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Research on Expression of Integrin and EGF in Sterile Women During Endometrial Implantation Window

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Abstract: Objective To study expression of integrin and epidermal growth factor in sterile patients during endometrial implantation window and discuss the relationship between the integrin and epidermal growth factor and endometrial receptivity. Methods: The research objects were divided into 5 groups with 30 women at the normal gestation age, 30 women exhibiting ovulation following PCOS ovulation induction treatment, 26 women exhibiting no ovulation following PCOS ovulation induction treatment, 38 women exhibiting oviduct obstruction, 32 women exhibiting hydrosalpinx. An immunohistochemical method was used to detect the expression of integrin and EGF in sterile women of the five groups of research objects during endometrial implantation window and a statistical analysis was conducted for all detection results. Results The expression level of the integrin in PCOS group is significantly lower than that in the control group and the difference is significant ($P<0.05$); the expression level of the integrin in PCOS anovulation group is significantly lower than that in PCOS ovulation group and there is statistical significance ($P<0.05$); the difference between the oviduct obstruction group and the control group is not significant ($P>0.05$); the expression level of the integrin in the hydrosalpinx group is lower than that in the oviduct obstruction group and the difference is significant ($P<0.05$). EGF is expressed in endometria of various groups of women and its expression is located in cytoplasm of epithelial cells of the endometrial gland. Conclusion Integrin and epidermal growth factor are expressed in endometria of various groups of women in the implantation phase indicating that they may be important regulatory factors for endometrial receptivity and embryonic implantation.

Keywords: Integrin, Epidermal Growth Factor, Sterile Women, Endometrium, Implantation Window Phase

1. Background

In recent years, reports both at home and abroad have shown that infertility morbidity is increasing gradually. The pregnancy success rate of sterile women still remains at 35%-40% and the bottleneck can not be broken through at all times although the assisted reproductive technology is maturing increasingly. Improving pregnancy success rate of sterile women has become one of the conundrums encountered in national and international reproductive medicine currently. During the reproductive process, oosperms can nidate, differentiate and mature in the uterus, where nidation is the key, while receptivity of embryo and endometrium having successful nidation capacity for embryo, i.e. endometrial receptivity, is the key to successful nidation [1-2]. Endometrial receptivity is the key to nidation after the embryo is obtained by clinical treatment and laboratory technique. A normal endometrium only allow for embryonic nidation in a very short period. In this period, the endometrial receptivity is the greatest and it is usually referred to as "implantation phase" [3]. In the implantation phase, the endometrium experiences morphological and physiological changes and transforms into receptivity state under fine regulation of ovarian hormone [4]. The endometrium expresses specific genes and combines specific protein enabling the endometrium to receive embryonic nidation [5]. These proteins can serve as biochemical markers for

endometrial receptivity and clinical detection of such markers helps determination of the implantation window phase.

As an important regulatory factor, studies on expression of integrin and epidermal growth factor (EGF) in endometria of sterile women are few [6]. Ovulation failure and oviduct are the main common factors for causing sterility when women of childbearing age have no dysplasia in their reproductive systems clinically. Polycystic ovary syndrome (PCOS) is one of the most common reasons for ovulation failure in women of child-bearing period and hydrosalpinx and oviduct obstruction are the most common reasons for sterility due to the oviduct factor [7].

Therefore, the research primarily detects expression of integrin and EGF in patients with polycystic ovarian syndrome and patients undergoing in vitro fertilization-embryo transfer due to the oviduct factor (IVF-ET) during endometrial implantation window

2. Material and Methods

2.1. Objects and Material of Study

All objects of study were selected from patients who sought medical advice in our Center for Reproductive Medicine at our hospital from June 2018 to May 2019 and all objects of study were notified and they agreed prior to selection.

DAB color developing agent was purchased from Hangzhou Biowish biotechnology Co. Ltd.; Bovine Serum Albumin was purchased from Shanghai Jianglai Biotechnology Co., Ltd.; rabbit anti human EGF polyclonal antibody and rabbit anti human integrin monoclonal antibody were purchased from Shanghai Boyan Biotechnology Co., Ltd.; S-P hypersensitivity reagent kits (rat/rabbit) were purchased from Beijing Ruixiang Biotechnology Co., Ltd.; Model XSZ-D2 inverted biological microscope was purchased from Japan MuPid Company; the full-automatic chemiluminiscence immunoassay analyzer was purchased from U.S. Thermo Company; the multifunctional microplate reader was purchased from U.S. Labnet Company; the low-temperature ultra centrifuge was purchased from Beijing Jingli Centrifuge Co. Ltd.

2.2. Experimental Grouping

Control Group: 30 women of normal child-bearing period, aged 24-35 with an average age of 29.4±5.7.

Inclusion criteria: (1) those whose menstrual cycle is regularly and usually 29-31 days; (2) those who have not use any hormonal medicine in recent 3 months; (3) those whose uteruses and ovaries show no signs of organic lesions after transvaginal ultrasonography is used; (4) those whose results of basic endocrine examination shows no anomaly; (5) those whose basal body temperatures are biphasic.

Experimental Group I: 56 PCOS patients aged 24-38 with an average age of 30.6±6.4. Clomifene citrate was administered to all PCOS sterile patients for ovulation induction and these patients were assigned to Group A and B based on whether the patients have dominant follicles and ovulate successfully. Group A is the group with ovulation consisting of 30 patients and Group B is the group without ovulation consisting of 26 patients. Experimental Group II: IVF-ET was performed for 38 sterile patients aged 24-38 with an average age of 29.7±6.2 due to oviduct obstruction. Experimental Group III: IVF-ET was performed for 32 sterile patients aged 24-38 with an average age of 30.4±6.7 due to hydrosalpinx.

Inclusion criteria: (1) those who suffer from infrequent ovulation or anovulation; (2) those who suffer from hyperandrogenism; (3) those who have unobstructed bilateral oviducts indicated by the uterus oviduct radiography; (4) those who have no abnormal reproductive organs; (5) those whose basal body temperatures are biphasic; (6) those who have not used any hormonal medicine in recent 3 months; (7) those whose spouse semen analysis is within the normal range [8].

2.3. Clinical Treatment and Observation

Monitoring of basal body temperature (BBT): the objects of study were ordered to measure the oral temperature with a clinical thermometer in early morning everyday from the first day of menstrual cycle. The temperature measured everyday would be recorded on a curve chart for basal body temperature indicating all extraneous factors, such as menstruation date, vaginal bleeding volume, sexual life date, common cold, fever, night shift, sleep insufficiency etc.

It was required that barrier contraception should be used by the objects of study in the menstrual cycle.

The therapeutic schedule for ovulation induction for 56 PCOS patients was clomifene citrate. 50mgClomifene citrate was orally administered on the 5th day of menstrual cycle or withdrawal bleeding, once daily for 5 days.

2.4. Specimen Collection and Treatment

Sampling was performed 6-8 days after rise of the basal body temperature; sampling was performed at 20-23 days of the menstrual cycle if the basal body temperature did not rise; vaginal B ultrasonic examination was preformed to measure the thickness and morphology of endometrium and ovarian volume.

Part of the endometrium specimen was immediately placed in the EP tube and stored in a refrigerator at -80℃ for later use; meanwhile another part of was immediately fixed in 10% neutral formalin, dehydrated in gradient alcohol, regularly embedded in paraffin, sectioned regularly and serially into 5μm-thick slices.

2.5. Detection of Expression Level of Integrin During the Endometrial Implantation Window

The immunohistochemical S-P hypersensitivity method and the horseradish peroxidase (HRP)-dimethylbenzidine (DAB) detection display system were used. Immumohistochemical staining was performed as per instructions of the reagent kit.

For immunohistochemical result judgement, brownish yellow particles of cell membrane or cytoplasm of tissue sections indicate positive reaction and absence of brownish

yellow particles indicates negative reaction. Grading was performed based on staining intensity under microscope: Grade0, i.e. negative reaction (-), free of deposition brownish yellow particles; Grade (+), i.e. weak positive, positive cells < 10%, but significantly stronger than the negative control and individual cells indicate intermediate to strong positive; Grade (++), i.e. intermediate positive, the positive cells account for 10%-60%; Grade (+++), i.e. strong positive, the positive cells >60%. An image analyzer was used to take images at random under microscope. 10 positive visual fields were taken for each positive section. The blank space was used for calibration. The optical density value for each visual fields and average optical density value were determined (Average optical density，AOD) [9].

2.6. Detection of Expression level of EGF During the Endometrial Implantation Window

Expression of EGF protein was detected as per instructions for the ELISA reagent kit.

For immunohistochemical result judgement, brownish yellow particles of cell membrane or cytoplasm of tissue sections indicate positive reaction and absence of brownish yellow particles indicates negative reaction. Grading was performed based on staining intensity under microscope: Grade0, i.e. negative reaction (-), free of deposition brownish yellow particles; Grade (+), i.e. weak positive, positive cells < 10%, but significantly stronger than the negative control and individual cells indicate intermediate to strong positive; Grade (++), i.e. intermediate positive, the positive cells account for 10%-60%; Grade (+++), i.e. strong positive, the positive cells >60%. An image analyzer was used to take images at random under microscope. 10 positive visual fields were taken for each positive section. The blank space was used for calibration. The optical density value for each visual fields and average optical density value were determined.

2.7. Statistical Analysis

The chi-square test, variance analysis and correlation analysis were performed for the data with the SPSS 15.0 software package. $P<0.05$ indicated statistical significance and all test results were expressed with x±s.

3. Results

3.1. Pathological Examination Results for Endometria of the Objects of Study

The pathological examination of endometria of the 5 groups of objects of study demonstrates that the endometrial gland exhibits proliferating phase or secretory phase. No pathological changes were observed. See Table 1 for results.

Table 1. *Pathological Examination Results for Endometria of Various Groups of Women.*

Group	Number of Cases	Proliferating Phase (number of cases)	Secretory Phase (number of cases)
Control Group	30	0	30
PCOS Group with Ovulation Reaction	30	0	30
PCOS Group without Ovulation Reaction	26	23	3
Oviduct Obstruction Group	38	3	35
Hydrosalpinx Group	32	1	31

3.2. Comparison of Sterility Years Among Various Groups of Women

The detailed personal medical histories of all clinical objects of study were inquired to exclude the interval of sterility due to contraceptives to visiting date. The variance homogeneity of sterility years among various groups of women was good. A F test was conducted. There was no significant difference of sterility years among sterile women ($P>0.05$). See Table 2.

Table 2. *Comparison of sterility years among various groups of women.*

Group	Number of Cases	Sterility Years
PCOS Group with Ovulation Reaction	30	3.82±1.63
PCOS Group without Ovulation Reaction	26	3.68±1.72
Oviduct Obstruction Group	38	3.94±1.47
Hydrosalpinx Group	32	3.52±1.56

3.3. Comparison of Endometrium Thickness Among Various Groups of Women During Implantation Window

The thickness of the endometrium of the PCOS group was lower than that of the control group. The thickness of the endometrium of the PCOS group without ovulation was lower than that of the PCOS group with ovulation; the thickness of the endometrium of the oviduct factor group was also lower than that of the normal group. There was no significant difference of endometrium thickness based on a pairwise comparison among various groups ($P>0.05$). See Table 3.

A linear correlation analysis was conducted for expression of endometrium thickness, endometrium integrin and EGF of various groups. The result has shown that there was no correlation between the expression level of endometrium integrin and EGF and endometrium thickness of the five groups of objects of study ($P>0.05$).

Table 3. *Comparison of Endometrium Thickness among Various Groups of Objects of Study during Implantation Window.*

Group	Number of Cases	Endometrium Thickness (mm)
Control Group	30	12.76±1.38
PCOS Group with Ovulation Reaction	30	11.42±1.35
PCOS Group without Ovulation Reaction	26	10.37±1.08
Oviduct Obstruction Group	38	11.24±1.26
Hydrosalpinx Group	32	10.87±1.19

3.4. Observation and Comparison of Number of Fertilization Women of the PCOS Group

Curettage was performed for the women of the PCOS group during the implantation window. CC ovulation induction was performed at later stage. Track and visit were performed to examine the β-HCG value. A positive β-HCG value indicates nidation success. See Table 4.

Table 4. *Observation and Comparison of the Number of Successful Fertilization of Various Groups of Objects.*

Group	Number of Cases	Primary Infertility (number)	Number of Nidation
PCOS Group with Ovulation Reaction	30	27	23
PCOS Group without Ovulation Reaction	26	26	18

3.5. Expression of Integrin During Endometrial Implantation Window

After immumohistochemical staining, deposition of brownish yellow substance was observed in endometrial glandular epithelium. The integrin specificity was expressed in endometrial glandular epithelium cytoplasm during the implantation window. The expression level of integrin of the PCOS group and the hydrosalpinx group significantly weakened (P<0.05). See Table 5 and Figure 1.

Table 5. *Qualitative Judgment of Integrin in Endometria of Various Women.*

Group	Number of Cases	Glandular Epithelial Cell			
		-	+	++	+++
Control Group	30	0	5	17	8
PCOS Group with Ovulation Reaction	30	0	4	19	7
PCOS Group without Ovulation Reaction	26	2	12	8	4
Oviduct Obstruction Group	38	0	9	22	7
Hydrosalpinx Group	32	0	15	11	6

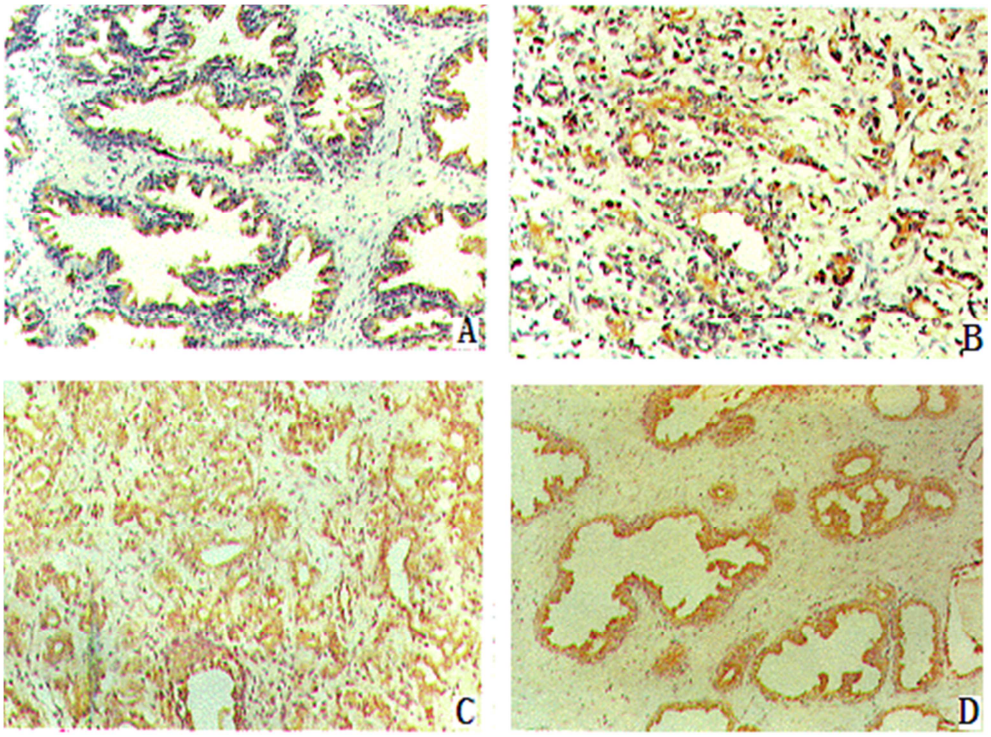

Figure 1. *Expression of Integrin during Endometrial Implantation Window.*

Legend: A. Expression of integrin in PCOS Group with ovulation reaction; B. Expression of integrin in PCOS Group without ovulation reaction; C. Expression of integrin in the oviduct obstruction group; D. Expression of integrin in the hydrosalpinx group.

The average optical density value result of the integrin in uteruses of various groups of women is as shown in Table 6. The expression level of the integrin in PCOS group is significantly lower than that in the control group and the difference is significant (P<0.05); the expression level of the integrin in PCOS anovulation group is significantly lower than that in PCOS ovulation group and there is statistical significance (P<0.05); the difference between the oviduct obstruction group and the the control group is not significant (P>0.05); the expression level of the integrin in the hydrosalpinx group is lower than that in the oviduct obstruction group and the difference is significant (P<0.05).

Table 6. *Average Optical Density of Integrin in Endometria of Various Groups of Women.*

Group	Number of Cases	Number of Cases Expressed	Average Optical Density Value
Control Group	30	30	0.5681±0.0836
PCOS Group with Ovulation Reaction	30	30	0.4128±0.0687 *#
PCOS Group without Ovulation Reaction	26	24	0.3096±0.0598 *#
Oviduct Obstruction Group	38	38	0.4838±0.0592 &
Hydrosalpinx Group	32	32	0.3685±0.0539 *&

Legend: * indicates that there is a significant difference compared with the control group (P<0.05); # indicates there is a significant difference between the PCOS anovulation group and PCOS ovulation group (P<0.05); & indicates that there is a significant difference between the hydrosalpinx group and the oviduct obstruction group ((P<0.05).

3.6. Expression of EGF in Endometria During Implantation Window

The expression sites of EGF of various groups of objects of study were detected with the immunothistochemical method. EGF was expressed in endometria of various groups of women. Its expression was located in endometrial glandular epithelium cytoplasm. See Table 7 and Figure 2.

See Table 8 for the average optical value results of endometrial EGF of various groups of women.

Table 7. *Comparison of EGF intensity at expression sites in endometria of various groups of women.*

Group	Number of Cases	Glandular Epithelial Cell			
		-	+	++	+++
Control Group	30	0	5	19	6
PCOS Group with Ovulation Reaction	30	2	6	15	7
PCOS Group without Ovulation Reaction	26	3	13	6	4
Oviduct Obstruction Group	38	2	5	23	8
Hydrosalpinx Group	32	3	18	8	3

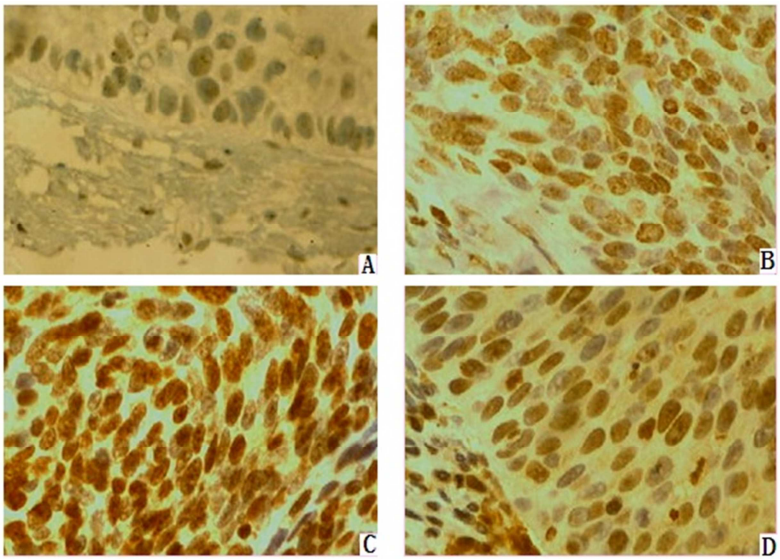

Figure 2. *Expression of EGF in Endometria during Implantation Window.*

Legend: A. Expression of EGF in PCOS Group with ovulation reaction; B. Expression of EGF in PCOS Group without ovulation reaction; C. Expression of EGF in the oviduct obstruction group; D. Expression of EGF in the hydrosalpinx group.

Table 8. *Average Optical Density of EGF in Endometria of Various Groups of Women.*

Group	Number of Cases	Number of Cases Expressed	Average Optical Density Value
Control Group	30	30	0.5128±0.0724
PCOS Group with Ovulation Reaction	30	28	0.3827±0.0483 *#
PCOS Group without Ovulation Reaction	26	23	0.2933±0.0479 *#
Oviduct Obstruction Group	38	36	0.4618±0.0658 &
Hydrosalpinx Group	32	29	0.3362±0.0492 *&

Legend: * indicates that there is a significant difference compared with the control group (P<0.05); # indicates there is a significant difference between the PCOS anovulation group and PCOS ovulation group (P<0.05); & indicates that there is a significant difference between the hydrosalpinx group and the oviduct obstruction group ((P<0.05).

4. Discussion

The pregnancy rate is low after PCOS ovulation induction treatment, which is closely associated with quality of egg cells. However, ovulation induction treatment impairs endometrial receptivity at the same time. Endometrial receptivity to embryo is decreasing thus leading to embryo implantation failure. This may be one of the causes for a high ovulation rate and low pregnancy rate after PCOS patients using ovulation induction medicine [10]. The oviduct factor is one of the common causes for clinical infertility. In vitro fertilization-embryo transplantation (IVF-ET) shows superiority in solving infertility due to oviduct [11]. However, many studies have shown that hydrosalpinx can reduce IVF-ET pregnancy success rate and increase abortion rate [12]. Hydrosalpinx is pathologic change process where expansion of the distal end of the oviduct wall and liquid accumulation occur due to obstruction of the distal end of oviduct as a result of various factors. It is generally considered that it is associated with previous pelvic cavity infection or endometriosis but the mechanism of hydrops formation still remains unclear [13].

Integrins are main cell surface receptors. It is a heterodimer composed of α and β chains. Currrently, 14 α subunits and 8 β subunits have been discovered and they can be divided into eight groups from β1 to β8 based on different β chains. α and β subunits jointly constitute coordinate bond sites, which mediate attachment of cells to extracellular matrixes [14]. Its special types can induce interaction among cells during adhesion of leukocytes [15]. Integrins are widely expressed in body. More than one integrins can be expressed on surface of most cells. They play a vital role in multiple life activities. E.g. Integrins are vital factors in leukocyte migration, platelet aggregation, development process and wound healing due to their adhesion [16]. In addition, some cells can only proliferate by means of adhesion. If any dysfunction occurs to adhesion of integrin-mediated cells to extracellular matrix apoptosis may be caused [17]. A majority of integrins are heterophilic cell adhesion molecules and their action depends on Ca^{2+}. Interaction between mediated cells and cells and interaction between cells and extracellular matrixes [18].

Epidermal growth factor (EGF) is a type of small peptide composed of 53 amino acid residues and one of the EGF-like family. It is multifunction growth factor and plays an important role in promoting division of cells of multiple tissues in vivo and in vitro [19]. EGF and specific receptors on the surface of response cells bind. The binding can promote receptor dimerization and cytoplasm phosphorylation. The activated receptors can bind with at least 5 proteins with different signal sequences for signal transduction and play a role in regulating protein synthesis at the translational level [20]. In addition, EGF can increase activity of DNA topoisomerase in cells as well as some genetic expression pertinent to proliferation, such as myc, fos etc.[21].

Embryonic nidation is the key to pregnancy and the beginning of a series of cellular signal transmission process where oosperms are implanted in the endometrium. Implantation success depends on blastocyst invasion ability and endometrial receptivity as well as synchronous development of endometrium and embryo [22]. Integrins are able to promote endometrium decidualization, maintain quiescent condition of the uterus, prevent uterine contraction before implantation, benefit embryo adhesion and nidation and influence polarity of endometrial glandular epithelium [23]. Endometrium decidualization plays an important role in embryonic nidation and creation and maintenance of pregnancy as well as delivery [24]. Integrins are able to promote inflow of extracellular Ca^{2+} by means of autocrine and paracrine thus decreasing level of Ca^{2+} in the uterine cavity and increasing concentration of Ca^{2+} in interstitial cells. Ca^{2+} and its calmodulin receptor bind to promote entery of endometrial interstitial cells into S phase from G1 phase and differentiation and growth of decidua [25]. Some studies also have shown that integrins secreted by the endometrium can lower the concentration of calcium ion in the uterine cavity by regulating flow direction of Ca^{2+} to maintain the quiescent condition of uterus and inhibit spontaneous and induced contraction of the mouse uterus [26].

Success of human pregnancy depends on interaction between the mother and her fetus. It is required to avoid exclusion of the mother against her fetus and prevent trophocytes from excessive invasion. Some studies have discovered that EGF can promote human chorion trophoderm cell adhesion to epithelial cells of the endometrial cavity to stimulate spread of blastosphere trophoderm and benefit embryonic nidation. Some scholars have reported that EGF is expressed in endometrium throughout the menstrual cycle of a normal female and exhibits regular variation with the menstrual cycle [29]. During early, middle and later proliferation period, weak expression of EGF is present in epithelial cells, interstitial cells and endothelial cells. The expression level reach its peak at the middle secretion phase (implantation window). EGF is expressed in endometrial glandular epithelium cells and coelomic epithelium cells. Positive products are secreted in the glandular cavity. The expression somewhat weakens during the late secretion period [30].

5. Conclusion

During ovulation induction treatment in the study, use of exogenous GnRH and Gn can directly or indirectly influence hormone level in the body, change endometrial environment, interfere with synchronism between cyclical development of endometrium and embryonic development thus affecting embryonic nidation and further development. During the nidation period, the endometrium changes morphologically and physiologically and converts into receptivity state under the effect of estrogenic and progestational hormones. The progestational hormone can proliferate and repair the endometrial glands and mesenchyme; the progestational hormone can convert the endometrium of the proliferation phase into endometrium of the secretory phase thus making appropriate preparation for oosperm nidation.

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