausal age were highly suggestive of malignancy. This deviation from norm was striking in malignant tumour (100%) compared to benign (86%) with proposed upper limit for OV in premenopausal women as 20cm<sup>3</sup> and for postmenopausal as 10cm<sup>3</sup> [Merz et al 1996]. In expert hands, OV and morphologic evaluation of complexity was shown to be inexpensive and accurate for differentiating benign from malignant tumours with sensitivity, specificity, PPV

and NPV of 0.981, 0.808, 0.409 and 0.997 respectively [Ueland et al 2003].

In this sample we did not encounter any patient with ovarian malignancy and hence could not provide a practical model. Ovarian cysts were seen in 2.9% of our subjects, slightly more prevalent among premenopausal women. Studies had shown that persistent lesions could be detected in about 3.6% of self referred, asymptomatic women at the first attendance of ultrasound screening. About 1.2% of screened subjects would have one benign tumour. The prevalence of OC was about 0.004%, more prevalent among postmenopausal women (over 94% of cases occurred in women over 40 years old) [Collins et al 1998]. In our experience, 69% of all ovarian tumours were benign with a younger peak age in the 3rd decade and most cancers were detected in the 4th to 5th decade. Tumours were rare before the 2nd decade and 77% were in the reproductive age [Thanikasalam et al 1992].

OV was shown to be associated with age, menopausal status, phases of the menstrual cycle and hormonal milieu during menopausal transition [Merz et al 1996; Opperman et al 2003; Giacobbe et al 2004], variables similarly found in this study. Possibly due to the higher presence of cyst on the right ovary, the predictors of ROV differed from LOV being only menopausal status whereas significant predictors of LOV were age of menarche and days of the menstrual cycle.

Data from this study did not reflect the general Malaysian population as the sample consisted of urban women with a Chinese majority instead of the usual population ratio. The sampled population had higher income, better education and access to health care. Nevertheless, this obtained data would be useful basis for further investigations particularly in high risk groups. Obtaining a complete data base is essential for delivering appropriate preventive services as incomplete data

may result in inaccurate risk assessment resulting in inappropriate interventions.

It is known that women with a first degree family history of breast cancer (BC) had a 1.7 fold increased risk of OC; an association with reciprocal ramifications. An increased risk of 2.2 fold was seen in women with a first degree relative affected with OC. Corresponding risks of 7.1 to 10.7 fold were observed for those with two or three affected relatives. Screening a population for OC with at least one first degree affected relative gave a prevalence of 3.8/1000 women. Screening women with BC/OC diseases gave a prevalence of 50/1000 [Collins et al 1998]. Thus OV and ET normogram should be made available for the local population to enable clinicians to tailor subsequent management and counselling.

In summary, the findings showed that the uterus atrophy with age and menopause regardless of ethnicity. Nearly one fifth of all subjects had uterine fibroids, significantly more among premenopausal women compared to postmenopausal (25% vs 10%). Early postmenopausal women demonstrated ET of <5mm, eventually reaching 2mm in those >70 years old. A cut-off <5.0mm was considered clinically acceptable as normal postmenopausal ET regardless of ethnicity. With a gradual decline in OV with age and menopause from about 7cm<sup>3</sup> at age 45-49 years to less than 1.5cm<sup>3</sup> at 70 years old, a clinical normal OV of <7.5 cm<sup>3</sup> and <3.5cm<sup>3</sup> respectively was suggested for pre and postmenopausal Malaysian women. Benign ovarian cysts were found in 2.9%.

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