



## Review Article

# Endometriosis - Pathogenesis and Sequelae

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### Abstract

Endometriosis is a gynaecological disorder characterised by the presence of endometrial-like tissue outside the uterus. It affects 10-15% of women during their reproductive age. Endometriosis is a highly variable condition in terms of presenting symptoms, anatomical extent of disease, rate of progression, incidence of infertility, response to treatment and the likelihood of recurrence. The aetiology and the pathogenesis of the disease are poorly understood. Endometriosis has a wide range of symptoms or can be asymptomatic, this makes the diagnosis of the disease difficult. The definitive diagnosis is surgical, usually via laparoscopy with histological confirmation. There is often a long delay in diagnosis, 8-12 years, from the onset of symptoms till a definitive diagnosis is made. Endometriosis is a progressive disease and long delays before effective treatment allows the disease to advance.

**Keywords:** Diagnostic; Endometriosis; Neuronal; Nerve fibres; Pain

### Endometriosis: Definition and Background

Endometriosis is an oestrogen-dependent gynaecological disorder that is characterized by the presence of endometrial-like tissue outside the uterus [1]. Endometriosis affects 10-15% of women during their reproductive age, 50 to 60% of women and teenage girls with pelvic pain and up to 50% of women with infertility [2,3].

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Endometriosis is considered as a highly variable condition in terms of symptoms, anatomical extent of the disease, rate of progression, incidence of infertility, response to treatment and likelihood of recurrence [3]. Endometriotic lesions can be spread through many areas, and are usually multiple. They are usually found in pelvic peritoneal and visceral surfaces, ovaries and rectovaginal septum [4]. They also can be rarely found in the pancreas, pleura, lung, umbilicus, on sciatic nerve roots, fallopian tubes, thorax and the kidneys, the vertebrae, the extremities or even the brain [5,6].

There are several factors that have been suggested that play a role in the establishment and development of endometriosis. These factors could be related to the genetic profile, inflammation, immune dysfunction, oxidative stress, hormonal activity, menstrual cyclicality, burden and immunological factors [7,8]. There are three symptomatic groups that are usually compared; these are asymptomatic patients, symptomatic (with pain) and infertile patients [9]. As a result the accurate, true prevalence and incidence of endometriosis in the general female population remains unclear, as some women with the disease can be completely asymptomatic, allied with the difficulty of a confirming diagnosis of the disease, which can only be reliably done by laparoscopy together with histological confirmation [3].

### Theories of Endometriosis

The definitive cause and the pathogenesis of endometriosis remains unclear. Many theories have been proposed to explain the development and establishment of endometriosis [8]. Three main theories have been proposed to explain this anomaly and are discussed below.

#### Retrograde menstruation/implantation theory

This is the oldest theory and the most widely accepted theory and was first hypothesised by Sampson in 1927. He suggested that the origin of endometriosis was from refluxed menstrual tissue and cells which implanted on the surface of the organs in the peritoneal cavity [10]. However, this theory was neglected as retrograde menstruation which occurs in 76-90% of women with fallopian tube disorders and not all of these women have endometriosis [11]. In addition, this theory failed to explain the existence of the disease in early puberty and also rarely in newborns and in women affected by the Mayer-Rokitansky-Küster-Hauser, a syndrome characterized by congenital aplasia of the uterus and the upper part of the vagina and in male endometriosis [12-16].

#### Coelomic metaplasia theory

This theory proposed that endometriosis initiated from abnormally trans-differentiated mesothelial lining of the visceral and abdominal peritoneum, which transformed into endometrial cells by metaplasia. This could be caused by infectious, hormonal, or other inductive stimuli [17]. The occurrence of endometriosis in prepubertal and adolescent girls, or in women who never menstruated and in unusual sites, including pleural cavity have often been considered as clinical evidence of the metaplasia theory [18-22].

## Induction theory

This theory can be considered as an extension of the coelomic metaplasia theory. It was proposed by Levander and Norman. This theory was built on the assumption that several endogenous biochemical or immunological factors could induce the transformation of undifferentiated peritoneal cells to differentiated endometrial tissue [23].

## Symptoms of Endometriosis

The clinical presentation of endometriosis has been highly variable which has led to a wide spectrum of symptoms. Symptoms that could be influenced by many factors such as age of presentation, anatomical extent of disease, incidence of infertility, response to treatment, likelihood of recurrence, rate of progression and natural long-term history of the condition. Some women will suffer from many symptoms, while others will have minimal symptoms and a small group of women with endometriosis will not present with any symptoms or will not be aware of any substantial symptoms [3]. It is unclear if this great variability in the symptoms presentation has been influenced by the genetic characteristics of the disease or other factors such as lifestyle and environment [24]. Although the symptoms are highly variable, the majority of women with advanced endometriosis will suffer from some form of pelvic pain [3].

## Pelvic Pain

Pelvic pain is the key symptom in endometriosis; and is the main reason why the patient consults her doctor [25,26]. There are common and classical forms of pelvic pain symptoms that women with endometriosis suffer from, these include: menstrual pain (dysmenorrhoea) which is often characterised as intense, unbearable, miserable, cramping, gnawing, crushing or pressing and pain during intercourse (dyspareunia) [27]. In addition, women with endometriosis may also suffer from pelvic pain with defaecation (dyschezia) and chronic pelvic pain [28].

## Infertility

Endometriosis may cause infertility and up to 50% of women with endometriosis may present with subfertility [29]. Despite a strong association between endometriosis and infertility, a true cause and effect relationship has yet to be established. It seems implausible to many that mild endometriosis could be the sole cause of long-standing infertility [30]. Some of the mechanisms that account for the adverse effects that endometriosis may have on fertility are listed in (Table 1) [31].

## Appearance of Endometriosis

Endometriotic lesions in the pelvic cavity can be classified into three types, these are (a) Peritoneal implants, (b) Deep infiltrating or adenomyomatous disease and (c) Endometriomas, which are chocolate brown like fluid-filled endometriotic cysts generally associated with the ovaries (Figure 1) [1,16].

## Superficial endometriosis

These occur in the form of peritoneal implants or lesions on the outer surfaces of the ovary. The peritoneal implants can be categorized into intraepithelial and sub-mesothelial lesions consisting of stromal and glandular tissue, which respond to menstrual cycle

hormones. Adhesions can sometimes accompany them. Depending on the severity of adhesion formation, the adhesions in the ovary can be sometimes intense and haemorrhagic in nature [1].

<b>Ovarian-Tubal Dysfunction</b>
Anatomical distortion of ovary and tube
Ovulation failure
Hyperprolactinemia
LUF (Luteinized Un-ruptured Follicle)
Abnormal follicle development
Reduced follicle development
Decreased estrogen production
Increased apoptosis of granulosa cells
<b>Immunological disorder</b>
Anti-endometrial antibody
<b>Abnormal peritoneal environment</b>
Increased peritoneal fluids and high concentration of cytokines
Activated macrophage
<b>Dysregulated endometrial function</b>

Table 1: Pathophysiology of endometriosis associated infertility.

## Deep infiltrating endometriosis

Also, known as adenomatous endometriosis, this type are mainly comprised of proliferative fibromuscular tissue with sparse glandular and stromal tissue with no surface epithelium. This deep infiltrating type does not obviously respond to menstrual cycle hormones. It is frequently seen in the uterosacral and rectovaginal ligaments [1].

## Ovarian endometriomas

An ovarian cyst, when encapsulated by endometriotic tissue, is known as an endometrioma. It is filled with a brown, almost chocolate-coloured fluid, resulting from metabolism of recurrent bleeding from the endometriotic surface implants. With time, this endometriotic tissue slowly gets replaced by fibrotic tissue causing the histological glandular appearance of the endometrioma to wane. The cyst wall is often found to consist of large scarred areas mixed with haemorrhagic, hyper vascularised endometriotic lesions [32].

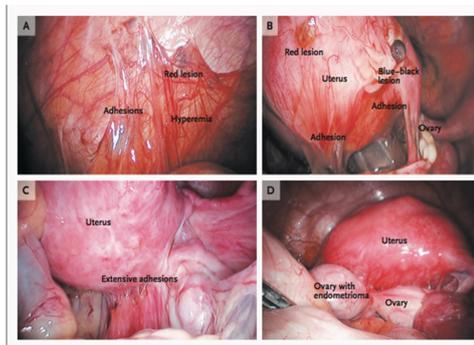


Figure 1: Peritoneal lesions and an ovarian endometrioma due to endometriosis.

Panel A shows an endometriotic implant (red lesion), adhesions, and hyperemia in the peritoneum. Panel B shows peritoneal implants, including red and blue-black lesions and adhesions. Panel C shows extensive adhesions distorting the normal pelvic anatomy. Panel D shows an endometrioma adherent to the posterior uterus and distending the ovarian capsule.

At surgery, it can be difficult to distinguish visually an endometrioma from a cyst of the corpus luteum, a haemorrhagic cyst, or a simple cyst. Although the cyst fluid in endometriomas is thick and dark brown because it contains haemosiderin (hence, the name “chocolate cysts”), this colour is not completely specific to endometriomas. Who acquired the images courtesy of Dr Christopher Herndon, University of California, San Francisco [1].

## Diagnosis of endometriosis

There is a lack of simple non-invasive tests for the diagnosis of endometriosis that could be applied in clinical practice. Although clinical history and pelvic examination can increase the possibility of a diagnosis of endometriosis, the usage of traditional clinical parameters to detect women with endometriosis has been limited [33]. The pain originally linked with menstruation causes delay in the time that women approach physicians about their gynaecological concerns [34]. From studying the narrative interviews of women with endometriosis-associated pelvic pain, there was a delay in the diagnosis and course of the treatment as the women believed that their pain was a natural biological side effect of being female [35].

## Gold Standard: Invasive Diagnostic Technique

A definitive diagnosis of endometriosis can be accomplished by laparoscopy and histological biopsy, which provides direct visualisation and histological confirmation [36,37]. However, laparoscopy is an invasive intervention and associated with considerable side effects and high costs [34]. Despite the controversy in the literature in regard to the advantage of one surgical modality over another in treating pelvic pathology, there is accumulative evidence suggesting that laparoscopy is the preferred technique to evaluate the pelvis and abdomen and to treat benign conditions such as ovarian endometriomas [33].

## Non-Invasive diagnostic imaging

Magnetic Resonance Imaging (MRI) and Ultrasonography (USS) (which includes transabdominal, transvaginal and transrectal approaches) have been used as diagnostic tools to identify endometriosis [34]. However, the primary role of USS in the diagnosis of endometriosis is to customize the management of patients. As the correct recording of endometriotic lesions may notify the surgeon on the presence of lesions that are not readily recognized at laparoscopy. It should be noted that superficial peritoneal endometrioses such as peritoneal bleb and “gunshot” lesions are too small to be detected at ultrasound examination [38]. These two techniques provide good options for the diagnosis of ovarian endometriosis (80-90% sensitivity and 60-98% specificity) however, are limited in detecting lesions outside the peritoneum, adhesions and infiltrations [39]. In addition, Doppler ultrasonography is a tool that may assist in the diagnosis of ovarian endometriosis; the blood flow changes according to the presence or absence of endometriomas [40].

## The need for biomarkers for the non-invasive diagnosis of endometriosis

In the last few years, many studies have been conducted or review articles published to discover a biomarker to detect the disease earlier and to avoid the use of laparoscopy [33,41-53]. The search for serum protein markers for endometriosis had commenced over several decades ago [54]. During this period, several proteins had

been identified, however, despite extensive research no reliable blood tests currently exist for the diagnosis of endometriosis [55]. Research into urinary biomarkers is an emerging field of research and little is currently known, despite published works [56-59]. A consensus of the World Endometriosis Society has been that the development of a reliable non-invasive diagnostic test is one of the top priorities in endometriosis [60]. A reliable biomarker must have high specificity, sensitivity and be inexpensive [34]. To date, there are no molecules that have been proven to be reliable biomarkers to be used in the diagnosis of endometriosis [45]. Over the last 25 years, more than 100 possible biomarkers have been investigated for potential diagnostic tests for endometriosis, however, none have proven to be clinically useful [61]. In symptomatic women, the use of CA 125 $\geq$ 30 units/ml is highly specific for diagnosing endometriosis, however, a CA 125 <30 units/ml does not exclude endometriosis and further investigation is required [62].

## Management of Endometriosis

The approaches to manage endometriosis can be classified into surgical and pharmacological. As the aetiology of the disease is not well understood, to-date there is no prevention or cure for endometriosis. Rather, the aim of the treatment options is mainly to manage the symptoms or to improve fertility rates [63].

### Surgical management of endometriosis

The aim of the surgical approach is to address both pain and fertility. Laparoscopy facilitates the removal of endometrial lesions and scar tissue, which may help to reduce pain and improve fertility.

#### Laparotomy

Laparotomy (open surgery) was considered the standard method for surgical therapy of endometriosis prior to the improvements in laparoscopic techniques [30]. In severe endometriosis, it was found that laparotomy and laparoscopy perform equally in treating pain and infertility problems, yet there was a trend towards a higher pregnancy rate and lower dyspareunia recurrence rate after laparotomy compared with laparoscopy in the 1990s [64]. This appeared to have been improved with developments in laparoscopic equipment, techniques and skill.

#### Laparoscopy

Laparoscopy is considered as the gold standard for treating mild and moderate stages of endometriosis [65]. Laparoscopy offers several advantages when compared with laparotomy procedures including decreased recovery time and cost [66]. Surgical procedures involve excision, fulguration, or laser ablation of endometriotic implants on the peritoneum, excision, drainage or ablation of endometriomas, resection of rectovaginal nodules, lysis of adhesions and interruption of nerve pathways [1]. Resection is preferred and is usually more effective in healing both pain and infertility. There are risks will all surgery, with laparoscopy, problems are rare, however can be severe.

#### Radical surgery

Radical surgery involves total abdominal hysterectomy with or without bilateral oophorectomy [67]. This option may suit women with chronic pelvic pain with endometriosis who have completed their families and have undergone other medical and or conservative

surgical treatments without complete symptom relief. However, this approach may not always alleviate pain symptoms especially in deep endometriotic disease [67].

## Medical Management of Endometriosis

Medical therapies are proposed as a temporary relief for pain management [68]. The effect of pharmacological treatment on fertility has been minimal and has been considered as ineffective in some cases such as ovarian endometriomas [69]. Medical treatments for endometriosis include hormonal suppression and analgesic management that are discussed below.

### Oral contraceptives

Combined oral contraceptive pills have been used to control endometriosis-related symptoms such as pelvic pain and dysmenorrhea [70]. Whilst the cyclical use of oral contraceptives has been used to manage heavy bleeding associated with endometriosis, the continuous use of oral contraceptives have been more effective in managing pelvic pain [71-73].

### Progestogens

Progestogens, which include Medroxyprogesterone Acetate (MPA) and 19-nortestosterone derivatives, help to control the pain associated with endometriosis by two mechanisms. It either stimulates decidualisation and atrophy of endometrial tissue, and inhibits matrix metalloproteinase-enzymes that play a fundamental role in the development and implantation of ectopic endometrium [74,75].

### GnRH agonists

GnRH agonists bind to pituitary receptors and have a longer half-life than native GnRH [76]. It stimulates the down-regulation of the pituitary-ovarian axis causing hypoestrogenism, which stimulates amenorrhea and endometrial atrophy [75]. In addition, the uses of GnRH analogue treatments have helped to reduce bleeding more than the IUD-administered progestin treatment [76]. Side effects of GnRH agonists, such as vasomotor symptoms and accelerated bone loss, limit treatment duration to six months. However, treatment can be extended beyond six months if add-back therapy is combined with the GnRH agonist [77].

### Danazol

Danazol is an androgen that is derived from 17 $\alpha$ -ethinyl testosterone and can be used as a treatment to manage the pain associated with endometriosis. It inhibits steroidogenesis and the LH surge leading to an increase in the level free testosterone. Danazol has androgenic side effects such as weight gain, acne and edema [78].

### Aromatase inhibitors

Aromatase is an enzyme, which converts steroidal precursors into estrogens. The estrogens trigger the growth of ectopic tissue, which leads to the onset of pelvic pain [79]. The inhibition of aromatase decreases the estrogen production [80]. The reduction of estrogen level in premenopausal women leads to an increase in FSH levels, which may cause ovarian follicular cysts [81]. Consequently, an “add-back therapy” and oral contraceptives are recommended to be used with aromatase inhibitors [81]. This combination therapy notably reduces abdominal and pelvic pain and shrinks endometriotic lesions at second-look surgery [81,82].

## Analgesics

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) have been indicated to be a reliable option for treating primary dysmenorrhea and they have an anti-inflammatory effect in endometriosis [83-85]. Although NSAIDs have been the most frequently used medications for pelvic pain, their efficacy in treating pain associated with endometriosis to date is not definite [86].

## Antioxidants

Recent evidence suggest that antioxidant supplements may reduce pelvic pain in patients with endometriosis [87,88].

## Endometriosis and Pain Mechanisms

The existence of close and complex a relationship between chronic pelvic pain and endometriosis has been widely recognised by gynaecologists. It is one of the consequences of the disease that most women with endometriosis complain about [26]. It affects the quality of life of women and has a negative impact on their ability to work, self-esteem and their personal relationships. The International Association for the Study of Pain has defined pain as “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [89]. Different types of pain are associated with endometriosis, which include dysmenorrhoea, dyspareunia and inter-menstrual pain, often over long periods and often considered as Chronic Pelvic Pain (CPP) [90]. Although there has been much research into the pain mechanisms of endometriosis, the associations between the severity of pain, extent of the disease and site of the lesions are still unclear and the mechanisms are still poorly understood [24,91].

Prostaglandins (PGs) have an important role in the pathogenesis of the symptom of pain in endometriosis due to an excess in the amount of PGs secreted from the endometrium during menstruation. Among PGs, PGF $\alpha$  is considered the most potent causal factor of pain [92]. Chronically elevated catecholamine levels are associated with pain and inflammatory disease, both often are associated with endometriosis [93-96]. Medina and Lebovic reported that Substance P (SP) and Calcitonin Gene-Related Peptide (CGRP) were both involved in the inflammatory and pain responses and both were present in the myometrial layer, this was reported as being indicative of the occurrence of sensory C and A $\delta$  fibres [97]. Bulletti observed a greater contractility at the time of menstruation in endometriosis subjects in comparison with control subjects, this was postulated as the possible roles of SP and CGRP nerve fibres in relation to the generation of pain in endometriosis and dysmenorrhea [98].

## Neurogenesis and Pain Perception

Sensory nerves are afferent nerves carrying nerve impulses from peripheral receptors to the Central Nervous System (CNS) [99]. Peripheral nerve fibers are also classified into three types according to their sizes (Table 2), which includes chemo-, mechano-, photo- and thermo-receptors, as well as nociceptors [100]. The perception of pain occurs as a result of crosstalk between the CNS and the Peripheral Nervous System (PNS) which is exerted by afferent and efferent nerves.

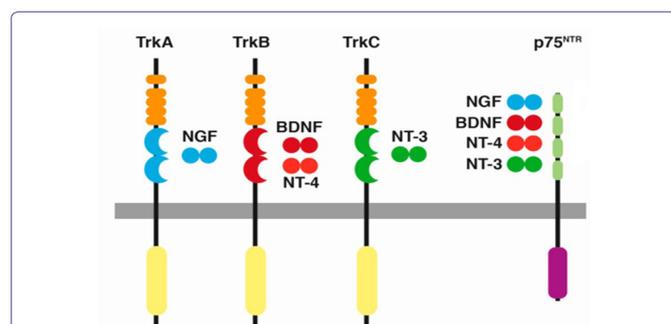
Type of Fibers		Function	Axonal Diameter (µm)	Conduction Velocity (m/s)	Direction of Conduction
A (Myelinated)	α	Proprioception, muscle contraction	12-22	70-120	Afferent and efferent
	β	Touch-Pressure, vibration	6-12	80	Afferent and efferent
	γ	Intrafusal fibers contraction	4-8	15-30	Efferent
	δ	Pain (acute, shallow), temperature (cold receptors), touch-pressure	1-5	4-30	Afferent
B (Myelinated)		Preganglionic fibers of ANS	1-3	3-15	Efferent
C (Unmyelinated)	Fibers of dorsal roots	Pain (chronic, deep), temperature (warmth receptors), touch-pressure (tactile or mechanoreceptors)	0.2-1.5	0.5-2	Afferent
		Postganglionic fibers of sympathetic nerves	0.2-1.5	0.5-2	Efferent

**Table 2:** Different types of peripheral nerve fibers. Source: Yan et al., [99]; Compiled from: Laverdet et al., [100] and Purves, 2012 [101].

### Neurotrophins and their receptors role in neurogenesis and pain

Neurotrophins are a family of structurally and functionally related proteins that play a role in regulating the growth, maintenance and apoptosis of neurons in the developing nervous system as well as injured neurons [102-104]. Neurotrophins consist of four members including Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin 3 (NT-3) and Neurotrophin 4 with the latter also known as Neurotrophin-5 (NT-4 or NT4/5) [102,103].

The biological effects of neurotrophins are facilitated through two major receptors including neurotrophic tyrosine kinase (Trks) receptors and the pan neurotrophin receptor at 75 kDa (p75<sup>NTR</sup>) [105]. Each neurotrophins binds with a specific Trk receptor in particular, NGF binds with TrkA, BDNF and NT-4 bind with TrkB, and NT-3 to TrkC [105]. NT-3 also binds with TrkA and TrkB however, with lower affinities and all four mature NTs bind with similar affinity to the p75<sup>NTR</sup> [105,106] (Figure 2).



**Figure 2:** Neurotrophins and their receptors. Each neurotrophin binds with a specific Trk receptor. NGF binds with TrkA, BDNF and NT-4 bind with TrkB, and NT-3 to TrkC. Trk: Tropomyosin Related Kinase; NGF: Neuronal Growth Factor; BDNF: Brain-Derived Neurotrophic Factor; NT: Neurotrophin. Source: Arevalo et al., [107] and Sanchez-Sanchez et al., [108].

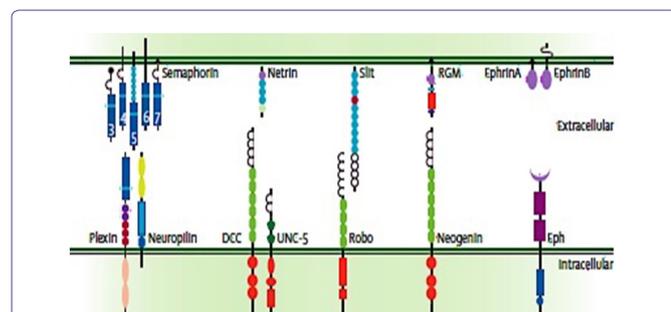
In addition, Glial cell line-Derived Neurotrophic Factor (GDNF) family, which includes GDNF, Neurturin, Artemin and Persephin and other neurotrophic factors that are crucial for the development, survival of the nervous system [109,110]. The activation of all GDNF family members are facilitated by binding with multicomponent GDNF Family ligand Receptor (GFR) α [110]. GDNF binds to GFRα1 and also interacts with GFRα2 and GFRα3 at lower affinities, Neurturin to GFRα2, Artemin to GFRα3 and Persephin to GFRα4 [110].

There is strong evidence that neurotrophins, specially NGF and BDNF, act as mediators and modulators of pain in different conditions [111]. Nociceptors express NGF receptors activating NGF that leads to the sensitisation of these nociceptors. In addition, BDNF is released from the spinal terminals of activated nociceptors. BDNF modulate and alter the effectiveness of the central nociceptive signals. NT3 and NT-4/5 has been shown to play reasonably modest roles in pain processing in most conditions [111]. Moreover, almost one-half of the nociceptor population has receptor components for GDNF, suggesting an important role for GDNF in the activation and maintenance of nociceptors [112,113].

### Neuronal guidance molecules and their receptors role in neurogenesis and pain

In the last two decades, work has led to the discovery of proteins that help to facilitate neuronal circuits through the guiding of neuronal axons to their specific targets during their development [114]. Neuronal guidance molecules can act as attractants or repellents. They can either guide axons towards a specific target or divert them away from a specific area. In addition, these molecules can be membrane-associated molecules and act with a limited effect or as secreted molecules with a wider range of effects [114]. Neuronal guidance molecules are divided into five families of canonical guidance proteins including Semaphorins, Netrins, Slits, Repulsive Guidance Molecules (RGMs) and Ephrins [115,116].

These neuronal guidance molecules are activated through binding to their specific receptors to trigger the intracellular signalling cascades, which cause axon routing through stimulation of changes in the growth-cone cytoskeleton [114,115]. Semaphorin family, which have attractant and repellent effects, bind to receptors from the plexin and neuropilin protein families [117]. Netrin molecules are activated through binding to DCC receptors and UNC-5 receptors to produce attractive and repulsive effects respectively [118]. Slit molecules have repellent effects which prevent axons re-crossing and through binding to the roundabout (Robo) family receptors [119]. RGMs have also repellent effects that signal through binding to Neogenin receptor [120]. While tethered to the membrane Ephrin A molecules interact with class A Eph receptors, the transmembrane Ephrin B interact with class B Eph receptors and both play a well-known role in organising axon connections between the eye and the brain [121] (Figure 3).



**Figure 3:** Five families of identified neuronal guidance molecules (top) and their binding receptors (bottom). Semaphorins binds to receptors from the Plexin and neuropilin protein families; Netrin molecules binds to DCC receptors and UNC-5 receptors; Slit molecules binds to the roundabout (Robo) family receptors, Repulsive Guidance Molecules (RGMs) binds to their receptors Neogenin; Ephrin A molecules interact with class A Eph receptors and Ephrin B interacts with class B Eph receptors. Source: [115].

## Neurogenesis and Endometriosis

Pain associated with endometriosis is as complex as the disease itself. As endometriosis is identified by the presence of lesions outside uterus, this suggests that the sensation of pain associated with endometriosis starts with sensory nerves that transduce noxious mediators, which are produced by lesions and other cells in their microenvironment, to CNS which is perceived as pain [1,99]. Interestingly, there is increasing evidence suggesting that the presence of nerve fibres in ectopic and eutopic endometrium play a possible role in the pain associated with endometriosis [122-124]. In addition, the relationship between endometriotic lesions and nerve fibers is bidirectional, as endometriotic lesions and nerve fibers are engaged in active cross-talks, which lead to the development of endometriosis and pain [99]. Numerous studies on pain associated with endometriosis have focused on the identification of nerve fibers and other factors that play a role in the development and maintenance of nerve fibres, to explain their possible role in pain triggering. Brief basic facts on nerve fibers and the possible role of nerve fibres in pain associated with endometriosis are discussed below.

### Nerve fibres in peritoneal endometriosis

Tulandi was the first study that investigated the presence of the nerve fibres in peritoneal endometriotic lesions compared to normal peritoneum in women with endometriosis using an antibody against Neurofilament (NF) protein [125]. However, no differences in the density of nerve fibres in peritoneal endometriotic lesions compared to normal peritoneum were detected. On the other hand, Tokushige demonstrated a higher density of small unmyelinated nerve fibres stained with protein gene product 9.5 (PGP 9.5) in peritoneal endometriotic lesions of women with endometriosis compared with normal peritoneum in women without endometriosis [122]. In addition, the density of nerve fibres was higher near endometriotic glands and blood vessels compared to the stroma [122]. Another study confirmed these results by finding nerve fibres stained with NF and Substance P (SP) in direct contact with endometriotic lesions in 74.5% (79/106) of the samples [123]. However, there were no significant differences in the total mean nerve scores in the peritoneum tissue from women with and without the disease. In another study by the same group demonstrated that the density of nerve fibres stained with NF and PGP

9.5 was significantly higher in the peritoneum of women with higher pain scores for dysmenorrhoea and pelvic pain in comparison with the peritoneum from women with a lower pain score. However, there was no correlation between the nerve fibre density and dyspareunia, dyschezia or dysuria [124].

In addition, some studies have also investigated the effect of hormonal treatment on nerve fibre density. Tokushige reported a decrease in the density of nerve fibres stained with PGP 9.5 in peritoneal endometriotic lesions of hormone-treated women in comparison to endometriotic lesion of untreated women [126]. However, Wang et al., showed no differences in the density of nerve fibres stained with NF or PGP 9.5 through different stages of the menstrual cycle [127].

### Nerves fibers in endometrium and myometrium

It has been suggested that endometrial biopsies could be used as a potential biomarker assay, due to the accessibility of it through a semi-invasive procedure [61,128]. A preliminary study on samples from the lower one half of the uterus collected after hysterectomy, reported an increase of nerve fibres stained with anti-S100 in the myometrium of patients with endometriosis or chronic pelvic pain, however, without endometriosis in comparison with controls [129]. In another study Tokushige demonstrated the presence of nerve fibres in the basal and functional layer of the endometrium in all patients of endometriosis [130]. In addition, no nerve fibres were found in the functional layer of the endometrium of women without endometriosis [130]. These results were confirmed by a subsequent study showing the presence of nerve fibres in the functional endometrial layer stained with Vasoactive Intestinal Peptide (VIP), Neuropeptide Y (NPY), SP and Calcitonin Gene-Related Peptide (CGRP), which suggest the presence of a mixture of sensory, adrenergic and cholinergic fibres [131]. Nerve fibres were also found in the myometrium of women with and without endometriosis. The density of endometrial nerve fibres has been suggested to be hormone dependent [132]. There was a decrease in density of the nerve fibres in the functional and basal endometrial layers of women using hormonal treatment in comparison to untreated women with endometriosis [132].

The results of previous studies have supported using endometrial nerve fibres as potential biomarkers for endometriosis [61]. Al-Jefout et al., was the first study to investigate this hypothesis. In this study nerve fibres were stained with PGP 9.5 and were reportedly detected with a specificity and sensitivity of 100% in the endometrial biopsies [128]. A further double-blinded study assessed efficacy of the detection of nerve fibres stained with PGP 9.5 in endometrial biopsies compared to laparoscopically verified endometriosis. This result demonstrated a specificity and sensitivity of 83% and 98%, respectively, with a positive predictive value of 91% and negative predictive value of 96% [133]. In addition, women with endometriosis and pain symptoms showed a significantly higher nerve fibre density compared to women with endometriosis and without [133]. However, the following studies have contradicted these encouraging results and it remains unclear why recent studies have disproved previous studies. Possible explanations could be the heterogeneity of the endometriosis, variability in tissue collection and processing protocols [134-138]. To find definite answers to the usefulness of the presence of nerve fibres in eutopic endometrium as a biomarker for endometriosis, the standardisation of these variable factors in large Randomized Controlled Trials (RCTs) with specific emphasis on minimal and mild endometriosis is needed [43,139].

## Neurotrophins and Endometriosis

There is evidence that neurotrophins and their receptors are involved in nerve fibre growth and are expressed in endometrial tissue and Peritoneal Fluid (PF) of women with endometriosis. Previous studies have shown that NT-3, NGF and their receptors: p75 and TrkA (respectively), are expressed in endometrial glands and stroma of peritoneal lesions, ovarian and Deep Infiltrating Endometrial (DIE) lesions [122,140,141]. In addition, Barcena de Arellano investigated the possible role of neurotrophins in eutopic endometrium and demonstrated that NGF, BDNF and NT-3 are expressed in the endometrium of women with and without endometriosis and there were no differences detected [142]. However, another study showed that the levels of NT-4/5 and BDNF were higher in the endometrium of women with endometriosis compared with controls, and there were no differences in the NGF level observed between the two study groups [143].

Barcena de Arellano also showed elevated levels of NGF, NT-3, but none in BDNF in the PF of women with peritoneal endometriosis compared with adenomyosis, adhesions or asymptomatic controls [144]. However, the concentrations of these neurotrophins did not show a correlation with the pain symptoms in any of the groups. Kajitani et al., demonstrated contrasting results, with a significant correlation between high NGF levels and the severity of dysmenorrhoea and moderate or severe dyspareunia in women with peritoneal or ovarian endometriosis [145]. Moreover, women with endometriosis showed elevated BDNF in their plasma [146]. These results are suggestive that neurotrophins may stimulate a differential nerve fibre growth pattern in women with endometriosis and potentially contributing to pain mechanisms associated with endometriosis.

## Neuronal Guidance Molecules and Endometriosis

Elevated neuronal guidance molecules activities were observed in women with endometriosis. Women with endometriosis showed a significantly higher Semaphorin 3A in endometrium, Semaphorin 3C in the endometrium and peritoneal endometriotic lesions and Semaphorin 3F in peritoneal endometriotic lesions [147-149]. Shen et al., reported a higher expression of Slit and Robo1 proteins, as well as an increased microvascular density, in cases of endometrioma recurrence [150]. The results of these studies suggested the possible role of neuronal guidance molecules in nerve fibres growth in women with endometriosis and potentially contributing to pain mechanisms associated with endometriosis.

## Conclusion

To-date the aetiology and the pathogenesis of the disease are still poorly understood. As discussed endometriosis has a wide range of symptoms or can be asymptomatic, this makes the diagnosis of the disease difficult. The definitive diagnosis is surgical, usually via laparoscopy with histological confirmation. There is often a long delay in diagnosis, 8-12 years, from the onset of symptoms till a definitive diagnosis is made. Endometriosis is a progressive disease and the long delays before effective treatment allows the disease to advance. Ideally there is a need for the discovery of a biomarker to detect the disease earlier and to avoid the use of laparoscopy.

## Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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