VULVAR HORMONAL RECEPTOR MODIFICATIONS DURING TOPICAL STEROID TREATMENT

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Summary: Four groups of 92 patients steroid pre-treated and non-treated vulvar tissues at delivery, during episiotomy, were used in determining androgen, estrogen and progesterone receptors. In 24 central specimens ER and AR concentrations turned out to be quite low when compared to the endometrium and the breast; PgR were much higher in both the cytoplasm and the nucleus, with a statistically significant difference. After estrogen, testosterone and progesterone topical treatment we observed interesting receptor status modifications which emphasize the use of vulvar receptors as marker during local therapy.

At the ISSVD Congress of the International Society for Studies in Vulvar Disease 1985 we presented the results regarding the correlations between androgen, estrogen and progesterone receptors in dystrophic tissues; results which seem to be at the base of vulvar dystrophy.

Since there is a great deal of confusion and subjectivism in the treatment of vulvar dystrophies, we have tried to verify the existence of a hormonal marker able to inform us of the modifications of the kinetic receptorial mechanism of the vulva during any steroidal treatment.

MATERIAL AND METHODS

In order to carry out such a study we needed to have an abundance of homogeneous healthy vulvar tissue at our disposal; since the difficulty in getting the material was well known to all, we asked ourselves the following question: Does an experimental vulvar tissue, to be used to study receptorial kinetics, exist? We may answer that, probably, the vulvar tissue at delivery, durig episiotomy, is a good basis for our research.

It was to this end that we selected 92 patients ranging in age from 20 to 35 yrs, who were giving birth for the first time, with a physiological pregnancy, who had undergone no therapy, came from the same geographical area, and were white people and who had spontaneous labor lasting from 8-12 hrs.

Episiotomy, relative vulvar biopsy and assays androgen, estrogen and progesterone receptors in the cytoplasm and in the nucleus with dextran-coated-charcoal technique were performed in specimen.

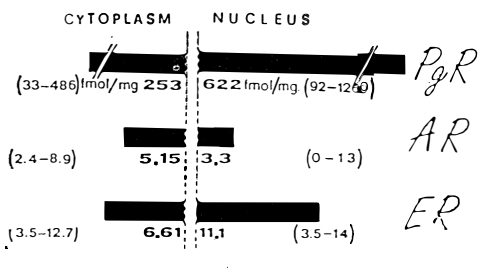
Three groups of selected patients were treated (24 pts.) with Propionate Testosterone in Vaseline 2% (1 g = 20 mg of steroid) (20 pts.), with progesterone Hydroalcholic gel 1% (2 g = 20 mg of steroid) and (24 pts.) with Estrone Sulphate cream (1 g = 0.625 mg of steroid). Moreover, we used 24 specimens from vulvar at delivery, as control.

RESULTS

Steroid receptors in vulvar tissues at delivery-non treated

We assayed Rn and Rc in 24 selected vulvar specimens at delivery (table 1).

Table 1. — *Steroid receptor status in 24 specimens of vulvar tissues at delivery, during episiotomy.*



In the cytoplasm we found important concentrations of the progesterone receptor, (253 fmol/mg), with maximum levels up to 486 fmol/mg; the nuclear acco-

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mulation turned out to be three times higher with concentrations of 622 fmol/mg up to maximum values of 1260 fmol/mg.

Androgen receptor concentrations were of 5.5 fmol/mg in the cytoplasm and 3.3 fmol/mg in the nucleus; estrogen receptor concentrations were at 6.6 fmol/mg in the cytoplasm and at 11.1 fmol/mg in the nucleus.

The results showed that in vulvar tissues, which were considered to be high in hormonal kinetics, the concentrations of estrogenic and androgenic receptors turned out to be quite low when compared to the endometrium and the breast.

On the other hand the progesterone concentrations were much higher in both the cytoplasm and the nucleus, the difference was statistically significant.

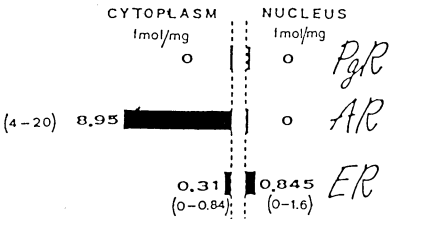
After our first try had given us unexpeted and anything but disappointing results we asked ourselves: since the vulva is richly vascularized at delivery, is it possible to manipulate the receptorial kinetics directly in vivo with topical steroids?

To answer this question we set up three groups of selected patients and treated them with testosterone (24 cases), progesterone (20 cases) and estrogen (24 cases). In order to keep the sample homogeneous we studied only those patients who had an 8-12 hours period of labour during which the vulva was intensively treated with steroids.

Hormonal receptors in estrogens pretreated vulvar tissues

The results obtained in 24 patients whose vulva were treated with estrogens are showed in table 2.

Table 2. — *Steroid receptor status in 24 specimens of vulvar tissues at delivery pre-treated with estrone sulphate cream (1 g = 0.625 mg of steroid).*



After such treatment, assays for PgR in the cytoplasm and the nucleus were impossible. The same was true for AR.

On the other hand, the concentration of AR in the cytoplasm was almost doubled with respect to the non-treated vulva.

Therefore, the topical estrogens were actually able to modify the receptorial kinetics of vulvar tissues, even at delivery. Later, we will discuss the interpretative and applicative hypotheses of this observation.

Hormonal receptors in testosterone pretreated vulvar tissues.

The receptorial status in 24 cases of vulva at delivery after treatment with testosterone is showed in table 3.

Table 3. — *Steroid receptor status in 24 specimens of vulvar tissues at delivery pre-treated with propionate testosterone in vaseline 2% (1 g = 20 mg of steroid).*

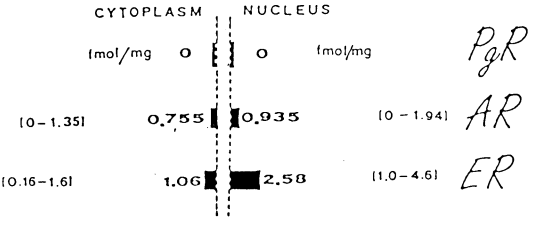
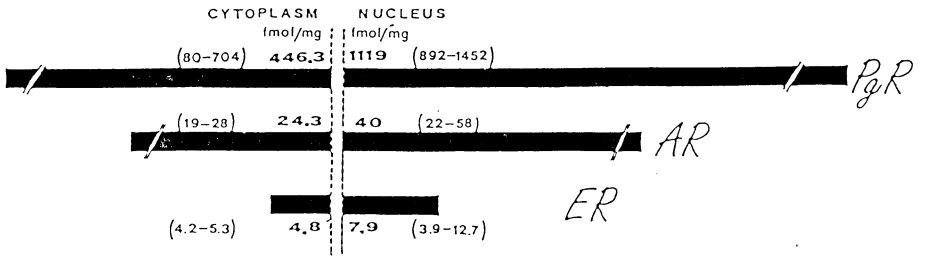


Table 4. — *Steroid receptor status in 20 specimens of vulvar tissues at delivery pre-treated with progesterone hydroalcholic gel 1% (2 g = 20 mg of steroid).*



We were not able to assay PgR after treatment in all of the tissues studied as the case was with ER. The concentrations of Ar and ER were very low compared to the corresponding values found in a non-treated vulva.

The common consequence of these two treatments (estrogens and testosterone) is, then, the undetectability of the PgR receptors in all of the 48 cases studied.

Hormonal receptors in progesterone pre-treated vulvar tissues

The phenomenon which was immediately evident (table 4) was the persistence of PgR and its concentrations. In fact, in the cytoplasm, values were found to range from 446 fmol/mg to 704 fmol/mg while in the non-treated vulva they ranged from 253 to 486 fmol/mg. The same phenomenon was observed in the nucleus in which the PgR concentrations were doubled compared to the ones of the no-treated vulva.

The concentrations of AR found in the cytoplasm are 5 times higher, and the ones in the nucleus 10 times higher than controls.

The fact that estrogenic receptors decreased in both the cytoplasm and the nucleus compared to the controls, was not unexpected since the Progesterone acted as an anti-Estrogen.

DISCUSSION

So, as to the question: Can the vulva at delivery be manipulated with topical steroids and therefore be used as an experimental model or control? We answer: Yes, since treatment with topical steroids even for only 8-10 hrs are capable of modifying the basic receptorial situation.

Thus it is only natural to ask: Can these receptors be utilized as markers and if so, in what way?

In order to answer this question we analyzed the behaviour of each Receptor with respect to the treatments carried out in these 98 cases and compared them to the corresponding values found in dystrophic and neoplastic tissues.

If we analyzed the behavior of AR it was evident that, when compared to non-treated tissues we were able to obtain an increase in AR only after treatment with Progesterone, and an apparent cytoplasmatic accumulation following treatment with ER.

What is more, if we compare AR concentration in non-treated vulva at the time of delivery to the concentrations of AR in dystrophic and neoplastic tissues (obtained in earlier studies) we found that the variations were unexpectedly weak and statistically insignificant.

If we analyzed the behavior of ER we found that, compared to tissues which were steroid non-treated, no treatment was able to modify this parameter deeply.

We did see, however, that regardless of the treatment, the nuclear concentrations are always present and are always higher than the cytoplasmatic concentrations.

In comparing the ER concentrations in non-treated vulvar tissues at delivery with the concentrations in dystrophic and cancerous tissues (obtained in earlier studies) we found that while the cytoplasmatic concentrations were similar statistically significantly, higher concentration is found in nucleus.

If we analyze the behavior of PgR, we find that this parameter is easily influenced by all of the treatments, both in a negative sense (treatment with ER and Testosterone) and in a positive sense (treatment with PgR). The results observed are quite interesting; on one hand because they demonstrate the doubling of PgR concentrations after treatment with PgR, and on the other, because they provoke an infinite series of questions which we are not yet able to answer.

Even so, we must point out that while cytoplasmatic concentrations in non-treated vulvar tissues, in dystrophic tissues and in neoplastic tissues that were quite similar in their range, the nuclear concentrations were statistically significantly higher in non-treated vulvar tissues.

Therefore, even if we consider that the tissue used in these studies was the vulva at delivery, and even with all of the hormonal implications that this organ undergoes for 9 months and particularly at delivery, we still believe this experimental model to be valid.

In fact, steroidal information in normal tissue must be carried from the cytoplasm to the nucleus and treated and non treated vulvar tissue at delivery fulfils requirement, while a deficit of nuclear transportation is frequently observed in dystrophic vulvar tissues.

CONCLUSIONS

Our observations derive from the fact that we always found a higher accumulation of ER in the nucleus than in the cytoplasm in vulvar tissues at delivery, while in dystrophies the ratio was always the opposite with a higher cytoplasmatic rather than nuclear accumulation.

In the future we hope to concentrate our studies only on the nuclear translocation of ER and PgR, since ER turned out to be stably represented in treated and non-treated vulvar tissues at delivery.

Which of the three steroidal treatments may be used in therapy in the light of this information? I would like to answer that PgR is the steroid that provokes the most changes at the receptorial level. Our group is experimenting with it now.

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