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Estrogen and progestin receptor levels in uterine leiomyomata: relation to the tumour histology and the phase of menstrual cycle

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Summary: Estrogen receptor (ER) and progestin receptor (PR) levels in the myometria and uterine leiomyomata of 26 normally menstruating women were studied. No significant menstrual cycle-related change in ER level was found in the leiomyomata or normal myometria. The ER levels in normal myometria and in cellular leiomyomata, but not in usual leiomyomata, tended to be higher in the follicular phase than in the luteal one. The "cytosolic" PR levels in cellular leiomyomata and in usual leiomyomata with no or with slight hyalinization as well as in their parental myometria were significantly lower in the luteal than in the follicular phase. This was not the case in usual leiomyomata with more intense hyalinization. The findings show that the reactivity of uterine leiomyomata to estrogens and/or progestins may be related to the histological features of the tumors. This should be realized when studying the steroid receptor levels in the tumours and possibly also when planning an endocrine therapy for the leiomyomata.

Key words: estrogen receptor; progestin receptors; menstrual cycle; uterine leiomyoma histology.

INTRODUCTION

Reactivity of uterine myomata to estrogens and progestins is evidenced by many data. The tumours tend to enlarge in pregnancy ([1, 2]) but may degenerate and regress in late pregnancy ([3]). Regression of uterine leiomyomata was observed after treatment with progestins ([3]), antiprogestin ([4]), and LH-RH agonists ([5]).

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Steroid hormones act through the specific receptors in target cell nuclei ([6, 7]). Estrogen receptor (ER) and progestin receptor (PR) levels in normal myometrium fluctuate regularly during the menstrual cycle; however, the reports on the menstrual cycle-dependent changes of ER and PR levels in the leiomyomata are conflicting ([8, 9, 10, 12, 13]).

It was our belief that greater importance should be given to the histological features of uterine myomata when studying the ER and PR patterns in these tumours. Thus the aim of our work was to compare the patterns of changes of the ER and PR levels in leiomyomata of diffe-

Table 1. – *Cytosol protein to tissue DNA ratio (means ±SD) in usual leiomyomas (LMu), cellular leiomyomas (LMc) and nomal myometrium (MM) of the same uteri. Number of samples is given in parentheses; p = significance level.*

Phase of the menstrual cycle	LMu — MM		LMc — MM		All leiomyomata	All myometria
					— p = 0.03 —	
Follicular	19.9 ±19.4 (6)	29.4 ±9.6 (4)	8.0 (2)	30.3 (2)	16.9 ±9.9 (8)	29.7 ±11.8 (6)
	— p = 0.01 —				— p = 0.001 —	
Luteal	19.8 ±16.8 (14)	31.5 ±11.9 (10)	11.1 ±5.3 (4)	29.2 ±16.7 (4)	17.9 ±15.3 (18)	29.4 ±11.9 (12)
	— p = 0.002 —		— p = 0.02 —		— p = -.—1 —	
Total	19.9 ±14.7 (20)	30.9 ±11.3 (14)	10.1 ±5.3 (6)	29.6 ±15.8 (6)	17.6 ±13.7 (26)	29.5 ±11.5 (18)

rent histological types and in their parental myometrium.

MATERIAL AND METHODS

Twenty-six normally menstruating women undergoing hysterectomy for leiomyomata were included in the study. The average age was 44±6 (32-51) and 43±6 (32-50) years for patients operated in follicular (n = 9) or luteal phase (n = 17) of the menstrual cycle, respectively. The patients did not receive any hormonal treatment prior to the operation. The phase of the menstrual cycle was verified by the histological features of the endometrium.

Two myomata from each of 12 uteri and one myoma from each of the remaining ones were taken, and a sample of myometrium adjacent to the leiomyoma(ta) was taken from each uterus. The details of tissue sampling, preparation of cytosol and nuclear extract, protein and DNA assays and receptor assays (a radioligand method was used in this study) have been described earlier [14, 15]. "Cytosolic" estrogen receptor (ERc) and progestin receptor (PRc) levels were expressed per mg of cytosol protein or per mg of tissue DNA. "Nuclear" estrogen receptor (ERn) and progestin receptor (PRn) levels were expressed per mg of DNA in KCl-extracted nuclear pellet. Student's "t"-test for paired and unpaired data was used to test for inter-tissue and menstrual cycle-related differences in receptor levels, respectively.

Histologically, the tumours were classified according to the degree of hyalinization and the cellularity as compared to that of the surrounding myometrium. Tumors showing usual pattern with no hypercellularity were classified as usual leiomyomata (LMu), and those with increased cellularity were classified as cellular ones (LMc). Hyalinization was graded as light, moderate or marked. Only the myometria with normal histological patterns and the respective leiomyomata with less than 2 mitoses per 10 high power fields showing no atypia or necrosis were used for receptor studies. Only the myometria with normal histological pattern and the corresponding leiomyomata with less than 2 mitoses per 10 high power showing no atypia or necrosis were used for receptor studies. Both the myometrium and the lemiomyoma(ta) had to be available to include a given uterus in the study.

RESULTS

Cytosol protein/DNA ratio did not change during the menstrual cycle in either leiomyomata or their parental myometria, but it was significantly higher in the myometria than in the leiomyomata, and tended to be higher in LMu than in LMc (Tab. 1).

Both in leiomyomata and their parental myometria, the ERc levels per mg of cytosol protein tended to be higher in the follicular phase than in the luteal one, whereas the ERc level per mg of DNA

Table 2. – *"Cytosolic" (ERc) and KCl-extractable "nuclear" (ERn) estrogen receptor levels (mean ±SD) in usual leiomyomas (LMu), cellular leiomyomas (LMc) and normal myometrium of menstruating women.*

		Leiomyoma		Myometrium	
		Follicular phase	Luteal phase	Follicular phase	Luteal phase
fmol ERc / mg protein	LMu	54±40 (8)	48±30 (20)	28±18 (6)	25±17 (13)
			p = 0.05	p = 0.01	
	LMc	98±71 (4)	38±20 (6)	37±25 (4)	24±16 (5)
	Total	69±53 (12)	46±28 (26)	28±18 (9)	25±17 (17)
			p = 0.02	p = 0.02	
fmol ERc / mg DNA	LMu	663±381 (6)	799±555 (14)	645±319 (4)	522±183 (10)
	LMc	639 (2)	328±233 (4)	907 (2)	665±239 (4)
	Total	656±406 (8)	694±535 (18)	733±284 (6)	556±202 (12)
fmol ERn / mg DNA	LMu	962±666 (6)	1083±600 (13)	804±401 (4)	705±302 (9)
				p = 0.05	
	LMc	706 (2)	357±478 (3)	378 (2)	497±404 (3)
	Total	898±575 (8)	947±636 (16)	662±329 (6)	625±324 (11)

tended to be higher in the follicular phase in normal myometria and in LMc but not in LMu. In both phases of menstrual cycle, ERc level per mg of cytosol protein was higher in leiomyomata than in their parental myometria, but no significant difference between the ERc titers per mg of DNA was found. No significant menstrual cycle-dependent change in ERn level was found in the leiomyomata or myometria. On the other hand, the ERn level was significantly higher in LMu than in their parental myometria in the luteal phase (Tab. 2).

In the myometria, the PRc level per mg of cytosol protein or per mg of DNA was significantly higher in the follicular phase than in the luteal one. PRc level in LMc, but not in LMu, was significantly higher in the follicular than in the luteal phase per mg of cytosol protein only. Both LMu and LMc contained more PRc per mg of cytosol protein than their parental myometria. In the luteal phase, the PRc and PRn levels per mg of DNA were significantly higher in LMu than in the myometria (Tab. 3). No relationship was observed between the phase of the menstrual cycle and the PRn/PRc ratio (data not shown).

No significant, hyalinization-related difference in ERc level was observed, and

Table 3. – *"Cytosolic" (PRc) and KCl-extractable "nuclear" (PRn) progestin receptor levels (mean ±SD) in usual leiomyomas (LMu), cellular leiomyomas (LMc) and normal myometrium of menstruating women.*

		Leiomyoma		Myometrium	
		Follicular phase	Luteal phase	Follicular phase	Luteal phase
pmol PRc / mg protein	LMu	1.67±0.86 (8)	1.23±0.60 (20)	0.91±0.60 (6)	0.49±0.16 (14)
			p = 0.02	p = 0.05	
	LMc	2.03±1.20 (4)	0.87±0.26 (6)	0.68±0.23 (4)	0.38±0.18 (5)
		p = 0.05		p = 0.02	
	Total	1.79±0.94 (12)	1.15±0.55 (26)	0.85±0.5 (9)	0.48±0.17 (17)
		p = 0.02	p = 0.03	p = 0.001	p = 0.01
pmol PRc / mg DNA	LMu	35.2±18.0 (6)	23.2±10.7 (14)	27.7±8.8 (6)	12.8±2.7 (10)
				p = 0.002	
				p = 0.001	
	LMc	16.39 (2)	8.1±3.0 (4)	19.5 (2)	10.8±3.5 (4)
	Total	30.5±17.7 (8)	19.9±11.4 (18)	25.0±8.3 (6)	12.4±3.1 (12)
				p = 0.01	
				p = 0.001	
pmol PRn / mg DNA	LMu	2.91 (2)	3.40±0.92 (8)	5.12 (2)	2.41±1.11 (6)
				p = 0.05	
	LMc	1.52±0.68	1.52±0.68 (3)		1.87±0.46 (3)
	Total		2.88±1.21 (11)		2.26±1.02 (8)

no menstrual cycle-related difference in the ERc level was found in LMu of either hyalinization degree. Mean PRc level per mg of cytosol protein was 2-3-fold higher in LMu showing slight no or hyalinization than in LMu with moderate to marked hyalinization. The PRc level was significantly higher in the follicular phase than in the luteal one but only in LMu showing no or slight hyalinization. LMu taken during the luteal phase of the menstrual cycle and showing slight or no hyalinization contained significantly more ERc/mg of cytosol protein than their parental myometria. In both follicular and luteal phase of the menstrual cycle, only the LMu showing no or slight hyalinization contained significantly more PRc/mg cytosol protein than their parental myometria (Tab. 4).

DISCUSSION

The reports on the menstrual cycle-related changes in the leiomyomal ER and PR levels are unequivocal. The changes in

Table 4. – *"Cytosolic" estrogen receptor (ERc) and progestin receptor (PRc) levels (means ±SD) in normal myometrium and in usual leiomyomas with slight to no (LM−) or moderate to marked (LM+) hyalinization.*

		Leiomyoma		Myometrium	
		Follicular phase	Luteal phase	Follicular phase	Lueal phase
fmol ERc / mg protein	LM±	77+49 (3)	44±42 (6)	34±24 (3)	20±11 (4)
				p = 0.02	
	LM−	41±31 (5)	50±26 (14)	22±10 (3)	27±19 (10)
fmol PRc / mg protein	LM+	0.74±0.20 (3)	0.64±0.29 (6)	0.55±0.02 (3)	0.48±0.17 (4)
		p = 0.003	p = 0.002		
		p = 0.02		p = 0.001	
	LM−	2.22±0.49 (5)	1.48±0.51 (14)	1.28±0.70 (3)	0.49±0.16 (10)
		p = 0.03			

leiomyomata were reported to parallel ([9, 10, 12, 13]) as well as to non-parallel ([8, 16]) changes in myometrium.

In our material, no decrease in ER (ERc+ERn) level was found in leiomyomata in the luteal phase, whereas in normal myometrium there was a slight tendency for the total ER level to decrease. Hovewer, no significant, menstrual cycle phase-related changes in either the leiomyomal or myometrial ERn and ERc levels were found in our patients. This may result from both the variability of ER level in the tumours and the pattern of ERn and ERc level fluctuations. Histologic features of the endometrium in one of nine uteri extirpated during the follicular phase corresponded to the middle, and in the remaining 8 to the late stage of the phase. According to our earlier study, the ERc and ERn levels in normal myometrium peak in the early and the middle stage of the follicular phase respectively; beginning from the late stage of the phase, only slight fluctuations of the receptor levels were observed ([11]). On the other hand, the menstrual cycle-related changes in PRc level can be seen in our material in both leiomyomata and their parental myometria. This is in agreement with the above study, which showed that the PRc level in normal myometrium peaks in the middle of the follicular phase and remains high up to the end of the phase ([11]). The cycle-related change in the leiomyomal PRc level was significant for the receptor level per mg of protein but not for that per mg of DNA. The cytosol protein/DNA ratio does not change in uterine leiomyomata or normal myometrium during the menstrual cycles; thus should be the same for both methods of expressing the receptor level. Some dissimilarities between the patterns obtained using these two methods resulted probably from the small number of samples for which DNA measurements were available.

The ERc, ERn, PRc and PRn levels in the luteal phase were lower in LMc than

in LMu, and the cycle-related change in the PRc level was less pronounced in LMu than in the myometrium or in LMc. These data point out that LMc may react better to circulating progesterone than LMu. Moreover, the PRc level in LMu tended to correlate negatively with the tumour hyalinization (Tab. 4). This may suggest a decreased reactivity to the estradiol of the leiomyomata showing moderate to marked hyalinization. However, also in their parental myometrium the PRc level was low and the cycle-related change in PRc level was negligible. Thus the hyalinization itself seems not to account for the decreased PRc receptor level in the leiomyomata showing hyalinization of higher degree.

Differences between the pattern of changes of ER and PR levels in leiomyomata and their parental myometria may result from a tumour-related modification of the local hormonal environment. Uterine leiomyomata can synthesize estrogens by the aromatization of circulating androgens ([17]). Aromatase activity was found to be many times higher in uterine leiomyomata than in their parental myometrium in both phases of the menstrual cycle ([18]). The local estrogen production may induce an increase in ERn, total ER (ERc+ERn) and PR, and decrease the phase-related fluctuations of the receptor levels. Prolactin may also play a role in increasing the ER and PR levels in the uterus ([19]). Uterine leiomyomata were shown to produce prolactin both under in vivo and in vitro conditions, whereas normal myometrium does not produce prolactin in vivo ([20]). It could be worth while studying the relation between the ability of the leiomyomata to modify their own hormonal environment and histological features of the tumours. In earlier reports, usually no respect has been paid to the histological features of uterine leiomyomata when studying the steroid receptor level. Our results point out that histologic heterogeneity of uterine leiomyomas may contribute both to the discrepancies between the earlier reports on the ER and PR regulation in the tumours and to the reported nonuniformity of the results of hormonal treatment of the tumours ([3, 4, 5]).

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