VAGINAL ADMINISTRATION OF GEMEPROST FOR PREOPERATIVE CERVICAL DILATATION IN NON PREGNANT PATIENTS

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Summary: The use of Gemeprost vaginal suppositories has been evaluated in a trial for induction of the cervical dilatation in non pregnant women.

30 voluntary patients, 22 nulliparous and 8 pluriparous, had to be subjected to biopsy of the endometrium; 24 were treated for the control of sterility and 6 for menstrual perimenopausal disorders. The biopsies of the sterility control were effected in the second half of the cycle, generally without having recourse to narcosis. A single Gemeprost pessary containing 1 mg of 16, 16-dimethyl-trans-Δ_2 PGE_1 methyl ester was intravaginal administered, deeply into the posterior fornix, 3 hours before the biopsy.

The success rate was 86.66 (26 pts.) with an average dilatation of 5.38 H (Hegar) $\pm$0.75 SD. For 4 patients (13.33%) having a dilatation less than 4 H, it was necessary to complete the dilatation mechanically.

All the observed side effects presented a modest intensity: cephalalgia 6.6% (no. 2), gastralgia 3.3% (no. 1), vaginal burning 6.6% (no. 2). No significant variation of vital function parameters was recorded.

In conclusion this type of preparation of the cervix has permitted us to achieve a more gradual dilatation and to prevent the traumata of the cervico-isthmic system due to forced mechanical dilatataions by the exclusive use of Hegar's dilators.

INTRODUCTION

The validity of the uterokinetic activity of prostaglandins has been widely demonstrated in a variety of obstetric situations ([1, 2, 5]), with a remarkable advantage over the conventional methods. Indeed, the efficient employment of the PGE_2 in the induction of labour in term-delivery ([3, 4, 5]) and of $PGF_{2\alpha}$ in obstetric conditions presenting danger, such as missed abortion, intrauterine fetal death and hydatiform mole ([1, 2]) is well known.

More recently, clinical practice has seen the introduction of the " analogues of prostaglandins ". These are synthetized derivatives which, with respect to the natural prostaglandins present many advantages, permitting a more handy use. These substances, indeed, owing to their chemical and metabolic characteristics, have half-life and an oxytocic activity which are remarkably superior in comparison with the natural PGs. The uterine stimulant potency of Gemeprost in rats on day 20 of pregnancy, after intravenous injection, can be seen to be some ten times greater than that of PGE_1 and PGE_2, and 100 times greater than $PGF_{\alpha 2}$. A single injection of Gemeprost (1μg/kg i.v.) has a very long-lasting uterine stimulant action. By comparison PGE_1 and PGE_2 at 10μg/kg i.v. produce uterine contractions of a comparable magnitude but with a shorter duration of action; therefore, it is possible to reduce dose of the drug utilized and the collateral effects which are typical of the natural prostaglandins ([6]).

Although this substance has already been employed effectively in the form of vaginal suppositories in missed abortion and intrauterine fetal death ([6]), data are not available in literature regarding the use of this drug in the induction of cervical dilatation, in a non pregnant state, in order to perform diagnostic endometrium biopsies. This is a very interesting field of application, since the employment of substances able to promote cervical dilatation in a more natural way may help to prevent the traumata due to the use of traditional mechanical methods.

In the present study the effectiveness and tolerability of ONO-802 in vaginal suppositories has been evaluated for cervical dilatation in a group of 30 patients subjected to endometrium biopsy.

MATERIAL AND METHODS

Altogether, 30 voluntary patients, aged between 18 and 43, were treated 22 of them being nulliparous and 8 pluriparous; 24 patients had to be subjected to endometrium biopsy for control of sterility, and 6 for menstrual perimenopausal disorders.

In the choice of the patients, it was decided to exclude all the patients whose anamnesis contained dispositions contraindicating the use of prostaglandins: cardiovascular insufficiency, obstructive airway diseases, ulcerous colitis, diabetes mellitus, coagulation disorders, convulsive syndromes, glomerulonephritis, renal insufficiency, previous hysterotomies and allergic reactions. After being informed, all the patients accepted the treatment.

The biopsies for the control of sterility were effected in the second half of the cycle, generally without having recourse to narcosis. On the other hand, the biopsies connected with perimenopausal menstrual disorders were always performed under general anaesthetic conditions.

The program of study considered the intravaginal administration, deeply into the posterior fornix, of a single vaginal suppository containing 1.0 mg of 16, 16-dimethyl PGE_1 methil ester (Cervidil - Serono), 3 hours before the biopsy.

All the vital parameters were recorded (body temperature, blood pressure, radical pulse) immediately before the introduction of the suppository, and then every hour until the biopsy. Any haematic vaginal loss or other adverse reaction was carefully evaluated and recorded on a case report form.

The evaluation of the effectiveness of the dilation was simply determined through the dilatation of the cervical duct immediately before and 3 hours after the treatment, through the use of cylindrical Hegar dilators, and considering the highest Hegar number that it was possible to introduce throughout the whole duct without any resistance. The possible haematic losses or any other possible complications relating to the intervention itself were accurately noted. During the 3 hours following the operation, the patients were checked every hour through the evaluation of the vital signs, haematic losses and any other complications. All the possible side effects (possibly taking place) were carefully evaluated as light, moderate or serious.

RESULT

In 26 patients (86.66%) good cervical maturation was achieved with an average dilatation of 5.38 H (Hegar) $\pm$ 0.7 SD.

Such cervical modification permitted us to perform the biopsy intervention easily with instruments having a moderate gauge, such as the Novak cannula or by curette, after a further moderate mechanical dilatation with Hegar 7 or 8.

For 4 patients (13.33%) the treatment was not effective because of a dilatation below 4 H, which was not sufficient to allow the passage of the bioptic instrument. Therefore a further mechanical dilatation by means of Hegar up to no. 6 or no. 7 was necessary (Tab. 1 and 2).

The endometrium biopsies for sterility control, effected without narcosis, were well tolerated by the patients; the pain felt was minimum and due only to the biopsy, since the action of Gemeprost allowed an easy introduction of the instrument through the uterine ostium.

In the biopsies carried out on account of peri-menopausal menstrual disorders, under general anaesthetic, a good maturation was also achieved, with a cervical dilatation which was easily completed by means of the Hegar's dilators.

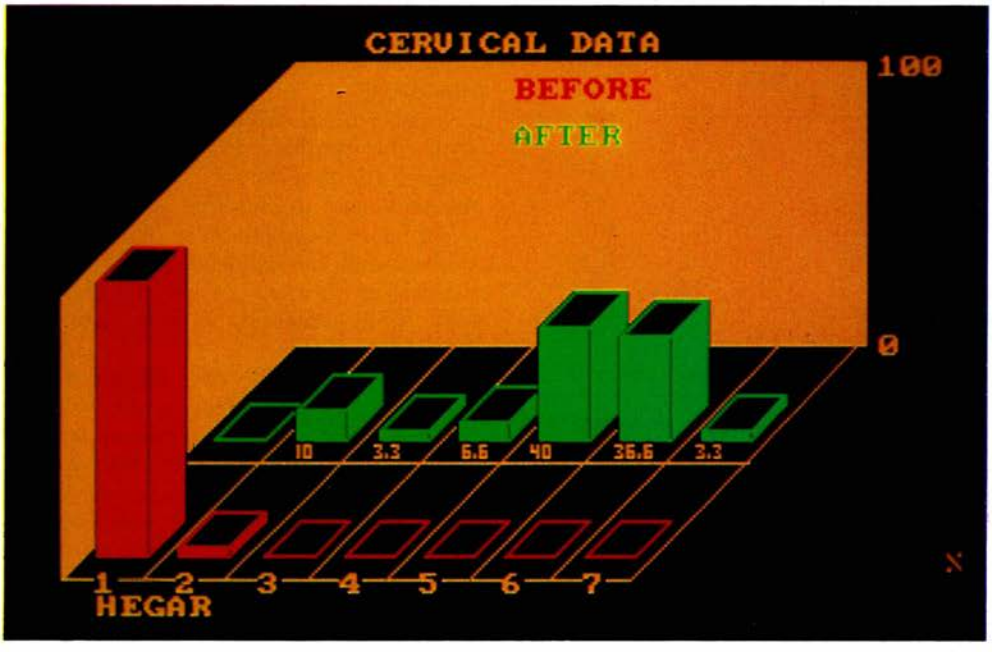

Fig. 1. — Cervical dilatation obtained with a single dose of Gemeprost 3 hours after vaginal administration.

As far as the tolerability of the drug is concerned, the following side effects were observed (Table 3):

All the observed side effects were mild and were well tolerated by the patients; therefore drug administration was not necessary.

Only 4 patients (13.3%) presented haematic losses of a menstrual type before the operation, but no significant variation on the haematochemical data was observed. Pulse rate, blood pressure and body temperature showed no significant changes.

DISCUSSION

On the basis of results obtained we can support the usefulness of this "analogous" form of PGE_1 (Gemeprost), administered vaginally, particularly in the performing of a diagnostic intervention, such as the endometrium biopsy by Novak's cannula, commonly performed in an out-patients' department and without narcosis. A single intravaginal administration of this drug determined, after 3 hours, in 86.66% of the treated patients, a

Table 1. — *Cervical data before treatment (Total no. of patients = 30).*

Consistency		Position		Dilatation (Hegar mm)	
Firm	13 (43.3%)	Posterior	30 (100%)	1	29 (96.6%)
Medium	16 (53.3%)	Mid	0	2	1 (3.4%)
Soft	1 (3.3%)	Anterior	0	>2	0

Table 2. – *Cervical data after treatment.*

Dilatation (Hegar mm)	No.	%
2	3	10
3	1	3.3
4	2	6.6
5	12	40
6	11	36.6
7	1	3.3

Table 3. – *The incidence of side effects.*

Cephalalgia	2 (6.6%)
Gastralgia	1 (3.3%)
Vaginal burning	2 (6.6%)

good preparation of the cervix and the cervical duct, with a dilatation which allowed the easy introduction of the bioptic instrument (fig. 1). Equally useful was the treatment of the patients subjected to the bioptic treatment in connection with perimenopausal disorders. This type of cervix preparation permitted us to achieve a more gradual dilatation and to prevent the traumata of the cervico-isthmic system (specially in the nulliparous patients) which may originate from forced mechanical dilatations achieved by the use of only Hegar's dilators.

These results demonstrate the oxytocic effectiveness of Gemeprost even on a non-pregnant uterus, also compared with the results obtained in a pregnant uterus by Karim ([2]), who reported 9.12 H dilatation in about 90% of the cases after 3 hours from the administration of the ONO-802 suppository.

Furthermore, similar studies conducted with other synthetic PG derivatives, administered in other ways ([7]), have not shown the same ease in handling.

As far as the tolerability of the product is concerned, the incidence of the observed side-effects was low (Table 3) and generally well tolerated without any drug support.

In conclusion, the easy administration, the scarcity of side effects which were encountered and the effectiveness ascertained after only 3 hours of latency, bear witness to the validity of this drug in the dilatation of the cervix of the non pregnant uterus.

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