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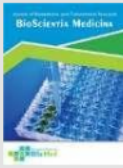
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Gynaecologic History During Adolescence to Predict Endometriosis Earlier

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ABSTRACT

Background. Endometriosis is a chronic gynaecological disorder that generally affects women of reproductive age which is characterized by implantation of endometrial tissue, both glands and stroma outside the uterus. Research shows that the initial onset of endometriosis patients begins in adolescence. The high prevalence with atypical symptoms leads to long term delay in establishing the appropriate diagnosis. Further developments in the field of early endometriosis screening will greatly assist clinicians, especially general practitioners in areas with limited health facilities, in early detection of endometriosis. **Methods:** Using the electronic databases, comprehensive literature searches were conducted with the specific keywords. Full-text manuscripts published were reviewed for relevancy and importantly, reference lists were cross-checked for additional relevant studies. **Results:** Dysmenorrhea, chronic pelvic pain, dyspareunia, dysuria, dyschezia, and glycoprotein were found dominantly in all analyzed literature. The occurrence of endometriosis affects the functioning of women in multiple aspects of life. Endometriosis places a significant burden on teens and adult women, their families, and society as a whole. **Conclusion:** Combination of structured past history taking, and several biomarker level might be useful as a screening tool that easy to use and cost effective, as early diagnosis is expected to prevent further progression of endometriosis especially in adolescence.

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1. Introduction

Endometriosis is a chronic gynaecological disorder that generally affects women of reproductive age which is characterized by implantation of endometrial tissue, both glands and stroma outside the uterus, starting from the pelvic peritoneum, ovaries, rectovaginal septum, to the pericardium, pleura, and even brain.^{1,2} The prevalence of endometriosis is estimated at 176 million women worldwide.³ In Indonesia, the prevalence of endometriosis still remain unclear as there has been no further research in the epidemiology of

endometriosis. Data from Cipto Mangunkusumo Hospital represent more than one hundred of patients with endometriosis in 5 years.⁴ The clinical manifestations of endometriosis are not typical, such as chronic pelvic pain, dysmenorrhea, dyspareunia and infertility, so that this disease is difficult to detect early, causing delays in the time of diagnosis.⁵ Women with endometriosis have a higher tendency to experience depressive symptoms and decreased sexual function.⁶ Symptoms of endometriosis contribute greatly to the

burden of disease and add huge costs to patients through reduced economic income and productivity.⁷

Research shows that the initial onset of endometriosis patients begins in adolescence.⁸ Other studies also mention the high incidence of endometriosis that occurs during adolescence. Adolescent girls with pelvic pain, including noncyclic pain with a first-degree family history of endometriosis, should be evaluated for possible endometriosis.⁹ Treatment for this age group can improve quality of life, reduce symptoms, prevent the development of more severe disease later in life and reduce the chances of future fertility problems, but further research to clarify this issue is essential.¹⁰ Until now, there is no endometriosis screening tool that can be used easily and cost effective.²⁹ The gold standard for definitive diagnosis of endometriosis is visualization of the lesion during laparoscopic or laparotomy procedures.¹¹ The high prevalence with atypical symptoms lead to long term delay in establishing the appropriate diagnosis.^{1,12}

Early screening tools for endometriosis that easy to access and cost-effective are in high demand, especially in developing countries such as Indonesia due to limited facilities and human resources in many health center. Various studies have been developed in the search for non-invasive methods of diagnosis of endometriosis, but until now there have been no satisfying results that can be used. Further developments in the field of early endometriosis screening will greatly assist clinicians, especially general practitioners in areas with limited health facilities, in early detection of endometriosis.

2. Methods

Using the electronic databases, PubMed, Science Direct and Google Scholar, comprehensive literature searches were conducted with the key words (Endometriosis) AND (adolescent OR teenager) AND (pelvic pain) OR (dyschezia) OR (polyuria) OR (dysuria) OR (dysmenorrhea) OR (CA125) OR (USG). In this Review, we discuss the symptoms of endometriosis that related to adolescents, setting these topics in the context of the “early diagnosis tools” model. Full-text manuscripts published were reviewed for relevancy and

importantly, reference lists were cross-checked for additional relevant studies.

3. Results

Dysmenorrhea

One of the most common symptoms that women with endometriosis will likely experience is dysmenorrhea.^{8,9,13} There is two type of dysmenorrhea, primary and secondary. Primary dysmenorrhea is defined as the presence of recurrent, crampy, lower abdominal pain of uterine origin that occur during menstruation without other organic diseases and it represents the most common menstrual in adolescents and young women.¹³ Secondary dysmenorrhea refers to painful menses due to other pathological conditions, such as endometriosis, adenomyosis, uterine fibroids and pelvic inflammatory disease.^{14,15} Endometriosis is the most common cause of secondary dysmenorrhea, the pain intensity is usually vary from mild to severe.^{16,17} Despite the high prevalence, many women with dysmenorrhea do not report it and seek medical care, because it is accepted as a normal aspect of the menstrual cycle and therefore is tolerated.¹⁸

The most widely accepted explanation for the pathogenesis of dysmenorrhea have been identified as a hyperproduction of uterine prostaglandins (PG), particularly PGF2a and PGE2 thus resulting in increased uterine tone and high amplitude contraction.^{14,17} Higher circulating levels of PGF2a and PGE2 have been reported in women with dysmenorrhea compared with asymptomatic women during menstruation.¹⁵ Peritoneal fluid of women with endometriosis consist more macrophage, the inflammatory environment of this disease points out an increased production of oestrogen, which in turn stimulates more PG through the activation of both NF-k Band Cyclooxygenase-2 (COX-2).¹² Clinical administration of exogenous PGs results in uterine contraction and often also produces the same systemic symptoms including nausea, vomiting and diarrhoea.¹⁹

In this review the author studied six articles about endometriosis (Table 1) and found that dysmenorrhea is the most common symptoms that women with endometriosis experience from adolescent to adult.

Case control study from Australia found that women who reported experiencing dysmenorrhea were more likely to have endometriosis develop than women reporting never or seldom experiencing pain during menstruation.²⁰ Another study about endometriosis symptoms difference in adolescents and adults with endometriosis, turns out that all participants report the first onset of dysmenorrhea happened around 14 – 16 years old. The same author also conclude the sooner women seek professional help for their dysmenorrhea the sooner the diagnosis of endometriosis obtained, meanwhile adults waited almost 3 times longer

between first seeing a clinician and achieving a surgical diagnosis.²¹ Study by Martire et al also found high percentage of dysmenorrhea among adolescent that went for USG examination, but ironically dysmenorrhea is not the chief complain for those girls, this could be because menstrual pain is commonly considered an inevitable manifestation of menses by many girls. Dysmenorrhea should be described in schools and other educational institutions as an important symptom that needs to be investigated.²²

Table 1. Studies about endometriosis symptoms

Title and Author	Country	Design Study	Sample		Variable	Study result
			Inclusion	Exclusion		
12 Prevalence of endometriosis among adolescent school girls with severe dysmenorrhea: A cross sectional prospective study ⁸	Republic of Sudan	Prospective cross sectional	Adolescent school girls	Improved pain with analgesia	Nausea	P>0,05
					Dysuria	P>0,05
					Dyschezia	P<0,05
					CA125	Sensitivity 78% Specificity 89,2%
					Abdominal USG	Sensitivity 100% Specificity 50%
16 Spectrum of symptoms in women diagnosed with endometriosis during adolescence vs adulthood ²¹	USA	Cross sectional	Adolescents and adults surgically confirmed endometriosis	Participants that never began the baseline questionnaire and no operative report	Dysmenorrhea	P<0,05
					Pelvic pain	P<0,05
					Nausea	P<0,05
					Dysuria	P<0,05
					Increased bowel movement	P>0,05
37 Adolescence and endometriosis: symptoms, ultrasound signs and early diagnosis ²²	Italy	Retrospective observational	Adolescent underwent transvaginal and transrectal ultrasound	Aged <12 y and >20y, pregnant, previous pelvic surgery, medical therapy with estrogens and progestin	Dysmenorrhea	P>0,05
					Pelvic pain	P>0,05
					Dyspareunia	P<0,05
					Dysuria	P>0,05
					Dyschezia	P<0,05
39 Early menstrual characteristics associated with subsequent diagnosis of endometriosis ²⁰	Australia	Case control	Women aged 18-55 y with and without endometriosis	Menstrual characteristics and symptom onset were both recorded in the 10-19 year age range	Dysmenorrhea	P<0,05
					Heavy menstrual bleeding	P>0,05
6 Evaluation of CA125 in relation to pain symptoms among adolescents and young adult women with and without surgically confirmed endometriosis	USA	Case control	Reproductive women with or without endometriosis	Participants that didn't complete questioner	CA125	P>0,05
4 The Diagnostic Accuracy of Combined Enolase/ Cr, CA125, and CA19-9 in the Detection of Endometriosis ²³	German	Cross sectional	Women aged 15-45 y with and without endometriosis	Usage of hormonal GnRH last 3 months, other gynaecologic disease or comorbid	CA125	P<0,05
					CA 19-9	P<0,05
					Enolase/ Cr urine	P>0,05

4. Discussion

Chronic pelvic pain

Chronic pelvic pain (CPP) accounts for 10% of outpatient gynaecologic visits. CPP that is described as chronic, cyclic, and persistent or progressive (worsening over time) increases the likelihood of an association with endometriosis.²⁴ Pelvic pain due to endometriosis is usually chronic (lasting ≥6 months) and is associated with dysmenorrhea (in 50 to 90% of cases), dyspareunia, deep pelvic pain, and lower abdominal pain with or without back and loin pain. The pain can occur unpredictably and intermittently throughout the menstrual cycle or it can be continuous, and it can be dull, throbbing, or sharp, and exacerbated by physical activity.¹³ Endometriosis is a disease in which hormonally dependent, inflammatory, ectopic endometrial lesions engage the reproductive, endocrine, vascular, musculoskeletal, and neuronal systems, there are several factors that may contribute to CPP.²⁵ Pain can be nociceptive, neuropathic and combination of those two, and endometriosis is thought to embrace all three types of pain mechanisms.²⁶

Peripheral mechanisms in endometriosis-associated CPP are numerous with interplay between endometriotic lesions, immune system, peripheral nerve fibres in both the lesions and adjacent peritoneum and peripheral neurons.²⁷ The mechanism of how ectopic endometrial lesions activate nervous system that caused pain has been investigated. That mechanism involves the innervation of lesions through neural sprouting of sensory and sympathetic fibers that innervate nearby blood vessels. Endometrial lesions must be vascularized to survive and grow,⁸ the branching of blood vessels during lesion development permits the simultaneous invasion of nerves, as the same factors that act on sprouting blood vessels act on nerve fibers. Newly sprouted nerve fibers may facilitate direct communication between the endometrial growths and the CNS, establishing a bridge for central integration of visceral sensory input.²⁵

CPP is one of the most common symptoms in endometriosis. An American study found that adolescent and adult with endometriosis feel acyclic pelvic pain over their life time, the pain usually last for

days and CPP highly interfered their daily activity at home, school, work, reduce their productivity and daily social activity.²¹ The concept of offering surgery to adolescents with chronic pelvic pain to derive a histologic diagnosis of the disease is inappropriate. A complete medical, surgical, social, and family history should be obtained from patients who present with this symptom, and they should undergo a physical examination that includes a pelvic examination, allowing both early diagnosis and adequate clinical management with surgery justified only for intractable cases.²²

Dyspareunia, dysuria and dyschezia

Deep dyspareunia is generally understood as pelvic pain occurring with deep penetration during intercourse or sexual activity.²⁸ Deep dyspareunia has been reported as one of the most frequent pain symptoms caused by endometriosis. A correlation has been demonstrated between lesion site and pain type. Dyspareunia has been associated with deep lesions infiltrating the uterosacral and cardinal ligaments, the pouch of Douglas, the posterior vaginal fornix and the anterior rectal wall. Deep dyspareunia affects approximately 50% of women with endometriosis and can result in sexual dysfunction and negative impacts on relationships.^{26,29,30}

Study by Martire et al report that most of adolescent with endometriosis that is already sexually active experience dyspareunia.²² Several studies have suggested that deep infiltrating endometriosis (DIE) lesions of the pouch of Douglas are more likely to be associated with deep dyspareunia compared with other sites. Deep dyspareunia was more frequent when DIE was found in a uterosacral ligament location than when it was not.^{29,31} Moreover, deep endometriotic lesions may be neurotrophic, as they have been consistently associated with higher expression of nerve growth factor (NGF) in comparison with peritoneal and ovarian implants.³²

Recent studies on clinical populations have reported posterior cul-de-sac and uterosacral lesions to be positively associated with dyspareunia, bladder and peritoneal lesions with dysuria, and deep vaginal

lesions with dyschezia.³³ As for distinct anatomic locations, severity of dyschezia was significantly greater in posterior vaginal wall, rectovaginal septum, and anterior rectal wall DIE, whereas mean VAS score was not significantly different in patients with uterosacral ligament involvement compared with control groups.³⁴ Pain remains the most important symptom for many women with endometriosis. Inflammation, peripheral and central pain generators, endocrine changes and structural alterations in the periphery and in the CNS may all contribute to endometriosis associated pain.^{25,27}

Glycoproteins

The discovery of a sufficiently sensitive and specific biomarker for nonsurgical detection of endometriosis would permit early diagnosis as well as prevent harmful sequelae of the disease.²³ Cancer Antigen125 (CA-125) is a high molecular-weight glycoprotein normally expressed on tissues derived from the coelomic and müllerian epithelia including the uterus endometrium. CA-125 has been reported to be elevated in endometriosis patients and is the most commonly described, extensively studied endometriosis biomarker to date.³⁵ CA-125 is often used in the diagnosis of ovarian cancer, but it can also be altered in endometriosis.³⁶ Although lacking both specificity and sensitivity for this pathology, the most representative glycoprotein used as a biomarker for endometriosis is CA-125. However, the simultaneous measurement of CA-125 with other molecules and their combination showed different sensitivities and specificities for endometriosis.¹² CA-125 seems to be hampered as a single clinically reliable diagnosis biomarker of endometriosis.

CA-19-9, also a tumor marker used in the investigation of ovarian cancer, has been tested in patients with endometriosis, and only a few studies detected a tendency of elevated levels in patients with endometriosis.³⁶ The cut off thresholds of CA-199 used to detect endometriosis in various studies are diverse, ranging from >7.5 to >37.0 IU/mL.³⁷ A review of the published literature suggests that an extremely high CA125 level combined with a high CA19-9 level is a

possible indicator of endometriosis. Study by Rokhgireh et al observed that combined CA-125 with CA-19-9 and enolase-1 as a biomarker for endometriosis, this combination gives a sensitivity of 65% and specificity of 66,6% for endometriosis.²³ The present study revealed that combined biomarkers possess greater sensitivity and specificity, and greater diagnostic power for the detection of endometriosis.

Retrospective study by Chen et al found the combination of haemoglobin, CA125, CA19-9 and H4 show a sensitivity of 85.4%, a specificity of 78.83%, and an area under the curve of 0.900, which was significantly higher than that of the individual index in endometriosis diagnosis.³⁸ Meta analysis has been conducted to study the diagnostic value of combined CA125 and CA19-9 as biomarker to diagnose endometriosis, in accordance with finding of others, Shen et al confirmed higher value of CA125 and CA19-9 in women with endometriosis compare to healthy women.³⁹ This conclude that endometriosis is highly associated with elevated serum CA125 and CA19-9, and the combination of this two may represent useful biomarker for the non-invasive diagnosis of endometriosis.

5. Conclusion

The occurrence of endometriosis affects the functioning of women in multiple aspects of life. Endometriosis places a significant burden on teens and adult women, their families, and society as a whole. Despite decades of research, there are still major challenges in the diagnosis and treatment of endometriosis. Recent literature on adolescent endometriosis has focused on the development of a clinical profile of adolescents with pelvic pain who are likely to be diagnosed with the disease. The importance of understanding patients is crucial. Endometriosis in adolescents is a disease to be considered as an important differential diagnosis in pelvic pain and adnexal cysts, especially among those with pain resistant to the use of commonly used medication. Medical professional should be aware of the signs and symptoms to make an early diagnosis, thereby preventing progression of the disease and providing the

most appropriate treatment for each patient. Combination of structured past history taking, and several biomarker level might be useful as a screening tools that easy to use and cost effective, as early diagnosis is expected to prevent further progression of endometriosis especially in adolescence.

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