

# Estrogen and Progesterone Receptors in Endometrium in Women with Unexplained Infertility

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## ABSTRACT

**Aim:** The purpose of the present study is to evaluate the relationship between endometrial concentrations of estrogen and progesterone receptors throughout the menstrual cycle in women with unexplained infertility. **Material and methods:** In forty four infertile women with unexplained infertility, biopsy of the endometrium was performed during simultaneous laparoscopy and hysteroscopy. Material was prepared for immunohistochemical staining. Forty four endometrial samples obtained from women with normal menstrual cycles were divided into four categories: early proliferative, late proliferative, early secretory and late secretory. Immunohistochemical localization of estrogen receptors (ER) and progesterone receptors (PR) was scored according to intensity of staining and proportion of cells specifically stained in glandular epithelium and stroma and results were analyzed. **Conclusion:** The early secretory phase appeared to be period of transition from the strong and ubiquitous staining for receptor characteristic of proliferative phase of endometrium to the weak, focal pattern of estrogen receptors. Progesterone receptors in early secretory phase were of strong staining and sufficient number of stained cells.

**Key words:** estrogen and progesterone receptors.

## 1. INTRODUCTION

The endometrium, as a target of estrogens and progestins, possesses the receptive receptor proteins. The concentration of estrogen receptors (ER) and progesterone receptors (PR) in different physiological and pathophysiological states such as the menstrual cycle, pregnancy, and endometrial cancer, has been determined by biochemical and immuno(cyto)chemical methods.

The levels of estrogens and progestins are important regulators of ER and PR gene expression. The human endometrium undergoes cyclical changes under the endocrine control of estrogens and progesterone acting via specific nuclear receptors.

The cross-talk between the endocrine system, growth factors and neurotransmitters can take place both at the receptor level, involving mainly phosphorylation reaction, and at the gene level, mainly through protein-protein interactions.

The molecular and cellular events mediating these changes are not fully understood. The factors responsible for the initial interaction between maternal and fetal epithelium leading to the establishment of pregnancy remain poorly understood. The progesterone receptor protein was determined using human progesterone receptor enzyme-linked immunoassay kit. The establishment of reliable biomarkers for the detection of

defects in endometrial receptivity has been a long-sought goal that remains an elusive target. The establishment of normal endometrial receptivity appears to be tightly associated with the down-regulation of epithelial PR (1).

## 2. MATERIAL AND METHODS

In forty four infertile women with unexplained infertility, biopsy of the endometrium was performed during simultaneous laparoscopy and hysteroscopy. Material was prepared for immunohistochemical staining. Forty four endometrial samples obtained from women with normal menstrual cycles were divided into four categories: early proliferative, late proliferative, early secretory and late secretory. Immunohistochemical localization of ER and PR was scored according to intensity of staining and proportion of cells specifically stained in glandular epithelium and stroma and results were analyzed.

## 3. RESULTS

### Early proliferative phase

- PR -Strong staining in stroma and glands
- In stroma 3+ 100%
- In glands 3+ 100%
- ER – In stroma weaker staining, but in glands strong

staining

- In stroma 1 < 80%
- In glands 3+ 100%

#### Late proliferative phase

- PR- In stroma and glands strong staining, but with smaller proportion of stained cells.
- In stroma 3+ 80%-100%
- In glands 3+ 70%-100%
- ER- Strong staining in stroma and glands cells
- In stroma 3+ 100%
- In glands 3+ 100%

#### Early secretory phase

- PR- In stroma and glands strong staining with sufficient proportion of stained cells
- In stroma 3+ 100%
- In glands 3+ 100%
- ER- In stroma weaker staining, with smaller proportion of stained cells.
- In glands strong staining and sufficient number of stained cells.
- In stroma 2+ 50%-80%
- In glands 3+ 100%

#### Late secretory phase

- PR- In stroma strong staining with sufficient proportion of stained cells. In glands weak staining with insufficient number of stained cells.
- In stroma 3+ 100%
- In glands 1+ 50%- 80%
- ER- In stroma and glands weak staining, and insufficient number of stained cells.
- In stroma 1 < 30%
- In glands 1 < 60%

## 4. DISCUSSION

Our results indicate that the early proliferating phase is characterized with strong staining PR in stroma and glands, while ER are weak stained in stroma and strong stained in glands.

Late proliferating phase is characterized with ER with strong staining in stroma and gland cells, which has been confirmed in our study, while PR is with strong staining in stroma and glands but with a smaller proportion of stained cells. The concentration of the progesterone receptors in the endometrium is highest during the late proliferative phase and is lowest in the late secretory phase (2). Estrogen receptor was detected in the nuclei of the vast majority of epithelial and stromal cells from early, middle, and late proliferative phase of endometrium. Middle and late secretory endometrium phase showed a dramatic reduction in the amount of localized estrogen receptors (3).

Early secretory phase is characterized with PR strongly stained in stroma and glands with sufficient proportion of stained cells, while ER is characterized with weak staining and smaller proportion of stained cells. Our results show that ER in the late secretory phase have weak staining in stroma and glands and insufficient number of stained cells. Specific staining for estrogen receptor in the functional middle and late secretory phase of endometrium was weak and limited to nuclei of scattered epithelial and stromal cells. Specific staining for estrogen receptors was always limited to nuclei, no specific cytoplasmic staining was observed (3). In our study, PR in late secretory phase were of strong staining and with sufficient proportion of stained cells, while glands were weak stained with insufficient

number of stained cells. In the natural cycle, PR-B expression increases in the luminal epithelium and in the stroma during the proliferative phase and then remains high well into the secretory phase (4).

Studies during the normal menstrual cycle have shown that the concentrations of endometrial progesterone receptor and its mRNA vary in glandular epithelia but remain steady in stromal cells.(5) Results suggest that there is a differential sensitivity of glandular and stromal progesterone receptors to steroid regulation during the normal menstrual cycle (5).

In the glandular epithelium many studies have shown a decline in PR-B expression during the late secretory phase immediately prior to menses (4).

Endometrial progesterone receptors and one of integrin cell adhesion molecules appear to undergo changes in expression around the time of implantation, and may be sensitive indicators of the receptive state (6).

Women with various gynecologic disorders appear to exhibit decreased uterine receptivity and abnormal expression of endometrial biomarkers (7). Certain types of uterine receptivity defects may be caused by the loss of appropriate ER alpha down-regulation in the mid-secretory phase, leading to defects in uterine receptivity (8).

## 5. CONCLUSION

The early secretory phase appeared to be period of transition from the strong and ubiquitous staining for receptor characteristic of proliferative phase of endometrium to the weak, focal pattern of ER. Our results show that ER in late secretory phase in stroma and glands are weak stained and there is insufficient proportion of stained cells, which might be an indicator of the defects in uterine receptivity. Progesterone receptors in early secretory phase were strong stained and with sufficient number of stained cells, while in the late secretory phase strong stained with sufficient proportion in stroma and weak stained with sufficient proportion in glands. Rapidly advancing technologies are bringing new biomarkers to the clinical arena that promise to further reveal the complexities of the endometrial receptivity.

**CONFLICT OF INTEREST: NONE DECLARED.**

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