Myometrial hypertrophy and uterine metropathy without apparent organic cause: rate or responsability

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Summary: Between 1971 and 1980 more than 6,000,000 hysterectomies were performed in the USA. Dysfunctional uterine hemorrhagia with non tumoral uterus and hypertrophic characteristic has been one of the principal indications, without possibility of definition as a pathological entity with its own characteristics.

With all these premises the Authors have attempted to see, by means of morphometric studies, the myocite characteristics and the proportion and composition of the uterine wall and at the same time eventual hormonedependence of this phenomenon. For this they turn to to determination of oestrogen and progesterone receptors.

Key words: Myometrial hypertrophy; Dysfunctional uterine hemorrhagia.

INTRODUCTION

Between 1971 and 1980 more than 6.000.000 hysterectomies were performed in the USA ([1]), the first indications were: leiomyoma, dysfunctional uterine hemorrhage and genital prolapse. For these Authors dysfunctional uterine hemorrage is an abnormal hemorrhage without known organic cause, they agree, for treatment, that hysterectomy must only be considered after curettage and hormonetherapy have failed. We think that the therapeutic properties of curettage and hormonotherapy, applied in this decade, have had a lot of failures and it is difficult to explain this situation when endometrial pathology is discarded by curettage.

Other Authors have found the same indications for hysterectomy ([2, 3, 4, 9]).

The discovery of enlarged uterus, no loss of symmetry, no adenomyosis and/or endometrial pathology has allowed the inclusion of some entities which were named "fibrosis uteri", uterine subinvolution, chronic passive congestion, etc. There is great confusion with regard to diagnostic judgements on hypertrophic ([6, 7, 8, 9, 10]). Many theories have existed regarding etiopathogenesis from von Scanzoni ([11]) in 1861 to Pellegri and Montanari ([12]) in 1981.

We suggest those references are both older lower and they differ from the present situation where hysterectomy represents the most frequent surgical operation in the western world, and without histopathological references regarding uterine hypertrophy and such eventual etiopathogenic factors.

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We think that the myometrium has not considered been as a protagonist in the responsability for "uterine metrorrhagia refractory to treatment", probably because of mechanical problems, where normal contractility defects can comprimise the hemostatic first phases on uterine cavity surface, even in normal endometrium. Naturally, the histological myometrial pattern is at first normal and it is difficult not to relate this eventual physiological uterine contractility defect to a certain degree of uterine wall with hypertrophy, or with fibroconnective tissue rate which those contain. We add to these hypermenorrheas without apparent cause, the uterus being slightly increased in size and of hard consistency.

If we accept the normal myometrium and uterine myoma ([13]) hormonedependence and some of the suggestions mentioned before, we can support our hypothesis in that "hypertrophic uterus" too may be conditioned by this hormonal factor and so respond to these variations.

The purpose of this study is to establish from these aspects an analysis reviewing of the concept of uterine hypertrophy (clinical and histopathological), and to estimate the eventual hormone dependence of this entity.

We have had to change the strategy of the study because it is not possible to compare a group with normal uterus and another group with hypertrophic uterus. First, it is impossible to find agreement among different Authors in defining a normal uterus. Without agreed definition between the two groups, tissue hormonedependence analysis is a problem. We think no significant differences exist between one uterus of 115 g and one of 125 g; according to Lewis *et al.* ([6]) that 120 g represents the lowerst limit for the diagnosis of hypertrophic uterus.

We have chosen the analysis of eventual relation between myometrial tissue morphohystology and hormonedependence in all physiologic situations which can be present in woman dating from puberty.

MATERIALS AND METHODS

Between 1986-87 we included in our study 24 patients undergoing hysterectomy for various reasons, except uterine tumour, diffuse adenomyosis, endometrial pathology, no parity or more than 3 pregnancies, previous hormonal treatments, hyperprolactinemia.

Previous surgery, a complete anamnesis and a systematic gynecological exploration were performed according to preoperation schedule.

Immediately after removing uterus we took a sample of myometrial fundus without endometrium. Each sample was divided into 2 parts. One was frozen and stored in liquid nitrogen for receptor study; the other was fixed in formalin and used for morphometric analysis.

A) *Prolactin, progesterone and oestradiol determinations.*

These were performed by direct radioimmunoassay without previous extraction using I 125 marker following manufacturer's kit instructions.

Prolactin: PROLK-PR, Sorin Biomedica: polyethylene glycol with excess of second antibody with intra and inter-assay about 3.9% and 9.5% respectively.

Oestradiol: Estradiol direct. Radio Isotopen Service: a second solid phase antibody was used. Sensitivity: 10 pg/ml, intra and inter-assay variation coefficients: 10.5% and 11.2% respectively for X=78.2 pg/ml.

Progesterone: RIA gnost Progesteron-Behring: solid phase antibody. Sensitivity: 0.6 ng/ml, intra and inter-assay variation coefficients: 6.1% and 7.3% respectively.

B) *Oestrogen and progesterone receptors.*

We used the Korennamn ([14]) method adapted by Viladiu and Figueras. The sample was taken during surgery after removing the uterus. We put it into a chriotub NUNC and then into a thermos with dry ice (−80° C). It was carried to the laboratory where it was stored in a chriogenic container with liquid nitrogen (−130° C). For sample preparation we took off the fat and connective tissue and washed it with physiological serum to eliminate blood. The hardened samples were pulverized, previously frozen, in a mechanical mortar steeped at low temperature. After it had homogeneised at 4° C with TEM buffer and centrifuged at 105000 x g at 4° C for one hour. We separated cytosol and determined the receptors.

Oestrogen: Specific activity 112 li/mM ([2, 4, 6, 7]) 3 H-17-β oestradiol (Amersham Radiochemical Centre). Radioactivity was measured by a liquid scintillation computer LKB-Wallac 1211, the results were shown in mol/mg proteins according to Scatchard's mathematic pattern.

Progesterone: It was the same as with 3 H ORG 2058 (Amersham) marker.

C) *Macroscopic study: anatomo-pathologic method.*

Once the annexes were removed the hysterectomy specimens were weighed in the operating-theatre prior to taking samples.

In the anatomo-pathologic department preparation, we measured the depth of the myometrium at the uterine fundu and in the anterior and posterior faces of the same fundus.

D) *Microscopic study: trichromic stainings. Anatomo-pathologic method.*

The samples were processed, conventionally, and were fixed with buffered formalin at 10% and embedded in paraffin. The histologic slices were stained with haematoxin, eosin and trichromic staining.

We performed conventional optic microscopy. We used trichromic staining to estimate the vessel, stromal cells and fibroconnective tissue by means of a simple cross appraisal system (+, ++, +++) always performed by the same observer.

E) *Anatomo-pathologic method. Morphometric analysis.*

The morphometric analysis was performed by:

- optic microscopy (Dialux, Leitz);
- planimetry equipment Videoplan Ibas 1 (Kontron, Bildanalyse, RFA);
- video camera (Saticon VK-C870, Hitachi).

We used YX program (Kontron software) for performing surface measures and cell counts.

15 different fields were examined of each histologic preparation for resulting homogeneity. The histologic flelds were selected according to: maximal cellular density, sectioned longitudinal sense kernels, no structural degenerative alterations.

By YX program (Kontron software) we performed:

a) relative nuclear area (NA) to determine the myometrial tissue rate that concerns the uterine myocites cytoplasm, interstitial stroma, vessels, etc.). There was an indirect cell hypertrophy estimation with a constant kernel/cytoplasm rate for each cellular type.

b) uterine myocite nuclear density (ND) was the arithmetical means of counting kernels in the 15 histopathological fields, expressed in numbers of kernels per myometrial tissue mm^2.

F) *Statistic method.*

Statistical inference:

1) Normality test: X2 for qualitative variable and Kolmogorov-Smirnov test for quantitative variable.

2) Mann-Whitney U test (no parametric test for means estimation).

3) Kruskal-Wallis 1-Way Anova (no parametric test for more than two means estimation).

4) Spearman correlation coefficient (no parametric test).

RESULTS

Statistical inference.

1) Normality test:

a) No normality distribution:

- X^2 test: vessel trichromic study
  smooth muscle trichromic study
  fibroconnective tissue trichromic study.
- Kolmogorov-Smirnov test:
  blood progesterone level
  blood prolactin level

b) Normality distribution: Kolmogorov-Smirnov test age, weight, height, blood oestrogen level, uterus weight, depth of myometrium, oestrogen receptor, progesterone receptors, nuclear density % nuclear area in field.

2) Mann-Whitney U test:

- The myometrial depth is greater according to the thickness of the smooth muscle component in the trichromic study (+++) and is less thick according to the smooth muscle when it is lower in the myometrium (error 3.61%).
- No correlation between smooth muscle tissue quantity in myometrium and more or less ER presence.
- No correlation between muscle component quantity and more or less PR presence.

- The ER/PR is greater the lesser the trichromic smooth muscle component quantification (++) than when is +++ (error 4.72%).
- The fibroconnective tissue variations do not influence depth of myometrium.
- The ER and PR levels do not influence the myometrium fibroconnective trichromic variations studied.
- The ER/PR does not influence the fibroconnective myometrium trichromic variations studied.

3) Kruskal-Wallis 1-Way Anova:

- There was no relation between myometrium depth and myometrial vessels trichromic variations studied.
- We found more ER when myometrium vessels trichromic study was +++ than when was it + (error 2.84%).
- There were no significant differences between PR levels and myometrium vessels trichromic study variations.
- ER and PR rate was greater when the trichromic vessels studied were +++ than when + (error 2.39%).

4) Spearman correlation coefficient:

- Myometrial depth was greater when: the weight of the uterus was greater ($p < 0.0005$).
  NA was greater ($p = 0.017$)
  ND was lower ($p < 0.0005$)
  NA/ND were greater (error 0.5%)
  ER were lower (error 0.5%)
  PR were greater ($p = 0.022$).
- There were no significant differences between:

* Myometrial depth and weight/height ($p = 0.548$)
PR and ND ($p = 0.063$)
ER and NA ($p = 0.123$)
Peripheric E level and PR quantity (4$p = 0.169$)
Peripheric P level and ER quantity ($p = 0.101$)
Peripheric P level and PR quantity ($p = 0.987$)
PR quantity and ER quantity ($p = 0.274$)
Uterus weight and NA ($p = 0.120$)
Uterus weight and weight/height ($p = 0.507$)

- Peripheric E level was greater when ER quantity was less ($p = 0.012$).
- ER/PR was greater when:
  ER quantity was greater ($p = 0.0005$)
  PR quantity was lesser ($p = 0.0022$)
  NA/ND was lesser ($p = 0.0005$)
  NA in field was lesser ($p = 0.004$)
  ND was greater ($p = 0.0005$)
- ER quantity was greater when:
  NA/ND was less ($p = 0.0005$)
  ND was greater ($p = 0.005$)
- PR quantity was greater when:
  NA/ND was less ($p = 0.01$)
  NA field was greater ($p = 0.0005$).
- Uterus weight was greater when:
  PR quantity was greater ($p = 0.023$)
  ND was less ($p = 0.0005$)
  NA/ND was greater ($p = 0.0005$)
  ER quantity was less ($p = 0.0005$)
  ER/PR was less ($p = 0.0005$)

DISCUSSION

We have only worked with normal histological myometrium. Certain Authors have estimated uterine hypertrophy when the myometrial depth was greater than 2 cm, thus they explained metropathy, that concerns uteri greater than 120-130 g [1, 15, 16].

We did not find correlation between myometrial depth and weight/height. Myometrial depth correlated positively with uterine weight (Fig. 1). Tables 1, 2, 3, present surgical indications, uterus weight and myometrium depth.

The percentage of NA/ND correspond to the mean nuclear size the myometrial cells. NA/ND correlated positively with myometrial depth (Fig. 2). ND correlated inversely with myometrial depth (Fig. 3).

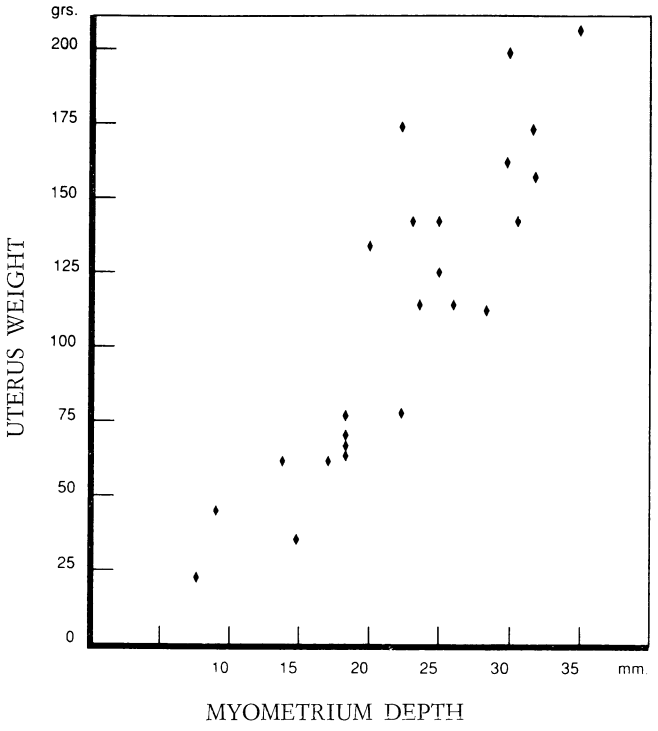

Fig. 1. — Rate between myometrial depth and uterine weigth in all patients studied.

We foresee these results correlating NA/ND with uterine weight (Fig. 4). We found hypertrophy but no hyperplasia for myocites in "hypertrophic" uterus.

By mean of trichromic stainings the results were: myometrial depth was greater when the smooth muscle rate was greater; fibroconnective tissue and observed vessels rate did not correlate with myometrial depth. We do not agree with Authors who explain "hypertrophic" uterus by the increase of myometrial fibroconnective element or by vessel sclerosis.

All patients had had 2-3 pregnancies and in this study we did not check correlation between fibroconnective tissue rate and parity.

We agree that uterine metropathy, without manifest or demonstrated organicity, correlated with diffuse uterine hypertrophy through the enlargement of the myometrium, conditioned by cell hypertrophy and, concretely by muscle element.

To us, endometrial hyperplasia alone does not explain this hyperme-

Table 1. – *Surgical indications in menopausal group. Weight and depth of myometrium.*

Indication	Weight uterus g.	Myometrial depth mm.
Urinary incontinence (UI) + Genital prolapse	22	7
Genital prolapse	38	15
UI + Genital prolapse	42	9
Genital prolapse	59	17
UI + Cystorectocel	60	14
UI + Cystorectocel	63	18
UI + Cystorectocel	80	22

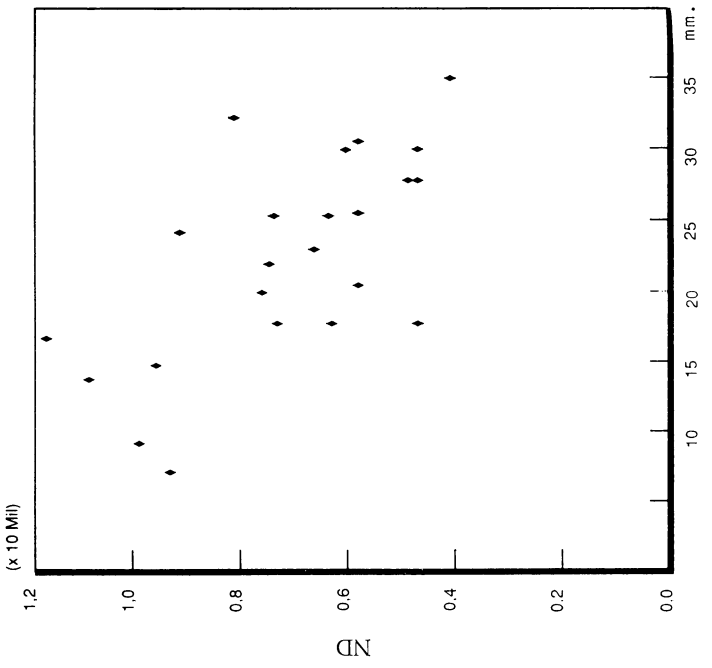

Fig. 3. — Myometrium depth and nuclear density/analysed area rate.

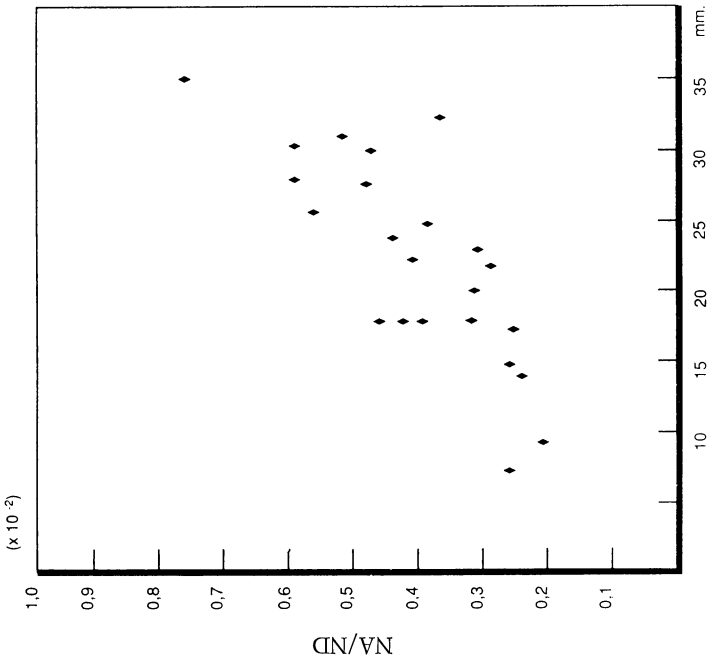

Fig. 2. — Mean nuclear size (NA/ND) and myometrium depth rate.

Table 2. – *Surgical indications in proliferative phase group. Weight and depth of myometrium.*

Indication	Weight uterus g.	Myometrial depth mm.
UI + Sterilization	66	18
UI + Metropathy + Cystorect.	70	18
UI + Cystorect. + Sterilizat.	115	24
Metropathy	125	25
Metropathy	133	20
Metropathy	138	23
Metropatry	140	25
Metropathy	140	28
Metropathy	160	28
Metropathy	170	32
Metropathy	171	22

norrhoea and/or menometrorrhagia but indeed dolico-menorrhagia and/or menorragia.

The symptoms are similar to myomatous uterus, and are often confused with it; it possesses demonstrable hormonsensibility ([13]), and is also associated with endometrial hyperplasia.

We determined myometrium ER and PR and serum 17β oestradiol and progesterone on the same day as the surgical operation in order to estimate the results better.

The myometrium is a target tissue for oestrogen and progesterone, and the ER and PR can be exact markers for studying the hormonsensibility of the tissue.

We rely on ER/PR ([17]) for correcting the reactions regarding different hormonal situations in the ER and PR concentration.

We can affirm that the myometrial depth is greater the lower ER concentration is (Fig. 5), the myometrial depth positively correlated with PR quantity ($p = 0.0005$). So, the myometrium depth is hormondependent parameter and positively oestrogendependent. PR high concentrations indicate an intracellular oestrogen activity and effective working of ER at nuclear level. Supposing progesterone controls its own receptors it shows progesterone deficiency in this tissue with consequent hyperoestrogenic effects.

With regard to ER concentration we must consider that after transference a cytoplasmic ER complex concentration decreases and nuclear accumulation of this complex is observed.

The figures 5 and 6 show the rate between myometrial depth and uterine weight respectively and ER/PR, whether myometrial depth or uterine weight have an exponential rate with ER/PR. We also compared ER/PR with mean nuclear size (NA/ND) of cells which compose these myometria, the rate is also exponential (Fig. 7).

It is the same for different hormonal phases in adult woman (proliferative, secretory and menopausal phases).

We cannot come to any conclusions as to the pregnant series.

In spayed female rats Martin *et al.* ([18]) showed that after oestrogen treatment an increased miometrial volume was produced by means of hypertrophy and oedema.

They observe in the stroma slight cell proliferation increase. They concluded that only epithelial cells respond to oestrogen stimulation presenting cell division. Clark ([19]), Tachi ([20]) had the same results. Quarmby and Korach ([21]) found, after oestradiol stimulation, timidine H3 was incorporated in epithelial cells but not in the myometrial or stromal uterine cells of spayed female rats. They also found

Table 3. – *Surgical indications in secretory phase group. Weight and depth of myometrium.*

Indication	Weight uterus g.	Myometrial depth mm.
UI + Cystorectocel	78	18
Metropathy	113	28
Metropathy	115	26
Metropathy	155	30
Metropathy	198	30
Metropathy	210	35

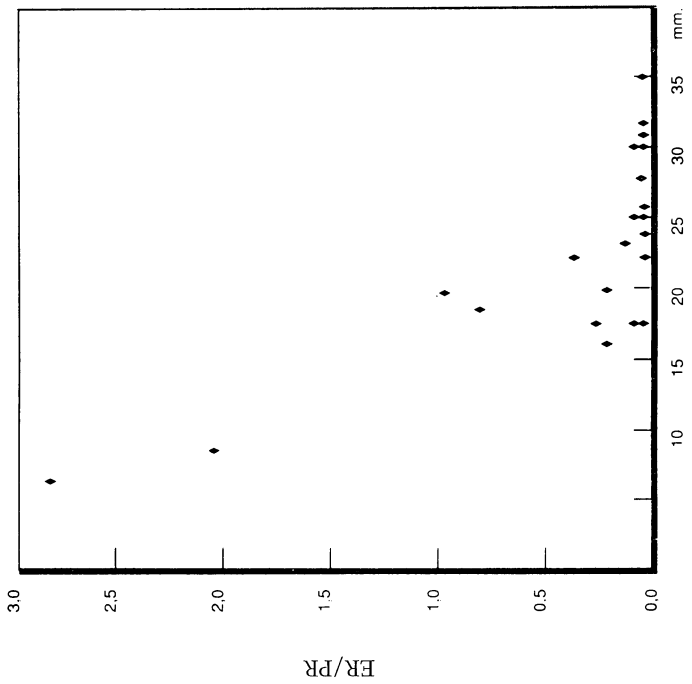

Fig. 5. — Myometrium depth and ER/PR rate.

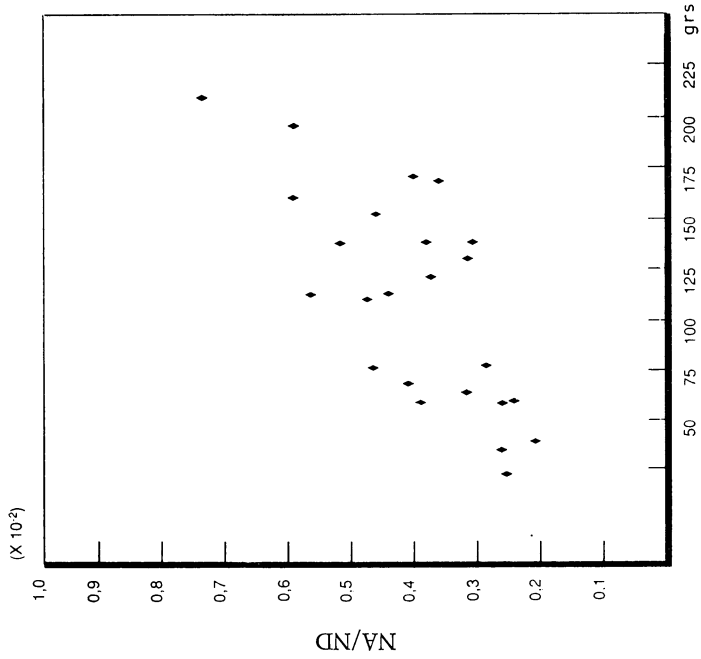

Fig. 4. — Mean nuclear size and uterus weight rate.

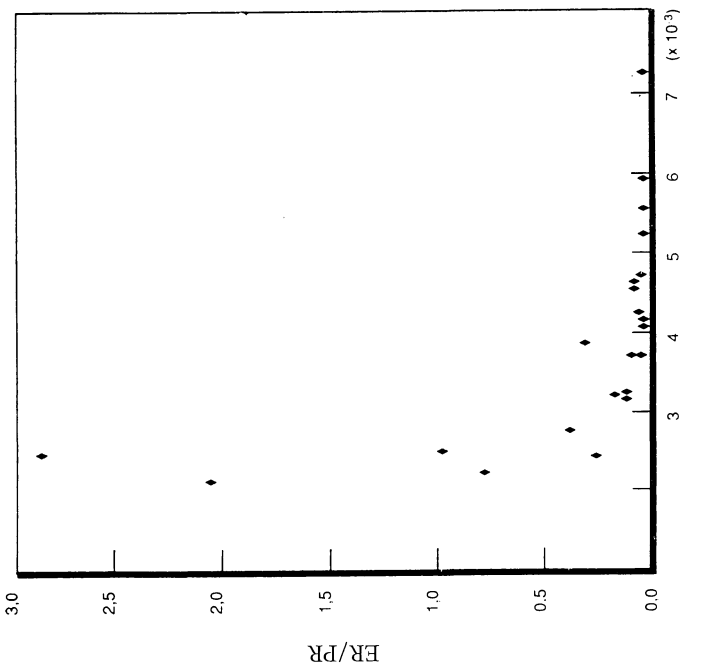

Fig. 7. — ER/PR and nuclear mean size rate.

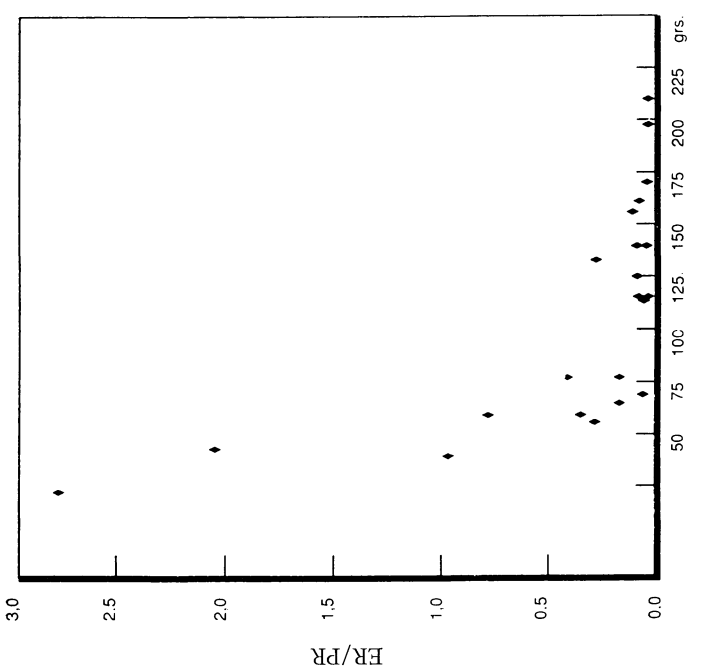

Fig. 6. — Uterus weight and ER/PR rate.

that 17β oestradiol reduces the time of growth in the time epithelium.

The turn over of stroma cells is very low and is not modified by oestrogen stimulation.

These results suggest oestrogens lead to epithelial hyperplasia and myometrial and stromal hypertrophy.

Martin, Finn and Frinder ([18]), Tachi *et al.* ([20]), Clark ([19]), and Quarmby and Korach ([21]) concluded that in spayed female rats only the uterine epithelial cells respond to oestrogen stimulation with DNA synthesis. Lobel *et al.* ([22]) confirm a low DNA synthesis in the myometrium during the rat oestral cycle. McCormach and Glasser ([23]) found an incorporation increase in epithelial DNA-RNA cells but not in myometrial and stromal cells.

The oestrogens have different effects on each uterine tissular component. Probably they also stimulate the protein synthesis differently in each tissular fraction.

ER number regulated itself, PR number was determined by oestrogen. Progesterone and certain progestative agents can affect ER complex crosses to target cell kernels. Taylor ([24]) demonstrated in the marked 17β oestradiol 80-90% of marked hormones go to the kernel in the follicular phase, that it to say by prevalent oestrogen action and at the same time, in the luteal phase, when the myometrium is exposed when the progesterone action, the cross to the kernel is about 20-30%. We do not know the mechanism but it is possible to observe progesterone caused changes in the lipidic layer which surrounds kernels.

Smith *et al.* ([25]) found in spayed rat uterus, after 3 days progesterone treatment protein increase both in epithelium and in the stroma. Progesterone produced in the epithelium a turn-over reduction of acid nuclear proteins though it did not abolish the following response to oestradiol. In the epithelium oestrogen administration after progesterone did not produce cell divisions but changes in nuclear proteins were similar to those appearing in the stroma.

King ([26]) affirms DNA synthesis is high in the epithelium and stroma where only oestrogens are present, this response is inhibited by progesterone agents in both cellular types.

So, we think "hypertrophic uterus" must have a pathological identity of its own and ovarian dysfunction in any form (deficient luteal phase, chronic or frequent anovulation, etc.) may be related to etiopathogenesis.

Relative or non compensated hyperoestrogenism leads to hypertrophy in the myometrium without histological alterations other than myocyte enlargement and this conditions the myometrial depth.

Pathologists do not consider these particulars to be necessarily pathological.

CONCLUSIONS

1) The hypertrophic uterus has its own hystopathogenic basis, with symptoms which are the first indications for hysterectomy.

2) A direct relation exists between uterine weight and myometrial depth by means of myometrial cell hypertrophy and so concretely of myocites.

3) This myometrial depth which, over 2 cm is a hormondependent parameter, can bring about well defined symptoms.

4) This hormondependence is expressed by:

a) PR concentration directly proportional to myocite trophism, myometrial depth or uterus weight.

b) ER/UR rate is inversely proportional to myocite trophism, myometrial depth or uterus weight.

5) The special ER distribution suggests:

a) A greater sensitivity of the more hypertrophic cell towards oestrogen.

b) A deficiency of progesterone action in this tissue.

c) A greater response receptivity towards progesterone.

REFERENCES

1) Easterday C. L., Grimes D. A., Riggs J. A.: "Hysterectomy in the United States". *Obstet. & Gynec., 62,* 203, 1983.
2) Thompson J. D., Birch H. W.: "Indication for hysterectomy". *Clin. Obst. Gyn., 24,* 1245, 1981.
3) Dicker R. C., Scally M. J., Greenspan J. R., Layde P. M., Ory H. W., Maze J. M., Smith J. C.: "Hysterectomy among women of reproductive age". Trends in the United States, 1970-1978. *JAMA, 248,* 323, 1982.
4) Van Keep P. A., Wildermeersch D., Lehert P.: "Hysterectomy in six European countries". *Maturitas, 5,* 69, 1983.
5) Selwood T., Wood C.: "Incidence of hysterectomy in Australia". *Med. J. Aust., 2,* 201, 1978.
6) Lewis P. L., Lee A. B. H., Easler R. S.: "Myometrial hypertrophy". *Am. J. Obst. Gyn., 84,* 1032, 1962.
7) Novak E., Woodruff J. D.: "Novak's gynecologic and obstetric pathology with clinical and endocrine relations". W. B. Saunders Company. Philadelphia P. A., 1979.
8) Langlois P. L.: "Diseases of the normal uterus". *J. Reprod. Med., 4,* 220, 1970.
9) Williams I. T., Kinney T. D., "Myometrial hypertrophy (socalled fibrosis uteri). *Am. J. Obst. Gyn., 47,* 380, 1944.
10) Robbins S.: "Textbook of pathology". W. B. Saunders Co., Philadelphia, 1974.
11) Von Scanzoni F. W.: "A practical treatise on the diseases of the sexual organs of women". B. M. Dewitt, New York, 1861.
12) Pellegri P. P., Montanari G. D.: "The preoperative diagnosis of pelvic congestion by means of 133 zenon injected into the cervical myometrium". *Acta Obst. Gyn. Scand., 60,* 447, 1981.
13) Callejo J.: "Estudio de los receptores de progesterona en el mioma uterino". Tesis Doctoral. Universidad de Barcelona, Barcelona, 1980.
14) Korenman S. G., Dukes B. A.: "Specific oestrogen binding by the cytoplasm of human breast carcinoma". *Clin. Endocr. Metab., 30,* 639, 1970.
15) Strobel E.: "Tumores benignos de útero". Käser O., Friedberg V., Ober K. G., Thomsen K., Zander J.: "Tratado de ginecología y obstetricia", tomo III, Ed. Salvat. Barcelona, 1974.
16) Honoré L. H.: "Menorrhagia, diffuse myometrial hypertrophy and the intrauterine contraceptive device: a report of fourteen cases". *Acta Obst. Gyn., Scand., 58,* 283, 1979.
17) Lyndrup J., Thorpe S., Glentho A., Obel E., Sele V.: "Alteraciones de los receptores de progesterona-estrogenos en la endometriosis". *Acta Obst. Gyn. Scand. Ed. esp. 1,* 407, 1988.
18) Martin L., Finn L. A., Frinder L.: "Hypertrophy and hyperplasia in the mouse uterus after oestrogen treatment: an autoradiographie study". *J. Endocrinology, 56,* 133, 1973.
19) Clark B. F.: "The effects of oestrogen and progesterone ou uterine cell division and epithelial morphology in spayed, adrenalectomized rats". *J. Endocrinology, 50,* 527, 1971.
20) Tachi C., Tachi S., Lindner H. R.: "Modification by progesterone and oestradiol induced cell proliferation RNA synthesis and oestradiol distribution in the rats uterus". *J. Reprod. Fertil., 31,* 59, 1972.
21) Quarmby V. E., Korach K. S.: "The influence of 17 oestradiol on patterns of cell division in the uterus". *Endocrinology, 114,* 694, 1984.
22) Lobel B. L., Levy F., Shelesnyakik: "Dynamics of cellular interchons during progestation and implantation in the rat". *Acta Endocrinol, 123,* 7, 1963.
23) McCormak S. A., Glasser S. R.: "Differential response of individual cell types from inmature rats traeted with oestradiol". *Endocrinology, 106,* 1634, 1980.
24) Taylor R. W.: "Female sex hormone receptors and their importance in clinical practice". *Am. J. Obst. Gyn., 134,* 385, 1979.
25) Smith J. A., Martin L., King R. T. B., Vertes M.: "Effects of oestradiol 17 and progesterone on total nuclear protein synthesis in epithelial and stromal tissue in the mouse uterus, and of progesterone on the ability of these tissues to bind oestradiol 17". *Biochem. J., 119,* 773, 1970.
26) King R. T. B.: "Efectos de los estrógenos y de los progestágenos sobre el endometrio normal y anormal". Pag. 126-131, en avances en receptores hormonales de M. A. Navarro Moreno. Ed. JARPYO, Madrid, 1984.

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