

Review Article

Endometriosis in Women is a Common Headache of This New Era: Review Article

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ABSTRACT

Endometriosis is a common, benign estrogen dependent gynaecological ailment in women of reproductive age with the presence of endometrial glandular epithelial and stromal cells, growing in the extra-uterine environment. A large amount of natural and man-made chemicals have co-morbid relationship with endometriosis, affecting 5% to 15% of child bearing age women and up to 3% to 5% of post-menopausal women. However, despite the prevalence, physical and psychological tolls and health care costs, a proper non recurrence cure for endometriosis has not yet been found. The review of the literature reveals that endometriosis, with indication of viscerovisceral hyperalgesia and suggestive of neuropathic pain, describes a progression of disease symptoms over the entire menstrual life. The leading worldwide cause of outstretched endometriosis is due to less awareness among women having lack of knowledge on observation, palpation and interference of proper diagnosis. This review aims to study the current trend of knowledge and awareness on the socio-psychological impact of endometriosis in women's lives; to provide updated knowledge of radio frequency and electromagnetic radiation impact on endometriosis disease; to make awareness among women regarding the effect of irrational food habits, use of planned and unplanned oral contraceptives to prevent unwanted pregnancy on endometriosis; to furnish the impact of environmental, chemicals and heavy metals on endometriosis disease; lastly to state the difference and link between endometriosis and malignancy for future research.

Keywords: endometriosis, dysmenorrhoea, prostaglandin, omega-6-fatty-acids, estrogenic-potency

INTRODUCTION

Endometriosis, as stated by Rokitansky⁽¹⁾ 150 years ago, is a common benign pleomorphic estrogen-dependent disorder, rooted by chronic pelvic pain (CPP) with sub fertility in young women in twenties and thirties age group.⁽²⁻⁶⁾ It is a stipulation, which occurs when functioning endometrium like tissue divorces uterus and grows to lodge themselves generally in an extra uterine environment, especially on the surface of peritoneal cavity, and also in the pleural cavity.^(3,7,8) These cells can also get implanted between the uterus and rectum or

between the rectum and vagina or on the ovaries, fallopian tubes, and the ligaments that support the uterus.⁽⁹⁾

The heterogeneity of endometriosis transmutes the development of a reliable classification system for diagnosis of different endometriotic stages and therapy.⁽¹⁰⁾ The label of endometriosis in females can be classified into four stages according to American Society of Reproductive Medicine; Stages 1 and 2 shows (minimal and mild endometriosis), Stages 3 and 4 (moderate to severe endometriosis). There are three subtypes of endometriosis in

accordance with localisation: i.e. Superficial-peritoneal, Deep-infiltrating and Ovarian endometriosis. The Superficial peritoneal endometriosis as detected by a laparoscope is surrounded by a white/blue/red/black area of scarring which is 1 to 2 cm wide and it is painful with less mass and implanted on the wall of peritoneum. ⁽¹¹⁾ The deep infiltrating endometriosis i.e. Recto vaginal is a rare and most painful type endometriosis which penetrates the bowel, bladder and vagina (\geq 5mm) as well as sciatic and obturator nerves. ⁽¹¹⁾ The ovarian endometriosis, also known as chocolate cysts forms in sizes ranging from 3-4 cm to 15cm, implants in the lining of ovaries and proliferates into fallopian tubes and bowels, which is often associated with infertility among young women of reproductive age. ⁽¹¹⁾

CELLULAR and MOLECULAR BASIS

The human endometrium is a dynamic tissue which endures monthly cyclic changes, including proliferation, differentiation and degeneration in females. There sequential modifications are generally associated with ischemic necrosis of the endometrium functional layer by the contraction of spiral-arteries, which are dependent on the concentration of sex hormones. ⁽¹²⁾ The Sex steroids particularly estrogen, released by ovaries, cause thickening of uterine lining due to endometrial tissue growth. Prostaglandin (PGE₂), a cytokine in turn is a potent inducer of estrogen-synthetase (aromatase) activity in endometriotic-stromal cells by autocrine-positive-feedback mechanism. ⁽¹³⁾ Programmed Cell Death (PCD) type-I (apoptosis) upholds the cellular homeostasis in endometrial epithelial cells during the late menstrual secretory phase for eliminating senescent endometrial cells from the functional layer of the human endometrium. ^(12,14) The reduced apoptosis for PCD was detected in the proliferative phase or at the beginning of secretory phase. ^(15,16) The molecular aspects of endometrial growth and progression may be embedded in response to a platelet derived growth factor

(PDGF), by a heat stable cationic hydrophilic protein. ⁽¹⁷⁾ The Platelet derived endothelial growth factor (PD-ECGF) is an angiogenic potential which may be prominently provided by uterine endometrial stromal cells associated with the stroke of progesterone and estrogen. ⁽¹⁸⁾ Ngo et al ⁽¹⁹⁾ reported that an endometriotic cells display activated pERK (phospho-extracellular regulated mitogen-activated kinase); growth-related-signaling pathway component, enhanced reactive-oxygen-species (ROS), superoxide anion, hydrogen peroxide, hydroxyl radical production and proliferative capability. The inflammatory cytokines or ROS can affect the signaling cascade activation and mitochondrial DNA damage, leading to apoptosis in endometriotic lesion. ⁽²⁰⁾ The presence of element like macrophages, iron or environmental contaminants disrupt the balance between ROS and antioxidants (protective mechanism of cells) in the peritoneal fluid of some women, leading to oxidative stress and endometriosis. ⁽²¹⁻²³⁾ The antioxidant enzymes are over expressed as a result of excessive free radical generation in endometriosis. ^(24,25) Asante and Taylor ⁽²⁶⁾ stated that the interference with neurotrophin (growth factor) production within endometrium itself might trigger the mitigation of pain-associated endometriosis. There is an increased lipid-protein complex modification in endometrium and ROS induced pro-inflammatory environment along with endometriosis, contributing neuro angiogenic milieu. ^(21,25) The cellular mechanism of endometriosis is schematically depicted in Figure 1. Kobayashi et al ⁽²⁷⁾ hypothesised that there are at least two distinct phases of endometriosis development: the initial wave of toll-like receptor (TLR; recognizer of endogenous-danger-associated-molecular-pattern (DAMP) activation which modulates innate immunity, followed by a second big wave of sterile inflammation. Oxidative stress is secondary to the influx of iron during retrograde menstruation which is

involved in the progression of endometriosis. (27,28)

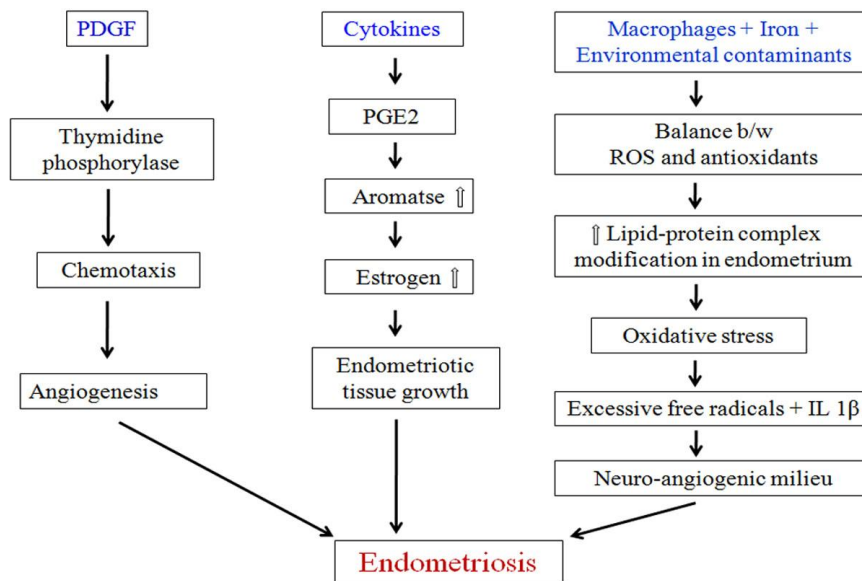


Figure1. The cellular mechanism of endometriosis

GLOBAL EMPHASIS

Endometriosis affects women in their prime fertile period of life. (29) One out of ten women in their reproductive age has endometriosis. The prevalence of endometriosis is not tracked easily in general women population who are living their respective life with this disease, without receiving proper treatment, as majority of symptoms in this disease are sub clinical (60%) or asymptomatic 1%. (30,31) According to “world-endometriosis-society” (32) the hidden toll and extraordinary negligence of endometriosis disease affects 176 million women in the world of which 6 to 10% of women are of child bearing age, 30 to 50% of women are experiencing infertility and remaining 30 to 60% of women are suffering from ovarian cancer. In USA, the prevalence of endometriosis ranged from 2 to 50% in women of reproductive age and among them 20 to 50% have infertility problems. (8) According to theguardian.com/society, (33) in UK, the onset of suffering age due to endometriosis is 11. In India endometriosis had affected 35% (25 million) of women in their fertile age as per 2007 census survey and endometriosisworld.org. The prevalence of endometriosis is highest in Cochin and Assam and lowest in Punjab.

A survey conducted by Endometriosis society in five schools of Kolkata, West Bengal, India, showed 5% of girls below 18, had dysmenorrhoea affected by endometrial disorder. Urbanization, modern lifestyle, choice of different lifestyle, use of pesticides, delay in marriage and 1st pregnancy, most marriages in women after post 30, non communicative fast life, use of unplanned oral contraceptive are the primary cause of endometriosis. (34)

AETIOLOGY OF ENDOMETRIOSIS

The pathophysiology of endometriosis is multi-factorial, involving interplay between several factors. (35) There are some theories to better understand the development of endometriosis. The most acceptable theory is the retrograde-menstruation-theory (implantation-theory or transplantation-theory) which suggests that some of endometrial debris exist in the uterus coming through fallopian tubes, attaches itself to the peritoneal surface for invading the tissue as endometriosis. (34) Mullerianosis, theory is supported by foetal autopsy which is a potential cell to become endometrial tissue due to lay down of tracts during embryonic development. (36) Vasculogenesis is the formation of micro vessels which originates from endothelial

progenitor cells of ectopic endometrial tissues. ⁽³⁷⁾ Endometriosis may also arise from the stem cells of bone marrow found in areas remote from the pelvis such as brain or lungs. ⁽³⁸⁾ Genetic inheritance and autoimmune reaction i.e. Graves disease, may be one of the cause in the development of endometriosis. ^(2,39) Persistent environmental-chemical exposure may also affect the endometrial risk among women. ⁽⁴⁰⁾

FAMILIAR ASPECTS

Endometriosis often results in a vast array of problems, including dyspareunia, dysmenorrhoea, pelvic pain and infertility. The histopathology of endometriosis is variable and dependent on the site of growth. It has been suspected of familial tendencies. ⁽¹⁰⁾ Magnitude of the augmented-risk of endometriosis (5% to 8% of first-degree relatives) is more reminiscent of polygenic/multifactorial tendencies. Lamb et al ⁽⁴¹⁾ in US, Moen and Magnus ⁽⁴²⁾ in Norway, Coxhead and Thomas ⁽⁴³⁾ in UK, reported the frequency of familial aggregates of endometriosis. The OXGENE (Oxford Endometriosis Gene) group recorded endometriosis from 19 mother-daughter pairs and 56 sibling-pairs. ⁽⁴⁴⁾ Higher concordance has been observed for monozygotic twins than dizygotic twins. ^(10,45) Pneumothoracic sisters may have pelvic endometriosis. ⁽⁴⁶⁾ Rahmioglu et al ⁽⁴⁷⁾ evaluated that women with one or two genetic variants (variation in DNA) may be prone to develop endometriosis. Linkage studies in pedigrees are likely to harbour variants implicated in familial endometriosis. ⁽⁴⁷⁾ Moreover the potential of gene-gene and gene-environment interactions are more influencing factors with the development of platforms to detect epigenetic genome-wide changes.

SOCIAL AND PSYCHOLOGICAL IMPACT

Endometriosis impairs Health-related quality of life (HRQoL) and work productivity across countries and ethnicities. ⁽⁴⁾ The diagnosis may be overlooked in the primary care, as patients think it causes

unnecessary suffering and reduces the quality of life. Hencefore, the influence on quality of life factors at disease stage, symptom severity stage, and care seeking stage has been poorly researched. ^(4,48,49) Nnoaham et al ⁽⁴⁾ evaluated that there is longer diagnostic delay with more “pelvic” symptoms (CPP, dysmenorrhoea and dyspareunia) and a higher body-mass-index (BMI). Delays are strongly associated with care-seeking experiences in primary care, discrediting nature of menstrual irregularities and risk of social stigmatization. ^(4,50-52) Endometriosis is of considerable importance, both directly in terms of its potentially and negative impact on the large number of women affected by its condition and indirectly on healthcare systems and society as a whole. ⁽⁶⁾ The thematic analysis of qualitative and quantitative studies revealed that the diagnostic delay and uncertainty, ⁽⁴⁾ quality of life and everyday activities, ⁽⁴⁹⁾ intimate relationships and planning for having children, ⁽⁵⁴⁾ Denny and Mann 2008, education and work, ⁽⁵³⁾ mental health and well-beings, ⁽⁵⁴⁾ medical follow up, ⁽⁵⁵⁾ and self management, ⁽⁵⁶⁾ may contribute “pain” as a significant symptom in endometriosis.

Women with endometriosis frequently experience significant delays from indication onset to diagnosis, ^(4,51,57) ranging from 5 to 8.9 years, ^(58,59) due to difficulty in distinguishing between normal and pathological symptoms. ⁽⁵⁰⁾ Women often consider themselves ‘unlucky’ as opposed to ‘unwell’ as well as the fear of disclosure would result in embarrassment and in them being perceived as weak. ^(6,50,56) In such circumstances, women were often initially referred to inappropriate secondary-care, or were misdiagnosed, most commonly with irritable bowel syndrome or pelvic inflammatory disease. ^(50,51,55,56,60) Henceforth, endometriotic women undergo symptomatic and trajectory uncertainty with delayed diagnosis. ^(55,61) Endometriotic pain has a detrimental impact on daily life and physical functioning (e.g. sleeping, eating and moving). ^(60,62) Women, between 16%

(63) and 61% (53) can tolerate difficulties with mobility, daily activities and/or self-care through endometriosis. Bernuit et al (57) and Fourquet et al (53) stated respectively that 23% and 71% household and housekeeping activities of women are also affected by endometriosis. Bernuit et al (57) and Fourquet et al (53) reported separately that 33.5% and 71% of women's sexual conjugal life was affected by endometriosis. Chene et al (64) reported that quality of conjugal-sex life was distressed in both types of women suffering from minimal and severe endometriosis. Fourquet et al (59) suggested that incapacitating pain and dyspareunia have a negative impact on conjugal-sex life. Infertility or concerns about the possibility of infertility, has accounted in worry, anxiety, depression and feelings of inadequacy among women who has contributed to relationship-breakdown. (6,60) Endometriosis affected women's education, studies and grades, causing drop out from education before completion. (65,66) Moreover, women do not inform their employers regarding their endometriosis diagnosis for a range of reasons due to difficulty in discussing a gender specific sex and infertility oriented disease condition with male employers. (66) Depression, anxiety and emotional distress are common symptomatic experiences of women suffering from endometriosis. (6,54,62,63) Endometriotic pain makes women depressed, moody, lonely and short tempered. (6,56) In response to the limitations of medical treatment, some women also attempt to handle endometriosis and alleviate symptoms through lifestyle changes including, diet and exercise and through complementary and/or alternative therapies. (56,65,66)

Women with endometriosis are more likely to have mood and pain related disorders, suffering from migraines. (67,68) Early menarche is a well known risk factor for endometriosis associated with an enhanced jeopardy of migraine. (69) Tietjen et al (70) demonstrated that menorrhagia, a frequent complaint among endometriosis

patient, has correlation with 63% of migraine patients. There is an existence of a co-morbid relationship between migraine and endometriosis. (68)

IMPACT OF ENDOMETRIOSIS ON WOMEN'S HEALTH DUE TO RADIO FREQUENCY AND ELECTRO-MAGNETIC RADIATION EXPOSURE

Human, in modern era are exposed to an ever increasing intensity of electromagnetic fields, (EMF; an array of waves arising due to the gathering of electric and magnetic fields) spawned from the production and supply of electricity, television, personal computers, radio communication and mobile communication. (71) The biological effect of EMF exposure is the consequence of amplified heat in the area of exposure or energy absorption without heating. (72) The biological hazard of EMF exposure was studied since in 1960s and the safety of human exposure to EMF at home and in occupational work zone both has become an imperative concern for public health. EMF may increase free radicals to lead cell growth inhibition, protein misfolding, DNA breakdown and disrupt Ca^{2+} dependent cell signaling. (71,73-77) According to Gye and Park, (71) EMF exposure can alter the concentration of reproductive hormones, gonadal function, pregnancy, embryonic and fetal and development. EMF increases the oxidative stress in the endometrium, leading to significant decrease in the number of ovarian follicles. (72) There are potential effects of radio frequency (RF) and electromagnetic radiation (EMR) exposure on human reproduction. (78) Cell phone communication which is an integral part of human activity in everyday life, also leads to RF-EMR exposure. The coverage of RF-EMR in cellular phones may indicate embryonic growth retardation. (79,80) RF-EMR alters granulosa cells, ovarian follicle numbers, endometrial tissues and sex steroids which are associated with oxidative stress and apoptosis, (78) thus leading to the risk of endometriosis among women. Liu et

al⁽⁸¹⁾ demonstrated that electromagnetic EMR membrane potential and lowers the calcium ion concentration of endometrial glandular cells. EMR exposure from Wi-Fi and mobile phones leads to increase in oxidative stress as well as over production of free radicals within the cel.⁽⁸²⁾ Such fettle induces inflammation and decreases the number of follicles leading to endometriosis.

IRRATIONAL FOOD HABITS

Differences in geographic location, monthly income and urbanization may affect endometriosis.⁽⁸³⁾ The diet and lifestyle may sway the presence of inflammation in the body, estrogen activity, menstrual cycle and prostaglandin metabolism.⁽⁸⁴⁾ In the developing countries the incidence of dysmenorrhea ranges from 45 to 90%, among women suffering from endometriosis.⁽⁸⁴⁻⁸⁶⁾ Diet plausibly has a role in the aetiology of endometriosis through effects on steroid hormone levels.⁽⁸⁷⁾ One of the possible pathogenic factor influencing both dysmenorrhea and endometriosis is enhancement of pro-inflammatory prostaglandin (PGE₂ and PGE₂α) levels derived from Omega-6-fatty acids in diet.^(84,88) However, Omega-3-fatty acids precursor of PGE₃ and PGE₃α, is linked to reduce inflammation and thus it alters the pain among endometriosis patient.⁽⁸⁹⁾ Trabert et al⁽⁸⁷⁾ revealed that there is a higher risk of endometriosis with daily consumption of fruits, whereas there is no connection between vegetables consumption and endometriosis risk. Savaris and Amarai⁽⁹⁰⁾ observed that consumption of dietary fiber is connected with higher risk of endometriosis. The risk of endometriosis may be lowered by decrease concentration of bio-available estrogen.^(87,91) High fat diets associates with increased serum estrogen, estrogen sulphate and estradiol levels in pre menopausal women may link the incidence of endometriosis.⁽⁸⁷⁾ Missmer et al⁽⁹²⁾ revealed that unsaturated fats especially palmitate and trans unsaturated fatty acids were directly linked to the risk of endometriosis development. There is no

correlation between fish consumption and peril of endometriosis as observed by Parazzini et al⁽⁹³⁾ and Heillier et al.⁽⁹⁴⁾ Endometriosis severity in correlation with blood phospholipid levels were checked by Khanaki et al.⁽⁹⁵⁾ and the result showed that relationship of Omega-6 and Omega-3-fatty (especially eicosapentaenic acid and arachidonic acid) acids is responsible for development of endometriosis. Phospholipids via diet intake have no role in the development of endometriosis. Saturated fatty acid is the main ingredient of red meat and butter. In three different studies by Trabert et al,⁽⁸⁷⁾ Heillier et al⁽⁹⁴⁾ and Parazzini et al⁽⁹³⁾ the result showed that amplification of endometriosis was high due to intake of red meat rather than butter. Soy and phytoestrogens in food can be connected with a higher risk of endometriosis.⁽⁹⁶⁾ Alcohol consumption emerges as a potential threat of endometriosis.^(87,94,97) Lucero et al⁽⁹⁸⁾ reported that caffeine rich product increase concentration of estrogen and estrone as well as sex-hormone binding globulin leading to endometriosis.

Nutrient deficiency due to irrational food habits may interfere with DNA methylation resulting in epigenetic abnormalities by silenced or altered cytosine-phosphate-guanine (CpG).⁽⁹¹⁾ CpG hypo-methylation leads to the over expression of steroidogenic factor 1 (SF1) or estrogen receptor β (ER-β), following an increase in estradiol and PGE₂ levels to favour inflammation and cell growth in endometriosis.⁽⁹⁹⁾

ORAL CONTRACEPTIVES

The public health data reveals that endometriosis disease is an important economic burden for young women in their fertile age.⁽⁴⁹⁾ Momoeda et al⁽¹⁰⁰⁾ stated dysmenorrhea is the early symptoms of endometriosis. Young women suffering from dysmenorrhea is not alleviated by non steroidal anti inflammatory drugs (NSAIDs).^(101,102) The treatment of Dysmenorrhea with oral contraceptive improves the ovarian function in young

women. ⁽¹⁰³⁾ Vessey et al ⁽¹⁰⁴⁾ reported lower risk of endometriosis in young women treated with oral contraceptive. However Parrazzini et al ⁽¹⁰⁵⁾ stated an increase risk of endometriosis among young women after they were using oral contraceptives.

The link between endometriosis and oral contraception is still debatable. ^(102,106,107) A cross sectional study regarding the relationship between use of oral contraceptive and endometriosis in non pregnant women ($\leq 42\%$, surgically explored) was conducted by Chapron et al. ⁽¹⁰²⁾ This study revealed that oral contraceptive increases the risk of deep infiltrating endometriosis due to selection biased prescription of oral contraceptive as the first line of treatment in dysmenorrhea.

ENVIRONMENTAL CHEMICALS AND HEAVY METALS

The collateral overuse of environmental resources leads to high-level of chemical contamination and undesirable toxic metal accumulation, leading to cellular damage. ⁽¹⁰⁸⁾ Rapid industrialization effects living-beings, exposed to chemical pollutants, having long half life, which can adversely influence physiological function and potentially cause different disease. ⁽⁸⁸⁾ Environmental chemicals such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), polyhalogenated hydrocarbons, polychlorinated dibenzo-p-dioxin (PCDD), polychlorinated dibenzofurans (PCDF) and polychlorinated biphenyls (PCBs) are endocrine disruptors, which impairs reproductive functions. ^(88,109) Several studies indicated a significant association between industrialized product, dioxin and endometriosis. ⁽¹¹⁰⁻¹¹²⁾ Dioxin and dioxin like compounds (chemically stable and lipid soluble) are polycyclic aromatic agents with chloral substitutes which are ubiquitous environmental pollutants. ⁽¹⁰⁹⁾ Dioxin and dioxin like compounds can enter nucleus via aryl hydrocarbon receptor nuclear translocator (AhRNT; heterodimer) to activate genes with xenobiotics response element at their regulatory sites. ⁽¹¹³⁾ Simultaneously, these environmental

chemicals trigger transforming growth factor β (TGF β) and cytokines which are involved in cell proliferation. ⁽¹¹⁴⁾ Endometrium and immune cells contain high concentration of Arh. ⁽¹⁰⁹⁾ Exposure to dioxin activates an inflammatory pathway of menstruation to promote the production of matrix metalloproteinases (MMP) in endometrial tissue. ^(115,116) MMP can degrade extra cellular matrix proteins in presence of normal concentration of progesterone, which down regulates endometrial MMP, ⁽¹¹⁷⁾ to cause auto-immune nature of endometriosis. ⁽⁸⁸⁾ There is a crosstalk between dioxin/AhR complex and estrogen receptor α to undergo an affinity dependent conformational change. ⁽¹¹⁸⁾ Moreover, prolonged persistence of dioxins allows the development of endometrial tissue within the peritoneal cavity. ⁽¹⁰⁹⁾

Heavy metals are gaining prominence as potential environmental pollutants, which can cause the prevalence of endometriosis following industrialization. ^(94,119,120) Martin et al ⁽¹²¹⁾ assessed the estrogenic potency of metals using the 50% effective concentration (EC50) of different metals as determined from dose response curves. Some heavy metals disrupt the hypothalamic pituitary ovarian (HPO) axis of endocrine function. ⁽¹²²⁾ Among them cadmium (Cd), lead (Pb) and mercury (Hg) have anti estrogenic effects to inhibit the binding of estradiol to estrogen receptor α . ^(94,121-123) Blood Cd level potentially effect endometriosis by rapid activation of kinases i.e. mitogen activated protein kinases (MAPs) and serine threonine specific protein kinase (Akt) through active and passive cigarette smoke, shell fish and green leafy vegetables food, directly contaminated with polluted water and soil. ⁽¹²⁴⁻¹²⁶⁾ Heilier et al ⁽⁹⁴⁾ and Brochin et al, ⁽¹²⁷⁾ stated that Pb exerts endocrine disruption of peritoneal endometriosis, via the bonding of activated G-protein and Calmodulin. Low level chronic Hg exposure causes endometriosis, ⁽¹²⁸⁻¹³⁰⁾ by inducing poor immune function and damaged enzyme activity in cell

membranes and DNA. Silva et al ⁽¹²⁰⁾ reported that occupational and environmental exposure of women to nickel (Ni) which is a potent metalloestrogen can also cause endometriosis.

DIFFERENCE AND LINK BETWEEN ENDOMETRIOSIS AND MALIGNANCY

Endometriosis is an auto-immune disease with a multifactorial pathogenesis. ⁽⁵⁾ There is an abnormal benign tissues implantation in other areas apart from their origin. Several studies have shown aberrant expression of genes/proteins in endometriosis, involving in regulating cellular processes like adhesion, proliferation, angiogenesis and immune dysfunction. ⁽¹³¹⁻¹³⁵⁾ Angiogenesis lesions are essential for endometriotic cell survival and development like tumor growth. ^(5,31) Regulators of angiogenesis (vascular endothelial growth factors (VEGF) and angiopoietins) are significantly high in peripheral blood, peritoneal fluid and endometrium along with endometriosis. ^(31,136) Moreover, glycodelin, an endometrium derived protein, is involved in the development of endometriosis and infertility due to its angiogenic, immunosuppressive and contraceptive effects. ^(31,137) The most crucial signalling node, the mitogen activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) or MEK pathway is a master regulator in the majority of signalling pathways and cascades in the pathogenesis of endometriosis. ^(31,138) Recent proteomics approach revealed that DJ-1 protein (a ubiquitous novel mitogen dependent oncogene) is up regulated in eutopic endometrium of women having endometriosis. ⁽¹³⁴⁾ The malignant transformation of endometriosis involved high estrogen stimulation in tumor pathogenesis. ⁽⁵⁾ The pathogenesis in endometriosis and endometrial cancer is complicated and multi factorial, but the putative linking mechanisms contain both estrogen stimulation and chronic inflammation. ⁽⁸³⁾ The malignant processes,

associated with endometriosis may be classified into three groups: i) epithelial ovarian cancers (endometrioid adenocarcinoma and clear cell carcinoma), ii) other Müllerian-type tumors, including Müllerian type mucinous borderline tumor and serous borderline tumor and iii) sarcomas such as adenosarcoma and endometrial stromal sarcoma in the female pelvic cavity. ⁽⁵⁾ Endometrioid adenocarcinoma, arise from endometriosis, exhibits activation of Wnt signalling and somatic mutations of CTNNB1 [encoding β -catenin [cadherin-associated protein)], PTEN (phosphatase and tensin homolog) and PIK3CA (phosphoinositide-3-kinase, catalytic, α polypeptide). ^(5,139) Endometriosis associated clear cell carcinoma has a high percentage of PIK3CA activating mutations. ⁽¹⁴⁰⁾ Mandai et al ⁽¹⁴¹⁾ established that micro environmental factors, including oxidative stress and inflammation, are crucial in endometriosis associated ovarian carcinogenesis. Epidemiological studies have suggested a specific link with endometrioid and clear-cell ovarian cancers, but no firm evidence established endometriosis as an ovarian cancer precursor lesion. ^(142,143)

CONCLUSION

Endometriosis has a protean emergence, confusing with other pelvic pathology. The overlapping appearance and characteristic-variations of endometriosis may alter with time. Lack of careful observation and palpation interfere the proper diagnosis. Neither medical nor surgical executive is efficacious in all circumstances. Heightened awareness of endometriosis in primary health care may lead to earlier diagnosis, reduced suffering and advanced the work life productivity of women. Edification pathogenesis of endometriosis may provide the betterment in treatment of this perplexing fettle.

FUTURE PROSPECTS

Mixed method approaches in endometriosis specific instruments can

explore the impact of endometriosis for more diverse populations. Imperative necessity is required to develop, tackle and evaluate the intervention for supporting females living with this debilitating chronic condition of this disease. Innovative strategies at molecular levels are future centre of interest to enlarge the newer achievement in optimal endometriosis treatment.

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