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Comparison of Relaxin Levels Between Premenopausal Women and Menopausal Women with and without Pelvic Organ Prolapse

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Abstract
Introduction: Aging has been associated with pelvic floor dysfunction, a condition related to secondary effects of various predisposing factors, including postmenomausal estrogenee levels. Decreasing estrogene levels during this period may manifest in degenerative changes in certain organs, including pelvic organ supporting structures. Other contributing predisposing factors for pelvic floor dysfunction include pregancy and delivery. This physiological condition has also been synergentically associated with the endocrine or hormonal system that prepares reproductive organs and supporting structures during pregancy, known as relaxin. This study was conducted to determine relaxin hormonal levels in premenopausal and menopasual women with and without pelvic organ prolapse
Methods: This cross-sectional study examined premenopausal and menopausal women to determine severity degrees of uterine prolapse using the Pelvic Organ Prolapse Quantification (POP-Q). Twenty five patients diagnosed with pelvic organ prolapse were allotted in to the case group whereas 38 non pelvic organ prolapsed patients comprised the control group. Relaxin serum was measured using Enzym Linked Immuno Sorbent Assay (ELISA). Statistics were analysed using the Mann Whitney test.
Results: Mean relaxin serum levels in premenopausal pelvic organ prolapsed and non pelvic organ prolapsed women were 91.450 ± 52.962 pq/ml and 109.441 ± 134.365 pq/ml, respectively, indicating no significant difference in relaxin serum levels between the two groups (p>0,05). Mean relaxin serum levels in menopausal pelvic organ prolapsed and non pelvic organ prolapsed women were 56.571 ± 37.875 pq/ml and 56.800 ± 57.097 pq/ml, respectively. Statistic testing also showed no significant difference in relaxin levels between the two groups (p>0,05).
Conclusion: Relaxin serum levels in premenopausal pelvic organ prolapsed women did not significantly differ with their non pelvic organ prolapsed counter parts. The same conclusion was drawn between menopausal pelvic organ prolapsed women and their non pelvic organ prolapsed counterparts.
Key words : Relaxin serum, menopause, Pelvic organ prolapse

Introduction

The premenopausal and menopausal period is an unavoidable period for a women approaching advanced age. During this period, a women may frequently have emotional and physical complaints. Menopause may cause decreased tissue remodelling, including decreased strength and flexibility of female reproductive organs. Approximately 50% of the female population aged 50 years old complained symptoms of pelvic organ prolapse.[1] Prevalence rates of gential prolapse reaches 35-50% of women, the incidence of which increases with increased parity and advanced age. Approximately 50% of women who previuosly delivered have genital prolapse, and almost 20% of gynecological cases that undergo surgery are cases of genital prolapse. Aging has been associated with secondary effects of various predisposing factors, including decreased estrogene levels during menopause, consequently manifesting in degenerative changes in certain organs, including the pelvic organ supporting structures.[2]

Other contributing predisposing factors for female pelvic floor dysfunction are pregnancy and delivery, conditions of which are charecterized by a biological adaptating process that prepares the pelvic organ supporting structures, including the fibrous connective tissues, to accomodate the undergoing physiological sequence. These physiological changes are also associated with relaxin, a hormone that prepares reproductive organs by regulating elasticity, including cervical effacement, uterine contractility, interpelvic ligamenter elongation, and affects the collagen turnover process.[2]

Relaxin was first introduced by Frederick L. Hisaw in 1926. Hudson first introduced it in hamsters and humans (1983-1984). Two forms of relaxin have been decoded in humans and other primates, using different genes, RLN1 and RLN2.[3,4,5] The underlying mechanism of interaction between relaxin and estogen has been studied in relation to uterine and supporting tissue growth. Estrogene functions by upregulating relaxin receptors. Latest studies have shown that both estrogene and relaxin inhibit uterine estrogene receptors, a matter of which has been postulated as an estrogene receptor down regulating process when a complete tropic effect of uterine

estrogene receptor activation is achieved.[6,7]

Methods

This cross sectional was conducted from July, 2012 until July, 2013 at the Department of Obstetrics and Gynecology Haji Adam Malik General Hospital, Faculty of Medicine, University of Sumatra Utara and Prodia Laboratory. Premenopausal and menopausal women with second to forth degree pelvic organ prolapse, with first degree or no pelvic organ prolapse, not diagnosed with liver disorders, diabetes, not on hormonal therapy for the last 6 months and not histopathologically or clinically diagnosed with malignancies, were included in this study, from which 25 pelvic organ and 38 non pelvic prolapsed patients were recruited.

All patients were identified for age, parity, mode of delivery, menopausal statuts, and body mass index and then underwent diagnostic physical and gynecological examination through external and internal genital inspection using speculum sim to assess pelvic organ prolpase severity degrees based on the pelvic organ prolapse quantification classification (POP-Q), uterine sondage and bimanual examination. Blood specimens were taken by vein punctures on the mediana cubiti region, as much as 10 cc using a vacumtainer.

Statistical Analysis

Variable analysis was performed on the distribution of the following data: age, parity, occupation, body mass index, menopausal status and relaxin levels. A chi-square test was used to compare the data distribution of age, parity, occupation and menopausal status. The Exact Fisher test was used on the data distribution of body mass index, whereas the t-uncoupled test was performed on data distribution for menopausal length. Data distirbution of relaxin levels was determined using the Mann Whitney U test. Numeric scale variables were transformed into categoric scala data. The significant difference level was set under for $p<0,5$. All data were statistically analysed using the SPSS version 15.

RESULTS

This study endrolled 25 pelvic organ and 38 non pelvic organ prolapsed patients.

Table 1. Patient Charecteristics

	Charecterisc variables	N
1	Age (n.%)	
	- ≤ 50 yo	26 (41.3%)
	- > 51 yo	37 (58.7%)
2	Pariy (n.%)	
	- 1-3	37 (58.7%)
	- ≥ 4	26 (41.3%)
3	Occupation (n.%)	
	- House hold wife	46 (73.0%)
	- Farmer	15 (23.8%)
	- Employee	2 (3.2%)
4	BMI (n.%)	
	- < 18.5	1 (1.6%)
	- 18.6 – 24.9	62 (98.4%)
5	Menopausal status (n.%)	
	- Pre menopause	
	- Menopause	24 (38.1%)
	POP (n.%)	39 (61.9%)
6	- With POP	
	- Without POP	26 (41.3%)
		37 (58.7%)

Patient characteristics in this study showed that patients were minimally aged 42 years old maximally aged 78 years old with a range of 54.22 ± 9.856, with the lowest and highest parity count of 1 and 12, respectively, with a range of 4.0 ± 2.924, minimal and maximal body mass index of 16 kg/m^2 and 31 kg/m^2, respectively, with a range of 9.69 ± 7.179, and minimal and maximal relaxin hormonal levels of 13.5 pq/ml and 490.4 pq/ml, respectively with a range of 76.196 ± 89.8244.

Table 2. Comparison of Subject Charecteristics Based on POP Groups

Charecteristics	POP (n=25)	Without POP (n=38)	Total	P
Age [a] (n,%)				
- ≤ 50 yo	1 (1.6%)	25 (39.7%)	26 (41.3%)	0.0001*
- > 51 yo	25 (39.7%)	12 (19.0%)	37 (58.7%)	
Parity [a] (n,%)				
- 1-3	10 (15.9%)	27 (42.9%)	37 (58.7%)	0.006*
- ≥ 4	16 (25.4%)	10 (15.9%)	26 (41.3%)	
Occupation [a]				
- Household wife	17 (27.0%)	29 (46.0%)	46 (73.0%)	0.140
- Farmer	9 (14.3%)	6 (9.5%)	15 (23.8%)	
- Employee	0 (0%)	2 (3.2%)	2 (3.2%)	
BMI [b]				
- < 18.5	1 (1.6%)	0 (0%)	1 (1.6%)	0.413
- 18.6 - 24.9	25 (39.7%)	37 (58.7%)	62 (98.4%)	
Menopausal Status [a]				
- Premenopause	2 (3.2%)	22 (34.9%)	24 (38.1%)	0.0001*
- Menopause	24 (38.1%)	15 (23.8%)	39 (61.9%)	
Menopausal Length [c]	24	15	39	0.0001*
(n, $\bar{x} \pm SD$)	13.67 ± 6.411	3.33 ± 1.397		
Relaxin Levels [d]	26	37	63	0.154
(n, $\bar{x} \pm SD$)	59.254 ± 39.001	88.100±111.740		

NB : a) Chi-Square Test
b) Exact Fisher
c) t-uncoupled test
d) Mann Whitney test
* Significance

Age, parity of 1-3, and parity ≥ 4, menopausal status and menopausal length of pelvic organ prolapse and non pelvic organ prolapsed groups significantly differed between premenopausal and menopausal women ($p<0.05$). Age, parity, menopausal status and menopausal length affected incidence of pelvic organ prolapse. Occupation, BMI, and relaxin hormon levels differed between pelvic organ prolapse and no pelvic organ prolapsed patients ($p > 0.05$), indicating that these factors did not affect prevalence rates of pelvic organ prolapse.

Statistical anaysis using the Mann Whitney U test showed that relaxin serum levels in premenopausal and menopasual groups did not significantly differ between pelvic organ and non pelvic organ prolapsed patients ($p>0.05$).

Table 3. Difference in Relaxin Levels in Premenopausal and Menopausal Groups With or Without Pelvic Organ Prolapse.

	With POP		Without POP		P
	n	$\bar{x} \pm SD$	n	$\bar{x} \pm SD$	
Premenopause	2	91.450 ± 52.962	26	109.441 ± 134.365	0.587
Menopause	31	56.571 ± 37.875	16	56.800 ± 57.097	0.989

DISCUSSION

Several risk factors that cause POP include menopause that is also associated with advanced age and menopausal condition that results in a hypoestronenism state. This study limits the menopausal age to > 51 years old, from which POP subjects aged > 51 years old (58,7%) were more dominant POP subjects aged ≤ 51 years old (41,3%). Menopausal length also differed between the POP and non POP group (p=0.0001). WHO studies show that 60-69 and 70-79 year old women have a 1.2 and 1.4 higher risk of having POP compared to 50-59 year old women. A cross sectional study on 21,449 menopausal women in Italy showed that the risk of pelvic organ prolapse increased 1.3 times and 1.7 times in 52-53 and 56 year old women than women aged younger than 51

year old.[8] Swift reported that first and second degree POP-Q was dominantly encountered in younger aged women, whereas third and forth degree POP-Q was evident in 2,6% of women aged > 40 years old and was increased to 21% in women aged > 70 years old.[9] Reay Jones et al reported that pelvic floor connective tissues weakens and detriorate in pelvic organ prolapsed patients, a condition that is associated with aging and menopause.[10,11]

Previous studies have proposed several predisposing factors for pelvic organ prolapse including mechanical alterations in the connective tissue or metabolisme and decreased collagen or collagen composition qualitative changes of pelvic organ supporting tissues.[2,3,7] Several studies have shown that injury during vaginal delivery increases risk of uterine prolapse in women delivering 3 times or more. Cervical ripening and dilatation during delivery occurs through activation of several collagens and elastases, that consequently reduces cervical connective tissue matrix. Bradley et al [12] in his three year study showed that in 1 and 2 parity women, vaginal descent increased 1.28 cm (0.49 - 3.32); in 3 and 4 parity women, vaginal descent increased 2.35 cm (0.98-5.67); and in 5 parity or more women, vaginal descent increased 4.82 cm (1.92-12,09).[9] MacLenna AH et al concluded that pregnancy more highly affects future prevalence rates of pelvic organ prolapse than the process of delivery. Cesarean section is the only mode of delivery that is not affected by reduced prevalence rates of POP compared to vaginal delivery. However, instrumental vaginal delivery apparently increases various tyoes of POP.[13]

Overweight (BMI of 25-30 kg/m^2) is associated with significantly increased prevalence rates of uterine prolapse (31%), rectocele and cystocele (38% and 39%, respectively), whereas obesity (BMI > 30 kg/m^2) is associated with a 40%, 75%, and 57% increase of uterine prolapse, rectocele, and cystocele, respectively. Hendrix et al (2002),[14] stated that overweight is associated with the incidence of uterine prolapse. A BMI of 25-30 kg/m^2 (overweight) is associated with significantly increased incidence of uterine prolapse (31%), whereas obesity (BMI > 30 kg/m^2) increased incidence rates till 40%. An abdominal circumference $\geq$ 88 cm may increase the risk of rectocele and cystocele up to 17%. Kuddish et al,[15] showed that women with BMI values of 25 or more had a 30-50% higher risk of developing uterine prolapse, cystocele, and rectocele than women with BMI values of 24,9 or lower. This study showed that BMI values of < 18.5 and 18.6 - 24.9 did not differ between the POP and non POP group (p=0,413).

Relaxin is responsible for reproductive organ elasticity, including cervical effacement, uterine contractility, intrapelvic ligament elongation, and may affect collagen turnover. One of its activities is to interact with estrogene. Increased relaxin serum affects tissue elasticity and elongation and may cause decreased type I:III collagen ratio, resulting in tissue weakening. Gabriel et al (2005) showed that relaxin serum was significantly lower in POP women. His results showed a 20% smooth muscle level detected in saccrouterine ligaments and stated that saccrouterine ligament type I collagen levels were similar between premenopausal women with or without POP, however, relaxin serum levels significantly declined in POP women.[16] This study showed that relaxin levels did between POP and non POP subjects (p=0.154).

Various studies have been conducted to prove that relaxin also has multi organ effects. Relaxin is structurally a part of the insulin hormon family. Relaxin has 7 homologous peptide structures and binds with leucine rich repeat G-protein containing receptors, which are LGR-7 dan LGR-8, that include the G-protein coupled receptor (GPCR) super family. Relaxin consists of a heptahelical transmembrane domain and is connected to the glycoproteo hormon recpetors, including LH and FSH receptors. Several studies show that relaxin is associated with the matrix metalloproteinase (MMP) enzyme, and therefore consequently decreases collagen synthesis and affects extracellular degradation of fibrous connective tissues.[17] Deitrech W et al,[18] reported that in women with POP and symtoms of pelvic floor disorders, examination of the ligamental relaxin receptors indicate regular expressions of LGR-7, with absent LGR-8. Women with pelvic organ prolapse usually have a longer exposure period to relaxin due to higher parity counts, a factor that apparently is associated pelvic organ prolapse through the expression of LGR-7.

Several researchers consider that relaxin serum levels affect pelvic floor dysfunction. Latest studies show that on comparing menopausal and premenopausal women, non-menopausal women had higher relaxin serum levels than menopausal patients, although these results were statistically insignificant. Relaxin may affect extracellular matrix. Collagen, elastin, and proteoglycan are important compartments of extracellular matrix and is associated with pelvic organ prolapse. If relaxin serum levels are low, collagen formation and degradation maybe altered and may weaken pelvic floor supporting system. On the other hand, decreased relaxin levels causes collagen connective tissues from the pelvic floor supporting system to excessively accumulate, that causes scars or form fibrosis, and eventually, the pelvic system looses its supporting dysfunction and causes pelvic organ prolapse. Relaxin from menopausal women especially originate from the endometrium and myometrium. Women without a uterus would have lower relaxin levels.[19]

Reisenauer et al,[20] found that the distribution of smooth muscle in the saccrouterine ligament is abnormal in women with POP. Assuming that increasing degrees of pelvic organ prolapse were lower, relaxin levels are usually lower, however, on performing statistical analysis to determine their correlation, results show that apparently pelvic organ prolapse does not affect relaxin serum levels.

Studies by Zhou yan-na et al revealed that hormonal relaxin levels in menopausal pelvic organ prolapse and non pelvic organ prolapse women were 226.2 ± 178.8 ng/L and 108.4 ± 98.7 ng/L, respectively. Relaxin levels in nonmenopausal women with and without pelvic organ prolapse were 1870.2 ± 264.4 ng/L and 373.7 ± 370.4 ng/L.[21]

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