ENDOMETRIAL HORMONAL RECEPTORS AS MARKER OF BENIGN BREAST DISEASE (B.B.D.)

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Summary: The problem of hormonal treatment of benign disease and mastodynia is still dividing Clinicians and Researchers.

The Authors, in order to select the patients suitable to be treated, propose the assay of Estradiol and Progesterone Receptors in the most accessible hormone-dependant tissue: the Endometrium.

Author's data point out a quite different behaviour of Estradiol and Progesterone cytoplasmic receptors in the Endometrium of women with B.B.D. and controls.

The knowledge of this information in the single patients will release from subjectivity when deciding about B.B.D. therapy or when trying to correct unsatisfactory treatment.

The clinical importance of the hormone-dependent pathology of the breast is well-known to be influenced by the endocrine modulation complex, synergic or antagonistic, of direct-action hormones (estrogens, progesterone, androgens, prolactin) and indirect (insulin, gonadotropins, adrenal steroids, somatotrope, prostglandins and others) ([1, 2, 3]).

Such action is mediated by the correlation between hormones and their own receptors and between hormones and receptors specific for other hormones.

Therefore in mammary physiopathology it is necessary to know the endocrine climate of the patient and the receptorial situation of the breast. The first is simple with radio-immunological assay; the second is more complex and necessitates invasive methods.

With regard to the role played by the hormonal receptors in benign diseases of the breast, we must remember that the site of origin of the mammary lesions is the terminal ductal alveolary unit.

The difficulties of nosological classification of the different pathologies generically defined as B.B.D. justifies the different levels of the receptorial concentrations related to the cellular heterogenicity, so much the greater as the lesion is small ([4, 5, 6, 7, 8]).

In the benign forms three grades of cellularity have been individuated:

1st grade: prevalent proliferation of epithelial cells;

2nd grade: intermediate picture;

3rd grade: high fibrosis.

Literature and our own experience (table 1) show a receptorial negativity of 67.3% in cases of B.B.D. and receptorial positivity of 25.1% of cases. Receptorial negativity is correlated to a cellularity of 2nd and 3rd grade (intermediate picture and/or high fibrosis) and therefore to a long-standing pathology.

Receptorial positivity is prevalently correlated to 1st grade cellularity (proliferation of epithelial cells and therefore a pathology of recent date). In cases of receptorial cellularity the cellular density is high, the level of fibrosis still scanty, and therefore estrogenic influence is still present.

The clinical usefulness of the study of hormone receptors in forms of B.B.D. is therefore evident.

It is, besides, important for the quantitative determination of the mammary receptors to bear in mind the plurality of the tissues and the consequent technical

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Table 1. — *Estrogen receptors in benign breast diseases.*

	Cases	E_2R+	E_2R-	$E_2R+/-$
Martin (7)	84	11 (13 %)	49 (58.3%)	24 (28.5%)
Singhakowinta (54)	58	34 (58.6%)	24 (41.4%)	0
Feherty (25)	41	3 (7.3%)	38 (92.6%)	0
Rosen (34)	27	3 (11.1%)	24 (88.9%)	0
Wittliff (8)	6	0	6 (100%)	0
Heuson (26)	12	6 (50.0%)	6 (100%)	0
Leclercq (52)	19	5 (26.3%)	14 (73.6%)	0
Nardelli (*)	16	0	16 (100%)	0
Total	263	62 (25.1%)	177 (67.3%)	24 (9.48%)

(*) Obst. Gyn. Inst. University of Padua.

difficulties. In fact the glandular parenchima and ducts are surrounded by adipose and connective tissue to sustain the veins, lymphatics and nerves. All these tissues are devoid of steroidal receptors and may therefore falsify the results of the quantitative assays.

In consideration of such difficulties and of the analogous hormone-sensitivity between breast and endometrium, our working group decided some years ago also to study the receptorial analogy of these tissues. We were lead into this research not only by the simplicity of the endometrial method but also by the analogy of benign and malign pathology between breast and endometrium.

We therefore evaluated the receptorial situation of the breast and of the endometrium between themselves and in relation to the histomorphological pictures of benign breast disease.

MATERIAL AND METHODS

The research was carried out on 80 patients of whom 28 were affected by mastodina with mastosic objectivity, and 50 in a control group.

The diagnosis of B.B.D. was decided on the basis of the following tests: clinical examination, thermography, diaphanoscopy, mammography, histological examination; in 16 cases the quantitative determination of ER and PgR was undertaken. The study of *mammary receptors* is today carried out in our institute by quantitative biochemical method (Carbon-Dextrano) and qualitative histochemical (Immunofluorescence); the results we obtained, presupposing quantitative measures, were obtained by the biochemical method (table 1).

The classification in ranges provides for the following distinctions:

1) range from 0 to 3 fmol/mg. The concentrations included in this are considered as negative responses.

2) range from 3 to 10 fmol/mg. The concentrations included in this range are considered borderline responses.

3) range from 10 to 100 fmol/m. The receptorial concentrations included between 10 and 100 fmol/mg are considered as positive responses.

4) range above 100 fmol/mg. The concentrations above 100 fmol/mg are considered highly significant responses.

The study of the endometrial receptors was carried out on material obtained in the out-patients department by aspiration with semiflexible probe, calibre 8, and with the Carbon-Dextrano quantitative method.

There were, besides, 42 patients with B.B.D. and 27 healthy patients in whom we carried out a study of the luteinic phase through RIA dosage of Progesterone, Estradiol, Prolactin and Testosterone on the 3rd, 9th and 12th days after the termic rise.

RESULTS

The variety of histomorphoolgical pictures and of evolutive phases in the form of B.B.D. hitherto considered do not allow us to indicate for each one of them a

typical mammary and endometrial receptorial state.

In spite of this the study of the cytoplasmatic receptors to Estradiol and Progesterone in the endometrium gave interesting and significant results.

In the control group the mammary receptors (Estrogen and Progesterone) were dosed in 20 patients and we noticed that they were consistently in the negativity range as, in fact is noted in the data in literature (table 2).

Table 2. — *Estrogen receptors in normal breast tissues.*

Author	Cases	RE-	RE-
Spaeren	9	——	9 (100%)
Heuson	16	——	16 (100%)
Leclercq	24	3 (12.5%)	21 (87.5%)
Rosen	81	——	81 (87.5%)
Wittliff	16	——	16 (100%)
Nardelli (*)	20	3	20 (100%)
Total	166 (1.80%)	3	163 (98.1%)

(*) Obst. Gyn. Inst. University of Padua.

On the other hand, regarding the endometrial receptors dosed in all 52 patients in the control group, the relation ER/PgR passes from 1:3.7 of the proliferative phase to 1:2 of the secretive phase, in agreement with the physiological nuclear translocation for progesterone and consequent antiestrogenic action of the progesterone itself (table 3). It was, besides, noted that the ER/PgR relation is progressively reduced in relation to the years of fertile age and therefore of exposure to the hormones because of lesser synthesis of PgR, while ER levels remain stable (table 4). This last datum is important since it shows how eventual hormone therapies cannot be identical and standardised in all periods of a woman's life but must instead be related to the actual receptorial capacity of the tissues.

Table 3. — *Hormonal receptors in relation to endometrial phases.*

Phases	E_2R fmol/mg	Ratio	PgR fmol/mg
Controls			
Proliferative	90.5	1 : 3.7	341.6
Secretive	79.7	1 / 2	172.3
B.B.D.			
Proliferative	184.4	1 : 5.4	1004.4
Secretive	166.2	1 / 5.6	929.2

B.B.D. = Benign Breast Disease.

Table 4. — *Hormonal receptors of the endometrium in relation to the number of years of exposition to the hormones.*

Years		E_2R fmol/mg	Ratio	PgR fmol/mg
Controls	<20	58.17	1 : 4.9	288.5
(52 cases)	20-30	100.1	1 : 3.6	365.35
	>30	101.95	1 : 1.7	174.26
B.B.D.	<20	297	1 : 4.8	142.4
(28 cases)	20-30	255	1 : 5.3	120.5
	>30	101	1 : 4.5	454

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Regarding the group of patients affected by BBD we obtained the following results (table 5):

– the mammary hormonal receptors, studied in 20 cases, were always within the negativity range (from 0 to 3 fmol/mg);

– with regard, instead, to the endometrial receptors dosed in all 28 patients we observed that the ER/PgR did not show the physiological decrease seen in relation to the passage from the proliferative to the secretive phase. This may be explained by a minor nuclear translocation of the receptor to Progesterone related to a reduced occupation of the receptorial sites to a cytoplasmatic level. In other

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	B.B.D.	225.0	1 : 5.3	1205.0
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words a reduced progenistic type of activity is shown;

– the ER/PgR relationship functioning in the years of exposure to the hormones (the fertile years) and in particular the PgR, not only demonstrates that progressive reduction observed in the control group, but, persisting at high levels in all the patients studied, was significantly different from the control groups;

– for a period of exposure to the hormones under 20 years the ER/PgR relation is similar to that shown in the controls, while the basic tone proved clearly increased. By way of hypothesis this picture might be an expression of an endocrine prodisposition to hormone-dependant mammary pathology;

– increasing the period of exposure from 20 to 30 years the ER/PgR relation proved to be one and a half times increased;

– finally for periods of exposure above 30 years the ER/PgR proves to be two and a half times increased in relation to the controls).

The significance of the dosages of the hormone receptors of the endometrium in cases of B.B.D. not only indicate hormone dependence but may also lead to useful indications in the choice of hormonal therapy. As we said, at the beginning of mammary hormone therapy it is important to know the endocrine climate and the receptorial situation. With regard to the receptorial situation, while the mammary one may give us indications relating to degrees of cellularity but anyway of no great significance, the endometrial, as we have seen, is indicative and of extreme interpretative interest.

Moreover, in the examined series, there was no significative difference of Progesterone, P.E.L. ratio, Prolactin and Testosterone plasma levels determined in the lutheal phase.

CONCLUSIONS

On the basis of our experience we may therefore conclude that hormonal dosages do not give a characterisation of B.B.D. of etiopathogenetic and consequently therapeutic order of hormonal type. In our experience, instead, it proved that the evaluation of the endometrial receptors allows for the indirect monitorising of the basic hormonal climate of the patient and again allows for non-invasive and even frequent follow-up in time.

For example in mastodinia without objectivity attributed to the breast and therefore symptom of B.B.D. in the initial phase, the receptorial situation of the endometrium proved abnormally high and remained so, as the mammary one has proved to be in our research.

In advanced stage B.B.D., with fibrosis and nodularity and therefore cellularity of the 2nd-3rd grade, the receptorial situation is negatived in the breast while the endometrial remains high, to indicate the persistant stimulative action of a hormonal pathological state.

In these conditions it is possible to establish personalised steroid treatment even on the basis of evaluation of the effects. In fact periodically repeating the endometrial extraction (by simple aspiration) we are able to know if the steroidal treatment is qualitatively and quantitati-

vely suitable and therefore monitorise the patient clinically with a reliable marker.

Thus it is possible to choose a therapy with progesterone, or with ovariostatics, with antiestrogens, with antiprolactinemics, with cyproterone acetate or with triphasic estroprogenistics, with Lh or again with topic progesterone etc. applicable in individual cases, also on the basis of the clinicians experience and of the confidence they have in hormonal therapy.

It is superfluous to underline the value of a precautionary measure, aimed at and monitorising of the mammary (and endometrial) hormonal dependant pathology, which otherwise might evolve into malignant neoplasias.

It is also important to consider the possibility of screening patients at risk of benign (and perhaps also malign) mammary pathology, on the basis of the endometrial receptor levels.

The study of estrogen and progesterone endometrium receptor levels in the periovulatory phase, because of the simplicity of its execution and the reliability of the assay, opens new and interesting diagnostic possibilities in gynecological endocrinology, and we think it will find ever increasing application as a marker of hormone dependance.

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