

Scoring of the Endometriosis: Relation to Nerve Fibers Density in Endometrial Biopsy

Thesis

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Introduction

Endometriosis is a chronic, complex gynecological disease affecting reproductive age women, characterized by endometrial-like tissue found outside of the uterine cavity. Clinical symptoms are manifested as dysmenorrhea, dysuria, dyspareunia and/or subfertility (*Valle and Sciarra, 2003*). Although the exact prevalence of endometriosis in the general population is not clear, the prevalence in women of reproductive age is estimated to range between 10 and 15% (*Lebovic et al., 2001*).

Endometriosis is commonly associated with a range of pelvic pain symptoms such as chronic dysmenorrhea, premenstrual abdominal and pelvic pain, back pain, dysuria, dyschesia and dyspareunia. However, the relationship between different types of pain and endometriosis is not well understood and there is poor correlation between the severity of pain symptoms and anatomical staging of the disease (*Chapron et al., 2003*).

There is now considerable evidence that eutopic endometrium from women with endometriosis exhibits many biochemical differences compared with that of women without endometriosis in terms of structure, proliferation, apoptosis,

immune components, cell adhesion molecules, proteases and their inhibitors, steroid and cytokine production and responsiveness, gene expression, protein synthesis, and angiogenesis (*Healy et al., 1998; Sharpe-Timms, 2001*).

Tokushige and colleagues demonstrated the presence of nerve fibers in the functional layers of the endometrium in women diagnosed with endometriosis. These nerve fibers were not detected in the functional layer of women without endometriosis. The functional layer of endometrium showed mostly sensory unmyelinated C nerve fibers responsible for transmitting dull, throbbing, and diffuse pain (*Tokushige et al., 2006 a,b*).

Women with endometriosis also had a highly significantly increased density of nerve fibers in the basal layer of endometrium and in the myometrium compared with women without endometriosis (*Tokushige et al., 2006a*).

These nerve fibers were also found in ectopic peritoneal endometriotic lesions and in deep infiltrating endometriosis (*Wang et al., 2009*).

Aim of the Work

The aim of this study is to determine the relationship between the severity of pain symptoms, scoring of the endometriosis & the density of nerve fibers in endometrial biopsy.

Endometriosis

Endometriosis is a common, chronic gynecological disease defined by presence of endometrial glands and stroma, most commonly in the pelvis. It is symptomatically associated with infertility and pelvic pain including dysmenorrhea dyspareunia, dyschesia and chronic pelvic pain (*Milingos et al., 2003*).

Historical Review:

Endometriosis was described in medical literature in the 1800s, but it was not until the 20th century that its common occurrence was appreciated (*Milingos et al., 2003*). Based on clinical observation and examination of histopathological specimens, John Sampson of Albany New York, in 1921, suggested that peritoneal endometriosis in the pelvis arose from seedings from ovarian endometriosis. Subsequently, in 1927, he published his classic paper, "Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity", which introduced the term "endometriosis" and established retrograde flow of endometrial tissue through the fallopian tubes and into the abdominal cavity as the probable cause of endometriosis (*Sampson, 1927*).

Epidemiology:

Endometriosis is primarily the disease of the reproductive years and is only rarely described in adolescence, when it is associated with obstructing genital tract abnormalities or in postmenopausal women where it has been reactivated because of hormonal replacement therapy. No racial differences in the incidence of the disease have been found except for Japanese women who have been reported to have twice the incidence of Caucasian women. Clinical experience based on gynecologic practice in Hawaii indicated a high incidence of endometriosis among Oriental women. To investigate this impression, a statistical analysis of gynecologic admissions and of diagnoses of endometriosis was performed by Miyazawa, on the basis of race at three hospitals, two in Hawaii and one in Japan. The result supports the impression that the Japanese female population has a high incidence of endometriosis. Approximately 10% of their gynecologic admissions were for endometriosis. The order of incidence in other racial groups was non-Japanese Oriental, white, and black (*Miyazawa, 1976*).

Sangi and colleagues studied epidemiology of endometriosis among parous women over a 6-year period, 3384 multiparous women underwent laparoscopy for tubal sterilization. Endometriosis was detected in 126 patients, who were consequently evaluated for severity of the disease. They conducted a case-control study, 504 control patients with no evidence of endometriosis were randomly selected from the most endometriosis lesions were minimal. They conclude that, factors associated with an increased risk for endometriosis included: advanced age, Asian race, long cycle length, one live birth, long duration of intrauterine device use, and long duration of uninterrupted menstrual cycles. Present oral contraceptive use was protective for disease. The role of these factors varied among different disease locations (ovary, uterus and tubes, posterior wall of the broad ligaments and cul-de-sac), and depth (superficial or deep). The prevalence of endometriosis was relatively low among multiparous women, and certain menstrual and reproductive characteristics were associated with its development. Furthermore, the relationship between various factors and endometriosis appeared to be site and depth specific. Their findings suggest that asymptomatic endometriosis may be clinically important (***Sangi and Ponidexter, 1995***).

Matorras and colleagues tried to assess the epidemiological factors linked to endometriosis in infertile women in Academic tertiary hospital by case-control study included one hundred seventy-four infertile women with endometriosis and one hundred seventy-four infertile women without endometriosis, all of them were studied by laparoscopy. They concluded that, cycles $<$ or $=$ 27 days was the only risk factor that seemed to be associated to endometriosis in infertile patients. However, predictive values were low. A trend to a protective effect of smoking was detected. Social class, reproductive history, infertility history, previous abortions, age, family history, age at menarche, and duration of menstrual flow were similar in both groups (*Matorras et al., 1995*).

The exact prevalence of endometriosis is unknown because invasive testing is needed to confirm the diagnosis. In addition much is still uncertain about this disease and its pathophysiology. However many women will seek treatment for pelvic pain, infertility or both. And until simple non invasive screening tests are developed, the true prevalence will remain unknown (*Eltabbakh and Bower, 2008*). Current prevalence therefore depends upon identification of women who are either symptomatic or undergoing various operative

procedures. The prevalence is markedly variable as the data shown in table (1).

Table (1): Prevalence of endometriosis through various presentations

Unexplained infertility	70-80% (<i>Kistener, 1977</i>).
Infertile women (all causes)	15-20% (<i>Kistener, 1977</i>).
At diagnostic laparoscopy	0-53% (<i>Houston, 1984</i>)
At treatment laparoscopy	0.1%-50% (<i>Houston, 1984</i>)
Women undergoing sterilizations	2% (<i>Strathy et al., 1982</i>)
In women with 1 st degree relatives	7% (<i>Simpson, 1980</i>)

Aetiology of endometriosis:

The precise aetiology of endometriosis still remains unknown. It has been called the disease of theories. Several theories were proposed to explain the process through which endometriosis develops, however, no single theory can explain the location of endometriotic deposits in all of the sites reported (*Shaw, 2003*).

1. Coelomic metaplasia:

The first complete theory of the histogenesis of endometriosis was advanced by Mayer: It stated that under certain stimuli, cells might change its character and even its physiologic function. More specifically ectopic endometrium

might arise from totipotent cells of the peritoneal mesothelium (*Meyer, 1919; Wenxin et al., 2005*).

Endometriosis occurring in unusual sites and instances was reviewed by Suginami for the purpose of exploring the pathogenesis of the disease. He concluded that, the affected sites in both common and uncommon endometriosis include cells arising from the coelomic membrane and include sites exposed to metaplasia-inducing substances such as estrogen and unknown factors liberated from the degenerating endometrium. This appears to strengthen the coelomic metaplasia theory (*Suginami, 1991*).

2. Transplantation theory:

The transplantation theory, originally proposed by Sampson in the mid -1920s, is based on the assumption that endometriosis is caused by the seeding or implantation of endometrial cells by transtubal regurgitation during menstruation (*Sampson, 1927*).

Seventy-five women admitted for sterilization were laparoscoped during menstruation by Liu and Hitchcock. Retrograde spillage of menstrual blood was observed in 76%. Mild or stage I endometriosis was detected in 43% of all the women but in only 54% of those who had retrograde spill.

Retrograde spill was seen in 97% of those with endometriosis. So they concluded that, retro grade spill is more common in women with endometriosis than in those without the disease (*Liu and Hitchcock, 1986*).

The Presence of endometrial cells in the peritoneal fluid, indicating retrograde menstruation, has been reported in up to 79% of women during early follicular phase, and these cells can be cultured in vitro, where Kruitwagen, and colleagues obtained peritoneal fluid (PF) during the early follicular phase in 24 women at laparoscopy as part of infertility investigation. The cells present in PF were pelleted and cultured. Developing endometrial epithelial cell colonies were identified in 19 women (79%). Identification of these cell colonies was facilitated using the monoclonal antibody BW 495/36 as specific marker. No significant distinction in incidence and number of cell colonies was found between women with minimal (n = 11) and without endometriosis (n = 12). A significant correlation with number of cell colonies was found in women with infertility who had no mechanical or male infertility factors. These data indicated that retrograde transport of viable endometrial cells during menstruation occurs in most women with patent tubes (*Kruitwagen et al., 1991*).

The high incidence of retrograde menstruation suggests that this phenomenon alone does not give rise to endometriosis but that some other factors must be involved in the development in the disease. These factors could include some alteration in the uterine endometrium; altered immune response to retrograde menstruation (hence failure to clear the peritoneal cavity of debris efficiently); or alternatively a more favorable peritoneal environment within the peritoneal cavity itself (*Shaw, 2003*).

3. Lymphatic, vascular and iatrogenic dissemination:

In order to explain the distant sites for endometriosis, Halban postulated that viable endometrial cells can gain entry into open basal lymph and blood vessels and are embolized to ectopic sites (*Halban, 1924*). Javert lent support to this theory by finding endometrium in lymph nodes (*Javert, 1949*). Even the common occurrence of endometriosis on the ovaries can be explained by lymphatic flow from the uterus to the ovary, as Ueki abstracted when he studied endometriosis histologically and investigated lymphatic drainage in and out of the uterus, where endometrial fragments in vessels were detected in 4.5% of cases of endometriosis. Confirmation of lymph flow into the ovary from the uterine body, strongly suggests that ovarian endometriosis arises as a consequence of vascular (lymphatic)

transport of endometrial fragments from adenomyosis lesions, serous endometriosis lesions, or the endometrium (*Ueki, 1991*).

Liang and colleagues diagnosed and managed twelve patients with scar endometriosis, and they conclude that, evidence of iatrogenic transplantation is seen not infrequently in surgical scars following cesarean section, hysterectomy, hystrotomy, or tubal ligation or in the lower genital tract following a surgical procedure as episiotomy, or delivery, and only rarely in the absence of trauma (*Liang et al., 1998*).

4. Genetic factors:

Many studies indicate that there may be a genetic factor related to endometriosis since the disease is more prevalent in certain families, Simpson and colleagues studied 123 patients with histologically proved endometriosis, 6.9% of all first-degree relatives were affected. By contrast, only 1.0% of female sibs of their husbands and only 0.9% of mothers of their husbands were affected. Several genetic etiologies can be postulated, but polygenic/multifactorial inheritance seems most likely because of: (1) the 6.9% risk for all first-degree relatives and (2) observations that the 18 patients with an affected first-degree relative were more likely to have severe endometriosis than those without an affected first-degree relative (*Simpson et al., 1980*).

Erica and colleagues discovered a new candidate genes located near known loci related to development and regulation of the female reproductive tract. And hereditary pathways for endometriosis have been identified using Molecular techniques, including linkage and genome-wide analysis and so, the possibility of prevention and treatment becomes more tangible for millions of women affected by endometriosis (**Erica et al., 2010**).

5. Environmental factors and dioxin:

Although an association between dioxin exposure and endometriosis has been proposed, the effects of this environmental toxin on human endometriosis are not known. To understand the potential underlying molecular mechanisms, Bulun and colleagues studied the expressions of cytochrome P-450 genes (*CYP1A1*, *CYP1A2*, and *CYP1B1*), which are induced by dioxin, and the expressions of cytosolic receptor for dioxin, in endometriotic and eutopic endometrial tissues. And levels of transcripts of *CYP1A1*, *CYP1A2*, *CYP1B1*, aryl hydrocarbon receptor, and aryl hydrocarbon receptor nuclear translocator protein were determined. They Concluded that the expression of dioxin-related transcription factors and target genes *CYP1A1*, *CYP1A2*, and *CYP1B1* in endometriotic tissues and stromal cells strikingly elevated. *CYP1A1* transcripts in