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RESEARCH ARTICLE

EFFECT OF INTRAVAGINAL DEHYDROEPIANDROSTERONE ON VAGINA AND ENDOMETRIUM IN POSTMENOPAUSAL WOMENS

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Abstract

Objective:- To examine the effect of intravaginal dehydroepiandrosterone on vagina and endometrium specially on symptoms and signs of vaginal atrophy and sexual dysfunction in postmenopausal women.

Material and Method:- Study was conducted on 128 postmenopausal women between 40-75 year of age, presented with symptoms of vaginal atrophy and sexual dysfunction. Vaginal pH was determined, vaginal smear was examined for maturation index and maturation value, and endometrial biopsy was taken before and after intravaginal application of 0.5%DHEA ovules daily for 12 weeks.

Results:- With DHEA, symptoms of sexual dysfunctions decreased significantly in 67% women ($p<0.05$), vaginal symptoms improved in 60% women ($p<0.05$).Vaginal pH was decreased by 1.1±0.06 unit ($p<0.0001$). Percentage of case with pH≤5 was increased to 79% from 34%, of parabasal cells decreased from 59.84±2.0 to 30.59±0.98 ($p<0.0001$) and of superficial cells increased by 8.66±0.18 ($p<0.0001$), maturation value increased by 20±0.63 ($p<0.0001$). Endometrial biopsy seen at the start of treatment remained unaffected by DHEA.

Conclusion:- DHEA has many benefits of estrogen, with no side effects, and helps women with vaginal atrophy to stimulate the cellular growth of the vaginal wall and increase vaginal secretion, thus restoring the vagina to its youthful condition.

Introduction:-

Dehyroepiandrosterone is naturally occurring steroid hormone produced by adrenal glands. DHEA provides a pool of prohormone for conversion to androgen and ultimately estrogens, Hence referred as "Mother of All Hormones". It is exclusive source of androgen and it was found that marked decrease in androgen can potentially lead to signs and symptoms of hypoandrogenicity in vagina and brain. After menopause, all estrogens and androgens are made locally from DHEA in peripheral target intracrine tissue. Strength of the vaginal wall is dependent on collagen structure, and because collagen formation is exclusively stimulated by androgens derived from DHEA in lamina propria fibroblasts, so it is true to say that DHEA plays an essential role in vaginal physiology and in correction of symptoms and signs of vaginal atrophy[1]. Advantage of DHEA over estrogen is that it exerts its effects in the three layers of vagina, especially on collagen formation in lamina propria. Vaginal dryness, a frequent accompaniment of menopause is often ignored or treated with estrogen, while estrogen replacement is generally the preferred treatment,

but it is not suitable for all women or the effect may not be sufficiently rapid. Therefore it is necessary to study other option.

The present study was undertaken to evaluate the effect of vaginal DHEA on sexual dysfunction symptoms i.e. desire, arousal, orgasm and pleasure, dyspareunia , vaginal dryness, atrophic changes, on vaginal pH and maturation index and also to find out effect of DHEA treatment on endometrial histology.

Material and methods:-

The study was conducted on 128 postmenopausal women of 40-75 years of age in 2012-2013. The cases were divided into two groups. Study group included 64 cases who received intravaginal DHEA 3 for months and the control group included 64 cases who either received vaginal lubricants or placebo treatment.

The inclusion criteria were: Postmenopausal women between 40 and 75 years of age. Women having self identified at least one of the following symptoms- vaginal dryness (defined by complained of inadequate lubrication at the time of sexual arousal and sexual intercourse), vaginal and vulval itching. All four aspects of sexual dysfunction i.e. desire, arousal, orgasm, dyspareunia.Women having low maturation index and women having vaginal pH≥5. The exclusion criteria were undiagnosed anbnormal genital bleeding, previous diagnosis of cancer (except skin cancer) or endometrial hyperplasia. Use of estrogen or progesterone within 3 months before study and blood pressure ≥140/90 mm Hg.

History was taken with reference to age, parity, habitat, socioeconomic status, education, dietary intake of soy and specially for vaginal, vasomotor and sexual dysfunction symptoms. Assessment of vaginal health was done by seeing quantity of secretion pooled in posterior vaginal vault, appearance and spread of the secretions coating the vaginal vault, epithelial integrity determined by colour, rugation and friability of vaginal surface. At first visit and then after12 week of therapy to find out effect of DHEA and placebo vaginal pH, vaginal cytology, vaginal maturation index, vaginal maturation value and endometrial biopsy was done.

Determination of pH was done by applying pH indicator strip in the pooled vaginal secretion on speculum or against the lateral vaginal wall with a forceps. The colour was then compared to the colours and corresponding pH values on a standard chart. For Vaginal cytology the vaginal scrape was collected, spread on slide and fixed with alcohol and stained with papanicolaou technique. Samples obtained were free from signs of inflammation (white blood cells) and endocervical cells, both of which might have falsely elevated the MI.

Maturation Index[3] is based on the assumption that the sex hormones estrogen, progesterone and androgens bring about maturation in squamous cells that can be detected by cytological examination.The higher the number of mature cells (superficial and intermediate), higher the Maturation Index or estrogen effect in body. MI is a ratio obtained through performing a 100 cell count of three major cell types (parabasal, intermediate and superficial cells) that are shed from the squamous epithelium. The cell count is expressed as a percentage. Parabasal cells are the least mature cells having not been affected by estrogen or progesterone, and superficial cells display the maximum maturity, having been affected by estrogen. MI is useful for evaluating hormonal function by cellular composition of the surface layer of vaginal tissue.[4]

A 100 cell count was performed to classify cells as: superficial(s)/intermediate(i)/parabasal(p) and were counted and result were expressed as the Maturation Value of meisels[3]. Superficial cells, intermediate cells and parabasal cells were assigned a point value of 1.0, 0.5 and 0 respectively. The number of cells in each category was multiplied by point value and the three results were added to get maturation value by using the equation (Px0)+(Ix0.5)+(Sx1). The VME has a range of 0-100. Maturation Value 0 to 49, 50 to 64 and 65 to 100 indicate low, moderate and high estrogen effect respectively. Increase in percentage of superficial cells and decrease in parabasal cells was derived from 100 cell count method. Endometrial biopsy was done after vaginal pH determination and taking smear cytology. Curetting from the anterior, posterior and lateral wall were taken.

Postmenopausal women of study group were given DHEA in daily dose of 0.5% by vaginal route for 12 weeks. Changes in vaginal symptoms and sexual dysfunction were observed after 12 week of treatment with DHEA. Vaginal pH & smear and endometrial biopsy were repeated after 12 week of DHEA treatment. Women of control group were given placebo treatment by vaginal route for 12 weeks, any change in the sexual dysfunction symptoms, vaginal pH and smear pattern, MI and endometrial histology was observed. Chi square test were carried out for

categorical variables and descriptive statistics were given as the mean±sd. For all statistical analysis $p<0.05$ was considered as significant.

Results:-

Among 128 postmenopausal women maximum number of patient were between the age group of 46-50 years 68.7% in study group and 62.5% in control group. The age at onset of menopause was from 44 to 56 years and average mean age onset of menopause was 48±3.3. A positive correlation between increasing parity and vaginal pH($r=0.4006$; $p=0.0009$) was found. The difference between study and control groups regarding habitat, socioeconomic status, educational status and parity was found to be statistically insignificant ($p>0.05$). Among all postmenopausal women, 82(64%) had symptoms related to sexual dysfunction like desire, arousal, orgasm, pleasure. More than 60% women had desire domain dysfunction. 46% women had one or more sexual problems. Placebo had no significant effect on desire domain, whereas with 0.5% DHEA treatment, 77% women showed significant improvement ($p<0.05$)(table-I). When the arousal/orgasm/pleasure domains were observed at 12 week time interval, a significant improvement ($p<0.05$) was observed in study group, when compared with placebo group. The presence of vaginal dryness, irritation/itching, and pain at sexual activity was reported by 82, 82 & 128 women respectively. Dyspareunia, identified as the most bothersome symptom by most women, remain unchanged in 66% of women in the placebo group, whereas it decreased up to 60% in the 0.5% DHEA treated group and was statistically significant ($p<0.05$)(table-I) For vaginal dryness and irritation/itching, a statistically significant difference was also seen in study and placebo group ($p<0.05$) (table-II). 34% women had vaginal pH ≤5 and 66% women had pH >5. In the study group the percentage of women with pH≤5 increased from 43% to 79% and with pH>5 decreased from 66% to21% and this difference was found to be statistically significant when compared with placebo group ($p<0.05$)(table-III). In DHEA treated group, the percentage of parabasal cells decreased by 29.25±1.02 from 59.84±2.01 to 30.59±0.99; ($p<0.0001$) and the percentage of superficial cell increased by 8.66±0.19 from 2.21±0.43 to 10.87±0.62; ($p<0.0001$) whereas no significant change in the percentage of superficial and parabasal cells was seen in placebo group (table-III&IV). Maturation value (MV) increased from 20.75±6.33 on day 1 to 40.75±5.70 after 12 weeks of treatment in DHEA treated group, while no change was observed in placebo group (table-V) and was statistically highly significant ($p<0.0001$). There was no effect on endometrial histology after 3 months of intravaginal administration of the hormone precursor DHEA. No drug related significant adverse event was observed on hematology, coagulation profile, liver function and renal function test.

Table -I: effect of DHEA on sexual symptoms.

Sexual symptoms	Study group				Control group			
	Improved		Not improved		Improved		Not improved	
	NO.	%	NO.	%	NO.	%	NO.	%
Desire	28/36	77	8/36	22	12/46	20	34/46	80
Arousal	16/24	66	8/24	33	10/36	27	26/36	72
Orgasm	16/24	66	8/24	33	10/36	27	26/36	72
Pleasure	16/24	66	8/24	33	10/36	27	26/36	72
All symptoms	16/24	66	8/24	33	10/36	27	26/36	72
Total	36				46			

Table – II: effect of DHEA on vaginal symptoms.

Vaginal symptoms	Study group		Control group	
	NO.	%	NO.	%
Dyspareunia	38/64	60	22/64	34
Vaginal dryness	22/64	58	16/44	36
Vaginal irritation	22/38	58	16/44	36
All	22/38	58	16/44	36
Total	40	62	22	34

Table- iii: effect of DHEA on superficial cells.

	Study group		Control group	
	PRE Tt	POST Tt	PRE Tt	POST Tt
MEAN±SD	2.06±2.40	11.19±3.40	2.03±2.49	2.34±2.53
	P<0.05		P>0.05	

Table- iv: effect of DHEA on parabasal cells.

	Study group		Control group	
	PRE Tt	POST Tt	PRE Tt	POST Tt
MEAN±SD	59.84±11.35	30.59±5.58	58.50±9.23	58.18±9.41
	P<0.05		P>0.05	

Table - v: effect of DHEA on maturation value.

Study group (n=64)	Maturation value	
	Pre treatment	Post treatment
32	12-20	35-45
32	22-35	35-65
Control group (n=64)	Pre treatment	Post treatment
34	15-20	No change
30	22-30	No change

Discussion:-

Postmenopausal women who do not have vaginal atrophy (estimated as 25% of the postmenopausal population) and the majority (75%) of postmenopausal women who have vaginal atrophy[1,2] is probably not related to the secretion of estrogen in the systemic circulation because estrogen secretion by ovaries has ceased in all women at time of menopause. Consequently, a deficit in estrogen secretion into the systemic circulation is not a valid explanation for the occurrence of symptoms of vaginal atrophy in 75% of postmenopausal women, whereas the remaining and more fortunate 25% of women live throughout all their postmenopausal years without significant bothersome or evident vaginal atrophy symptoms. Therefore, estrogens may not be a physiological replacement therapy for the 75% of postmenopausal women who have vaginal atrophy, as other factors may be at play. Contrary to the estrogens of ovarian origin, which are secreted into general circulation where they are exposed to all tissues that possess the required steroidogenic enzymes with no significant release of active steroids into circulation, thus avoiding exposure of the other tissue not physiologically in need of these active sex steroids. Secretion of DHEA, the only source of sex steroids after menopause, markedly and variably decreases with age, with an average 60% loss being already observed at time of menopause. Consequently the only difference between the symptomatic (75%) and asymptomatic (25%) postmenopausal women is the amount of DHEA secreted by the adrenal glands, the ability of each tissue to transform DHEA into active sex steroids, and /or the sensitivity of vaginal tissue to DHEA. With this knowledge, it is clear that DHEA and not estrogens should be the physiological hormone therapy at menopause. Low sexual desire is strongly associated with a decrease in the other aspects of the sexual response namely, arousal, orgasm and pleasure. DHEA, a compound inactive by itself acts as a precursor for the cell specific local formation of all androgen and estrogen after menopause. This specific androgenic effect of DHEA on collagen formation could play major role in the particularly positive results obtained in the present study. Time and dose dependent improvement in four domains of sexual function with intravaginal DHEA therapy was observed at 12 week time interval, the 1.0% DHEA dose led, compared with placebo, to 49% (p=0.0061) and 23% (0.0257) improvements of desire domains[5]. Hackbert studied the effect of DHEA on sexual arousal in 16 sexually functional post menopausal women and found that the concentration of DHEAS to be increased 2-5 folds following DHEA administration[6].

In present study, dyspareunia was identified as the most bothersome problem, remained unchanged in 66% of women in placebo group, whereas it decreased to 38% in 0.5 % DHEA treated group (table-I). The effect of DHEA on vaginal atrophy was found to be significant (p==0.04) when compared with placebo (Table-I). Labrie et al and Panjari et al also found improvement after 12 weeks of treatment with 0.5% DHEA daily doses, in 82.4%, thus leaving only 17.8% women with no reported improvement of their most bothersome symptoms[5,7].

In present study, vaginal pH was decreased at 12 weeks by 1.1±0.06 units ($p<0.0001$) from 5.9±0.80 units to 4.78±0.87 units ($p<0.0001$) in 0.50% DHEA treated groups, where as in the placebo group, pH decreased by 0.5±0.08 unit at 12 weeks from 5.9±0.87 to 5.3±0.79 unit.(Table-3). The result was comparable with that of Labrie et al. In their study, vaginal pH was decreased at 12 weeks by 1.3±0.13 units ($p<0.0001$) from 6.6±0.07 units, with 0.50% DHEA treated groups[5].

In present study with DHEA treatment, vaginal cytology showed decreased in parabasal cells and increase in superficial cells. Labrie et al in their study with intravaginal DHEA also observed decrease in percentage of parabasal cells of 45.9±5.31, with 0.5%, whereas no significant effect was observed in the placebo group at any interval. In DHEA treated group increase in percentage of superficial was by 6.8±1.29 (from0.5±0.16 to 7.2±1.29, $p=0.0001$) and no significant change was observed in placebo group[5].

MV is a useful marker to examine vaginal maturation and reveal vaginal estrogen deficiency regardless of the presence of inflammation. The maturation value went from 20.75±6.33 on day 1 to 40.75±5.70, after 12 weeks respectively, with 0.5% DHEA dose. The difference in MV between treatment and placebo group was highly significant ($p<0.0001$). Labrie et al also observed rise in maturation value from 21.0±2.72 on day 1 to 41.2±1.84, 45.2±1.67, 46.5±1.51 and 47.3±1.58 at 2, 4, 8 and 12 weeks respectively with the 0.5% DHEA dose[5].

Conclusion:-

The new knowledge gained about intracrinology in women clearly indicates that apperanace of symptoms of vaginal atrophy in postmenopausal women is due to a lack of DHEA and/or insufficient transformation of this precursor into active androgen and/or estrogens in the vagina. By local action in the vagina, DHEA applied daily at doses at which serum steroids remain well within normal postmenopausal values exerts relatively potent beneficial effect on all four aspects of sexual dysfunction. The androgenic component of DHEA plays a role in improvement in desire, arousal, orgasm, and pleasure. Intravaginal DHEA has many of the benefits of estrogens, with no side effects, and helps women with vaginal atrophy to stimulate the cellular growth of the vaginal wall and increases vaginal secretion, thus restoring the vagina to its youthful condition.

This approach avoids the fear of systemic effects common to all presently available estrogen formulations and adds a novel physiological androgens component to therapy.

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