The effect of clomiphene and conjugated oestrogens on cervical mucus

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Summary

The analysis of 157 menstrual cycles in 50 patients on ovulation-inducing regimens showed that in restoring ovulation clomiphene citrate inhibited cervical mucus production and caused hypersecretion of oestradiol. The inhibitory effect was inversely proportional to serum oestradiol levels, and the addition of conjugated oestrogens did not rectify the inhibitory effect, increase plasma oestradiol levels or increase cycle length. Doubling the clomiphene dosage made no significant difference to any of the parameters examined. The mechanism of this inhibitory effect is still obscure.

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Clomiphene citrate is the agent most widely used in the induction of ovulation. Although specifically indicated in the case of the anovulatory patient[1] with an intact reproductive centre [2] and normal blood oestrogen levels, [1-3] it is often arbitrarily used in conditions such as luteal phase defects[4,5] and when precise timing of ovulation is important, for example in the patient who requires artificial insemination.[6]

One of the side-effects of this form of induction of ovulation is inhibition of cervical mucus production;[7,8] this is not universally accepted,[9,10] but is often said to be one explanation for the dichotomy between pregnancies achieved and ovulatory cycles.[11] The inhibition of cervical mucus production is thought to be due to the anti-oestrogenic effect of clomiphene on the cells which secrete cervical mucus.[12] A logical solution, widely practised, is to prescribe oestrogens for 5 - 7 days after clomiphene to counteract this effect.[1,12] This has been shown not to affect ovulation.[13] Conjugated oestrogens are often used for this purpose.[12]

This paper deals with the inhibitory effect of clomiphene citrate on cervical mucus production and the value of conjugated oestrogens in restoring this production.

Patients and methods

A retrospective analysis was made of the records of 50 patients (32 with anovulation, 12 with oligo-ovulation and 6 with luteal phase defects) on an ovulation-inducing regimen. A total of 157 cycles was analysed and divided into the groups shown in Table I. The patients' initial cycles, before they had received any treatment, served as the control group.

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TABLE I. PATIENT GROUPS

Group No.	No. of cycles
I Control group	50
II Clomiphene 50 mg	51
III Clomiphene 100 mg	17
IV Clomiphene 50 and 100 mg plus 2,5 mg conjugated oestrogens	39
	157

Patients were started on clomiphene citrate 50 mg/d; this dose was doubled if ovulation, as judged by the basal body temperature chart and a rise in serum progesterone levels during the luteal phase, was not achieved. The clomiphene was taken from day 5 to day 9 of the cycle, counted from the start of menstruation. Conjugated oestrogens 2,5 mg/d for 7 days beginning on day 10 of the cycle were added if mucus production had been poor during the preceding cycle.

Patients attended the clinic from day 13 to day 16, as well as once between day 24 and day 26 for determination of the serum progesterone level. During the mid-cycle visits, cervical mucus was aspirated, and blood was taken for serum oestradiol determinations. Patients kept a basal body temperature chart and noted the length of the cycles accurately.

A cervical score was calculated, taking into consideration the colour of the cervix, the presence of a cervical mucus tongue (receptaculum cervicis), the quantity, translucency, viscosity and *spinnbarkeit* of the mucus, and whether it formed a fern pattern on drying. Values were allocated for all these parameters according to a scale ranging from 0 to 3, with a maximum score of 21 (Table II).

Oestradiol assay was performed with radio-immunoassay kits supplied by Internation CIS, Immeuble P3, 2 rue Stephenson, 78181 St Quentin Yvelines, Cédex, France. All statistical comparisons between groups were performed by the one-way analysis of variance.[14]

Results

From Fig. 1 it can be seen that there was significant inhibition of cervical mucus production in the patients on clomiphene ($P <$ 0,0001). This was true for the total cervical score as well as for ferning, *spinnbarkeit* and the presence of a receptaculum cervicis (Fig. 2). There were no significant differences between the groups receiving different doses of clomiphene. The same inhibitory effect was present in the group receiving conjugated oestrogens ($P <$ 0,0001), with no statistically significant improvement when compared with the groups receiving clomiphene alone.

Blood oestradiol levels (Fig. 3) were significantly higher ($P <$ 0,0001) in the clomiphene groups (II, III and IV), with no significant differences between the group receiving 50 mg clomiphene and that receiving 100 mg or between these groups and the group which also received oestrogen. Furthermore, if patients treated with clomiphene were divided into groups according to their blood oestradiol levels an inverse relationship to cervical mucus production was noted (Fig. 4).

TABLE II. CERVICAL SCORING SYSTEM

	Score 0	1	2	3
Colour of mucus	Pale	Pale pink	Pink	Hyperaemic
Mucus tongue (receptaculum cervicis)	No mucus	Secretion confined to borders of external os	Mucus forming tongue on posterior cervical lip	Mucus secretion reaching vaginal epithelium
Quantity	No mucus	Small amount on glass slide	Mucus covers $^1/_4$ of slide surface	Mucus covers $^1/_2$ or more of slide surface
Translucency	No mucus	Opaque	Slightly opaque — becoming translucent	Clear translucent mucus
Viscosity	No mucus	Thick, gelatinous mucus	Becomes viscous	Watery (like white of egg)
Spinnbarkeit	Nil	1-4 cm	5-7 cm	$\geqslant$ 8 cm
Ferning	Nil	Linear ferning with patchy distribution	Linear ferning with side-branches in areas on slide	Complete ferning on largest portion of slide, with well-developed side-branches

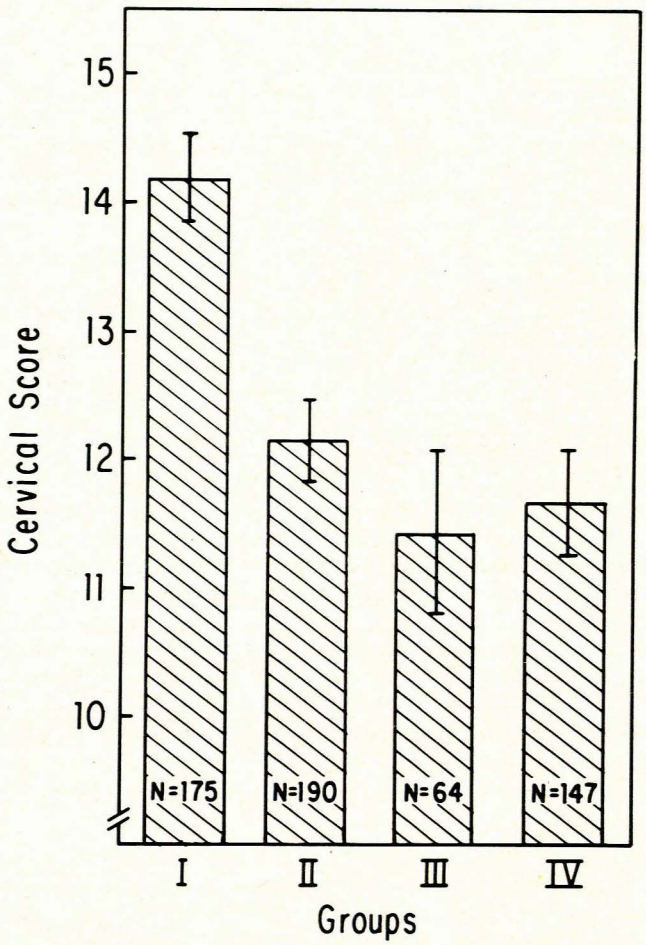

Fig. 1. Representation of the cervical score in the four groups. The number of observations, mean and standard error for each group are shown.

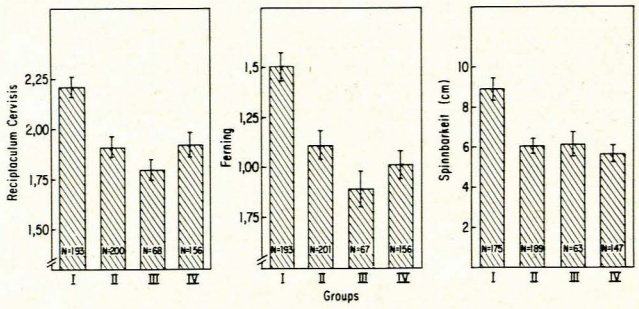

Fig. 2. Representation of observations of ferning pattern, *spinnbarkeit* and receptaculum cervicis. The number of observations, mean and standard error are shown.

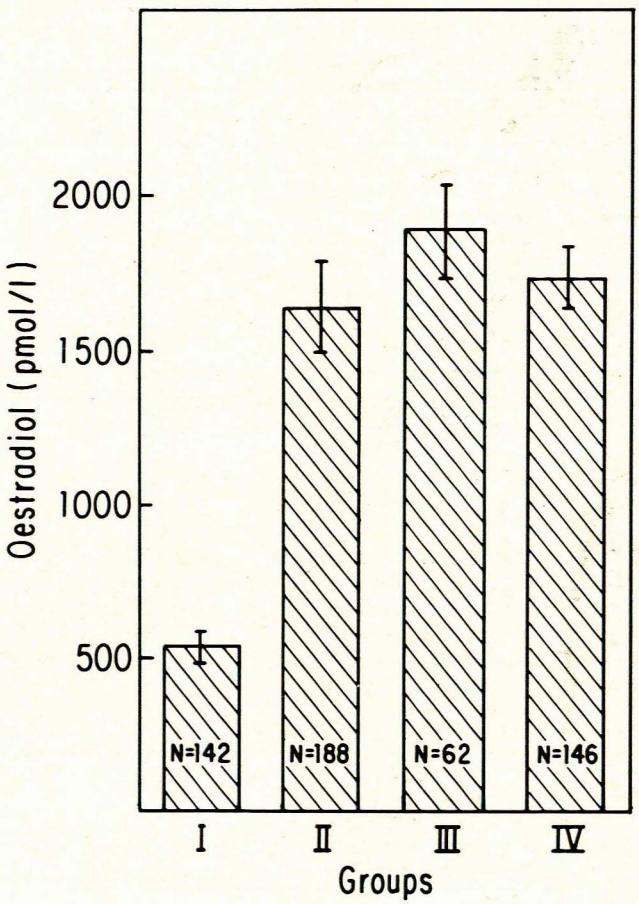

Fig. 3. Representation of serum oestradiol levels in the four groups. The number of observations, mean and standard error are shown.

As would have been expected, serum progesterone levels during the late luteal phase (Table III) were significantly greater in the treated groups than in the control group ($P < 0{,}001$), with no statistically significant differences between the different treatment groups. There were no significant differences in cycle duration (Table IV) between the different groups.

Comment

Several interesting points emerge from this study. In restoring ovulation, clomiphene citrate: (*a*) inhibits cervical mucus

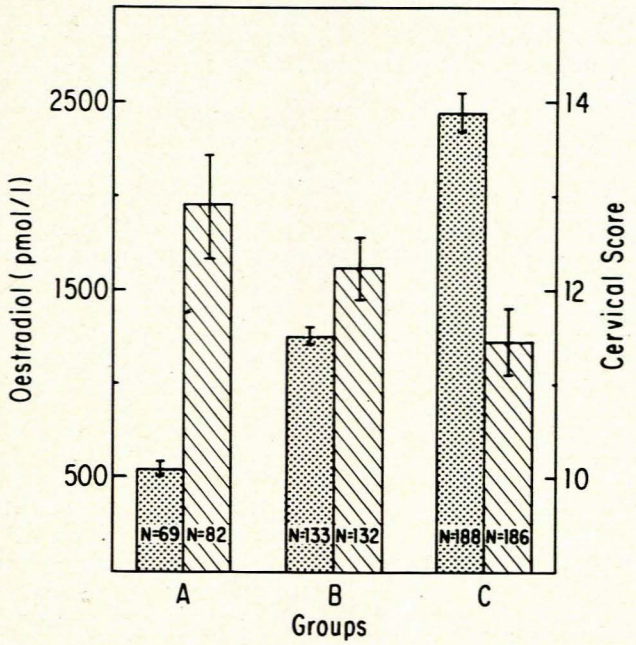

Fig. 4. Representation of the inverse relationship between serum oestradiol levels and cervical score if treatment cycles are arbitrarily divided into three groups, depending on serum oestradiol levels (group A — oestradiol < 1 000 pmol/l; group B — 1 000 - 2 000 pmol/l; group C — >2 000 pmol/l). The number of observations, mean and standard error are shown. The cervical score differed significantly ($P < 0,02$).

TABLE III. SERUM PROGESTERONE LEVELS (nmol/l)

Group No.	No. of observations	Mean ± SE
I	47	9,92 ± 1,11
II	50	18,29 ± 1,65
III	17	21,34 ± 2,96
IV	39	23,49 ± 2,35

TABLE IV. CYCLE DURATION IN DAYS

Group No.	No. of observations	Mean ± SE
I	50	28,63 ± 0,57
II	51	28,55 ± 0,82
III	17	29,76 ± 0,59
IV	39	29,14 ± 0,41

production (the total cervical score as well as its individual components being affected); and (*b*) causes hypersecretion of oestradiol, with an inverse relationship between serum oestradiol levels and cervical mucus production.

The inhibitory effect of clomiphene on cervical mucus production may be explained by a prolonged anti-oestrogen effect on the endocervical glands or perhaps an excessive production of androgens, as seen during the clomiphene-induced ovulation.[15] However, patients with elevated blood androgen levels due to the polycystic ovary syndrome, as well as those being given gonadotrophins to induce ovulation, resulting in increased follicular apparatus steroid secretion, have been found to produce sufficient cervical mucus. It therefore seems that despite increased oestradiol levels the inhibition of cervical mucus production in patients on clomiphene is due to a continuing anti-oestrogenic effect on the cervical glands.

No statistically significant differences as regards any of the parameters examined existed between the group receiving clomiphene 50 mg and that receiving 100 mg. Although the analysis was not specifically designed to compare serum progesterone levels on a time-related basis, there are no significant differences in either serum oestradiol or progesterone levels between the lower and higher clomiphene dosage groups in this study. It therefore does not seem necessary to increase the clomiphene dosage to stimulate further hormone production by the follicular apparatus in those patients who ovulate on clomiphene 50 mg.

The addition of conjugated oestrogens to the treatment regimen did not neutralize the inhibitory effect of clomiphene on the cervical mucus, nor did it serve to increase plasma oestradiol values or increase cycle length. It is therefore pointless to prescribe conjugated oestrogens to rectify the inhibitory effect of clomiphene in a particular patient.

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