Int Urogynecol J (1993) 4:259–261

International Urogynecology Journal

Original Article

Does Progesterone Cause an Irritable Bladder?

A. Cutner[1], G. Burton[2], L. D. Cardozo[1], B. G. Wise[1], D. Abbott[1] and J. Studd[1]
[1]King's College Hospital, and [2]Lister Hospital, London, UK

Abstract: Nine women with primary ovarian failure, who were having their artificial menstrual cycles manipulated with physiological levels of estrogen and high doses of progesterone, were entered into the study. They filled in urinary symptom questionnaires and had urodynamic investigations in the two phases of treatment: estrogen and progesterone, and estrogen alone. The number of voids per 24 hours was significantly greater in the progesterone phase, as was the end filling pressure on cystometry. This is the first report in the literature of the effects of high-dose progesterone on the lower urinary tract.

Keywords: Lower urinary tract; Progesterone

Introduction

Detrusor instability is present in about 40% of incontinent women. Although it may be secondary to upper motor neuron damage, the majority of cases are of unknown etiology and referred to as idiopathic. There is increasing evidence to suggest that detrusor activity may be related to hormonal status. Several authors have suggested an association with pregnancy [1,2], and indeed there is definite evidence that in women on hormone replacement therapy the degree of urinary incontinence on pad testing is more severe in the progestogenic phase [3].

Although Wall and Warrell [4] have reported a case of detrusor instability at the time of menstruation, but not mid-cycle, changes in urodynamic parameters at different stages of the menstrual cycle are not supported by Sorensen et al. [5]. The aim of this study was to determine whether high-dose progesterone results in irritative bladder symptoms and detrusor instability in young women.

Correspondence and offprint requests to: Dr A. Cutner, Registrar in Obstetrics and Gynaecology, King's College Hospital Registrar Rotation, Urodynamic Unit, King's College Hospital, Denmark Hill, London SE5, UK.

Methods

Women who were undergoing in-vitro fertilization with egg donation for primary ovarian failure were entered into the study. They were having 'dummy' cycles to examine whether this improved the pregnancy success rate. They were treated with estrogen (estradiol valerate 4 mg orally per day) from day 2 to day 10, and with high-dose progesterone (Utrogestan 100 mg vaginally three times per day) and estrogen (estradiol valerate 6 mg orally per day) from day 11 to day 25. Thus although the level of estrogen is slightly different in the two phases, the only variable showing marked change was progesterone.

As an extension to the above protocol, consenting women completed a urinary symptom qustionnaire and underwent subtracted provocative cystometry on two occasions: first during the progesterone and estrogen phase, and secondly during the estrogen alone phase.

The symptom questionnaire enquired about their frequency of micturition and symptoms of stress incontinence, urgency and urge incontinence.

Urodynamic assessment included uroflowmetry, with determination of the peak flow rate and volume voided. A urethral filling catheter and a 1 mm fluid-filled pressure catheter were then passed into the bladder, and a 2 mm fluid-filled tube covered by a condom was passed into the rectum. The residual urine was measured. Subtracted provoked cystometry was performed. The bladder was filled with 0.9% saline at room temper-

ature with the patient in the supine position, and the first sensation of desire to void and the bladder capacity were determined. In the erect position the patient was asked to cough and also to heel bounce, and any rise in detrusor pressure or leakage was noted. Detrusor pressure and peak flow rate were measured during voiding while the patient was seated. Provocative tests used were fast filling, coughing, change in position from supine to erect, and heel bouncing.

Non-parametric statistics were used. A Wilcoxon's matched-pairs signed rank test was employed for ordinal paired data, and a McNemar's test was used for paired dichotomous data. Definitions and units conform to the standards proposed by the International Continence society [6]. This study had full local ethical committee approval.

Results

Nine women were included in the study. They were all nulliparous. The youngest was 28 and the oldest 45.

The medium number of voids per 24 hours in the estrogen phase was five (inter-quartile range, 5–6), whereas in the high-progesterone phase it was seven (inter-quartile range, 5–9) (Table 1). This difference is statistically significant ($p<0.05$). Although 5 women complained of urgency in the high-progesterone phase, all of which resolved in the estrogen phase, there was 1 new case in the estrogen phase. This difference is not significant. None of the women complained of urge incontinence in either phase, and only 2 of stress incontinence, both in the high-progesterone phase.

Comparing the first sensation of desire to void and the bladder capacity in the two phases of treatment, there were no significance differences (Table 2).

We compared the detrusor pressure rise on filling in the two phases of the treatment cycle (Table 1). Where the bladder capacity in the two phases of treatment were different, the detrusor pressure rise at the same capacity was compared. Seven out of the 9 women had a greater end filling pressure in the high-progesterone phase, and none were worse in the estrogen phase. This difference is significant (McNemar's test, $p<0.05$).

In the estrogen and progesterone phase, 2 women had stable bladders, 6 had low compliance alone, and 1 had low compliance and provoked detrusor instability. There were no new cases of abnormal detrusor activity in the estrogen-only phase. Of the 6 women with initial low compliance, 3 became stable, 2 had a smaller rise in detrusor pressure, and 1 remained the same. In addition, the 1 woman with phasic detrusor instability and low compliance while taking progesterone had low compliance only during the estrogen-only phase. Thus overall 3 women remained the same in the two phases of treatment, and 6 improved in the estrogen phase. This change approaches significance (McNemar's test, $p=0.06$).

Table 1. The number of voids per 24 hours and the detrusor pressure rise on filling in each phase of treatment

Patient number	Estrogen & progesterone		Estrogen	
	Voids per 24 hours (number)	End filling pressure (cmH_2O)	Voides per 24 hours (number)	End filling pressure (cmH_2O)
1	6	7	4	0
2	9	15	6	5
3	7	14	5	5
4	13	20	10	15
5	5	20	5	15
6*	11	25	7	25
7	4	20	3	20
8	7	17.5	5	5
9	5	15	6	5

* This patient also had provoked detrusor instability in the estrogen and progesterone phase

Table 2. The first sensation of desire to void, and bladder capacity in the two phases of treatment

		Estrogen & progesterone	Estrogen
First sensation	Median	200 ml	250 ml
	Inter-quartile range	140–250	140–270
	Range	70–430	100–350
Bladder capacity	Median	450 ml	450 ml
	Inter-quartile range	405–500	450–480
	Range	300–550	375–550

Discussion

The reproducibility of repeated urodynamic investigations has been addressed by several authors, with some demonstrating good reproducibility while others would not agree. Sorensen et al. [7] found significant increases in the first sensation of desire to void and the bladder capacity between the first and fourth tests. However, they found no differences in bladder compliance. Other studies have failed to show these differences using two tests [8,9]. In addition, the incidence of detrusor instability appears to vary with repeated tests [10–13]. One unit has looked at the urodynamic findings in healthy fertile females at different stages at the menstrual cycle [14], and followed them up to look at the long-term reproducibility [15]. They found all parameters to be reproducible in both the short term and long term, and this was confirmed by studies in healthy postmenopausal women [16].

Ideally, in this study the patients should have been randomly allocated as to whether the first investigation was performed in the estrogen and progesterone phase,

or the estrogen-only phase. However, the small numbers would make random allocation less meaningful.

Although the number of women included in this study is small, they form a unique group. Since they have no endogenous sex hormones, levels may be artificially manipulated. It is interesting that in animal studies estrogen has been shown to enhance α-adrenergic responses [17–19], and progesterone β-adrenergic responses [20,21]. This would suggest that progesterone would increase bladder compliance rather than decrease it. However, the effect on human detrusor muscle has not been determined.

This is the first report of the isolated effects of high-dose progesterone on the lower urinary tract. It demonstrates both subjectively and objectively an association between high levels of circulating progesterone and detrusor 'irritability'.

References

1. Clow WM. Effect of posture on bladder and urethral function in normal pregnancy. *Urol Int* 1975;30:9–15
2. Cutner A, Cardozo LD, Benness CJ. Assessment of urinary symptoms in early pregnancy. *Br J Obstet Gynaecol* 1991;98:1283–1286
3. Benness C, Gangar K, Cardozo L, Cutner A, Whitehead M. Do progestagens exacerbate urinary incontinence in women on HRT? *Neurourol Urodyn* 1991;10:315–316
4. Wall LL, Warrell DW. Detrusor instability associated with menstruation. Case report. *Br J Obstet Gynaecol* 1989;96:737–738
5. Sorensen S, Knudsen UB, Kirkeby HJ, Djurhuus JC. Urodynamic investigations in healthy fertile females during the menstrual cycle. *Scand J Urol Nephrol* 1988; Suppl 114:28–34
6. Abrams P, Blaivas JG, Stanton SL, Anderson JT. The standardization of terminology of lower urinary tract function. *Int Urogynecol J* 1990;1:45–58
7. Sorensen SS, Nielsen, JB, Norgaard JP, Knudsen LM, Djurhuus JC. Changes in bladder volumes with repetition of water cystometry. *Urol Res* 1984;12:205–208
8. Cass AS, Ward BD, Markland C. Comparison of slow and rapid fill cystometry using liquid and air. *J Urol* 1970;104:104–106
9. Ramsden PD, Smith JC, Pierce JM, Ardran GM. The unstable bladder – fact or artefact? *Br J Urol* 1977;49:633–639
10. Benness CJ, Barnick CG, Cardozo L. Is there a place for routine videocystourethrography in the assessment of lower urinary tract function? *Neurourol Urodyn* 1989;8:299–300
11. Wein AJ, Hanno PM, Dixon DO, Raezer D, Benson GS. The reproducibility and interpretation of carbon dioxide cystometry. *J Urol* 1978;120:205–206
12. Jensen D. Pharmacological studies of the uninhibited neurogenic bladder. 1. The influence of repeated filling and various filling rates on the cystometrogram of neurological patients with normal and uninhibited neurogenic bladder. *Acta Neurol Scand* 1981;64:145–174
13. Awad SA, McGinnis RH. Factors that influence the incidence of detrusor instability in women. *J Urol* 1983;130:114–115
14. Sorensen S, Knudsen UB, Kirkeby HJ, Djurhuus JC. Urodynamic investigations in healthy fertile females during the menstrual cycle. *Scand J Urol Nephrol* 1988; Suppl 114:28–34
15. Sorensen S, Gregersen H, Sorensen SM. Long-term reproducibility of urodynamic investigations in healthy fertile females. *Scand J Urol Nephrol* 1988; Suppl 114:35–41
16. Sorensen S. Urodynamic investigations and their reproducibility in healthy postmenopausal females. *Scand J Urol Nephrol* 1988; Suppl 114:42–47
17. Raz S, Zeiger M, Adoni A. Hormonal environment and uterine response to epinephrine. *Am J Obstet Gynecol* 1971;111:345–349
18. Raz S, Zeigler M, Caine M. Hormonal influence on the adrenergic receptors of the ureter. *Br J Urol* 1972;44:405–410
19. Roberts JM, Insel PA, Goldfien RD, Goldfien A. Alpha receptors but not beta receptors increase in rabbit uterus with estrogen. *Nature* 1977;270:624–625
20. Hodgson BJ, Dumas S, Bolling DR, Heesch CM. Effect of estrogen on sensitivity of rabbit bladder and urethra to phenylephrine. *Invest Urol* 1978;16:67–69
21. Levin RM, Shofer FS, Wein AJ. Estrogen-induced alterations in the autonomic responses of the rabbit urinary bladder. *J Pharmacol Exp Ther* 1980;215:614–618

EDITORIAL COMMENT: This is an interesting article on the effects of progesterone on lower urinary tract complaints in females. It reports an increase in urgency and decrease in bladder volume in patients receiving progesterone as part of their hormone replacement. This may have clinical relevance in patients on hormone replacement therapy. Currently there are few data on the effects of progesterone on the bladder outside of pregnancy. However, most of the studies indicate that progesterone causes relaxation of the detrusor muscle, either through a β-agonist or an anticholinergic effect. This study suggests the opposite, and points out the fact that further studies need to be done before any recommendations regarding its clinical use can be made.