S9. CONSERVATIVE MANAGEMENT OF ATYPICAL ENDOMETRIAL HYPERPLASIA AND EARLY INVASIVE CARCINOMA WITH INTRAUTERINE LEVONORGESTREL: A PROGESTERONE RECEPTOR STUDY

Tjalma[a] WAA, Janssens[b] D, Wildemeersch[c] D, Colpaert[d] C, Watty[a] K.
[a]*Department of Gynecology and Gynecological Oncology, University Hospital Antwerpen, University Antwerpen, Belgium;* [b]*Department of Gynecology, Turnhout, Belgium;* [c]*Contrel Research, Technology Park, Ghent (Zwijnaarde) Belgium*; [d]*Department of Pathology, University Hospital Antwerpen, University Antwerpen, Belgium*

Introduction: Promising clinical results with the levonorgestrel–intrauterine drug delivery system (LNG-IUS) in women with atypical endometrial hyperplasia have been published previously.[1] This treatment could, therefore, be useful for patients with atypical hyperplasia or early endometrial malignancy who are poor surgical candidates or who do not want to be operated upon, e.g., patients wishing to preserve their fertility. However, a small number of women treated with systemic progestogen show persistence or progression of the condition which has been attributed to the non-availability of progesterone receptors (PR) at treatment initiation and/or to an alteration in regular progesterone function.[2] Several research groups have noted a downregulation of PR in LNG-IUS-treated endometrium in pre-menopausal fertile women.[2,3] The aim of this study was to analyse the feasibility of such a treatment with a novel, frameless LNG-IUS and the potential significance of quantitative PR assessment in this management.

Patients and methods: Eight post-menopausal women (7 with atypical endometrial hyperplasia and 1 with endometrial cancer International Federation of Gynecology and Obstetrics (FIGO) stage 1A) were treated with a LNG-IUS, releasing 14 g of LNG/day. Mean age was 58 years (range 46-58 years) and mean

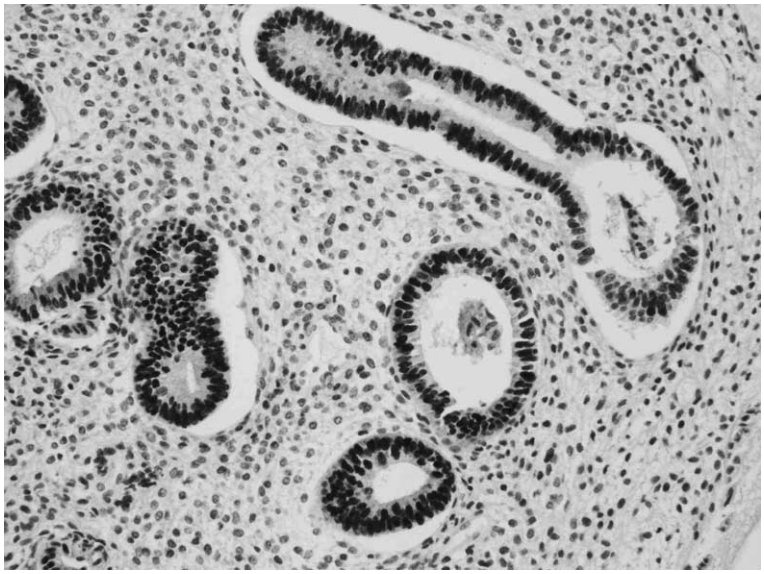

Fig. 1. Atypical endometrial hyperplasia prior to treatment, showing immunoreactivity for progesterone receptor (PR) in almost all epithelial cells (original magnification 200x).

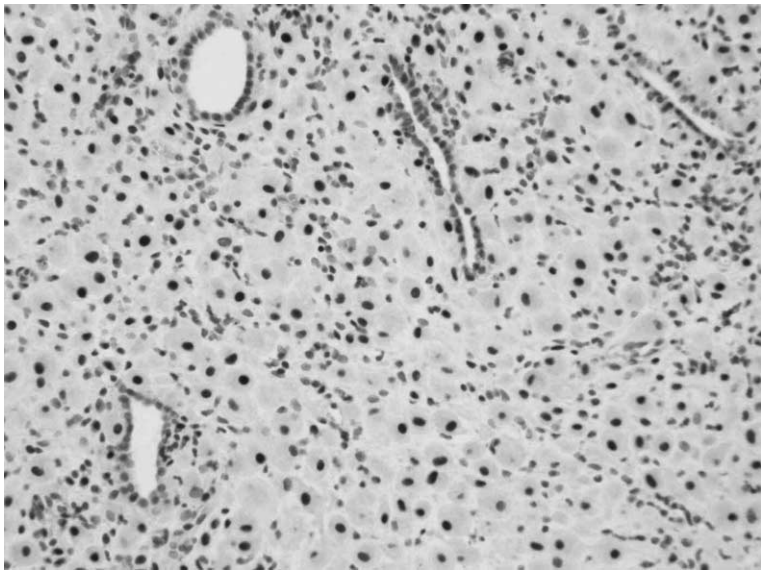

Fig. 2. Endometrium of the same patient during treatment with the LNG-IUS. The endometrium shows atrophy with low expression of progesterone receptor in the epithelial cells of the atrophic glands, but preserved immunoreactivity in many decidualised stromal cells (original magnification 200x).

1359-6349/$ - see front matter
doi:10.1016/j.ejcsup.2004.08.043

follow-up 29 months (range 11-51 months). All had clinical examination, transvaginal ultrasound (TVU), D&C or pipelle biopsy and consented to receive treatment. The use of the LNG-IUS was approved by the Ethics Committee of the University of Ghent, Belgium. Patients were seen on a regular basis every 3–6 months including clinical examination, TVU and endometrial biopsy.

To determine the endometrial PR status, paraffin-embedded tissue sections were immunohistochemically stained with a mouse monoclonal antibody (NCL-PGR-312, Novo Castra Laboratories, Newcastle-upon-Tyne, UK). The percentage of immunoreactive nuclei was scored, both in the endometrial epithelium and stroma.

Results: At study initiation, all eight women showed expression of PR in the epithelial cells, ranging from 50% to 95% (Fig. 1). The percentage declined over time during treatment (range 5–50%) (Fig. 2). No recurrence or progression of disease was noticed in any of the women. The endometrial histology specimen showed profound endometrial suppression with glandular atrophy and stromal decidualisation in all women.

Discussion: Intrauterine progestogen delivery, particularly LNG, acts throughout the whole thickness of the mucosa caused by the high tissue concentrations[3] and could, therefore, be a promising alternative treatment. Continuous intrauterine progestogen administration could enhance the success rate. The significant reduction of the PR expression observed during treatment with the LNG-IUS in our study appears to be a marker for the strong antiproliferative effect of the hormone at a cellular level resulting in an inhibition of oestrogen bioactivity and endometrial suppression. In the absence or where there is a low content of PRs before treatment, this cascade of events may be hindered and may explain why, at least in some cases, persistence or progression of disease occurs. Women with this condition should be carefully followed.

References

1. Wildemeersch D, Dhont M. Treatment of non-atypical and atypical endometrial hyperplasia with a levonorgestrel-releasing intrauterine system. *Am J Obstet Gynecol* 2003, **138**, 1297-1298.
2. Hurskainen R, Salmi A, Paavonen J, Teperi J, Rutanen E. Expression of sex steroid receptors and Ki-67 in the endometria of menorrhagic women: effects of intrauterine levonorgestrel. *Mol Hum Reprod* 2000, **6**, 1013-8.
3. Critchley HO, Wang H, Jones RL, Kelly RW, Drudy TA, Gebbie AE, Buckley CH, McNeolly AS, Glasier AF. Morphololical and functional features of endometrial decidualization following long-term intrauterine levonorgestrel delivery. *Hum Reprod* 1998, **13**, 1218-24.