AlphaVBeta3 Integrin Expression within Uterine Endometrium in Unexplained Infertility

Thesis

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Alaa Mohamed Atef Karim El-Din

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List of Abbreviations

- **2D** : Two dimensional
- **3D** : Three dimensional
- **4D** : Four dimensional
- **BBT** : Basal body temperature
- **CAMP** : Cyclic Adenosine Monophosphate
- **CAMs** : Cell Adhesion Mollecules
- **CC** : Clomiphene Citrate
- **COH** : Contolled ovarian stimulation
- **COX** : Cyclooxygenase
- **cPLA** : Cytosolic Phospholipase A
- **CSF** : Colony Stimulating Factor
- **ECM** : Extracellular matrix components
- **EDPA** : Intraendometrial power Doppler area.
- **EEC** : Endometrial Epithelial cells
- **ELISA** : Enzyme-linked immunosorbent assay
- **ER** : Estrogen receptor
- **ER** : Estrogen receptor
- **ESC** : Endometrial Stromal Cells
- **ET** : Embryo transfer
- **ET** : Endometrial thickness
- **EV** : Endometrial volume
- **FAK** : Focal adhesion kinase
- **FN** : Fibronectin

List of Abbreviations *(Cont.)*

- **FSH** : Follicle Stimulation Hormone
- **HG-EGF** : Heparin binding epidermal growth factor
- **HOXA** : Homeobox gene
- **HSG** : Human Chorionic Gonadotrophin
- **HSG** : Hysterosalpingography
- **ICAM**-1 : Intercellular adhesion molecules 1
- **ICSI** : Intracytoplasmic Sperm Injection
- **IGF** : Insulin like growth factor
- **IHC** : Immunohistochemistry
- **IL** : Interlukin
- **ILK** : Integrin linked kinase
- **IUD** : Intrauterine Device
- **IUI** : Intrauterine Insemination
- **IVF** : In Vitro fertilization
- **LH** : Luteinizing Hormone
- **LIF** : Leukemia inhibiting factor
- **LTs** : Leukotrienes
- **MAP** : Mitogen-activated protein
- **MCP** : Membrane Co-factor protein
- **MMPs** : Matrix metalloproteinases
- **MUC** : Mucin
- **OC** : Oral contraceptives
- **OPN** : Osteopontin
- **PCOs** : Polcystic ovary syndrome

List of Abbreviations *(Cont.)*

- **PCT** : Post coital test
- **PGI2** : Prostacyclin
- **PGS** : Prostaglandin Synthase
- **PGs** : Prostaglandins
- **PGT** : Prostaglandin transporter
- **PI** : Pulsatility Index
- **PID** : Pelvic Inflammatory Disease
- **PKC** : plausible substrates for cellular kinases C
- **PR** : Progesterone receptor
- **RGD** : Arginine- Glycine- Aspartic acid
- **RI** : Resistance Index
- **ROC** : Reciever Operating Characteristic curve
- **RPL** : Recurrent Pregnancy loss
- **SEM** : Scanning electron microscope
- **TGF** : Transforming growth factor
- **TNF-α** : Tumor Necrosis Factor α
- **TXa** : Thromboxanes
- **VEGF** : Vascular endothelial growth factor

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Introduction

Unexplained infertility refers to the absence of a definable cause for a couple's failure to achieve pregnancy after 12 months of attempting conception despite a thorough evaluation ***(Abusief et al., 2007).***

The Practice Committee of the American Society for Reproductive Medicine (ASRM) has published guidelines for a standard infertility evaluation ***(The Practice Committee of the American Society for Reproductive Medicine, 2006).*** It includes a semen analysis, assessment of ovulation, a hysterosalpingogram, and, if indicated, tests for ovarian reserve and laparoscopy. When the results of a standard infertility evaluation are normal, practitioners assign a diagnosis of unexplained infertility. Although estimates vary, the likelihood that all such test results for an infertile couple are normal (ie, that the couple has unexplained infertility) is approximately 15% to 30% ***(The Practice Committee of the American Society for Reproductive Medicine, 2006).***

The average incidence of unexplained infertility has been reported to approximately 15%. The incidence varies from 0% to 37%. This variation may be attributed to selection bias in referral-based infertility practice ***(Balasch, 2000).***

In the absence of a correctable abnormality, the therapy for unexplained infertility is, by default, empiric. Proposed treatment regimens include intrauterine insemination (IUI), ovulation induction with oral or injectable medications, combination of IUI with ovulation induction, and assisted reproductive technologies (ART) ***(ASRM, 2006).***

Embryo implantation represents the most critical step of the reproductive process in many species. It consists of a unique biological phenomenon, by which the blastocyst becomes intimately connected to the maternal endometrial surface to form the placenta that will provide an interface between the growing fetus and the maternal circulation ***(Denker, 1993; Aplin, 2000).***

Successful implantation requires a receptive endometrium, a normal and functional embryo at the blastocyst developmental stage and a synchronized dialogue between maternal and embryonic tissues ***(Simonet al., 2000).***

The process of implantation may be classified into three stages: apposition, adhesion and invasion ***(Enders, 1967).***

The endometrium is receptive to blastocyst implantation during a spatially and temporally restricted window, called the implantation window. In humans, this period begins 6-10 days after the LH surge and lasts for 48 hours ***(Simon et al., 2000).***

Endometrial receptivity consists in the acquisition of adhesion ligands together with the loss of inhibitory components that may act as a barrier to an attaching embryo ***(Aplin, 2000).***

The relative inefficiency of the implantation process is paradoxical in view of the fact that reproduction is critical to species survival. Implantation failure remains an unsolved problem in reproductive medicine and is considered as a major cause of infertility in otherwise healthy women. Indeed, the average implantation rate in IVF is around 25% ***(de los Santoset al., 2003).***

Inadequate uterine receptivity is responsible for approximately two-thirds of implantation failures, whereas the embryo itself is responsible for only one-third of these failures ***(Simon et al., 1998; Ledee-Bataille et al., 2002).***

The recent discovery of molecules crucial for successful embryo implantation has offered researchers precious insight into this field. Primary adhesion molecules that are implicated in implantation include selectins, galectins, heparan sulfate proteoglycans, MUC1, integrins, cadherins, and the trophinin-tastin-bystin complex ***(Dey et al., 2004).***

Integrins are a family of transmembrane glycoproteins, formed by the association of two different, non-covalently

linked, α and β subunits. To date, 18 α and eight β chains have been identified in mammals. When paired, they form 24 distinct integrin heterodimers that differ in their function ***(Hynes, 2002).***

Integrins whose expression is increased in the mid-luteal phase were proposed as markers for the frame of the window of implantation ***(Lessey et al., 2000).***

Three cycle-specific integrins are co-expressed by the human endometrium defined histologically on days 20–24 of the human menstrual cycle: α1β1, α4β1 and αvβ3, but only the β3 mRNA subunit expression was shown to increase after day 19 and is not detected beforehand. Moreover, αvβ3 integrin as well as its ligand osteopontin was positively detected by Immunohistochemistry on the endometrial luminal epithelial surface, which first interacts with the trophoblast ***(Apparao et al., 2001).***

In regard to its expression pattern along with its epithelial localization, αvβ3 has been proposed as a potential receptor for embryonic attachment ***(Lessey, 2003).***

Integrins are also expressed by the human trophoblast at the time of implantation ***(Wang and Armant, 2002).***

During the proliferative phase, high estrogen levels act via the estrogen receptor-α (ERα) to inhibit integrin