Biomedical Research 2012; 23 (2): 301-306

Surgical treatment of hydrosalpinx improves the expressions of integrin αvβ3 and L-selectin ligand in the endometrium in implantation window

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Abstract

Clinical importance of the improved expressions of integrin αvβ3 and L-selectin ligand in the endometrium following the surgical treatment for hydrosalpinx has been studied. A total of 60 patients with hydrosalpinx and 30 patients with fallopian tube obstruction were recruited. In the implantation window, immnohistochemistry was carried out to detect the expressions of integrin αvβ3 and L-selectin ligand in the endometrium of the hydrosalpinx patients before and after surgery and of patients with fallopian tube obstruction. In the implantation window, the expressions of integrin αvβ3 and L-selectin ligand in the endometrium of hydrosalpinx patients before surgery were significantly lower than those in patients with fallopian tube obstruction ($P<0.05$). However, there were no marked differences in the expressions of integrin αvβ3 and L-selectin ligand in the implantation window between hydrosalpinx patients after surgical intervention and fallopian tube obstruction patients ($P>0.05$). Furthermore, for patients with hydrosalpinx, the expressions of integrin αvβ3 and L-selectin ligand in the implantation window were dramatically increased after surgery ($P<0.05$). Hydrosalpinx decreases the expressions of integrin αvβ3 and L-selectin ligand in the endometrium in implantation window, and integrin αvβ3 and L-selectin ligand may be important factors influencing the endometrial receptivity of hydrosalpinx patients. Surgical treatment for hydrosalpinx can improve the expressions of integrin αvβ3 and L-selectin ligand in the endometrium in implantation window.

Key words: Hydrosalpinx, integrin αvβ3; L-selectin ligand, endometrium in implantation window

Accepted March 04 2012

Introduction

Under the influence of steroid from the ovaries, the endometrium undergoes periodical changes. Thus, the embryos can implant in the endometrium only in the proper phase [1]. The blastocyst implantation is shared by all mammals in nature and usually occurs between 3 days and 6 days after fertilization, which is corresponding to the days 21~24 or 5~8 days after the LH peak. That is to say, the embryos enter the uterus in the implantation window. The embryos and endometrium secret some related proteins and cytokines in a strictly spatial-temporal sequence. These proteins and cytokines recognize each other and cooperate leading to the implantation [2]. These bioactive cytokines and proteins are known as markers of the endometrial receptivity.

Tubal factors are the main causes of female infertility and account for about 40% of all causes. Furthermore, the hydrosalpinx accounts for 10~30% of the tubal factors causing infertility. *in vitro* fertilization-embryo transfer (IVF-ET) was initially applied in women with tubal factor infertility. However, numerous studies show the hydrosalpinx can reduce the implantation rate and pregnancy rate [3]. The mechanisms underlying the impact of hydrosalpinx on the IVF-ET are poorly understood. There is evidence that the influence of hydrosalpinx on the endometrial receptivity is one of the mechanisms [4]. In the present study, the expressions of integrin αvβ3 and L-selectin ligand in the endometrium in implantation window was compared between hydrosalpinx patients and those with fallopian tube obstruction, and the expression of integrin αvβ3 and L-selectin ligand in the endometrium in the implantation window in hydrosalpinx patients were also compared before and after surgery. Our results may be helpful to elucidate the cause of poor outcome of hydrosalpinx patients following IVF-ET.

Materials and Methods

Patients

A total of 60 patients with hydrosalpinx and 30 patients with fallopian tube obstruction were recruited from April 2010 to December 2010 from the Center of Reproductive Medicine of the Affiliated First Hospital of Sun Yat-sen University.

All patients were aged <40 years and had regular menstrual cycle. Endocrine examinations revealed normal and the basal body temperature was biphasic. Hormones were not administered within 6 months before study. Endometriosis, uterine fibroids, polycystic ovary syndrome, ovarian cancer, infertility of unknown causes, immune infertility, chronic systemic disease, sexually transmitted disease, trophoblastic disease, smoking and drinking as well as male infertility were excluded before study.

Diagnosis

Hydrosalpinx: The bilateral or unilateral hydrosalpinx was diagnosed by hysterosalpingography (HSG) or laparoscopy (LAP) and untrasonography.

Fallopian tube obstruction

The fallopian tube obstruction was diagnosed by HSG or LAP, and ultrasonography was performed to exclude the presence of hydrosalpinx.

Surgical intervention of hydrosalpinx

Vaginal ultrasound-guided hydrosalpinx aspiration, laparoscopic salpingostomy, laparoscopic proximal tubal ligation or laparoscopic salpingectomy was performed.

Sample collection and processing

The LH peak was measured by using LH strip since the 10^{th} day of menstrual cycle. In addition, transvaginal ultrasonography and test of serum sex hormones were also performed. At days 7~8 after ovulation, the endometrium was collected at the bottom of uterus by using a curette and washed in normal saline to remove the blood. Samples were fixed in fixation solution, embedded in paraffin and sectioned. Pathological examination was carried out to confirm that the endometrium was in the secretory phase. For patients with hydrosalpinx, the endometrium was collected in the implantation window before and after surgery, but collection of endometrium was done once in patients with fallopian tube obstruction.

Immunohistochemistry

Mouse anti-human integrin αvβ3 monoclonal antibody (Abcam) (1:80) and mouse anti-human L-selectin ligand monoclonal antibody (1:200) (SANTA CRUZ) were used for immunohistochemistry which was performed according to the manufacturer's instructions.

Determination of findings

Five fields were randomly selected from each section at a magnification of 400, and the integrated optical density (IOD) was determined by using the Image-Pro Plus 5.1 Chinese.

Statistical analysis

The IOD was expressed as means ± standard deviation (x±s). Statistical analysis was performed with SPSS version 13.0. A value of two-tailed P<0.05 was considered statistically significant.

Results

Under light microscope, the integrin αvβ3 and L-selectin ligand were mainly expressed on the membrane and in the cytoplasm of the endometrial gland epithelial cells, and the endometrial interstitium had weak expressions of integrin αvβ3 and L-selectin ligand. In the hydrosalpinx patients, the expressions of integrin αvβ3 and L-selectin ligand were significantly different between before and after surgery (P<0.05). Before surgery, the expressions of integrin αvβ3 and L-selectin ligand in the endometrium of hydrosalpinx patients (Figure 1 A and D) were markedly lower than those in the controls (Figure 1 C and F) (P<0.05). However, no dramatic differences were found in the expressions of integrin αvβ3 and L-selectin ligand in the endometrium between hydrosalpinx patients after surgery (Figure 1 B and E) and control patients (P>0.05) (Table 1).

Table 1. *Expressions of integrin αvβ3 and L-selectin ligand in patients of both groups*

	Hydrosalpinx patients		**Fallopian tube obstruction patients** (n=30)
	Before surgery(n=60)	After surgery (n=60)	
Integrin αvβ3	0.29±0.10	0.58±0.17	0.55±0.11
L-selectin ligand	0.37±0.11	0.54±0.15	0.50±0.15

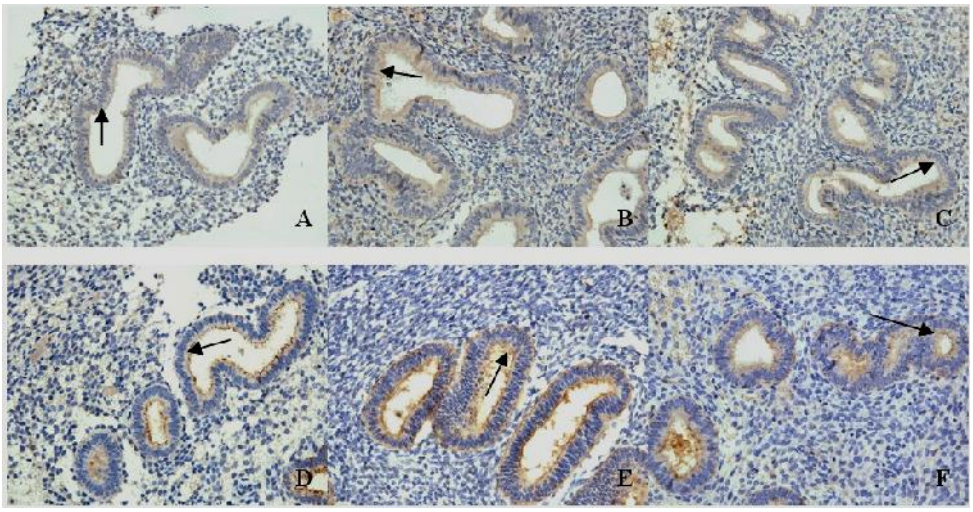

Figure 1. *A: Expression of endometrial integrin αvβ3 in hydrosalpinx patients before surgery; B: Expression of endometrial integrin αvβ3 in hydrosalpinx patients after surgery ; C: Expression of endometrial integrin αvβ3 in fallopian tube obstruction patients ; D: Expression of endometrial L-selectin ligand in hydrosalpinx patients before surgery ; E: Expression of endometrial L-selectin ligand in hydrosalpinx patients after surgery ; F: Expression of endometrial L-selectin ligand in fallopian tube obstruction (Immunohistochemistry, ×400).*

Discussion

The histologically normal endometrium not always has normal function and can not reflect the receptivity. Currently, the indicators for the evaluation of endometrium are limited. There are dozens of cytokines and molecules that are being applied to evaluate the successful implantation of embryos. In the present study, we employed integrin αvβ3 and L-selectin ligand as markers of emdometrial receptivity. To date, few studies have been conducted to investigate the integrins and their ligands and no study has been conducted to explore the effect of hydrosalpinx on the expressions of integrins and their ligands in the endometrium. The influence of hydrosalpinx on the integrin αvβ3 and L-selectin ligand has never been investigated.

Integrin αvβ3

Biochemical characteristics of integrin

Integrins are a type of cellular adhesion molecule and widely expressed on the cell membrane. They are receptors shared by extracellular matrix and are heterodimers consisting of subunits α and β in a non-covalent manner. A total of 14 α subunits and 9 β subunits have been identified and can form more than 20 integrins. Both subunits α and β are composed of extracellular domain, transmembrane domain and intracellular domain. The α subunit is 120-180 kDa in molecular weight and is indispensable for the integrin function. The β subunit is 90-110 kDa in molecular weight. Different α subunits and β subunits have different structures. The N terminal of the heterodimers of subunits α and β is extracellular and long and forms a spherical domain. In addition, the N terminal also contains a divalent cation-binding site which can specifically bind to the laminin (LN), fibronectin (FN), vitroneetin (VN) and the Arg-Gly-Asp (RGD) in the human complement C3. The C terminal is intracellular and short. Different α and β subunits have distinct structures of C terminal. Dou et al [5] found the expressions of α2, α3, α4, α5, α6.1, α6.2, αv, β1, β2, β3 and β5 in the endometrium in the whole menstrual cycle, the α2, α3 and α5 were predominantly expressed in the proliferative phase, and the α4, α6.2, αv, β1, β2, β3 and β5 were mainly expressed in the secretory phase. However, the α6.1 expression was constant in the whole menstrual cycle. In addition, the changes in the expressions of αv and β3 in the menstrual cycle were more obvious than other subunits. Moreover, different types of cells had expressions of different integrins. In mammals, the integrins are widely expressed on the cell membrane. Currently, integrins have become an acceptable marker of endometrial receptivity.

Role and regulation of integrins in the reproduction

The integrins function via binding to the corresponding ligands. An integrin can recognize some ligands and a ligand may recognize different integrins. The integrin αvβ3 is related to the endometrial receptivity and its ligands include osteopontin (OPN) [6], perlecan, FN, VN, tenascin, von willebrand factor (vWF), etc. During the establishment of endometrial receptivity, OPN can recognize αvβ3, which is closely related to the implantation window. In the proliferative phase, the mRNA expression of OPN is weak. In the middle or later secretory phase,

the endometrial epithelial cells, lymphocytes and endometrial secretions have high mRNA expression of OPN [7]. Lessey et al [8] proposed the Sandwich model in the implantation of embryos: The integrins expressed on the embryos and in the endometrium can bind to the OPN, which facilitates the adhesion of embryos to the endometrium. In the implantation window, the expressions of integrins in the endometrium are significantly increased due to the regulation by steroids and a series of cytokines and growth factors, and the affinity of integrins is also elevated, which maximizes the endometrial receptivity. At the same time, the trophoblast cells in the embryos also have the expressions of integrins. Thus, the integrins in the endometrium and on the trophoblast cells bind to the OPN which mediates the crosstalk between embryos and endometrium. The integrins are expressed on the cell membrane in a cluster manner but the individual integrin has a low affinity to the ligands. However, the accumulated affinity of clustered integrins significantly consolidates the bindings between the embryos and endometrium. Therefore, in the Sandwich manner, the endometrium becomes to accept the embryos finally leading to the endometrial receptivity. In addition, integrins might act as activators and can activate the endometrium, increase the vascular permeability, promote the dilation of local blood vessels and involve in the decidualization of endometrium, which are beneficial for the adhesion between embryos and endometrium and subsequent implantation.

Before the endometrial receptivity is established and after the endometrial receptivity disappears, the expressions of estrogen receptor (ER) and progesterone receptor (PR) in the endometrial epithelial cells have a decreasing tendency which is dependent on the P. The failure of P regulation may significantly affect the endometrial receptivity [9]. The P binds to the PR and then regulates the αvβ3 and its ligands in two ways: (1) Direct regulation: P directly acts on the PR on the epithelial cells of endometrium and then promotes the expressions of αvβ3, OPN and other endometrial receptivity related molecules (such as α1β1 and α4β1) on the epithelial cells; (2) indirect regulation: P acts on the PR on the endometrial stroma cells which stimulates the transcription of down-stream genes and increases the expression of epithelium growth factor (EGF) or heparin-binding EGF-like growth factor (HB-EGF). These factors then function on the corresponding receptors on the endometrial epithelial cells leading to the production of αvβ3, OPN, etc [10]. At the site where the embryos implant in, a series of cytokines are expressed and form a network, which can coordinate the expressions of some factors mediating the endometrial receptivity. The integrins are also regulated by these factors and thus, the endometrium can achieve the receptivity at the designed time. The embryos can secret hCG and other cytokines (such as IL-1) which then bind to the corresponding receptors on the endometrium and regulate the expressions of molecules in the endometrium (such as integrins) and subsequent the endometrial receptivity. There is evidence showing that integrin αvβ3 binds to the RGD sequence both of which are expressed on the embryos [11]. RGD might bridge the recognition between the integrin αvβ3 in the endometrium and that on the embryo, but the specific mechanism is unclear. The findings above show the integrin αvβ3 is critical for the implantation of embryos, and it is expressed not only in the endometrium but on the surface of embryos.

Effect of hydrosalpinx on the integrin αvβ3 expression in the endometrium

Our results showed the integrin αvβ3 expression in the hydrosalpinx patients before surgery was markedly lower than that in patients with fallopian tube obstruction. After surgical intervention for hydrosalpinx, the integrin αvβ3 expression was comparable between patients in two groups. In addition, when compared with before surgery, the integrin αvβ3 expression was dramatically increased in the hydrosalpinx patients. These findings suggest hydrosalpinx inhibits the integrin αvβ3 expression in the endometrium in the implantation window, which is upregulated following surgical intervention. These findings were consistent with previous reported. Lessey and Castelbaum [8] found that the integrin αvβ3 expression in the endometrium in the implantation window was decreased in the hydrosalpinx patients, but returned to normal after surgical treatment for hydrosalpinx. Bildirici et al [12] also draw the same conclusion. In study of Bildirici et al, they investigated 10 patients with hydrosalpinx. Before surgery, the HSCORE score of integrin αvβ3 expression was <0.7 in the implantation window in 8 hydrosalpinx patients, and the mean HSCORE score was increased by 2.1 after surgery (criterion for positive: 0.7). The statistical analysis showed the significant difference in the integrin αvβ3 expression in the endometrium before and after surgery. We speculate that hydrosalpinx may reduce the endometrial receptivity via decreasing the integrin expression in the endometrium.

Selectin

L-selectin is one of members of cellular adhesion molecule family which mediate the interaction between leukocytes and endothelial cells, migration of leukocytes across the endothelial cells into inflammatory tissues and lymphocyte homing and re-circulation [13][14]. In recent years, studies show some key processes in the reproduction, immunity and vascular functions share some features at the molecular level [15][16].

Biochemical characteristics of L-selectin and its ligands

Selectin family is a group of important cell adhesion molecules and includes three molecules with similar structure: L-selectin, P-selectin and E-selectin which were initially identified on the leukocytes, platelets and endothelial cells, respectively. These molecules are type I transmembrane glycoprotein consisting of extracellular do-

main, transmembrane domain and intracellular domain. Different integrins have high homology and similar structure in the extracellular domain. The extracellular domain is composed of three groups: (1) The N terminal is a calcium-dependent type C exogenous agglutinin-binding-domain, and can bind to the ligand. (2) Epidermal growth factor-like domain is necessary for the maintenance of molecular configuration. (3) Complement regulatory protein repeated sequence or complement binding protein repeated sequence. There is no homology in the transmembrane domain and intracellular domain among selectins. The human selectin gene locates in the chromosome 1 and is arranged in the ~300-kb region in an order of P/L/E.

The molecular weight of L-selectin is about 75~80 ku, and the ligands of selectin are largely oligosaccharide groups. The 3 selectins can recognize sialyl Lewis sugar or related molecules. Five glycoprotein ligands have been identified: (1) glycosylation dependent cellular adhesion molecule-1 (GlyCAM-1) is a secretory salivary mucin with the molecular weight of 50 ku and can bind to all selectins. The sulfated oligosaccharide chain can bind to the L-selectin. G1yCAM-1 can also bind to lymphocytes resulting in activation of integrins β2 and β1. (2) CD34 is a 90-ku glycoprotein and a transmembrane salivary mucin. CD34 is widely expressed on the endothelial cells, hematopoietic precursor cells, brain and multiple embryonic fibroblast lines. (3) Mucosal vascular addressin cell adhesion molecule (MAdCAM-1) is identified by MECA-367 and also a ligand of integrin a4β7 on the lymphocytes. (4) Sgp200 is a sulfated glycoprotein in the isolation of high endothelial vein (HEV) in the mouse lymph nodes by L-selectin Fc chimeras. Its molecular weight is 200 ku and can be secreted. The molecular characteristics of Sgp200 are still unclear. (5) P-selectin glycoprotein ligand (PSGL-1) can also act as a ligand of L-selectin.

Role and regulation of L-selectin and its ligand

L-selectin is constitutively expressed on the majority of leukocytes and mediates the adhesion between leukocytes and endothelial cells. L-selectin involves in the migration of leukocytes across the endothelial cells into the inflammatory tissues and participates in the homing and recirculation of lymphocytes as well as the adhesion between lymphocytes. In the inflammation region, L-selectin initiates the adhesion between leukocytes and endothelial cells which may be realized by the regulation of the expression of ligands on the endothelial cells. Genbacev et al [17] speculated that, morphologically, the crossing of leukocytes from the blood vessels was similar to the adhesion of embryos to the uterus. In the adhesion of embryos to the uterus, the embryos locate in a liquid environment of mucin secreted by uterus. In respect of this, Genbacev et al hypothesized that the binding of L-selectin to its ligands might be an initial step in the implantation of embryos. In the implantation window, the expression of L-selectin on the embryos and that of oligosaccharide ligand of L-selectin in the endometrium have an increasing tendency. Their study also confirmed the binding of L-selectin to its ligand was an important regulator of human pregnancy. L-selectin is also expressed on the surface of sperms and might be involved in the fertilization.

The ligand of L-selectin was initially identified by the MECA-79 in the HEV of mouse lymph nodes, and its corresponding antigens are called peripheral lymph node addressins (PNAd) including the ligands of G1yCAM-1, CD34 and Sgp200.

In a study, the antibody against the ligand of L-selectin was used to detect the endometrium in the follicular phase and luteal phase of two egg donors by immunofluorescence assay. Results showed the MECA-79 was weakly expressed in the follicular phase and mainly found in the endometrial gland and on the endometrial cells. In the luteal phase, MECA-79 was strong expressed, especially on the endometrial cells. Western blot assay was employed to detect the MECA-79 expression in the endometrium of both donors at different time points. Results revealed the expression of MECA-79 was markedly increased at days 3 and 6 when compared with that at days 0 (day of egg retrieval) and 2. These findings suggest the expression of ligand of L-selectin increases with the alteration of endometrial receptivity, and the MECA-79 expression in the endometrium also has a periodic alteration over the menstrual cycle.

Effect of hydrosalpinx on the expression of L-selectin and its ligand

A few studies reported the expressions of L-selectin and its ligand in the endometriun in China, and no study has been conducted to investigate the effect of hydrosalpinx on the expression of L-selectin and its ligand.

Our results showed, in the implantation window, the expression of L-selectin ligand in the endometrium of hydrosalpinx patients before surgery were significantly lower than those in patients with fallopian tube obstruction. However, there were no marked differences in the expression of L-selectin ligand between hydrosalpinx patients after surgical intervention and fallopian tube obstruction patients. Furthermore, for patients with hydrosalpinx, the expression of L-selectin ligand in the implantation window were dramatically increased after surgery ($P<0.05$). These findings imply that hydrosalpinx affects the expression of L-selectin ligand in the endometrium in the implantation window since the expression of L-selectin ligand has increased following surgical intervention for hydrosalpinx.

Hydrosalpinx is a feature of chronic pelvic inflammation. Copperman et al [18] compared the endometrium between patients with hydrosalpinx and subjects with normal fallopian tube. Their results showed the number of inflam-

matory cells in the endometrium of hydrosalpinx patients was significantly higher than that in subjects with normal fallopian tube, and the expressions of inflammatory cytokines including IL-2 were also markedly increased when compared with control group. IL-2 is a cytokine specific to Th-1 cells. Piccinni et al [19] found Th-1 cytokines could down-regulate the expression of leukemia inhibitory factor (LIF). The increase of IL-2 expression in the endometrium of hydrosalpinx patients might also reduce the LIF expression. In the hydrosalpinx patients, the contents of toxic substances including cytokines in the lesions are very high [20]. These toxic substances can enter the uterus, affecting the expressions of L-selectin and its ligand. Our previous studies have shown that hydrosalpinx reduced the expressions of αvβ3 and LIF in the endometrium, both of which are the markers of endometrial receptivity. In the present study, the expressions of L-selectin and its ligand were also reduced in the endometrium of hydrosalpinx patients. According to the findings that the expressions of integrin αvβ3, LIF and L-selectin are reduced in the hydrosalpinx patients, we speculate that L-selectin and its ligand can be used as markers of endometrial receptivity. However, this hypothesis should be further confirmed in future multicenter randomized, controlled prospective studies.

Taken together, the endometrium undergoes periodic changes which vary in individuals. To accurately evaluate the endometrial receptivity is basic for the improvement of endometrial receptivity. In the present study, we investigated the effect of hydrosalpinx on the expressions of integrin αvβ3 and L-selectin in the endometrium in the implantation window. Our results demonstrate the hydrosalpinx influences the expressions of integrin αvβ3 and L-selectin in the endometrium in the implantation window, reduces the receptivity of endometrium for the implantation of embryos and compromises the ability to maintain the pregnancy. After surgical treatment for hydrosalpinx, the expressions of integrin αvβ3 and L-selectin in the endometrium are increased. L-selectin and its ligand may be important factors influencing the endometrial receptivity of hydrosalpinx patients.

Acknowledgment

This study was funded by Guangdong Science and Technology Program (No. 2009B030801155) and Guangdong Population and Family Planning Project (No. 2010243).

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