# Adenogenesis Factors FGF7, FGF10, FGF23, IFN-τ and HGF in Endometriosis Tissue Respect to Eutopic Endometrium: An Immunohistochemical Study

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**ABSTRACT:** Endometriosis is a pathological condition defined by the occurrence of endometrial glandular and stromal structures in anatomical compartments different from the uterine cavity. Endometriosis is a genetic polymorphism, estrogen-dependent inflammatory disease. This very common pathological entity causes a high level of morbidity in patients; it is also considered one of the most important causes of infertility. We and others have proposed as a pathogenetic mechanism of endometriosis a modification in the fine tuning of the processes of organogenesis of the uterus. We have correlated the immunohistochemical expression in deep endometriotic lesions and in normal endometrial tissue of several molecular factors that are implicated in the embryonic development of the uterine glands. We noticed a significant higher expression both for epithelium and stroma in the controls respect to the endometriosis samples for FGF7, FGF-10 and HGF. Interestingly, regarding FGF-23 and IFN-τ, we observed a significant higher expression in the ectopic endometrial stroma compared to the eutopic endometrium, while thepithetlium expression did not display a significant differential expression in endometriosis tissues respect to normal endometrium. The data generated support the fact that endometriosis tissues, both the epithelial and stromal component, have a different phenotype respect to the eutopic endometrium and sustain the hypothesis that alterations in the molecular mechanisms in control for adenogenesis and survival of endometrial structures are linked to the genesis and survival of endometriosis lesions outside of the uterus.

**KEY WORDS:** adenogenesis, endometriosis, endometrium, growth factors, uterus

## I. INTRODUCTION

Endometriosis can be defined as the presence of endometrial glands and stroma outside its normal site, the uterine cavity.[1] Endometriosis is a common benign estrogen-dependent inflammatory disease that causes various symptoms such as chronic pelvic pain, dysmenorrhea, and dyspareunia. It is recognized as the main cause of infertility.[2,3] The prevalence of endometriosis appears to have a range between 10% and 15% in the general population.[4] Despite this, the pathogenesis of endometriosis is not fully defined, the diagnosis is often late, and there is no effective therapy for its elimination.[5]

The most accepted theory for the etiology of endometriosis is Sampson's theory, which suggests endometriosis develops as a result of retrograde menstruation through the Fallopian tubes.[6] Sampson's theory is supported by data showing that women commonly have retrograde menstrual flow; increased retrograde flow caused by outflow tract obstructive defects substantially increase the prevalence of endometriosis.[7] Despite this, endometriosis is also identified outside the pelvis, in women without a uterus, carrying the Mayer-Rokitansky-Kuster-Hauser syndrome, and in men, indicating that retrograde menstruation does not represent the only route for endometriosis development.[8,9]

Moreover, several studies have elucidated the differences that distinguish endometriotic cells from *eutopic* endometrial cells, such as reduced progesterone responsiveness,[10] increased resistance to apoptosis,[11] as well as increased cell adhesion/migration/invasion capacity.[12] Previously, we and other groups postulated how the

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presence of ectopic endometrium in fetal age has been demonstrated in the same anatomical compartments where endometriosis is normally found in adult patients.[13–15] This observation made it possible to define as one of the sure pathogenetic mechanisms of endometriosis, an alteration of the processes of organogenesis of the uterus, and to include this disease in the complex of anomalies of the Müllerian ducts.[16] The molecular pathways in charge for this modification of the fine regulation of uterus organogenesis are still not identified.[5] Indeed, the link between Müllerian duct anomalies and endometriosis has long been recognized and has so far been explained in the framework of the theory of retrograde menstruation.[17] Interestingly, we have recently proved that the transcriptome of endometriotic tissue expresses numerous genes involved in embryogenesis differentially with respect to endometrial tissue and that this dissimilar expression is not linked to the phase of the hormonal cycle.[18]

It is well known from embryology studies that epithelial–mesenchymal interactions are key factors for an accurate uterine development.[19] Indeed, these relations are in charge for local control and synchronization of morphogenetic crucial cell actions, such as cell movement and adhesion, cell differentiation, and cell proliferation.[20] In concert with this assumption, fibroblast growth factors (FGFs) play a wide range of roles in physiological and pathological conditions, such as embryonic development and angiogenesis.[21] We know that angiogenesis represents a crucial step in the pathogenesis of endometriosis, because endometriotic lesions require neovascularization.[22] In addition to the FGF family, it has been shown that the growth of endometriosis can be regulated by many other cytokines.[23,24] Following this pathway, we decided to focus our attention on the following angiogenesis related genes: fibroblast growth factor 7 (*FGF7*), fibroblast growth factor 10 (*FGF10*), fibroblast growth factor 23 (*FGF23*), hepatocyte growth factor (*HGF*) and interferon-τ (IFN-τ). The main aim of this study was to investigate the protein expression of these angiogenesis-related growth factors, via immunohistochemical (IHC) evaluation, in the ectopic endometrium of women with endometriosis, both in its epithelial and stromal compound, and compare this expression with the results found in eutopic endometrium. The data generated may suggest some of the molecular mechanisms in charge for the growth and persistence of endometriosis structures outside of the uterus.

## II. MATERIALS AND METHODS

### A. Case Selection

Surgical specimens from patients who experienced surgery for infertility, pelvic pain symptoms, or adnexal masses between 2000 and 2010 at the "Centro Italiano Endometriosi" were retrospectively collected and analyzed for the presence of deep endometriosis lesions, as already described.[25] All the cases where the occurrence of endometriotic glands was histologically recognized were selected for this study. Forty-two cases were considered eligible for the analysis. All patients signed an informed consent before enrollment in the study to permit the use of the data generated in retrospective analyses. The Human Normal Endometrium Tissue MicroArray CYN1 (SUPER BIO CHIPS, Seoul, Korea), including 59 normal endometrial samples both in the proliferative and secretive phase, was selected to describe the expression of each antigen examined in the physiological endometrium. Main characteristics are described in Table 1. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000 and 2008. The study was approved by the Scientific Committee of Fondazione Italiana Endometriosi.

### B. Immunohistochemical Analysis

Immunohistochemistry was performed as earlier described.[26,27] In detail, 5 μm paraffin embedded sections were cut, mounted on glass and dried overnight at 37°C. Sections were deparaffinized in xylene, rehydrated through a graded alcohol series, and washed in phosphate-buffered saline (PBS). PBS was used for all subsequent washes and for antiserum dilution. Tissue sections were quenched

**TABLE 1:** Characteristics of the 42 patients included in the study

| | No. | Mean ± SD | % |
|---|---|---|---|
| Age (years) | 42 | 35 ± 5 | |
| AFS stage* | | | |
| I | 0 | | 0 |
| II | 1 | | 3 |
| III | 3 | | 7 |
| IV | 38 | | 90 |

*American Fertility Society stage, based on The American Fertility Society, 1985.

sequentially in 3% hydrogen peroxide in aqueous solution and blocked with PBS-6% non-fat dry milk (Biorad, Hercules, CA, USA) for 1 h at room temperature. Slides were then incubated at room temperature at 1:100 dilutions with the following antibodies: FGF7 antibody (abx176437; Abbexa, Cambridge, UK), FGF10 antibody (abx176398; Abbexa), FGF23 antibody (abx10281; Abbexa), HGF antibody (abx117058; Abbexa) and IFN-τ antibody (abx177051; Abbexa). After washes in PBS, the slides were incubated with UltraTek HRP secondary antibody (ScyTek Laboratories, Logan, UT, USA) for 1 h. All the slides were then processed by the ABC method (Vector Laboratories, Burlingame, CA, USA) for 30 min at room temperature. Diaminobenzidine (ScyTek Laboratories, Logan, UT, USA) was used as the final chromogen, and hematoxylin was used as the nuclear counterstain. Negative controls for each tissue section were prepared by leaving out the primary antiserum. As positive controls, tissue samples expressing the antigen of interest, as indicated in the data sheets of the antibodies used, were selected. All samples were processed under the same conditions. The IHC expression was evaluated in both epithelium and stromal compound of the ectopic and eutopic endometrium. In order to define a score, the level of each protein expression was defined considering the number of positive cells and the intensity of the expression and described as: score 1 (absent to very low); score 2 (low); score 3 (moderate), score 4 (intense). An average of 25 fields was analyzed for each specimen. The level of concordance, expressed as the percentage of agreement between the observers was 95% (40 cases over 42). In the remaining specimens, the score was obtained after collegial revision and agreement.

### C. Statistical Analyses

Descriptive analysis was performed by using median values and 95% confidence interval (CI) and percentages when appropriate. Differences between two groups of patients were assessed using Mann-Witney U test for nonparametric continuous variables. Moreover, the different distribution of other variables between groups was assessed using Chi-square test. SPSS software (version 17.00, SPSS, Chicago) was used for statistical analysis. A P value of less than 0.01 was considered to indicate statistical significance.

## III. RESULTS

### A. Morphological Examination

Stromal and epithelial deep endometriosis samples and normal epithelial and stromal endometrium controls were examined. No significant differences were observed between the proliferative and secretory phases. Morphologically, endometriotic lesions showed the distinctive presence of both endometriotic glands and stroma, despite the site of the endometriosis. The glands observed displayed classical endometrioid appearance, while the endometriotic stroma was similar to eutopic inactive or proliferative endometrial stroma. Infiltrate rich in histocytes and siderophages was commonly observed, possibly caused by hemorrhage and menstrual changes in endometriosis. Finally, the

presence of a network of small blood vessels, and proliferation of fibroblasts was commonly detected in the stroma.

## B. Immunohistochemical Analysis

We analyzed the immunohistochemical expression of IFN-τ, FGF-7, FGF-10, FGF-23, and HGF in normal human endometrium and stroma and compared this expression with the one detected in the epithelium and stroma of a series of 42 deep endometriosis samples. For all the antibodies tested, we detected a specific cytoplasmic immunopositivity. In Figs. 1–3 the Student's *t*-test analysis of the differential expression of all these antigens in epithelium and stroma of endometriosis lesions respect to normal human endometrium tissues are depicted.

Significantly higher expressions of FGF7, FGF-10, and HGF were detected in both epithelium and stroma in the controls as compared to the endometriosis samples. Interestingly, regarding FGF-23 and IFN-τ, we observed a significant higher expression in the ectopic endometrial stroma compared to the eutopic endometrium, while the epithelium expression did not display a significant differential expression in endometriosis tissues respect to normal endometrium. In Fig. 4, examples of immunohistochemical staining are shown.

A statistical analysis was performed of the immunohistochemical expression of these growth factors in the proliferative and secretive phase of the normal human endometrium samples used as control to estimate whether estrogen and progesterone levels could modify their expression levels.

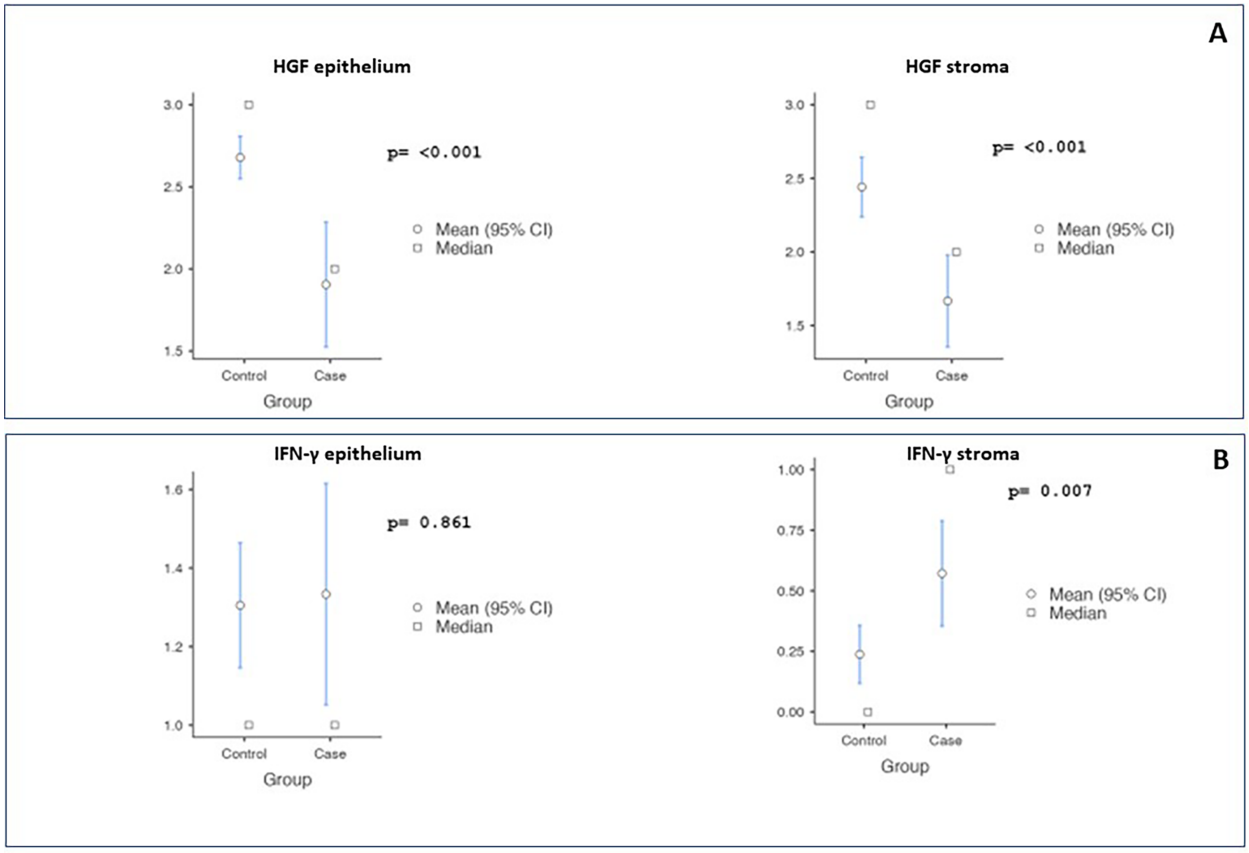


**FIG. 1:** Statistical analysis by means of Student's *t*-test of the differential expression of HGF (panel A) and IFN-τ (panel B) in epithelium and stroma of endometriosis lesions respect to normal human endometrium tissues

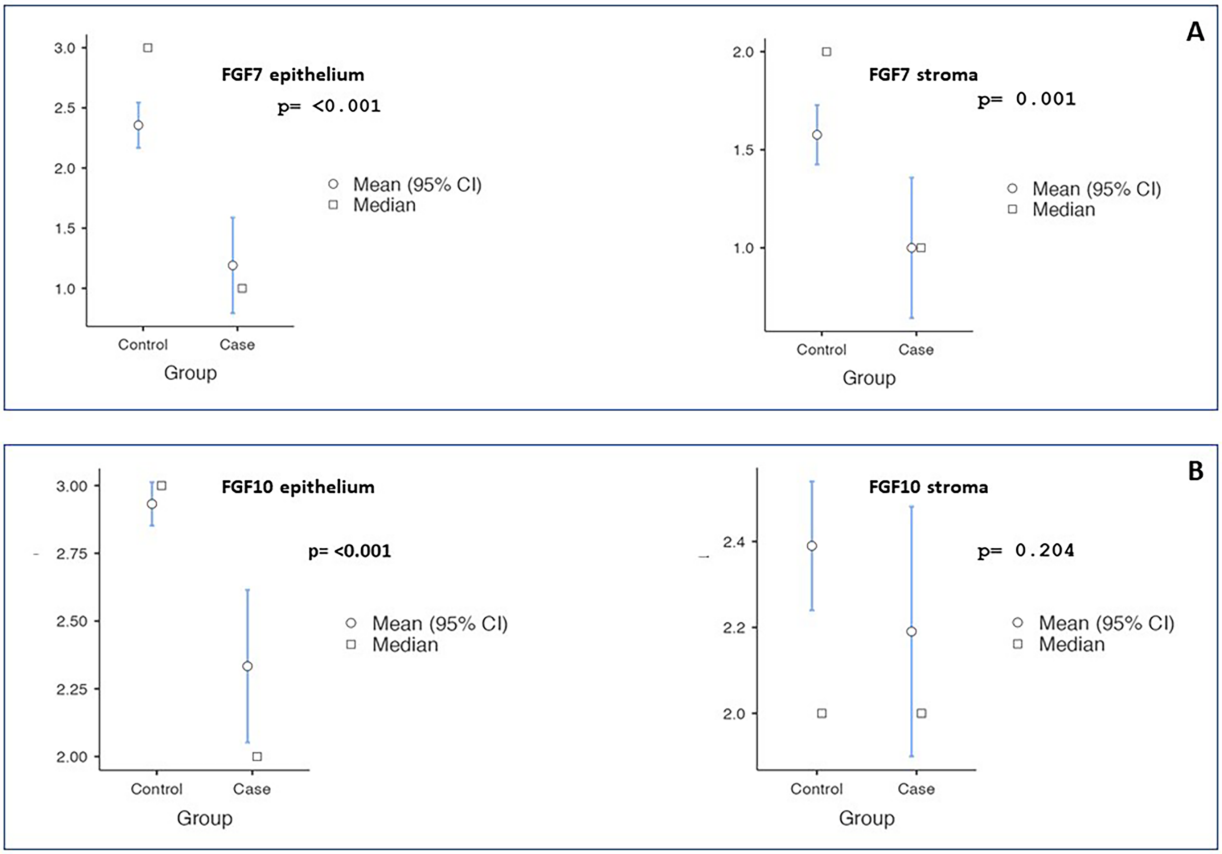


**FIG. 2:** Statistical analysis by means of Student's *t*-test of the differential expression of FGF7 (panel A) and FGF10 (panel B) in epithelium and stroma of endometriosis lesions respect to normal human endometrium tissues

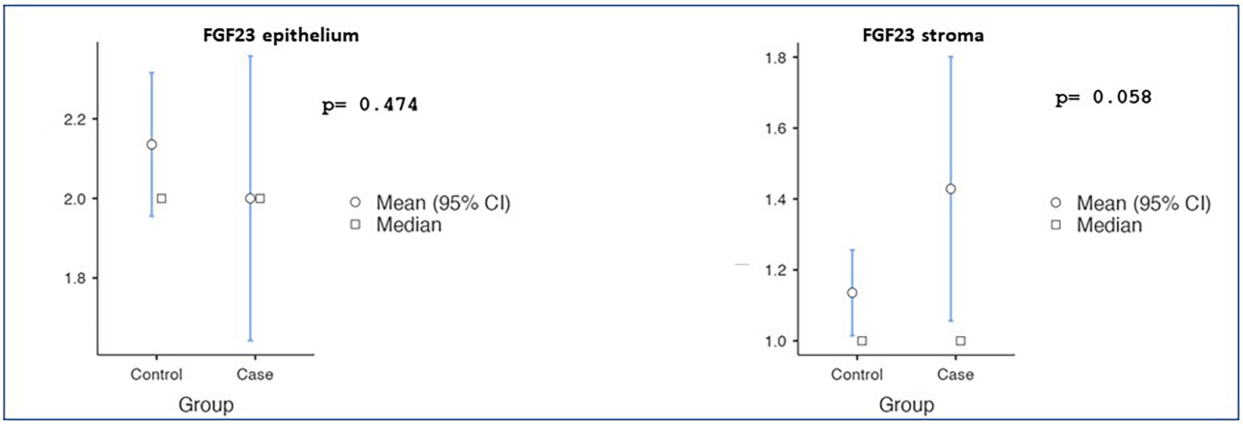


**FIG. 3:** Statistical analysis by means of Student's *t*-test of the differential expression of FGF23 in epithelium and stroma of endometriosis lesions respect to normal human endometrium tissues

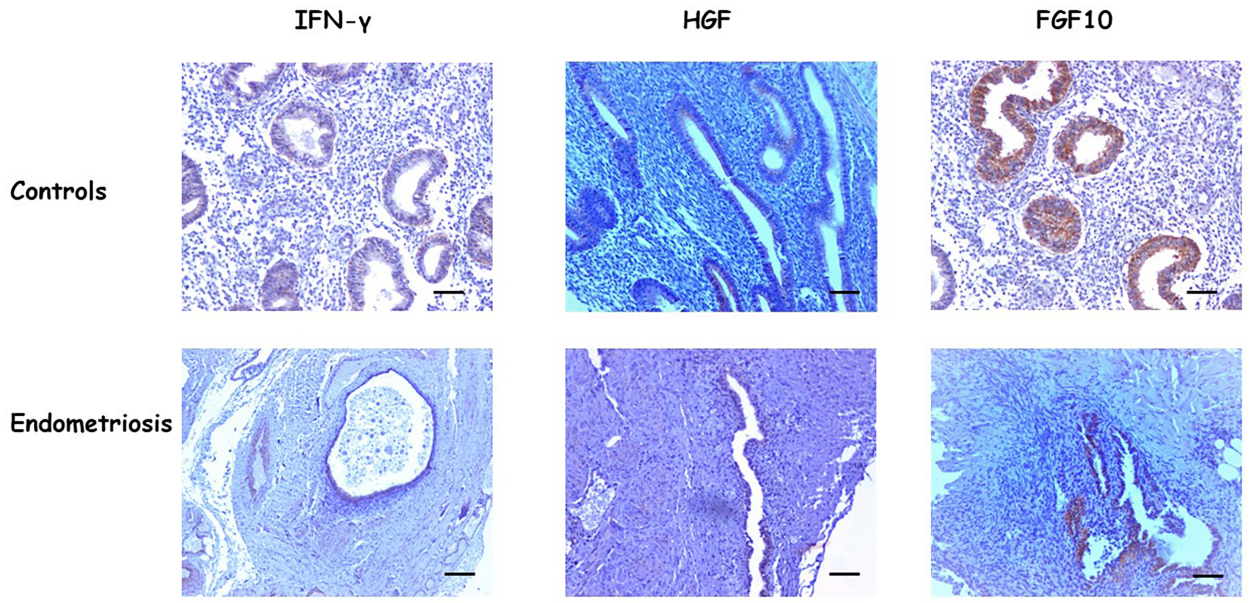


**FIG. 4:** Exemplificative immunostainings for IFN-τ, HGF, and FGF10 in human endometrium and endometriosis lesions displaying different levels of expression (scale bar = 100 μ) (original magnification ×10)

Indeed, we did not find statistically significant differences in the immunohistochemical expressions of all the antigens analyzed, both in the epithelium and in the stroma in the two different phases of the cycle, proliferative and secretory. This trend was confirmed (data not shown) in endometriotic tissue.

## IV. DISCUSSION

Endometriosis is a common disease affecting 5%–10% of women of reproductive age globally.[28] Endometriosis is defined as an ectopic localization of endometrial cells supported by a stromal compartment containing a rich blood supply and fibroblasts.[29] Diagnosis of endometriosis is only considered definitive when the presence of endometrial-like tissue (''lesions'') outside the uterus is confirmed during surgery.[1] Endometriosis lesions can be found in asymptomatic women and are detected in up to 50% of women seeking treatment for infertility.[30] Despite its high prevalence in female population, many theories on the pathogenesis of endometriosis have been postulated but none yet seems to have truly prevailed over the others.[31]

The most widely accepted theory of origin is Sampson's theory of reflux menstruation.[6] According to this, if endometriosis is an auto transplant, such tissue should be expected to have a close similarity with eutopic endometrium, because that is the nature of an auto transplant. Nevertheless, several studies have indicated that there are distinctive features in endometriotic cells when related to eutopic endometrial cells. These dissimilarities comprise reduced progesterone responsiveness,[32] augmented resistances to apoptosis,[33] as well as augmented cell adhesion/migration/invasion capacity.[34]

Consistently, in several previous works we and others have highlighted several points that are not in common between eutopic and ectopic endometrium, and we believe that this is the key to really understanding the processes underlying the development of endometriosis, especially in the process of adenogenesis and epithelial-mesenchymal interaction.[18,25]

In fact, uterine development as well as endometriosis, depend at least in part on epithelial–mesenchymal interactions mainly regulated by stromal-derived growth factors, whose interactions, play important roles in epithelial proliferation, differentiation, and proliferation.[19]

Fibroblast growth factors (FGFs) play a wide range of roles in physiological and pathological conditions, such as embryonic development and angiogenesis. In detail, FGF-7 stimulates epithelial cell proliferation and differentiation,[35] while FGF-10 is essential for the patterning of early events in branching morphogenesis.[36] On the other hand, HGF functions as a paracrine mediator of mesenchymal–epithelial interactions that govern mitogenic and morphogenic behaviors of epithelia in developing lung and mammary tissues.[37]

In a compared model of the developing neonatal ovine uterus, FGF-7, FGF-10, HGF, and their epithelial receptors were identified as being organizationally important growth factor systems associated with endometrial morphogenesis.[19] We found that, in both epithelial and stromal compound of the ectopic endometrium, FGF-7, FGF-10, and HGF expressions were significantly decreased. Considering the well-defined role of these growth-factors, in promoting cellular proliferation and reducing cell–cell adhesion, it is possible to hypothesize that, during embryogenesis, a higher expression, could allow individual cells to break away from their parental architecture and could contribute to the formation of the primitive endometriosis lesions. The reduced expression in endometriosis may be related to the progression of the disease in adult, probably related to the hyper estrogenic environment of endometriosic structures.[38] Indeed, the fact that some FGFs and HGF are strictly linked to steroidogenesis has long been documented, and confirmed by observation in several *in vivo* and *in vitro* models.[39,40] Stromal FGF10 serves as potential paracrine factor for estrogen-dependent regulation of epithelial proliferation in the uterus.[41] On the other hand, FGF7 and FGF10 expressions are influenced by estradiol in mammary glands of mice, in rat prostate gland during embryogenesis, and during follicular growth in a cattle model.[41–44] Finally, HGF secretion is uniquely regulated in the uterus, but not in ecto- and endo-cervix, by estradiol.[45]

Interestingly, we found for FGF23 and IFN-τ a higher expression in the stroma of endometriosis lesions as compared to normal endometrium. FGF23 belongs to the metabolic FGF subfamily and is a physiological regulator for phosphate and active vitamin D levels in serum.[46] Consistently, IFN-τ has been shown to be involved in the regulation of phosphate, calcium, and vitamin D signaling during the peri-implantation period of pregnancy.[47] Several works have linked low levels of vitamin D with endometriosis, leading to the idea that vitamin D deficiency plays a role in the pathogenesis of endometriosis.[48] The observation that some of molecular mediators of vitamin D metabolism have an altered expression in endometriosis tissues respect to normal endometrium is in agreement with this hypothesis and deserves further investigation. Nevertheless, the data produced in our work about the lower levels of HGF in endometriosis as compared to the controls are also in accordance with this hypothesis. In fact, it has been recently showed that treatment with vitamin D significantly reduce the protein expression of HGF in endometrial stromal cells of patients with endometriosis compared with controls.[49]

FGF23 levels are linked also to estrogen expression.[50] It has been suggested that exposure to estrogen in the form of estrogen therapy may abort or counteract the postmenopausal increase in serum FGF-23 and phosphorus levels.[51] Moreover, an experimental study designed to investigate the factors and mechanisms involved in the effect of estrogens on the parathyroid gland established that female rats treated with estrogen had significantly higher serum and bone FGF-23 levels.[52]

In our study, we performed a statistical analysis of the immunohistochemical expression of these growth factors with respect to the phase of the hormonal cycle of the uterine tissue samples used as controls and we observed no correlation with changes by ovarian cycle. Several articles[1–4] on endometriosis refer to it as an ‘‘estrogen-dependent’’ disorder, and we suggest, based on our data, that this definition should be updated to ‘‘steroid-dependent’’ to reflect the importance of other steroids and their receptors in regulation of cells in both eutopic and ectopic endometrium. Indeed, estrogen regulates the survival and growth of endometriotic structures not directly and not exclusively, but through the modulation of other factors also depending on the patient’s genetic background.[38] In conclusion, our data suggest that some factors of adenogenesis in endometriotic tissue could display a regulation partially

disengaged by the action of female sex hormones in the formation and sustenance of the disease and could be considered as a potential target for therapy.

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The study was approved by the Scientific Committee of Fondazione Italiana Endometriosi.

All patients provided written informed consent before enrollment in the study to permit the use of the data generated in retrospective analyses.

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