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A randomized controlled trial of goserelin and medroxyprogesterone acetate in the treatment of pelvic congestion

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Following identification of the proportion of pelvic congestion among symptomatic patients complaining of chronic pelvic pain, and in a totally asymptomatic group of patients requesting tubal ligation, the efficiency of goserelin acetate versus medroxyprogesterone acetate was compared objectively using pelvic venogram scores, and subjectively by symptom resolution, improvement of psychological status and sexual functioning in a prospective randomized trial in 47 patients with pure pelvic congestion syndrome. Patients received either goserelin acetate (3.6 mg/month for 6 months) or medroxyprogesterone acetate (MPA; 30 mg/day for 6 months). Among patients with chronic pelvic pain, those with pure pelvic congestion were mostly parous, had the most severe pelvic signs and symptom scores, lowest rates of sexual functioning, and higher states of anxiety and depression as compared with others. At 1 year after treatment, goserelin remained superior to MPA in terms of pelvic venographic improvement as an objective measure. In alleviation of signs and symptomatology, improvement of sexual functioning and reduction of anxiety and depressive states as subjective measures, goserelin acetate achieved a statistically significant advantage ($P = 0.0001$) compared with MPA.

Key words: goserelin acetate/medroxyprogesterone acetate/pelvic congestion syndrome

Introduction

The pelvic congestion syndrome is a distinct clinical entity which is often overlooked in everyday practice (Beard *et al*., 1986; Porpora and Gomel, 1997; Venbrux and Lambert, 1999). Although this syndrome has been intermittently recognized for many years, its aetiology is unclear, and proposed treatments are not uniform. In 1949, there seemed no doubt that this syndrome was a stress disorder (Taylor, 1949a–c), but by 1964 opinion had changed (Lefevre, 1964). Despite the early observations of Lefevre, clinicians who did not include venography in the evaluation armamentarium of chronic pelvic pain continued to refer these patients for psychotherapy, with a presumed diagnosis of undetectable organic pathology (Beard *et al*., 1986).

During the past two decades, a number of authors have reintroduced peruterine venography in addition to ultrasound and diagnostic laparoscopy to evaluate chronic pelvic pain patients (Beard *et al*., 1984, 1986). These studies have shown that pelvic congestion syndrome is responsible for pain in a high proportion of patients with no detectable organic pathology (Beard *et al*., 1984, 1986; Adams *et al*., 1990; Venbrux and Lambert, 1999).

Currently, it is not clear whether congestion is a result of ovarian dysfunction or mechanical factors. Proponents of ovarian dysfunction claim that induced or natural hypo-oestrogenic hormonal milieu results in the diminution of varicose vein diameters. It has been suggested that oestrogen is a venous dilator, and that hypo-oestrogenic states or antagonizing the effects of oestrogen by progesterone results in resolution of symptoms (Farquhar *et al*., 1989; Reginald *et al*., 1989; Adams *et al*., 1990). On the other hand, according to the mechanical theory which is easy to speculate, a 60-fold increase in the capacity of pelvic veins during successive late pregnancies makes these vessels vulnerable, and eventually leads to vascular incompetence, resulting in dilatation of veins and retrograde vascular flow in the non-pregnant state (Reginald *et al*., 1987; Sichlau *et al*., 1994). It is probable that both of these hypotheses of aetiology are cooperative (Hobbs, 1990). The cause of pain due to the pelvic congestion remains unclear, but the most likely possibility is that increased dilatation, concomitant with stasis, leads to the release of local pain-producing substances (Beard *et al*., 1986; Reginald *et al*., 1989; Porpora and Gomel, 1997; Venbrux and Lambert, 1999).

In the past, medroxyprogesterone acetate (MPA) has been

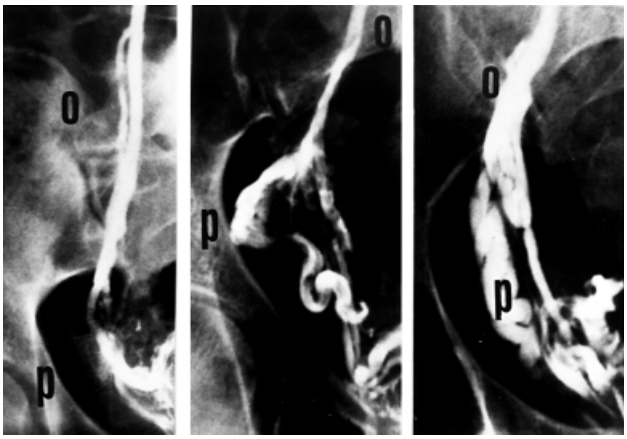

Figure 1. Venograms showing successive deterioration of scores of different patients. The scores are (left to right): 3, 5, 9. For perspective, compare label 'p' (congestion of ovarian plexus) and 'o' (ovarian vein diameter) that indicates venous circulation at the right side.

used to suppress ovarian function of pelvic congestion syndrome patients, and proved to be effective. It was shown that MPA given at 30 mg/day for 6 months was effective in terms of objective (venography) and subjective (pain) improvement, both during and immediately after treatment of pelvic congestion syndrome. In another trial, long-term benefits (9 months after the end of treatment) of MPA (30 mg/day for 4 months) and psychotherapy on subjective outcome measures were demonstrated. Gonadotrophin-releasing hormone (GnRH) agonists, combined with hormone replacement therapy (HRT), have been used for the treatment of this syndrome (Gangar *et al.*, 1993). These authors reported that, after a treatment period of 4 months, combined goserelin and HRT was not effective in the treatment of pelvic congestion syndrome, despite effective ovarian suppression.

Since 1994, pelvic venography has been used in our institution as a diagnostic tool in combination with other established modalities such as laparoscopy and transvaginal ultrasonography to determine the aetiology of chronic pelvic pain.

The purposes of this prospective randomized trial in patients with pure pelvic congestion were first, to identify the proportion of venographically proven pelvic congestion both in a group of patients complaining of chronic pelvic pain, and in a group of totally asymptomatic patients requesting tubal ligation; second, in parallel with this prospective evaluation, the efficiency of the GnRH analogue goserelin acetate and MPA was compared objectively by obtaining pelvic venogram scores, and subjectively by monitoring symptom resolution, improvement of psychological status, and sexual functioning.

Materials and methods

This prospective trial was undertaken between March 1996 and March 2000, and designed to serve two purposes: (i) to identify the proportion of venographically proven pelvic congestion in chronic pelvic pain patients, as well as in asymptomatic patients requesting tubal ligation; and (ii) to assess the effect of two different regimens [MPA 30 mg/day for 6 months, and goserelin acetate (Zoladex; Zeneca, Macclesfield, UK) 3.6 mg for six monthly injections] in the treatment of pure pelvic

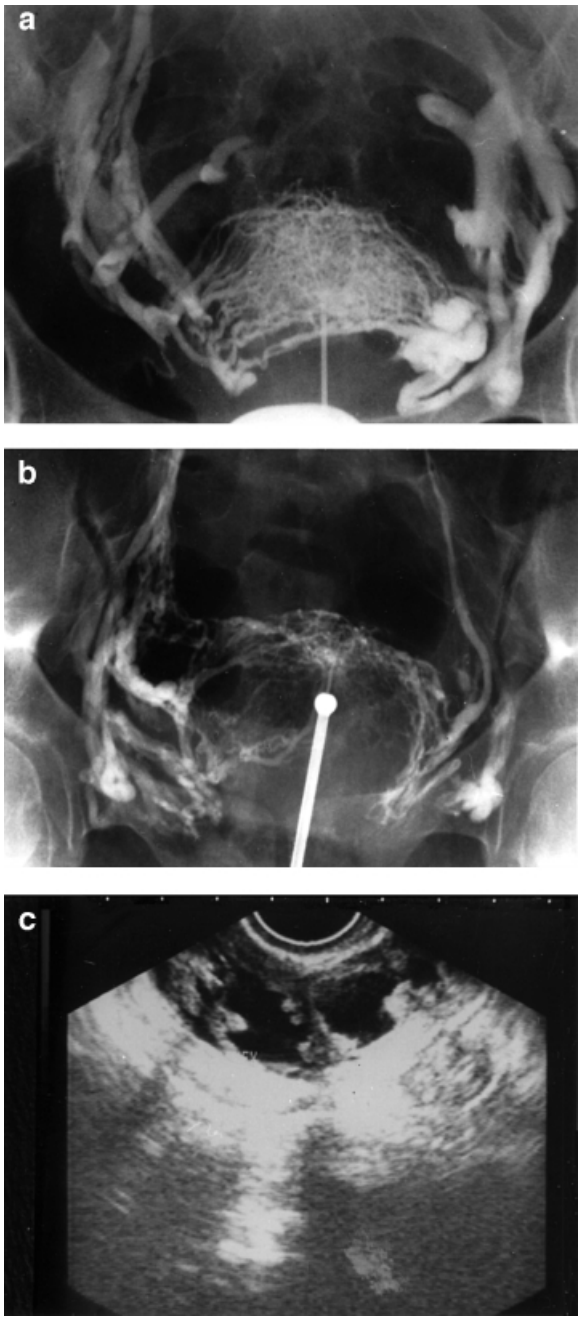

Figure 2. Concomitant pelvic congestion in patients with chronic pelvic pain. (**a**) In a patient with moderate endometriosis; the film was taken 40 s after dye injection. (**b**) In a patient with chronic pelvic inflammatory disease (PID); the film was taken 20 s after dye injection. (**c**) The hydrosalpinx of the chronic PID patient in (**b**).

congestion (cases without any other detectable organic pathology other than pelvic congestion) in a prospective randomized manner. This investigation was conducted in the teaching department of a university medical centre, the trial protocol having been approved by the Ethics Committee of the institution. All subjects gave their informed consent before entering the study.

During this study, 148 patients complaining of chronic pelvic pain were prospectively evaluated by adherence to a strict protocol that consisted of pelvic examination, venography, laparoscopy, ultrasonography and questionnaires to determine psychological status and sexual functioning. The existence of pelvic congestion or other pertinent abnormality in 30 asymptomatic patients requesting sterilization was

Table I. Baseline clinical characteristics of study patients[a]

Parameter (n = 30)	Tube ligation	Chronic pelvic pain patients (n = 148)		
		Organic pathology (n = 93)	Pure pelvic congestion (n = 47)	Referral to psychiatry (n = 8)
Age (years)	33.1 ± 3.3	32.9 ± 5.1	32.2 ± 2.8	34.3 ± 2.4
Parity (n)	3.4 ± 1.3	2.8 ± 1.3	3.4 ± 1.2	3.2 ± 1.3
Venography score	3.2 ± 0.5	4.6 ± 1.5	8.6 ± 0.5	3.1 ± 0.7
Pelvic symptom score	0.7 ± 0.7	6.7 ± 1.8	10.5 ± 1.3	9.5 ± 1.3
HADS score				
Anxiety	5.2 ± 1.4	5.7 ± 1.4	7.4 ± 0.9	8.3 ± 1.7.
Depression	3.6 ± 1.5	4.9 ± 1.3	6.3 ± 1.02	15.6 ± 2.1
Total	8.7 ± 2.3	10.6 ± 2.1	13.7 ± 1.4	23.0 ± 1.9
rSSRS score	82.8 ± 5.5	33.9 ± 10.1	18.1 ± 4.1	20.8 ± 6.9

[a]Values are mean ± SD.
HADS = Hospital Anxiety and Depression Scale; rSSRS = revised Sabbatsberg Sexual Rating Scale.

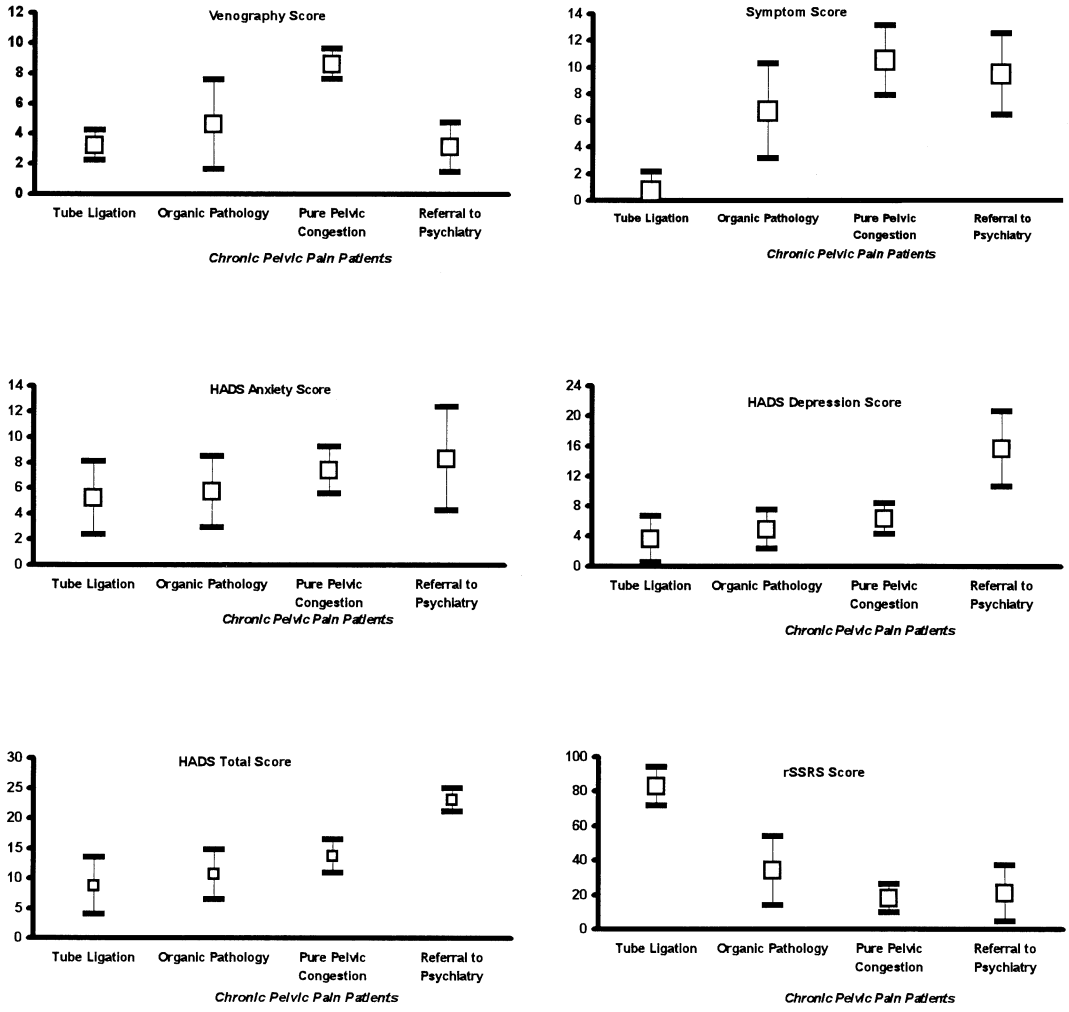

Figure 3. Mean and 95% confidence interval for venography score, pelvic symptom score, HADS score (Anxiety, Depression, Total) and revised Sabbatsberg Sexual Rating Scale (rSSRS) score of study subjects.

investigated using venography and ultrasonography before laparoscopy. These patients were also requested to complete the questionnaires.

All patients in the study underwent peruterine venography, high-resolution transvaginal and/or transabdominal ultrasound examination and diagnostic laparoscopy. Pelvic symptoms and physical findings were assessed by the same physicians. All patients were asked to complete the submitted forms of the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), and the revised Sabbatsberg Sexual Rating Scale (rSSRS) (Garrat *et al*., 1995).

Grading of symptoms and physical findings were assessed at each

clinic visit on a modification of a published scale (Biberoglu and Behrman, 1981) that was modified by excluding induration. Pelvic pain, dyspareunia, dysmenorrhoea and pelvic tenderness were each scored as: none (0 points); mild (1); moderate (2); and severe (3). The sum of these variables comprised the total pelvic symptom score in this study. The scale and its scoring (and modifications of it) have been used frequently as a reliable tool in the assessment of pelvic pain.

In all cases, peruterine venography was performed before diagnostic laparoscopy in the first week after menses. Fluoroscopic screening was performed to observe the spread of contrast material into myometrial, uterine and ovarian venous plexuses. Routine films were taken at the end of injection, and 20 and 40 s later. Peruterine venographies were assessed by a pelvic venogram scoring system (Beard *et al*., 1986), according to which ovarian vein dilatation, dye disappearance and congestion are considered as three variables. Each variable is assigned a value of 1 to 3, depending on the degree of abnormality. Ovarian vein diameter was measured at the point of maximum diameter of the segment of the vein that could be clearly visualized. If the diameter was <4 mm, it was assigned a value of 1, 5–8 mm a value of 2, and >8 mm a value of 3. The disappearance interval was determined from the films taken at the end of injection, and at 20 and 40s after injection. When the dye disappeared at the end of injection, it was assigned a value of 1; when the time was >20 s it was valued as 2, while a time >40 s was valued as 3. Congestion was assessed from the calibre and the tortuous appearance of individual pelvic veins. Normally, the veins are small, straight, similar in calibre, and easily visualized. Such an appearance was assigned a value of 1. In moderate congestion, the veins were of variable calibre and tortuous, and difficult to discern individually (value of 2). In extensive congestion, the veins were wide, obscured by a pool of contrast medium around the ovarian plexus, showed great variation in calibre, and appeared highly tortuous (value of 3). Thus, a total score of 3 indicated a normal venogram, while a score of 9 indicated the most abnormal venogram. A venogram score of $\geqslant 5$ was found to be an objective measure of pelvic congestion with a high sensitivity (91%) and specificity (89%) (Beard *et al*., 1984, 1986). In this trial, all patients (controls, organic pain, pure pelvic congestion) were assessed according to the above-mentioned scoring system. A venography score of $\geqslant 5$ was accepted as a threshold to diagnose pelvic congestion. To improve the comparison and the perspective, three venograms from different patients were presented, each showing successive deterioration in ovarian vein diameter and ovarian plexus at the right side (Figure 1). During the performance of the venography, the ovarian plexus is straightened by a strong downward traction of the tenaculum for purposes of demonstration.

High-resolution ultrasound examinations were carried out using commercially available instruments. The investigators were aware of the physical changes in the pelvic organs (uterine and endometrial changes, cystic ovaries) of women with pelvic congestion (Taylor, 1949a,b,c; Adams *et al*., 1990). However in this study, the aim of the sonography was to examine the detailed internal consistency of the uterus and adnexa in order to detect, suspect or exclude organic pathology such as myoma, adenomyosis, endometrioma and hydrosalpinx. General endotracheal anaesthesia was used in all patients for multiple puncture diagnostic laparoscopy. Those in the control group were sterilized by bipolar electrocoagulation; patients with organic pathology other than pure pelvic congestion, were appropriately treated in the same session via laparoscopy or laparotomy.

The HADS is a self-assessment mood scale designed specifically for use in non-psychiatric hospital outpatients to determine states of anxiety and depression (Zigmond and Snaith, 1983). The scale is composed of 14 items, seven for the anxiety and seven for the depression subscales. Five mutually exclusive answers, rated from 0 to 4 according to increasing psychiatric severity, are provided for each of the questions. The points are then summed to give anxiety and depression subtotals, and a total score. For the subscales, a score of $\leqslant 7$ indicates non-psychiatric cases, whereas a score of 8–10 indicates doubtful cases, and a score >11 indicates definitive psychiatric cases. The HADS has been shown to be a reliable instrument for screening, and a valid measure of severity of these mood disorders in patients under investigation in medical and surgical departments. Its validity and reliability have been

Table II. Clinical characteristics of randomized subjects by allocated treatment[a]

Parameter	MPA (n = 24)	Goserelin (n = 23)	P
Age (years)	32.3 ± 3.0	33.1 ± 3.3	0.76
Parity (n)	3.4 ± 1.2	3.4 ± 1.3	0.37
Venography score	8.6 ± 0.5	8.5 ± 0.6	0.42
Pelvic symptom score	10.9 ± 1.0	10.2 ± 1.4	0.07
HADS score			
Anxiety	7.2 ± 0.9	7.5 ± 0.9	0.20
Depression	6.4 ± 0.8	6.2 ± 1.1	0.62
Total	13.6 ± 1.3	13.8 ± 1.4	0.49
rSSRS score	18.6 ± 4.4	17.6 ± 3.8	0.41

[a]Values are mean ± SD.
HADS = Hospital Anxiety and Depression Scale; MPA = medroxyprogesterone acetate; rSSRS = revised Sabbatsberg Sexual Rating Scale.

Table III. The effects of pharmacological agents on each group

Parameter	MPA (n = 24)				Goserelin (n = 23)			
	Baseline	First[a]	Final[b]	P[c]	Baseline	First[a]	Final[b]	P[c]
Venography score	8.6 ± 0.5	–	4.5 ± 1.2	0.001	8.5 ± 0.6	–	3.2 ± 0.5	0.001
Pelvic symptom score	10.9 ± 1.1	5.1 ± 1.3	6.2 ± 1.1	0.001	10.2 ± 1.4	2.3 ± 1.1	2.5 ± 1.3	0.001
HADS score								
Anxiety	7.2 ± 0.9	5.5 ± 1.1	5.6 ± 1.1	0.001	7.5 ± 0.9	5.0 ± 0.7	4.9 ± 0.7	0.001
Depression	6.4 ± 0.8	4.4 ± 0.8	4.8 ± 0.9	0.001	6.2 ± 1.1	4.3 ± 1.1	4.3 ± 0.6	0.001
Total	13.6 ± 1.4	9.9 ± 1.6	10.3 ± 1.7	0.001	13.8 ± 1.4	9.4 ± 1.3	9.2 ± 1.1	0.001
rSSRS score	18.6 ± 4.4	71.7 ± 7.3	66.4 ± 8.3	0.001	17.6 ± 3.8	81.1 ± 3.1	80.2 ± 2.7	0.001

Values are mean ± SD.
[a]First evaluation was made at the end of treatment, after the first menses, and searched for the impact of medications on subjective outcome variables.
[b]Final evaluation was made at 12 months from the end of treatment, and searched for the impact of medications both on objective and subjective outcome variables.
[c]Friedman two-way ANOVA test.
HADS = Hospital Anxiety and Depression Scale; rSSRS = revised Sabbatsberg Sexual Rating Scale.

tested in the present patient population. In the present study, HADS was used to diagnose, and to assess the states of anxiety and depression, as well as to determine the impact of treatment on health-related quality of life.

The rSSRS is a 12-item questionnaire for the assessment of sexual functioning (Garrat *et al*., 1995). For each item, there are five possible answers, scored from 0 to 4 points (from the lowest to the highest sexual satisfaction). The scores of 12 items are then summed and transformed to a scale of 0 to 100. Scores between these values represent the percentage of the total possible score achieved. This scale has the potential to be widely used as an adjunct to clinical measures of health in order to assess the impact of interventions on sexual functioning within clinical trials (Garrat *et al*., 1995). The validity and reliability of this scale have been demonstrated and tested in the present patient population.

Table IV. Comparison of medroxyprogesterone acetate (MPA) and goserelin in pure pelvic congestion syndrome: mean changes (Δ mean ± SD) in objective and subjective clinical outcome data

Parameter	MPA (n = 24)	Goserelin (n = 23)	P
Venography score	4.2 ± 0.9	5.3 ± 0.7	0.0002
Pelvic symptom score	4.7 ± 1.4	7.7 ± 1.8	0.00001
HADS score			
Anxiety	1.6 ± 1.2	2.6 ± 0.8	0.002
Depression	1.6 ± 1.3	1.9 ± 0.9	0.38
Total	3.3 ± 1.9	4.6 ± 1.1	0.002
rSSRS score	47.0 ± 7.8	62.5 ± 5.0	0.00001

HADS = Hospital Anxiety and Depression Scale; rSSRS = revised Sabbatsberg Sexual Rating Scale.

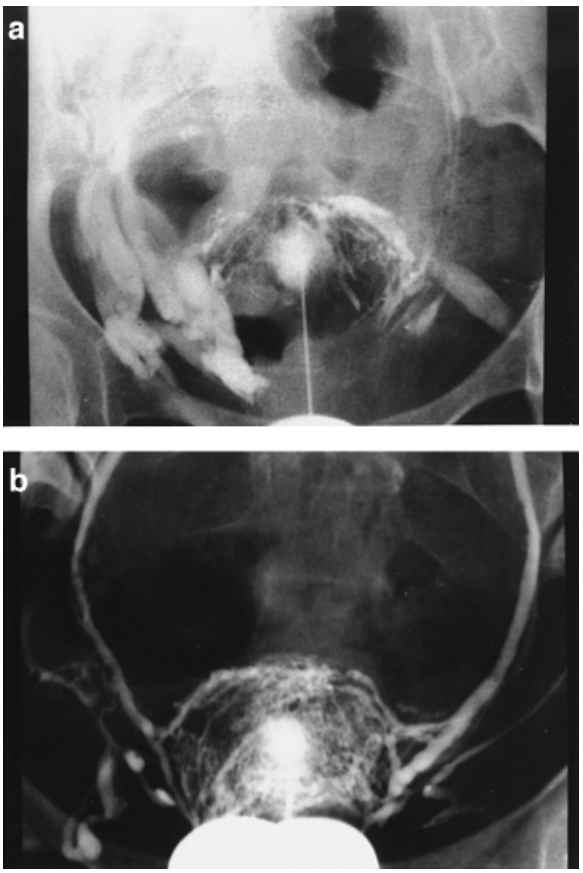

Figure 4. (**a**) Pure pelvic congestion; venography score of 9; the film was taken 40 s after dye injection. (**b**) The same patient after 12 months of treatment with goserelin; normal venography scores. Note the residual tiny varicosities of broad ligament; the film was taken after dye injection.

The submitted HADS and rSSRS forms were interpreted by one of the authors (S.O.) in a different psychiatry department in a different city. During interpretation, she was blinded to the patients and treatment, and was unaware of the venography scores and pelvic symptom scores.

In parallel with evaluating and gathering data from chronic pelvic pain patients, those with pure pelvic congestion were randomized prospectively to treatment arms of goserelin or MPA. Thus, all patients with pure pelvic congestion had pretreatment objective venogram scores, subjective pelvic pain scores, and pre-filled questionnaire of rSSRS and HADS.

On completion of the pre-trial evaluation, eligible subjects (i.e. those with pure pelvic congestion) were randomized in a ratio of 1:1 that was performed in accordance with a computer-generated randomization sequence using numbered, opaque, sealed envelopes to MPA or goserelin. Goserelin was administered as six monthly injections, whereas MPA was administered 30 mg/day for 6 months.

To assess the impact of pharmacological regimens on outcome variables, the patients were re-evaluated twice: (i) at the end of treatment after the first menses, when patients were evaluated for the impact of treatment on subjective outcome measures; and (iii) 12 months after the end of treatment.

All patients underwent peruterine venography to assess the long-term objective response to treatment, and pelvic symptom score, HADS and rSSRS were re-evaluated for residual pelvic findings, sexual response and for mood as subjective outcome variables at 12 months after treatment. None of the patients with pure pelvic congestion had psychotherapy as an adjunct to medications. None of them used oral contraceptives after the original treatment as an adjunctive measure. At the final evaluation during the performance of peruterine venography the operators were blinded.

Statistical analysis

Statistical analysis was performed using SPSS for Windows 6.0. Variables were compared statistically using the Mann–Whitney *U*-test, Wilcoxon test and Friedman two-way ANOVA where appropriate. A P-value of < 0.05 was considered to be significant.

Results

By strict adherence to the protocol for diagnostic evaluation of chronic pelvic pain, organic pathology was detected in 93 of 148 patients, 11 of whom had concomitant pelvic congestion (venography score >5) (Figure 2a–c). The most common organic pathology detected was endometriosis (n = 58, 39%), followed by chronic pelvic inflammatory disease (PID) (n = 17, 11%), postoperative adhesions (n = 15, 10%), uterine disease (myoma, n = 4, 2.7%; adenomyosis, n = 1, <1%), Allen–Masters syndrome (n = 1, <1%) and ovarian mass (n = 1 dermoid cyst, <1%). In the group in which organic pathology was detected, concomitant pelvic congestion was observed in 11 patients (12%). Those patients with concomitant congestion were observed in five cases of endometriosis, four of PID, one case with myoma, and one case with adenomyosis.

In 47 patients (31%), pelvic congestion was the only detected abnormality. In the remaining eight patients (5.4%), referral to the psychiatry department was offered after a negative evaluation for disease (ultrasonographic examination, venography and

laparoscopy were all normal in this subset of patients) and HADS scores relevant for depression (HADS depression subscale was ⩾12). Among the patients with depression, a strikingly high HADS depression subscale was noted, a normal venogram score, and a high pelvic symptom score in addition to diminished sexual functioning. In the group of asymptomatic patients (those requesting tubal ligation), only a single case of mild pelvic congestion with a venography score of 4 was detected, whereas there were two cases of adhesive disease, three of minimal endometriosis, and one case with a small myoma.

The baseline clinical characteristics and mean pelvic pain, venography, rSSRS and HADS scores of all patients are listed in Table I. The mean and 95% confidence interval for venography score, pelvic symptom score, HADS score (anxiety, depression, total) and rSSRS score of study subjects are given in Figure 3. The parity (mean ± SD) of patients with pelvic congestion syndrome was higher than the parity of those with organic pathology (3.4 ± 1.3 versus 2.8 ± 1.3; $P = 0.0001$), whereas statistically significant difference of parity was seen among patients requesting tubal ligation as compared with pelvic congestion syndrome. Even though patients with organic pathology had venography scores significantly higher (4.6 ± 1.5 versus 3.2 ± 0.5; $P = 0.0001$) than those requesting tubal ligation, their venography scores were significantly lower (8.6 ± 0.5 versus 4.6 ± 1.5; $P = 0.00001$) than those with pure pelvic congestion. Pelvic symptom scores were significantly higher in those patients with pelvic congestion syndrome as compared with those patients with organic pathology (10.5 ± 1.3 versus 6.7 ± 1.8; $P = 0.00001$). HADS scores of patients with pelvic congestion syndrome were significantly higher among all patients. Significantly higher total HADS scores of 13.7 ± 1.4 were noted for patients with pure pelvic congestion as compared with total HADS scores of 10.6 ± 2.1 for patients with organic pathology ($P = 0.0001$); the significantly elevated scores were also observed in anxiety and depression subscale scores (anxiety subscale score 7.4 ± 0.9 versus 5.7 ± 1.4; $P = 0.0001$; depression subscale score 6.3 ± 1.02 versus 4.9 ± 1.3; $P = 0.0001$ for patients with pure pelvic congestion syndrome as compared with those patients with organic pathology respectively). The rSSRS scores were significantly lower in patients with pelvic congestion syndrome than in those with organic pathology (18.1 ± 4.1 versus 33.9 ± 10.1; $P = 0.0001$). As expected, significantly lower scores of HADS and higher scores of rSSRS were noted in patients requesting tubal ligation.

After identification, 47 patients with pure pelvic congestion were randomized to receive either goserelin or MPA for 6 months. At the start of treatment, the groups were comparable in terms of age, parity, venography scores, pelvic symptom scores and HADS and rSSRS scores. The baseline clinical characteristics of this group are listed in Table II. All patients were cycling regularly, suggesting a normal hormonal milieu. None of them was using oral contraception, and none used oral contraceptives after the treatment as an adjunctive measure. Randomization resulted in statistically similar baseline characteristics.

The first evaluation was performed to determine subjective outcome data at the end of treatment, immediately after the first menstrual period. Initially, results seemed to indicate a statistically significant improvement in subjective outcome measures in both arms (Table III). However, this improvement was found to be statistically not consistent in the MPA arm at the end of 12 months treatment. Even though MPA was still significantly effective in improving the subjective outcome of patients at the final evaluation, as time progressed the positive effects of MPA on subjective outcome measures declined in a statistically significant manner. In the MPA arm, mean pelvic symptom score, after declining to 5.1 ± 1.3 from baseline, rose to 6.2 ± 1.1 ($P = 0.0004$). The HADS anxiety subscale score did not change significantly from the first evaluation to the final one (5.5 ± 1.1 versus 5.6 ± 1.1; $P = 0.42$). However, the HADS depression subscale, after declining to 4.4 ± 0.8 from baseline, rose to 4.8 ± 0.9 ($P = 0.0026$), and the total HADS score, after declining to 9.9 ± 1.6 from baseline, rose to 10.3 ± 1.7 ($P = 0.033$). The same deterioration was noted in the rSSRS scores which, after improving to 71.7 ± 7.3 from baseline, declined to 66.4 ± 8.3 ($P = 0.0001$). In contrast, the improvement of subjective outcome measures in the goserelin arm did not change as time progressed from the end of treatment to 12 months after treatment. In the goserelin arm, none of the variables showed a statistically significant change from the end of treatment to 12 months after treatment.

At the final evaluation (12 months from the end of treatment), although both agents were effective in the treatment of pure pelvic congestion syndrome (venography score reduction, pelvic symptom score reduction, HADS score reduction and rSSRS score improvement) (Table III), a statistical comparison of these agents pointed to a better outcome for goserelin (Table IV). Goserelin was shown statistically to be more effective in reducing pelvic venography score (Figure 4a,b) than MPA (Δ mean scores 4.2 ± 0.9 for MPA and 5.3 ± 0.7 for goserelin; $P = 0.0002$). Goserelin proved also to be more effective in decreasing pelvic symptom score (Δ mean score 4.7 ± 1.4 for MPA, 7.7 ± 1.8 for goserelin; $P = 0.00001$). Goserelin was also statistically more efficient in decreasing HADS anxiety subscale and total scores, whereas in decreasing the depression subscale of HADS scores both agents were similarly effective [Δ mean score 1.6 ± 1.2 for MPA, 2.6 ±0.8 for goserelin ($P = 0.002$); for depression subscale Δ mean score 1.6 ± 1.3 for MPA, 1.9 ± 0.9 for goserelin (P = NS); for HADS total score Δ mean 3.3 ± 1.9 for MPA, 4.6 ± 1.1 for goserelin ($P = 0.002$)]. Goserelin improved rSSRS scores more efficiently than MPA (Δ mean score 47 ± 7.8 for MPA, 62.5 ± 5 for goserelin; $P = 0.00001$).

Discussion

Among women who suffer from otherwise unexplained chronic pelvic pain, venography studies have shown that pelvic congestion syndrome is responsible for the incapacitating chronic pelvic pain in many cases (Beard *et al.*, 1986). Symptoms of pelvic congestion syndrome include deep dyspareunia, congestive dysmenorrhoea, post-coital pain, and a dull chronic pelvic pain with sharp exacerbation triggered by postural changes. Pain can sometimes be lessened simply by lying down and elevating the legs. The pain of pelvic congestion syndrome is typically aggravated by states of pelvic vessel engorgement

(many hours of standing or working in a sitting position, premenstrually, and most notably after coitus). Tenderness of the ovarian point (the junction of the upper and middle thirds of a line drawn between the umbilicus and anterior superior iliac spine) and directly elicited ovarian tenderness are well described signs of this condition, other than tenderness of the uterus, posterior parametrium and uterosacral ligaments (Beard *et al*., 1986, 1988). Diagnosis of this condition can sometimes be achieved using laparoscopy, transvaginal ultrasonography (with/without colour Doppler equipment), magnetic resonance imaging and computed tomography (Desimpelaere *et al*., 1999), but none of these methods can delineate the detailed pathological anatomy of pelvic varicose veins as accurately as pelvic peruterine venography. Venous stasis can also be studied using fluoroscopic peruterine venography. Modalities other than pelvic venography (in their current state) can be used only as screening modalities as they have variable specificity and sensitivity.

One hallmark of pelvic congestion syndrome is its disappearance after the menopause (Beard *et al*., 1986, 1988; Porpora and Gomel, 1997). As induced hypo-oestrogenic stages or venoconstriction and/or occlusion of varicose veins (by medical or surgical as well as interventional radiological treatment) results in ameloriation of symptoms, this syndrome is suspected to occur as a result of gonadal dysfunction, cooperative with mechanical factors (Farquhar *et al*., 1989; Reginald *et al*., 1989; Venbrux and Lambert, 1999). Medical treatment of pelvic congestion includes progestins, danazol, phelobotonics and non-steroidal anti-inflammatory drugs (Charles, 1995). In addition to these agents, GnRH agonists combined with HRT have been used for the treatment of this syndrome (Gangar *et al*., 1993). These authors reported that, after a treatment period of 4 months, combined goserelin and hormone replacement therapy was not effective in treating pelvic congestion syndrome, despite effective ovarian suppression. However, these authors have stated that 'it is also possible that relief of pain and congestion is not obtained because the treatment period of four months is not sufficiently long'. In a survey of the literature, not a single report could be found on the use of GnRH analogues only, for 6 months, for the treatment of pelvic congestion syndrome. Nonetheless, the use of GnRH analogues was highly attractive in the present study because they had very often been used during the past decades to suppress ovarian function, and to create an artificial menopause for a variety of gynaecological disorders of variable duration. The other well-studied compound used to suppress ovarian function, namely MPA, produced a variable effect that in the main was short-lasting (Farquhar *et al*., 1989; Reginald *et al*., 1989; Adams *et al*., 1990). Other treatment modalities of pelvic congestion syndrome were simply mechanical, by the use of a variety of techniques including extraperitoneal or laparoscopic ligation of pelvic varices and/or ovarian veins, embolization of varices and/or ovarian veins by interventional radiological procedures, and hysterectomy with bilateral adnexectomy (Hobbs, 1990; Mathis *et al*., 1995; Capasso *et al*., 1997; Cordts *et al*., 1997; Venbrux and Lambert, 1999). Even though definitive surgery (hysterectomy with bilateral adnexectomy) is an effective treatment (both in terms of pain relief and restoration of normal sexual function), it must always remain as the last option (Beard *et al*., 1991).

In this study, the following points were postulated: (i) Pelvic congestion syndrome is a distinct clinical entity. (ii) As once believed, the syndrome was not a stress disorder, and the deprived psychological status of these patients was the result of unidentified, unclear origin of their pain and undertreatment of the syndrome, and that the situation was reversible by using the appropriate treatment. (iii) Sexual satisfaction can be regained by appropriate medical treatment. (iv) If a hypo-oestrogenic hormonal milieu can be created by the most effective medical modality, the outcome of this treatment will be more effective than other studied medical regimens.

Although controversy persists, we believe that pelvic congestion syndrome is a distinct clinical entity. In the present cohort of 148 chronic pelvic pain patients, pure pelvic congestion was identified in 30% of patients. These results confirmed the findings of others (Beard *et al*., 1986, 1988) in that only a single case of minimal pelvic congestion was found among a group of asymptomatic patients, whereas 15% of variable degree congestion was detected in a group patients with organic pathology demonstrable by laparoscopy or ultrasonography (Beard *et al*., 1986, 1988). Among those women who were sexually active, asymptomatic, and requesting tubal ligation, not one case of severe pelvic congestion was identified. While this was the main conclusion drawn from this patient group, a low pelvic symptom score, and a low HADS score in addition to higher scores of sexual functioning were noted. Typical examples of concomitant pelvic congestion syndrome are shown in Figure 2a–c, and in these cases it is believed that pelvic congestion occurs secondary to tissue distortion and destruction and results in altered pathways of venous drainage. It cannot be assumed that, when pelvic pathology is found at laparoscopy in women with chronic pelvic pain, the two are necessarily related. The cause of pain (organic pathology or congestion) in concomitant pelvic congestion is unclear (Beard *et al*., 1991). To quote Beard and his co-authors, 'What is certain, is that pelvic congestion in the absence of endometriosis, does cause pain, whereas the converse is not proven' (Beard *et al*., 1991). This statement may hold true for the PID-associated pelvic pain patient shown (Figure 2a and b). Further clinical investigations are necessary in concomitant pelvic congestion syndrome. However, during the study period the organic pathologies were treated irrespective of the venography scores.

Patients with pure pelvic congestion syndrome had higher HADS scores than any other pathology, but their scores responded to medical treatment and reassuring clinical care. It was stated that psychological disturbances may exist in this syndrome; even psychotherapy was recommended and tested in a prospective randomized manner (Farquhar *et al*., 1989). Sexual abuse history, experience of insecure family life in childhood and psychological stressors were all claimed in the aetiology of this syndrome (Farquhar *et al*., 1989; Porpora and Gomel, 1997). Although a high score of anxiety and depression was noted in the present pelvic congestion syndrome patients, it is believed that the chronic pelvic pain of the condition is the result of varicosities, while the greater anxiety and depression of the patient is a natural human response to an undiagnosed, unclear aetiology of debilitating chronic pain. Psychotherapy was not used instead of any proposed treatment for aetiology, and a

significant reduction of HADS scores accompanied by an objective reduction in the diameters of pelvic veins was noted. It has been shown that surgical, interventional radiological treatments, venoconstrictors and MPA all reduce the diameter of veins and ameloriate symptoms, irrespective of the psychological status of the patient (Reginald *et al*., 1987; Mathis *et al*., 1995; Venbrux and Lambert 1999). In the present study, the GnRH analogue goserelin acetate induced a statistically more profound reduction in objective venogram scores compared with MPA, and also resulted in a more profound reduction in anxiety and total scores of HADS. The depression subscale was also reduced significantly in both groups, in parallel with venography score reduction. These results indicate that the symptoms of this syndrome cannot be regarded as a somatization because diminution of vein diameters improves psychological status by ameliorating the pain itself.

Somatization is simply the persistent, unexplained medical symptoms, and may be associated with current and lifetime depression; moreover, it is the construct that links apparently dissimilar disorders. Somatization is frequently considered as a maladaptive coping strategy gained in the early family life. Anxiety and depression on the other hand can have physical symptoms. Chronic pelvic pain without any anatomical basis may be seen in depression; it can be a somatization disorder, or the presence of a co-morbid anxiety or depression may render the patient at risk of somatic amplification. It has been shown that 70–80% of psychiatric patients initially have physical symptoms (Walker, 1997).

Despite the fact that the terms 'illness' and 'disease' are frequently used interchangeably, medical sociologists have made useful distinctions between these concepts (Walker, 1997). Disease describes the objective, physiological changes associated with organic pathology and physical signs. In patients with pelvic congestion, these are venography scores and ovarian point tenderness, as well as enlargement of the uterus and cystic ovaries. Illness, on the other hand, refers to subjective decrements in emotional, role, social and occupational functioning. Thus, the patient can complain of coital–post-coital pain and abandonment of sexual life, and may also complain of the marital consequences of this role. This distinction is very useful in characterizing the process of somatization (Walker, 1997). Patients can have disease with illness (such as those in the pure pelvic congestion group, in the organic pathology group), patients can have illness without organic disease, i.e. somatization (such as those referred for psychiatry), and patients can have disease without illness (this has been sought in the tube ligation group, where pelvic congestion might have been a normal finding in parous, sexually active women).

Accordingly, in the present study no significant pelvic congestion was noted in the tube ligation group. Eight patients were referred for psychiatry, despite their initial complaint being chronic pelvic pain. It was not possible to diagnose pelvic congestion objectively in 47 patients who, unfortunately, had deprived psychological and sexual status in terms of HADS and rSSRS scores when compared with other organic pathologies. However, after appropriate treatment these patients responded favourably both as a disease (venography score improvement) or as an illness (mood and sexual functioning improvement).

The human sexual cycle is characterized by vascular engorgement; in an already incompetent vascular system this engorgement leads to venous stasis characterized by dsypareunia and the long-lasting post-coital ache of pelvic congestion syndrome. Post-coital pain is the most common reason for abandonment of sexual activity in pelvic congestion syndrome (Beard *et al*., 1988). Indeed, it has been shown that correct treatment of pelvic congestion syndrome improves sexual satisfaction (Farquhar *et al*., 1989; Hobbs, 1990; Beard *et al*., 1991; Sichlau *et al*., 1994). In the present study, in patients with pelvic congestion syndrome a strikingly low rSSRS baseline score was found compared with other scores, indicating the negative impact of varices on sexual functioning, and treatment in both study arms was effective in restoring the scores. Again, goserelin, by achieving a significantly greater reduction in pelvic venogram scores, had a more favourable impact on sexual satisfaction of patients than did MPA. It has been shown previously that any treatment modality capable of decreasing either vein diameters or venography scores will ameloriate most of the symptomatology of pelvic congestion syndrome. As goserelin was more effective than MPA in reducing the venogram scores, the patients' symptomatology regarding sexual functioning improved more favourably in the goserelin arm.

The cause of pelvic congestion is speculative; it may be either oestrogen-dependent or simply mechanical, but it is most probably cooperative. Currently, it is known that in order to overcome the symptomatology, an effective treatment should reduce the diameters of veins and improve venous drainage of the pelvis (Hobbs, 1990). Long-term benefits of MPA (30 mg/day for 4–6 months) have been demonstrated previously, and the authors of these studies have used MPA to produce a hormonal milieu of hypo-oestrogenism and a reduced end-organ response to oestrogens (Farquhar *et al*., 1989; Reginald *et al*., 1989; Adams *et al*., 1990). These authors were successful in reducing both venogram scores and pain using this regimen, and considered MPA in the above-mentioned doses to represent first-line therapy of pelvic congestion syndrome (Farquhar *et al*., 1989). In the published literature it was noted that in some cases, unresponsiveness to MPA was the result of an unsatisfactory hypo-oestrogenic state caused by the drug itself (Farquhar *et al*., 1989). In the present study, the efficiency of goserelin compared with MPA was tested in a prospective, randomized manner. In the present authors' opinion the most important feature of pelvic congestion syndrome is its disappearance after menopause. However, it is unlikely that a temporary artificial menopause of 6 months will achieve permanent cure of the syndrome. However, we postulated that the most effective suppression of ovarian function would have a longer-lasting effect on the syndrome, and this was the reason for choosing an arbitrary 1-year interval after treatment. In fact, 1 year was longer than the term reported earlier regarding MPA. Goserelin, with its natural pharmacological consequence of creating hypo-oestrogenism, was more effective than MPA, and also found to reduce more effectively the pelvic venogram scores. Therefore, goserelin was better to ameliorate symptoms, reduce patients' anxiety and improve sexual satisfaction during the long-term treatment of pelvic congestion syndrome. According to our data, both agents improve the subjective outcome of

patients immediately after treatment. However, even though effective at the final evaluation as compared with baseline, the effectiveness of MPA was reduced statistically at 1 year after treatment. Such a trend was not observed in the goserelin arm. On final evaluation, although both agents were found to be effective in terms of both objective and subjective improvement, goserelin was found to be more effective. In other words, a greater degree of subjective improvement was noted at the end of treatment with MPA as compared with the long term. It was noted that the subjective improvement in the goserelin arm persisted for 1 year after treatment. Unfortunately, the objective data outlining the temporal effects of medications on vasculature are not yet available, although it is possible to conclude that goserelin has a longer-lasting effect than MPA on the vasculature.

Pelvic congestion syndrome is responsible for a significant percentage of chronic pelvic pain, and its identification will undoubtedly aid the clinician in the correct management of chronic pelvic pain patients. Peruterine pelvic venography is a safe, painless, rapid procedure that, in our opinion, should be supplementary to laparoscopic evaluation. When pelvic congestion patients were compared with patients having pure forms of pelvic congestion, they were found to have the most unfavourable presentation. Their pelvic symptom scores were high, and they were more deprived, both psychologically and sexually. This underlines the fact that, without venographic studies, those patients without a detectable organic pathology might easily have a diagnosis of a somatization. However, with simple venography the unfavourable signs and symptoms can be linked to a specific disorder, and correct treatment instituted that results in a much more favourable outcome than endless consultations and psychological support.

We believe that, to improve the effectiveness of medical treatment of pelvic congestion syndrome, this novel approach of using GnRH analogues should be tested in larger prospective studies, with particular emphasis on longer-term effects and safety. Moreover, it is clear that basic laboratory research is necessary in order to further clarify the aetiology of the hormonal effects, especially of oestrogens and local pain-/dilatation-producing substances. During the past decade, interventional radiological methods have been in the frontline of treatment, and these concentrated mainly on ovarian vein embolization, while disregarding the 'pelvic field' portion (varicose veins noted in the broad ligament) of the congestion; this was in contrast to the mainly dual visceral drainage (uterine and ovarian) and multiple collaterals with the parietal system of pelvic venous circulation. The use of surgical, interventional radiological or medical treatment approaches should be considered for optimal treatment that achieves long-term success both in objective and subjective outcome measures of this debilitating condition. It follows that prospective comparative studies with larger patient population sizes are necessary to provide such information.

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