The Effects Of Different Sex Hormones On Female Rabbit Urodynamics: An Experimental Study

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Abstract

Background: We previously reported the effects of different sex hormones on the bladder urodynamics in male rabbits. The aim of this study was to investigate the effects of different sex hormones on the bladder urodynamics in female rabbits.

Methods: Mature female New Zealand white non-pregnant rabbits were studied in five groups. G-I: Low midline laparotomy (LML) + %0.9 NaCl. G-II: LML+estrogen. G-III: LML+ bilateral ovariectomy (BO)+estrogen. G-IV: LML+BO+ progesterone. G-V: LML+BO+testosterone. Baseline urodynamic records and the blood sex hormone levels were measured. In the follow-up all rabbits from each group underwent urodynamics on the 5th, 10th and 30th post-injection days. Estrogen, progesterone and testosterone levels were also measured during the follow-up period.

Results: There were no significant changes in bladder capacity and compliance in G-I. The bladder capacity and compliance were found increased in G-II and G-III on the 5th and 10th days (p<0.05). There were no significant changes in G-IV. The bladder capacity and compliance declined on the 10th day in G-V, but this was statistically non-significant (p>0.05).

Conclusion: In female rabbits, after the injection, progesterone and testosterone reduced slightly the bladder capacity and compliance. On the contrary, there was an increase in bladder capacity and compliance in correlation with high estrogen levels.

INTRODUCTION

With the use of sex hormones, notable changes have been achieved in adult patients as far as incontinence problem is considered ([1],[2],[3],[4]). The effects of estrogen on urodynamics have been investigated previously in clinical studies ([5],[6]). However experimental urodynamic investigations in this field had been rarely reported. This preliminary report describes the effects of estrogen, progesterone and testosterone on urodynamic findings in female rabbits.

METHODS

Animals: Mature female New Zealand white non-pregnant rabbits were used. Five groups were set up for this study.

Sex hormone levels: Blood estradiol-17 B, progesterone and testosterone levels were measured (Chemilumina Scent Immunoassay technique) to determine baseline hormonal status.

Cystometry: For cystometry, rabbits were sedated by an intramuscular injection with 0.7 mL/kg of a mixture of ketamine (25 mg/mL) and xylazine (6 mg/mL). With the

animal secured supine, a balloon catheter (4 F) was inserted into the bladder through the urethra and connected to a Mallinckrodt pressure transducer via a three-way stopcock. The urodynamic responses were recorded (Synectics PC Polygraph, Synectics, USA) and evaluated in an IBM PC II computer using 'Polygraph' software (Urology edition version 6.0B26 and 600P4). After catheterisation, normal saline was instilled into the bladder with at room temperature at a speed of 10% of bladder capacity (3-4ml/min) and the intraabdominal and intravesicals pressure recorded continuously. The procedure was repeated as necessary. Typical volume-pressure profiles were obtained. The bladder capacity was defined as that at start of the rapid increase in intravesical pressure or the deflection point in the curve. The rate of change of volume per unit pressure during the initial phase of the cystometrogram was used as a relative measurement of compliance ([7]).

Technique and study groups: Prophylactic antibiotic was used preoperatively. Oral feeding was stopped 6 hours before the operation. Postoperatively all rabbits received free

access to water in the first day and food the next day.

G-I; n=5: Only low midline laparotomy (LML) was done. These animals received one dose %0.9 NaCl 4 weeks after the operation.

G-II, n=5: Only LML was done. These animals received one dose estrogen after 4 weeks (i.m. injection of 4 mg polyestradiol phosphate - prepared by Organon Ilac Ltd., Turkey).

G-III, n=5: LML+ bilateral ovariectomy (BO) was done. These animals also received the same dose estrogen on the 4th postoperative week.

G-IV, n=5: LML+BO was done. These animals received one dose i.m progesterone on the 4th postoperative week and followed-up (Progesterone acetate 4mg/kg- prepared by Organon Ilac Ltd., Turkey).

G-V, n=3: LML+BO+ these animals received testosterone on the 4th postoperative week for 10 days (Testosterone proprionate 10mg/day subcutaneously - prepared by Organon Ilaç Ltd., Turkey).

Follow-up: All rabbits in each group underwent urodynamics for baseline records and on the 5th, 10th and 30th post-injection days. Blood estradiol-17 B, testosterone and progesterone levels were determined in on the 5th, 10th and 30th days.

The animal welfare committee approved all experimental protocols. For statistical verification Mann Whitney U – Wilcoxon and Cruscal-Wallis-x2 test were done.

RESULTS

The changes in sex hormone levels and the mean bladder capacity and compliance are summarised separately for each group. %0.9 NaCl, LML don't have any significant effect on measurements. BO decrease the estradiol-17 B levels, but does not effect the capacity and compliance and likewise the response after injection.

Sex hormone levels: Estrogen: There was no statistically significant change in G-I. With the mentioned treatment, high levels of estradiol-17 B are maintained in blood for at least 10 days ($_2$). The estradiol-17 B levels were found increased after the injection of estrogen on the 5th and 10th days and decreased thereafter and returned to baseline level at the postinjection 30th day in G-II & G-III. Progesterone: With the mentioned treatment, high levels of progesterone

are reached in the blood ($_8$). Progesterone level was found increased at the 5th day and then returned near to baseline level on the 30th postinjection day in G-IV. Testosterone: With the mentioned treatment, high levels of testosterone are reached in the blood ($_9$). We found the testosterone level increased on the 5th and 10th postinjection days and then returned to baseline levels on the 30th postinjection day in G-V.

CYSTOMETROGRAMS
TABLES ABREVIATIONS

1: Preoperative, 2: 4th week postoperative, 3: postinjection 5th day, 4: postinjection 10th day, 5: postinjection 30th day.

G-I: There was no statistically significant change in bladder capacity and compliance (Table 1).
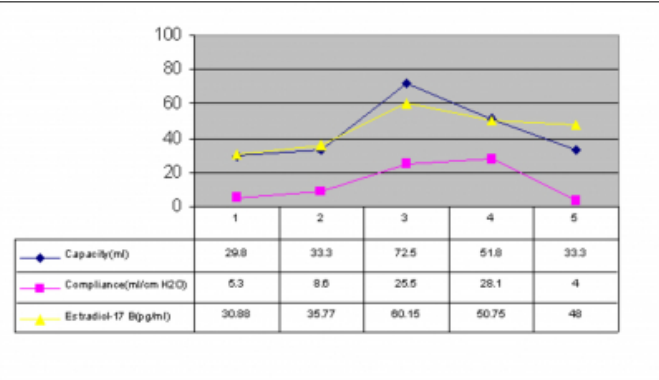
Figure 1

Table 1 (G-I): Low midline laparotomy + %0.9 NaCl only. In this group the changes were statistically not significant (p>0.05).
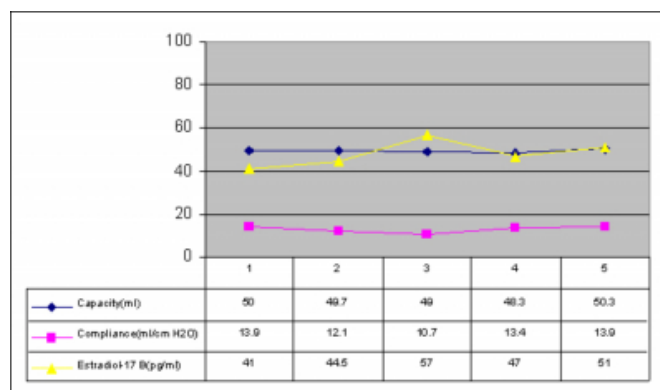
G-II: The mean bladder capacity and compliance found increased after estrogen injection on the 5th and 10th days and decreased thereafter and returned on the 30th day to the baseline levels (Table 2). These changes were statistically significant (p<0.05).
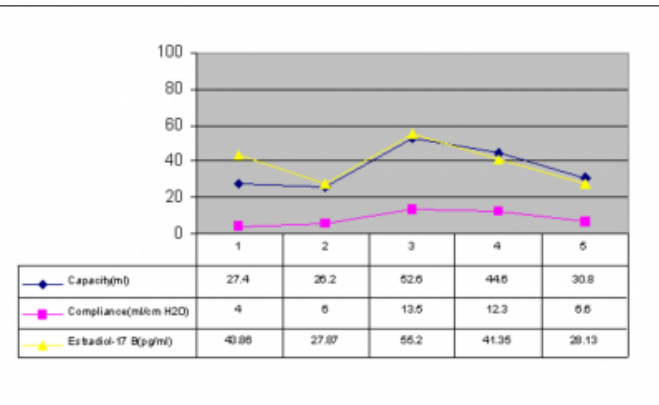
Figure 2

Table 2 (G-II): Low midline laparotomy+ estrogen. In this group after the injection of estrogen the bladder capacity and compliance increased on 5th and 10th days. The capacity and compliance decreased thereafter and returned near to baseline levels on the 30th day. The changes were statistically significant p<0.05).

	1	2	3	4	5
Capacity(ml)	29.8	33.3	72.5	51.8	33.3
Compliance(ml/cm H2O)	5.3	8.6	25.5	28.1	4
Estradiol-17 B(pg/ml)	30.88	35.77	60.15	50.75	48

G-III: The mean bladder capacity and compliance found increased after estrogen injection on the 5th and 10th days and decreased thereafter and returned at 30th day to the baseline levels (Table 3). These changes were statistically significant (p<0.05).

Figure 3

Table 3 (G-III): Low midline laparotomy + bilateral oopherectomy + estrogen.

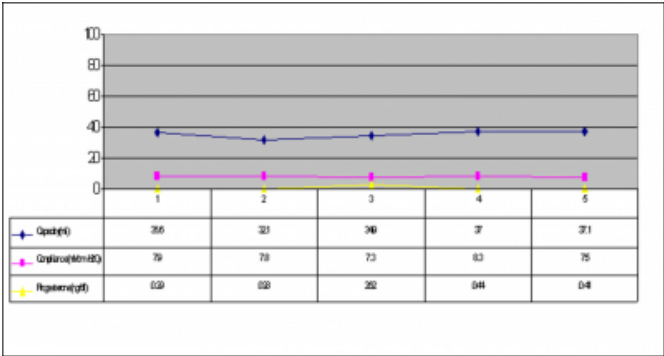|	1	2	3	4	5
Capacity(ml)	27.4	25.2	52.6	44.6	30.8
Compliance(ml/cm H2O)	4	6	13.5	12.3	6.6
Estradiol-17 B(pg/ml)	43.86	27.87	55.2	41.35	28.13

Estrogen level decreased after oopherectomy, without any change in capacity and compliance . In this group after the injection of estrogen the bladder capacity and compliance increased on 5th and 10th days. The capacity and compliance decreased thereafter and returned near to baseline levels on the 30th day. The changes were statistically significant (p<0.05).

G-IV: There was no statistically significant changes in bladder capacity and compliance (Table 4).

Figure 4

Table 4 (G-IV): Low midline laparotomy + bilateral oopherectomy + progesterone.

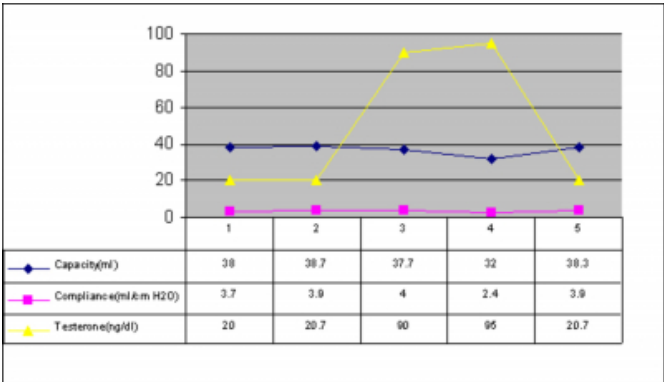|	1	2	3	4	5
Capacity(ml)	35.6	32.1	34.9	37	37.1
Compliance(ml/cm H2O)	7.9	7.9	7.3	8.3	7.5
Progesterone(ng/l)	0.29	0.28	2.52	0.44	0.4

Changes in bladder capacity and compliance after the injection of progesterone were statistically non-significant.

G-V: The bladder capacity and compliance was found declined on the 10th day (Table 5). The changes were statistically non-significant (p>0.05).

Figure 5

Table 5 (G-V): Low midline laparotomy + bilateral oopherectomy + testosterone. After the injection of testosterone the capacity and the compliance were found decreased on the 10th day. The changes were statistically non-significant (p>0.05).

	1	2	3	4	5
Capacity(ml)	38	38.7	37.7	32	38.3
Compliance(ml/cm H2O)	3.7	3.9	4	2.4	3.9
Testerone(ng/dl)	20	20.7	90	95	20.7

DISCUSSION

The effects of female sex hormones on bladder function were evaluated in female adults especially for postmenopausal incontinence and bladder irritability syndromes ([1,3,8,10]). The mechanism by which estrogen replacement may improve the incontinent condition could be related to one of the several factors that contribute to the maintenance of a positive intraurethral pressure, such as urethral smooth muscle tone or blood flow in the urethra ([2]).

There is evidence, that estrogen was associated with an increased density of a-adrenoreceptors in animal studies.

This strongly suggests an important role for a-receptors in the female bladder outlet ([11]). It has been shown that, estrogen selectively regulates adrenergic receptors in various parts of the lower urinary tract. Additionally estrogens influence a-adrenergic receptors in the body and midbladder and urethra ([12]) by increasing the densities of a-adrenoreceptors and their sensitivity to norepinephrine ([13]). These investigators also observed, that estrogen treatment did not affect b-adrenoreceptor density and their response to b-adrenoreceptor agonists in any part of the bladder ([14]).

On the other side estrogen receptors are also demonstrated experimentally and clinically in female subjects. Although this study demonstrated significant increase in bladder capacity and compliance after the injection of estrogen, it is still not clear, how this action is took place at cellular level in regard to the hormone-receptor relation.

Progesterone is generally looked upon as an antagonist to estrogen, and high levels of progesterone during late pregnancy have been associated with the onset of urinary incontinence ([15]). However the effects of progesterone were found to be small and these influence were explained, by improving the maintenance of urethral closure ([16]). Some studies suggest that progesterone had little effect on the urethral pressure profile ([17]). The antagonist effect can be explained as in this study by the fact that these receptors were not found in appreciable concentrations in the bladder and urethra ([18]). Additionally progesterone antagonises the effects of estrogen on the bladder neck by blocking estrogen induced increase in urethral flow ([13],[14]).

Androgen receptors have been demonstrated in a female rabbit model as well ([1]). They were found in the highest concentration in urethral and bladder epithelium. Low to low/moderate concentration was found in smooth muscle fibres. Similar to progesterone this can explain the slight antagonist effect of testosterone in female subjects.

In each gender, the sex specific hormones may affect bladder function. These hormones interact at the bladder neck and regulate the bladder outlet ([2],[3],[9]). Testosterone in male and estrogen in female adults may induce considerable changes in bladder functions in terms of incontinence problems ([4],[9],[19],[20]). On contrary, progesterone and testosterone act as antagonist in females.

The sex hormone receptors in bladder (estrogen, progesterone and androgen) were also demonstrated in experimental and clinical studies ([9],[17],[20],[21],[22]). These receptors were found frequently at bladder neck similar to the adrenoreceptor's. This suggests that there could be a relation between the hormones, these hormone receptors and bladder functions.

As the hormone concentrations achieved by the interventions were high compared with those observed in the controls, the responses should be viewed as pharmacological responses not those achieved in the physiological situation. Additionally the number of animals studied is small, so caution needs to be exercised where no effect is observed and we recommend caution on the interpretation of these data and conduct further studies in this area.

CONCLUSION

This preliminary report describes the bladder capacity and compliance alterations in the female rabbits after the injection of different sex hormones. In this study, by a single injection of estrogen, a change in bladder capacity and compliance was demonstrated in short-term follow-up. Under the influence of estrogen, the capacity, compliance increased and stayed in correlation with the levels of this female sex hormone. On the contrary the use of progesterone and testosterone acted as antagonist and reduced the bladder capacity and compliance.

AUTHORS' CONTRIBUTIONS

Sinan Celayir design the study and participated partly in laboratory work.

Zekeriya Ilce carried out the main laboratory work and performed the statistical analysis.

All authors read and approved the final manuscript.

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