Role of Uterine Natural Killer Cells in Women with Infertility and Associated Endometriosis: A Case Control Study

Thesis

Submitted for Partial Fulfillment of Master Deg ree in Obstetrics and Gynecology

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Marwa Hamdy Abdelhafeez

Contents

List of Abbreviations

Abbrev.	Meaning
ADCC	Antibody dependent cellular cytotoxicity
CD	Cluster of differentiation
COCP	Combined oral contraceptive pills
DIE	Deep infiltrating endometriosis
dNK	Decidual NK
EIF	Endometriosis inducing factor
GnRH	Gonadotropin-releasing hormone agonist
IFN-y	Interferon-y
IL	Interleukin
IVF	In vitro fertilization
IVF-ET	In vitro fertilization and embryo transfer
KARs	Killing activating receptors
KIRs	Killer inhibitory receptors
LIF	Leukemia inhibitory factor
LUNA	Laparoscopic uterine nerve ablation
NK	Natural killer
RSA	Recurrent spontaneous abortion
TNF-a	Tumour necrosis factor-a
TVS	Transvaginal ultrasound
UNK	Uterine NK

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Protocol

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A Protocol of Thesis
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INTRODUCTION

Infertility affects about 10-15% of reproductive age couples ***(Boivin et al., 2007)***. The presence of patent fallopian tubes, normal ovulation, and normal sperm parameters may still be associated with subfertility because of distortion of the uterine cavity or the presence of intraperitoneal endometriosis ***(Hart, 2003)***.

Endometriosis is characterized by the presence, outside the endometrial cavity, of tissue that is morphologically and biologically similar to normal endometrium. This ectopic endometrial tissue responds to ovarian hormones undergoing cyclical changes similar to those seen in eutopic endometrium ***(Overton et al., 2007)***.

The clinical diagnosis of endometriosis is primarily made at the time of laparoscopy, although there is increasing support for empirical treatment with laparoscopy if symptoms persist. The classic appearance is of blue-black lesions, but many subtler appearances are now recognized ***(Husby et al., 2003)***.

Endometriosis is present in 20-40% of women who complain of subfertility, although it can be found in 5% of fertile women. Postulated explanations include intraperitoneal inflammation, immunological factors, unruptured luteinized follicles, and an increase in the rate of miscarriage ***(Hart, 2003)***.

Uterine natural killer (NK) cells are the predominant leukocyte population in normal human endometrium ***(Nagler et al., 1989)***. Approximately 70–80% of uterine NK cells are characterized as $CD56^{bright}CD16^{-}$ ***(King and Loke, 1991)***. Their content varies throughout the normal menstrual cycle, likely due to recruitment of peripheral NK cells and/or in utero proliferation/differentiation of stem uterine NK cells ***(Tang et al., 2011)***.

Another minor subpopulation of uterine NK cells, characterized as$CD56^{dim}CD16^{+}$, displays cytotoxic activity toward the extravillous trophoblast and autologous endometrial cells and may create a hostile environment for implantation ***(Verma et al., 2000)***.Successful embryo implantation requires a receptive endometrium, a functional embryoat the blastocyst developmental stage and a synchronized dialog between maternal and embryonic tissues ***(Cakmak and Taylor, 2011)***.

Only few studies have examined changes in uterine NK cell numbers in endometriosis, demonstrating a lower percentage of $CD56^{bright}$ NK cells and adefect in NK activity in the eutopic endometrium of women with endometriosis ***(Klentzeris et al., 1995; Jones et al., 1996; Petta et al., 2010)***.

Recently, it was concluded that women who have larger populations of cytotoxic $CD16^{+}$ uterine NK cells and/or higher populations of $CD56^{bright}$cells may be at greater risk of infertility disorders resulting from an inflammatory environment

occurring during implantation or later during decidualization ***(Giulian et al., 2014)***.

Aim of the work

The aim of this study is to evaluate the expressionof CD56 and CD16 uterine natural killer cells in the endometrium of women with infertility associated with endometriosis.

Research question: do women with infertility associated with endometriosis express CD56 and CD16 uterine natural killer cells in their endometrium?

Research hypothesis: the expression of CD56 and CD16 uterine natural killer cells in the endometrium is not correlated to infertility associated with endometriosis.