Prevalence of Endometriosis Among Infertile Women Undergoing Laparoscopy

Thesis

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قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

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Marwan Osama Saleh Elkady

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List of Abbreviations

AIDS	:	Acquired Immune Deficiency Syndrome
BMI	:	Body mass index
CA-١٢٥	:	Cancer antigen ١٢٥
COX-٢	:	Cyclooxygenase ٢
FSH	:	Follicle stimulating hormone
GnRH	:	Gonadotrophin releasing hormone
HDS١٧B٢	:	١٧β-hydroxysteriod dedydrogenase ٢
IL-٦	:	Interleukin-٦
LH	:	Luteinizing hormone
LOH	:	Loss of heterozygosity
LUNA	:	Laparoscopic uterosacral nerve ablation
MDPA	:	Medroxy progesterone acetate
NK cells	:	Natural killer cells
NSAID	:	Non-steroidal anti-inflammatory drug
OCP	:	Oral contraceptive pill
PF	:	Peritoneal fluid
PGE٢	:	Prostaglandin E٢
PHAH	:	Polyhalogenated aromatic hydrocarbon

R-AFS	:	Revised classification of the American fertility society
RCT	:	Randomized controlled trial
TCDD	:	٢،٣،٧،٨-tetrachlorodibenzo-p-dioxin
TSH	:	Thyroid stimulating hormone
WHO	:	World health organization

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Introduction

Endometriosis is a benign condition in which endometrial glands and stroma are present outside the endometrial cavity, usually in the ovary or on the pelvic peritoneum. ***(Harada, ٢٠٠١).***

It is a common disorder of the female reproductive organs and the leading cause of chronic pelvic pain in women occuring in ١٠-٣٣٪ of women aged ٢٥-٣٥ years. Half of adolescents with chronic pelvic pain will have endometriosis. The average age at diagnosis is ٢٧ years, but many women have symptoms for years before a definitive diagnosis is made ***(Hernandez & McNamara, ٢٠٠٢).***

Estimates of the numbers of women who suffer from endometriosis vary widely, nearly ٩٠ million women worldwide have been proposed as a conservative Fig.. The fact is that there is no way to establish accurate Fig.s because the only way to confirm a diagnosis is by laparoscopy. If only ١٠٪ of women have it, that makes endometriosis one of the most common disease on the face of the earth., more common than AIDS and more common than cancer ***(Browne & Heather, ٢٠٠٣).***

Due to atypical presentation and/or microscopic disease; at least some patients with no apparent disease during laparoscopy do in fact have minimal & invisible disease. This fact supports the contention that some patients with unexplained infertility must suffer from a very early stage of

endometriosis this concept is further supported by a variety of immunological observations amongst which are observation on abnormal autoimmune function which suggest that patients with unexplained infertility exhibit the same immunologic profile as those with endometriosis ***(Ota & Igarashi, ١٩٩٣).***

Moreover, after extended researches in center for human reproduction, Chicago' USA it was concluded that many patients with unexplained infertility are patients with minimal endometriosis presenting as a precursor. Stage to visible endometriosis, also it's believed that autoimmune abnormalities precede endometriosis ***(Gallova, ٢٠٠٢).***

Aim of work

The aim of this study is to determine the prevalence of endometriosis in women undergoing laparoscopy for evaluation of infertility.

Pathogenesis of Endometriosis

Endometriosis is a disease of complex aetiopathogenesis. It is often called the disease of theories. Several theories to explain the evolution of endometriosis have been suggested, but no single theory explains all types and sites of endometriosis **(Amer, ٢٠٠٨).**

Retrograde Menstruation and Implantation Theory (Sampson's Theory)

This theory proposes that viable endometrial tissue is refluxed through the fallopian tubes during menstruation and implants on peritoneal surface or pelvic organs **(Sampson, ١٩٢٧)**. Women with Müllerian anomalies that increase retrograde menstrual flow, prolong menstruation, or shorten cycles (٢٧ days or fewer) have an increased incidence of endometriosis **(Berube *et al.*, ١٩٩٨; Vigano *et al.*, ٢٠٠٤; Cramer and Missmer, ٢٠٠٢)**. Such observations lend evidence to support the role of retrograde menstruation as an etiology of endometriosis **(Bohler *et al.*, ٢٠٠٧)**.

Retrograde menstruation has been found in the peritoneal cavity in women with patent tubes who underwent laparotomy or laparoscopy during menstruation and in women undergoing chronic peritoneal dialysis. Also there is an increased frequency of endometriotic implants in the dependent areas of the pelvis. This anatomic distribution of endometriosis also supports the concept of retrograde menstruation **(Seli *et al.*, ٢٠٠٣).** Retrograde menstruation is a widely accepted proposed mechanism that may explain mostly the presence of endometrial cells in ectopic sites. However, it does not account for the fact that these misplaced cells survive in women with endometriosis and not in healthy women **(Kyama *et al.*, ٢٠٠٣).**

Because this phenomenon is prevalent in most women, several other fundamental processes must contribute to the implantation of endometrial cells and their subsequent development into endometriotic lesions. Indeed, retrogradely seeded endometrial cells must escape apoptosis, adhere to the mesothelium, proliferate and establish a new blood supply **(Gagne *et al.*, ٢٠٠٣).**

Most investigators agree that additional factors are essential for the implantation and growth of endometriotic lesions **(Fowler *et al.*, ٢٠٠٧)**, these additional factors leading to the development of endometriosis appear to be a multifaceted complex of genetic, immunologic, hormonal, and environmental components **(Mihalyi *et al.*, ٢٠٠٥; Bohler *et al.*, ٢٠٠٧; Ulukus *et al.*, ٢٠٠٩).**

Coelomic Metaplasia Theory (Meyer's Theory)

This theory was introduced at the turn of the twentieth century by Meyer. It proposed that endometriosis develops from metaplasia of cells that line the pelvic endometrium. Meyer suggested that infectious, hormonal, or other inductive stimuli may result in metaplasia, which in turn could result in endometriosis **(Meyer, ١٩١٩; Meyer, ١٩٢٧).**

Embryologic studies demonstrated that pelvic peritoneum, germinal epithelium of ovary, and müllerian ducts are derived from epithelium of the coelomic wall. This type of transformation may cause ovarian surface endometriosis.

Clinical evidence that supports the theory of coelomic metaplasia lies in case reports of endometriosis that occurs in men **(Giannarini *et al.*, ٢٠٠٦)**, in prepubertal, and adolescent girls **(Schifrin *et al.*, ١٩٧٣),** in women who never menstruated **(El-Mahgoub *et al.*, ١٩٨٠)** and in unusual sites, including pleural cavity **(Van Schil *et al.*, ١٩٩٦; Roberts *et al.*, ٢٠٠٣)**. The men with endometriosis were undergoing estrogen

therapy, however, and the possibility of estrogen stimulation of mullerian rests cannot be excluded. Similarly, although pleural endometriosis could result from local metaplasia of pleural mesothelium, it also might result from transdiaphragmatic passage of endometrial fragments. If coelomic metaplasia is similar to metaplasia elsewhere, an increase in its frequency would be expected with aging. Proofs for the theory of coelomic metaplasia are far from being conclusive **(Seli *et al.*, ٢٠٠٣).**

Induction Theory

The induction theory is an extension of the coelomic metaplasia theory and proposes that endogenous biochemical or immunologic factors can induce undifferentiated cells to differentiate into endometrial tissue **(Matsuura *et al.*, ١٩٩٩; Levander and Normann, ١٩٥٥).**

Embryonic Rest Theory

In the ١٨٩٠s, Von Recklinghausen and Russell introduced the embryonic rest theory **(Laschke and Menger, ٢٠٠٧).** This theory proposed that cell rests of müllerian origin could be activated to differentiate into endometrium in the presence of a specific stimulus. Both Coelomic Metaplasia and Embryonic rest theories might explain the rare phenomenon that endometriotic lesions have been found in male patients **(Giannarini *et al.*, ٢٠٠٦).**

Vascular and Lymphatic Metastasis (Halban's Theory)

In the ١٩٢٠s, Halban suggested that distant endometriosis occurs via vascular or lymphatic spread of viable endometrial cells. This theory explains the rare endometriotic lesions occurring in extrapelvic sites (eg, brain, lung) but does not explain the more common pelvic lesions

(Dhanaworavibul *et al*., ٢٠٠٦; Amer, ٢٠٠٨). Lymphatic spread has also been thought to explain the presence of endometriosis in lymph nodes **(Fujii, ١٩٩١).**

Immunological Factors

Immunologic factors may affect a woman's susceptibility to implantation of exfoliated endometrial cells. Immune alterations include increased number and activation of peritoneal macrophages, decreased T cell reactivity and natural killer cell cytotoxicity, increased circulating antibodies, and changes in the cytokine network **(Berkkanoglu and Arici, ٢٠٠٣)**, and eventually chronic inflammation and infertility.

Molecular Mechanisms of the disease

Accumulating evidence suggests that eutopic endometrium from women with endometriosis has aberrant properties compared with that from women without the disease, and that these aberrant properties may play central roles in the pathogenesis and pathophysiology associated with the disease **(Sharpe-Timms, ٢٠٠١).**

One of two mechanisms could explain the successful implantation of refluxed endometrium onto the peritoneal surface: molecular defects or immnnologic abnormalities (or both). In endometriosis, the eutopic endometrium exhibits multiple subtle but biologically important molecular abnormalities, including the activation of oncogenic pathways or biosynthetic cascades favoring increased production of estrogen, cytokines, prostaglandins, and metalloproteinases. When the eutopic endometrium, biologically distinct tissue, attaches to mesothelial cells, the magnitude of the molecular abnormalities is amplified drastically, enhancing the survival of the implant. A possible second mechanism of implant survival entails a failure of the immune system to clear implants from the peritoneal surface. Both mechanisms may