THE ASSOCIATION BETWEEN CLINICAL MANIFESTATION, BIOCHEMICAL MARKER (CA 125) AND DIAGNOSTIC LAPAROSCOPY OR LAPAROTOMY FINDINGS WITH/WITHOUT HISTOPATHOLOGICAL CONFIRMATION IN THE DIAGNOSIS OF ENDOMETRIOSIS

BY

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Introduction

Endometriosis is known to be a devastating disease, not only because of its association with abdominal pain and infertility, but also the poor outcome of treatment given especially to those with associated fertility problem. However, detection and treatment given at early stage of disease may give better prognosis compared to those in advanced stage. Making an early diagnosis of endometriosis is therefore important for these patients. Direct visualization of the endometriotic lesions, with or without being confirmed histologically is at present the gold standard tool to make the diagnosis of endometriosis. Clinical manifestation alone could not confirmed the diagnosis. Tumour marker eg. CA 125 is not specific to endometriosis. Ultrasonography studies could not be of much value unless there is presence of endometrioma. Many patients are reluctant to undergo surgery in our centre. Therefore, we are to find a non-invasive way to make the diagnosis of endometriosis so that early treatment with better outcome could be offered to the patients.

Objective

This study was performed to create a scoring system name Cli-Endomet, which suggestive of endometriosis, by evaluating the association between the medical history, clinical examination, ultrasound findings and biochemical marker (CA 125).

Methodology

This was a cross sectional study, performed over 18 months duration from November 1st, 2011 until April 31st 2013. 176 patients with pelvic pain, which include dysmenorrhea, dyspareunia, ovulation pain, dyschezia or any chronic non-specific pelvic pain were recruited into the study. Detailed history and a thorough clinical examination were performed on each patient. A transvaginal ultrasound scan was performed and 2 mls of blood was taken from each patients either during menstruation or late luteal phase to determine the level of serum CA 125. All patients were then been subjected to either laparoscopy or laparotomy operation and/or tissue biopsy was taken for histopathology examination whenever was possible. In the presence of endometriosis, the staging of disease was determined using revised American Society of Reproductive Medicine (rASRM) scoring system. The clinical criterias which were strongly associated with diagnosis of endometriosis were extracted from statistical model, and were transformed for development of the clinical criteria scoring system, the Cli-Endomet.

Results

Among 176 patients recruited, 103 of them (58.5%) were confirmed to have endometriosis. The clinical manifestations and CA 125 level were analyzed via simple logistic regression then followed by multiple logistic regression, to determine the association between clinical presentation, CA 125 and endometriosis. The ROC (Receiver Operating Characteristic) curve of CA 125 was plotted and the cutoff points of CA 125 level in association with endometriosis were 50 to 200 U/mL with p value < 0.001. The clinical parameters which were statistically significant were dysmenorrhea (especially severe type, p < 0.015), ultrasonography finding of ovarian mass (if present) with ground-glass appearance or thick with sediments content (p < 0.001) and CA 125 level (p < 0.001). From this analysis results, a scoring system Cli-Endomet was then developed.

Conclusion

CliEndomet scoring system, which takes into consideration of several significant clinical parameters, can be used as an alternative tool that suggestive of endometriosis. However, the accuracy of CliEndomet is not fully validated yet. Should it proven to be accurate, it may avoid patient from unnecessary diagnostic surgical procedure and further medical treatment may be instituted accordingly.

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LISTS OF ABBREVIATIONS

AFS	American Fertility Society
ASRM	American Society for Reproductive Medicine
AUR	Area Under Curve
BMI	Body Mass Index
CA 125	Cancer Antigen 125
COC	Combined Oral Contraceptives
COX 2	Cyclooxygenase type 2
DMPA	Depot Medroxyprogesterone Acetate
GnRH	Gonadotrophin Releasing Hormone
GDG	Guideline Development Group
HPE	Histopathology examination
HRPZ II	Hospital Raja Perempuan Zainab II
HUSM	Hospital Universiti Sains Malaysia
LUNA	Laparoscopic Uterosacral Nerve Ablation
MIRENA	Levonogestrel-releasing intrauterine device
MRI	Magnetic Resonance Imanging
NK	Natural Killer cell
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
PGE_2	Prostaglandin E2
POD	Pouch of Douglas
R-ASRM	Revised American Society for Reproductive Medicine
RCOG	Royal College of Obstetrician and Gynaecology
ROC	Receiver Operating Characteristic
SPRM	Selective Progesterone-receptor Modulators
TVS	Transvaginal ultrasound
VEGF	Vascular Endothelial Growth Factor

ABSTRAK

Objektif

Kajian ini telah dilaksanakan untuk merumuskan satu system pemarkahan yang dinamakan Cli-Endomet, yang mencadangkan penyakit endometriosis, dengan menilai keberkesanan dalam persatuan antara sejarah perubatan, pemeriksaan klinikal, penemuan ciri ultrasound dan penanda biokimia (CA 125) dari pemeriksaan darah pesakit.

Kaedah Kajian

Ini adalah satu kajian keratan rentas, yang dilaksanakan dalam tempoh 18 bulan, mulai 1hb November 2011 hingga 31hb April 2013. Sebanyak 176 pesakit dengan simptoms seperti sakit senggugut, sakit semasa melakukan hubungan seksual, sakit semasa membuang air besar, sakit pada bahagian bawah abdomen sama ada semasa ovulasi atau masa yang tidak spesifik, telah dipilih untuk menyertai kajian ini. Sejarah perubatan yang terperinci dan pemeriksaan klinikal yang teliti telah dijalankan ke atas setiap pesakit. Imbasan ultrasound melalui faraj telah dilaksanakan dan 2 mls darah telah diambil dari setiap pesakit sama ada semasa haid atau fasa luteal lewat untuk menentukan tahap serum CA 125. Semua pesakit kemudiannya telah menjalani pembedahan secara laparoscopy atau laparotomy dan tisu biopsy diambil, sekiranya ada, untuk pemeriksaan histopatologi. Pesakit-pesakit yang mempunyai endometriosis telah dikategorikan kepada 4 peringkat menggunakan klasifikasi “revised American Society for Reproductive Medicine (rASRM) scoring system”. Kriteria klinikal yang berkait rapat dengan diagnosa endometriosis ini dikumpulkan dari model statistic, dan telah digunakan untuk penciptaan system pemarkahan dengan kriteria klinikal, dengan nama Cli-Endomet.

Keputusan

Antara 176 pesakit , 103 daripada mereka (58.5 %) telah disahkan mempunyai endometriosis. Manifestasi klinikal dan tahap CA 125 dianalisis melalui ‘simple logistic regression’ kemudian diikuti oleh ‘multiple logistic regression’ , untuk menentukan hubungan antara persembahan klinikal, CA 125 dan endometriosis. “ROC” (Receiver Operating Characteristic) lengkung CA 125 diplot dan tahap CA 125 yang berkait rapat dengan endometriosis adalah 50-200 U / mL dengan nilai $p < 0.001$. Parameter klinikal yang secara statistik penting adalah sakit senggugut (kesakitan yang teruk, $p < 0.015$) , imbasan jisim ovari dengan ultrasound (jika ada) dengan penampilan “ground-glass” atau tebal dengan sedimen kandungan ($p <0.001$) dan keputusan darah CA 125 ($p < 0.001$) . Dari keputusan analisis ini, sistem pemarkahan Cli- Endomet telah dirumuskan.

Kesimpulan

Sistem pemarkahan CliEndomet, yang mengambil kira beberapa parameter klinikal yang ketara, boleh digunakan sebagai alat alternatif yang menandakan endometriosis. Walau bagaimanapun, ketepatan CliEndomet ini tidak disahkan sepenuhnya lagi. Sekiranya ia terbukti tepat, ia boleh mengelakkan pesakit daripada prosedur pembedahan dignostik yang tidak diperlukan dan rawatan perubatan selanjutnya boleh dimulakan dengan sewajarnya.

ABSTRACT

Objective

This study was performed to create a scoring system name Cli-Endomet, which suggestive of endometriosis, by evaluating the association between the medical history, clinical examination, ultrasound findings and biochemical marker (CA 125).

Methodology

This was a cross sectional study, performed over 18 months duration from November 1st, 2011 until April 31st 2013. 176 patients with pelvic pain, which include dysmenorrhea, dyspareunia, ovulation pain, dyschezia or any chronic non-specific pelvic pain were recruited into the study. Detailed history and a thorough clinical examination were performed on each patient. A transvaginal ultrasound scan was performed and 2 mls of blood was taken from each patients either during menstruation or late luteal phase to determine the level of serum CA 125. All patients were then been subjected to either laparoscopy or laparotomy operation and/or tissue biopsy was taken for histopathology examination whenever was possible. In the presence of endometriosis, the staging of disease was determined using revised American Society of Reproductive Medicine (rASRM) scoring system. The clinical criterias which were strongly associated with diagnosis of endometriosis were extracted from statistical model, and were transformed for development of the clinical criteria scoring system, the Cli-Endomet.

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Conclusion

CliEndomet scoring system, which takes into consideration of several significant clinical parameters, can be used as an alternative tool that suggestive of endometriosis. However, the accuracy of CliEndomet is not fully validated yet. Should it proven to be accurate, it may avoid patient from unnecessary diagnostic surgical procedure and further medical treatment may be instituted accordingly.

1.0 INTRODUCTION

Endometriosis is a common gynecological disorder affecting women of reproductive age. It was first identified in the mid-nineteenth century (Von Rokitansky, 1860). It is defined as a disease characterized by the presence of tissue that is biologically and morphologically similar to normal endometrium, contains endometrial glands and stroma, in ectopic locations outside the uterine cavity. This ectopic endometrial tissue responds to hormones and drugs in a generally similar manner to eutopic endometrium undergoing cyclical changes. Cyclical bleeding from the endometriotic deposits appears to contribute to the induction of a local inflammatory reaction and fibrous adhesions; in the case of deep implants in the ovary, it can lead to formation of endometriomas (Pratibha, 2006).

Women with endometriosis may be asymptomatic, subfertile or suffer varying degree of pelvic pain. Incidence of endometriosis ranges from 1% to 10% of general population, up to 30 – 40% in women with infertility, the incidence is higher in women with pelvic pain with an incidence of 82% (Othman, 2008; Hooghe, 2002; Mounsey, 2006). However, the diagnosis of this condition remains difficult. The 'gold standard' of diagnosing endometriosis is by direct visualization of the lesions with or without histology confirmation. Unfortunately, this invasive procedure has potential complications, with positive predictive value differs if lesions are typical focal (76%) or atypical adhesion-forming (25-50%) (Walter, 2001).

Besides, the use of laparoscopy is limited by available finding, the surgeon's experience, and human error, including missing non-specific lesions (Razvan et al, 2011).

The predictive value of any one or set of symptoms or clinical manifestations of endometriosis remain uncertain. A normal physical examination also does not rule out the diagnosis of endometriosis with poor sensitivity (38-79%), specificity (32-80%) and positive predictive value (54-62%) (Eskenazi B, 2004). Ultrasound has limited value in diagnosis but it is useful to exclude ovarian endometrioma (Moore J, 2002).

Thus, development of a simple blood test as a marker for screening patients at risk for endometriosis would reduce the number of unnecessary interventions and would therefore be very useful (Stefan et al, 2010). Increasingly efforts are made to use less invasive tests with a low cost and high negative predictive value (Patrelli, 2011).

CA -125 is the cell surface antigen expressed by derivatives of coelomic and mullerian epithelia. The antigenic determinant of high-molecular-weight glycoprotein is detected by monoclonal antibody CA-125 (Robert et al., 2006).

Barbieri et al. reported higher concentrations of CA 125 in the glandular epithelium of endometriotic lesions than in the endometrium (Barbieri et al, 1986). Indeed, Koninckx et al (1996) after evaluating CA-125 in peritoneum and in the blood, concluded that superficial disease causes its elevation in peritoneal fluid, whereas deep disease causes its elevation in blood. The performance of CA-125 for the diagnosis of endometriosis has been assessed in a meta-analysis, with estimated sensitivity of 28% and specificity of 90% (corresponding likelihood ratio of raised level is 2.8). This test performance for moderate to severe endometriosis is better, with sensitivity of 47%, and specificity of 89% (corresponding likelihood ratio of raised level is 4.3) (Chapron, 2004). Despite poor sensitivity, several reports have demonstrated that serum CA-125 level may predict the response to medical and surgical treatment.

We are now trying to find a clinical diagnostic criteria, named Cli - Endomet to assist in diagnosis of endometriosis based on the clinical manifestations, radiological imaging and laboratory marker, comparing with direct visual inspection of pelvis at laparoscopy or laparotomy, with or without histology confirmation, to improve diagnostic sensitivity and specificity, hoping that surgical intervention can be avoided and medical therapy can be instituted according to the Cli-Endomet. According to Tommaso et al., a nonsurgical diagnosis of endometriosis is useful even if the management is surgical rather than medical (Tommaso et al., 2003). If it is proven that Cli-Endomet is a reliable tool that highly suggestive of endometriosis, then the high possibility of endometriosis could be made without surgical procedure and the appropriate treatment could be started accordingly.

2.0 LITERATURE REVIEW

2.1 PATHOPHYSIOLOGY

2.1.1 Aetiology

The definitive cause of endometriosis remains unknown, it is often called the disease of theories as several theories with supporting evidence have been put forward:

a. Retrograde menstruation
b. Coelomic metaplasia
c. Induction theory
d. Genetic and immunological factors
e. Defects in embryogenesis theory

2.1.1(a) Retrograde Menstruation (Implantation Metastasis theory)

The most widely accepted theory, proposed in the 1920s by Sampson, that claim the adhesion and growth of endometrial fragments deposited into the peritoneal cavity via retrograde menstruation (Sampson, 1927). The refluxed endometrial fragments adhere to and invade the peritoneal mesothelium and develop a blood supply, which leads to continued implant survival and growth (Giudice, 2004). This theory is supported by the fact that endometriosis is commonly found in young girls with obstructive abnormalities of genital tract, which is often relieved by surgical correction of the obstruction (Sanfilippo, 1986). It has been suggested that enhanced angiogenesis could be a factor in the development of this lesions as the endometriotic areas are frequently found to have increased vascularity. This is further supported by the presence of potent angiogenic growth factor (vascular endothelial growth factor, VEGF), which is found in the peritoneal fluid of patients with endometriosis together with transforming growth factor-β and intracellular adhesion molecule-1 (1 CAM). Their levels decrease significantly after treatment with gonadotrophin-releasing hormone (GnRH) analogues (Pratibha et al., 2006)

2.1.1(b) Coelomic Metaplasia

First described in 1919 by Meyer, postulates the possibility of coelomic membrane metaplasia to endometrium-like tissue following chronic irritation and stimulation by oestrogen (Pratibha et al., 2006). Because the ovary and the progenitor of endometrium, the mullerian ducts are both derived from coelomic epithelium, metaplasia may explain the development of ovarian endometriosis (Chapron, 2004). This theory also explain the peritoneal endometriosis due to proliferative and differentiation potential of the peritoneal mesothelium. This theory is attractive in instance of endometriosis in the absence of menstruation, such as in premenarchal and post-menopausal women, and in males treated with estrogen and orchidectomy for prostatic carcinoma (Dictor, 1988; Pinkert, 1979). However, the absence of endometriosis in other tissues derived from coelomic epithelium argues against this theory.

2.1.1(c) Induction theory

This theory was introduced by Levander and Norman in 1955, was based on the assumption that endometriosis results from the differentiation of mesenchymal cells, induced by substances (hormonal or biologic factors), which may be exogenous or released by degenerating endometrium (Bontis, 1997; Pratibha, 2006). In vitro studies have demonstrated the potential for ovarian surface epithelium, in response to estrogens, to undergo transformation to form endometriotic lesions (Matsuura, 1999).

2.1.1(d) Genetic and Immunological factors

Endometriosis is more prevalent in certain families, and it has been shown that there is seven fold higher risk of developing endometriosis of a severe grade in women with first-degree relatives with the disorder (Robert, 2006). There is also high incidence found in monozygotic twins compared with dizygotic twins, suggesting some genetic link in endometriosis.

2.1.1(e) Defects in Embryogenesis Theory

This theory postulates that endometriosis is caused by small defects of embryogenesis (Knapp, 1999; Benagiano and Brosens, 2006), suggested that the endometrial tissue, misplaced outside the uterine cavity during the earlier steps of organogenesis and displaying identical molecular phenotype to the endometrium present in uterus. This ectopic endometrium would remain quiescent and asymptomatic until puberty, where the hormonal changes cause its regrowth and subsequently the onset of symptoms of endometriosis.

2.1.2 Hormonal Dependence

Oestrogen has been definitely established as having a causative role in the development of endometriosis (Gurates, 2003). Estrogen mainly produced by ovaries, minimal amount by peripheral tissues, through aromatization of ovarian and adrenal androgens.

The endometriotic implants express aromatase and 17β-hydroxysteroid dehydrogenase type 1, which convert androstenedione to estrone and of estrone to estradiol, respectively, but these implants are deficient in 17β-hydroxysteroid dehydrogenase type 2, which inactivate estrogen (Kitawaki, 1997; Zeitoun, 1998). Thus, implants will be exposed to an estrogenic environment.

Normal endometrium does not express aromatase and has elevated 17β-hydroxysteroid dehydrogenase type 2 in response to progesterone (Satyaswaroop, 1982), the progesterone inhibit the estrogen effects during luteal phase of menstrual cycle. Prostaglandin E2 (PGE_2) is the most potent inducer of aromatase activity in endometrial stromal cells, the aromatase activity produces estradiol, which further augments PGE_2 production by stimulating the cyclooxygenase type 2 (COX-2) enzyme in uterine endothelial cells (Bulun, 2002; Gurates, 2003). This causes a positive feedback loop and potentiates the estrogenic effects on proliferation of endometriosis.

2.1.3 Role of Immune System

In retrograde menstruation, the menstrual tissue and endometrium is usually cleared by immune cells e.g. macrophages, natural killer (NK) cells, and lymphocytes. Thus, immune system dysfunction is one likely mechanism for the genesis of endometriosis in retrograde menstruation (Seli, 2003). One study showed the macrophages in women with endometriosis have a stimulatory effect on endometriotic tissue, enhanced the proliferation of endometrial cells, whereas the monocytes from women without endometrioses had the opposite effect (Braun, 1994), this shows there is impaired function of macrophages allows endometriotic tissue proliferation. Besides, Wilson et al (1994) & Ho et al (2001) had demonstrated the decrease in NK cell cytotoxicity against endometrium.

The cellular immunity may be disordered and T lymphocytes are implicated in women with endometriosis. Humoral immunity, including endometrial antibodies (IgG), are detected in serum of women with endometriosis (Odukoya, 1995), suggest that endometriosis may be, in part, an autoimmune disease. This may explain lower pregnancy and in vitro fertilization (IVF) implantation rates in affected women (Dmowski, 1995).

Cytokines, especially interleukins IL-1β, IL-6, IL-8) and TNF-α are elevated in affected individuals and stimulate proliferation of endometrial stromal cells (Arici, 1996; Arici, 1998; Ryan, 1995).

2.2 CLASSIFICATION

The gold standard of endometriosis diagnosis is visualization of endometriotic lesions by laparoscopy, with or without histological confirmation. The initial classification created by the American Fertility Society (AFS) in 1979, which has been subsequently renamed the American Society for Reproductive Medicine (ASRM), was revised for the third time in 1996 but still with limitations. In this system, endometriosis is classified as stage I (minimal), stage II (mild), stage III (moderate), stage IV (severe). This classification system (r-ASRM) did not provide any prognostic information with respect to subsequent fertility or severity of pelvic pain (Guzick, 1982, 1997).

2.3 DIAGNOSIS OF ENDOMETRIOSIS

2.3.1 Clinical Manifestation

The main presenting symptoms of endometriosis include pelvic pain and infertility. The pain include dysmenorrhea, dyspareunia, chronic pelvic pain, ovulation pain, dyschezia (pain on defecation), and non-cyclical pelvic pain. There may be other associated urinary and bowel symptoms in cases of the bladder and bowel involvement.

The underlying cause of this pain is unclear, but proinflammatory cytokines and prostaglandins released by endometriotic implants into the peritoneal fluid may be one source (Giudice, 2004). Recent data suggest that endometriosis pain may result from neuronal invasion of endometriotic implants that subsequently develop a sensory and sympathetic nerve supply, which may undergo central sensitization (Berkley, 2005).

Dysmenorrhea in endometriosis patient is most often related to rectovaginal septum or uterosacral ligament disease (Murphy, 2002 ; Vercellini, 1996).

Painful defecation typically reflects rectosigmoid involvement with endometriotic implants, may be chronic or cyclic, and associated with constipation, diarrhea or cyclic hematochezia (Azzena, 1998; Remorgida, 2007).

Infertility may result from adhesions which are caused by endometriosis and impair normal oocyte pick-up and transport by the fallopian tube. Beyond mechanical impairment of ovulation and fertilization, perturbations in ovarian and immune function as well as implantation appear to be involved in the pathogenesis of infertility in women with endometriosis (Chapron, 2004). Some researchers have suggested that folliculogenesis is impaired in women with endometriosis (Pellicer, 1995). Other investigations found that oocyte number may be decreased or apoptosis with decreased oocyte competence in women with endometriosis cause infertility, but well-designed studies are lacking (Garrido, 2002 ; Harlow. 1996).

Abnormality in endometrial development supports the possibility that implantation defects may be responsible for subfertility associated with endometriosis. Deficient $\alpha_v\beta_3$ integrin expression in the peri-implantation endometrium of women with endometriosis has been demonstrated, and this may be the cause of decreased uterine receptivity (Lessey, 1994).

Sperm function may be affected as studies showed increased phagocytosis of spermatozoa by macrophages from women with endometriosis (Haney, 1981; Muscato,

1982) and sperm binding to the zona pellucida appears to be adversely affected (Qiao, 1998).

2.3.2 Physical Examination

2.3.2.(a) Visual inspection

Rarely, endometriosis may develop spontaneously within perineum or perianal area (Watanabe, 2003), or other sites such as an episiotomy or surgical scar (e.g. Pfannenstiel scar).

2.3.2.(b) Speculum examination

14% of patients with deeply infiltrating endometriosis have positive findings on speculum examination (Chapron, 2002). Occasionally, bluish or red powder burn lesions may be seen on posterior fornix or cervix, with tender or contact bleeding.

2.3.2.(c) Bimanual examination

Uterosacral ligament nodularity, thickened and tenderness may indicate active disease of endometriosis. Ovarian endometrioma may be felt as cystic adnexal mass, which may mobile or adherent. The pouch of Douglas may be obliterated with retroverted, fixed and tender uterus (Chapron, 2004).

2.3.3 Laboratory Testing

2.3.3. (a) Serum CA125

CA 125 is an antigenic determinant on a glycoprotein, found in several adult tissues such as epithelium of fallopian tube, endometrium, endocervix, pleura and peritoneum (Chapron, 2004). Marked increase are observed during pregnancy and peritoneal irritation by infection or surgery, and also found in over 80% of cases of epithelial ovarian carcinoma. Elevated serum CA 125 has been shown to positively correlate with

the severity of endometriosis (Hornstein, 1995). Elevated plasma CA125 post-treatment can be used as an argument that treatment is not complete or the condition has recurred. However, it has poor sensitivity in detecting mild endometriosis. A study by Mol.et.al (1998) revealed a sensitivity of 28% and specificity of 90% (corresponding likelihood ratio of a raised level is 2.8). It appeared to be a better test in detecting stage III and IV endometriosis, for a specificity of 89% and sensitivity was 47% (RCOG greentop guideline, 2006).

2.3.3. (b) Other serum markers

Serum CA 19-9, placental protein 14, interleukin-6, tumor necrosis factor -α have been studied, with limited diagnostic accuracy and rarely used (Bedaiwy, 2004).

2.3.4 Diagnostic Laparoscopy

The gold standard for detecting endometriosis disease is direct visualization via laparoscopy or laparotomy with or without histopathology confirmation (Gerard A. et. al, 2012). The findings are variable, include discrete endometriotic lesions, endometrioma and adhesion formation. The endometriotic lesions can be red polypoid lesions, clear lesions, red flame or powder burn lesions, blue black or brown lesions, yellow, white lesions or peritoneal windows (Pratibha, 2006). The endometriosis commonly located at ovaries, ligaments around the uterus, space between the rectum and vagina or cervix (Women's Health, 2007). Latest guideline by ESHRE on endometriosis (ESHRE, 2013) stated that the combination of laparoscopy and the histological verification of endometrial glands and/or stroma is considered for the diagnosis of endometriosis. The GDG (Guideline Development Group) recommends that endometriosis diagnosed by a positive laparoscopy with histology, even though negative histology does not exclude it.

Endometriomas are cystic endometrial lesions contained within the ovary. Laparoscopic visualization of ovarian endometriomas has a sensitivity and specificity of 97% and 95%, respectively (Vercellini, 1991).

2.3.5 Diagnostic Imaging

Transvaginal ultrasound (TVS) has limited value in diagnosing peritoneal endometriosis but it is a useful tool both to make and to exclude the diagnosis of an ovarian endometrioma (RCOG, 2006). The sensitivity is range from 64% to 90% and specificity is range from 22% to 100% of TVS to diagnose endometriomas (Moore, 2002). At present, there is insufficient evidence to indicate that magnetic resonance imaging (MRI) is a useful test to diagnose or exclude endometriosis compared to laparoscopy (RCOG, 2006).

2.4 TREATMENT

Endometriosis is difficult to treat, since with the most treatment modalities there is eventual recurrence in up to 60%. It is thought that the only definitive treatment is total abdominal hysterectomy with bilateral salpingo-oophorectomy, but even after radical surgery the recurrence rate is 5-10% (Pratibha, 2006). Treatment for endometriosis depends on symptoms and its severity, location of endometriotic lesions, goals for treatment and desire to conserve future fertility (Olive, 2001). The current treatments are medical, surgical or a combination of both.

2.4.1 Medical Treatment

2.4.1 (a) Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Endometriotic tissue has been shown to express cyclooxygenase-2 (COX-2) at greater levels than eutopic endometrium (Ota, 2001). Therefore, NSAIDs, are often first line

therapy, aimed at lowering the prostaglandin levels may play a role in alleviating endometriosis-associated pain.

2.4.1 (b) Combined Oral Contraceptives (COC)

The COC is usually drug of choice in women who do not wish to conceive. These drugs act by inhibiting gonadotropin release, decreasing menstrual flow, and decidualizing implants (Chapron, 2004). It can be used continuously in long term for controlling symptoms.

2.4.1 (c) Progesterone

Progesterone are known to antagonize estrogenic effects on the endometrium, causing initial decidualization and subsequent endometrial atrophy, produce a state of pseudopregnancy. It can be administered in multiple ways, such as oral progestins, depot medroxyprogesterone acetate (DMPA), a levonogestrel-releasing intrauterine device (MIRENA), and selective progesterone-receptor modulators (SPRM) (Chapron, 2004). The SPRM suppress estrogen-dependent endometrial growth and induce reversible amenorrhoea without the adverse side-effects of estrogen-deficiency (Pratibha, 2006).

2.4.1. (d) Danazol

Danazol is an isoxazol derivative of 17α-ethinyl testosterone, has both androgenic and anabolic properties. It suppress the hypothalamic-pituitary axis with an interference of the pulsatile gonadotrophin surge with no change in basal gonadotrophin levels (Robert.S, 2006). Danazol is highly effective in treatment of endometriosis, with symptomatic improvement in 55-93% of cases. But the recurrence rate is up to 40% within 36 months of completion of the danazol treatment (Pratibha, 2006).

2.4.1. (e) Gonadotrophin-releasing hormone agonists (GnRH agonists)

GnRH agonists induce pituitary gonadotrophin desensitization via the downregulation of the GnRH receptors, with an eventual state of hypogonadotrophic-hypogonadism-pseudomenopause (Pratibha, 2006). GnRH agonist therapy is limited due to possible loss of up to 6% of bone mineral density in the first 6 months and the loss may not always be entirely reversible (RCOG, 2006).

Add- back therapy (low-dose estrogen, low-dose progestin or tibolone) may be added to GnRH agonist therapy to counteract the bone loss (Carr, 1995). In a meta-analysis, bone mineral density was significantly higher in women taking add-back therapy with GnRH agonist compared with a GnRH alone, for 6 months duration. Besides, hypoestrogenic adverse effects were significantly less severe in women who received 'add-back' (RCOG, 2006).

2.4.2 Surgical Treatment

2.4.2 (a) Conservative surgery

The principles of surgical treatment of endometriosis include ablation, vaporization or excision of peritoneal implants, excision or ablation of endometriomas, excision of deep infiltrating nodular endometriosis and restoration of pelvic anatomy by adhesiolysis (Francesca,2010). It is reported at 5- year follow up, the disease recurred about 20% for surgery compared to about 50% for medical treatment, and 30% will not experience any improvement in symptoms after surgery (Saad.A, 2010).

Laparoscopic uterosacral nerve ablation (LUNA) can be performed during diagnostic laparoscopy. The results seem beneficial in reducing the dysmenorrhea but adequate randomized trials have not been performed.

2.4.2 (b) Radical surgery

Radical surgery is reserved for patients with severe symptoms and no desired potential for fertility, especially when other forms of treatment have failed (Robert, 2006). This includes total abdominal hysterectomy with or without bilateral oophorectomy along with resection of any endometriotic lesions as completely as possible. Pre-operative trial of GnRH agonist may be helpful and hormone replacement therapy may be commenced post-operatively in young patients (Francesca, 2010), but there is insufficient evidence of any effect on outcome measures such as pain relief to justify its usage (RCOG, 2006).

Endometriomas are often treated surgically, as ovarian masses often prompt surgical investigations. One randomized controlled trial has compared cystectomy with surgical drainage and bipolar coagulation of endometrioma's inner lining (Beretta, 1998). Cystectomy lead to lower rates of pelvic pain compared with drainage and coagulation (10% versus 53%), cumulative pregnancy rates were also higher following cystectomy during 24-month surveillance (67% versus 24%).

In some patients, transection of presacral nerves lying within interiliac triangle may provide relief of chronic pelvic pain. Presacral neurectomy may be performed laparoscopically, but it is technically challenging, thus it is used in a limited manner and not recommended routinely for management of endometriosis (Chapron, 2004).

2.4.3 Treatment of Endometriosis-related Infertility

30-40% of women with endometriosis suffer from infertility. Medical treatment of endometriosis does not improve fertility. In minimal-mild cases, ablation of endometriotic lesions plus adhesiolysis can improve fertility, compared with diagnostic laparoscopy alone (RCOG, 2006). The role of surgery in improving pregnancy rates for

moderate-severe disease is uncertain. Post-operative hormonal treatment has no beneficial effect on pregnancy rates after surgery (RCOG, 2006). Alternatively, patients with endometriosis and infertility are candidates for fertility treatments such as controlled ovarian hyperstimulation, intrauterine insemination, and in vitro fertilization (Chapron, 2004).

3.0 HYPOTHESIS AND OBJECTIVES

3.1 RESEARCH HYPOTHESIS

The new CliEndomet could be used to diagnose endometriosis.

3.2 OBJECTIVE

3.2.1 General objective :

- To create a scoring system, i.e. CliEndomet as a reliable tool to suggest endometriosis

3.2.2 Specific objectives :

- To determine the correlation between the clinical manifestation (including medical history, physical examination and ultrasonographic features) and biochemical marker (Ca125) with the diagnosis of endometriosis.

- To identify the prognostic factors among the clinical manifestation, and biochemical marker towards the diagnosis of endometriosis.

- To formulate a scoring system which highly suggestive of endometriosis.

4.0 METHODOLOGY

4.1 STUDY DESIGN, SETTING AND DURATION

This was a cross sectional study with a goal to develop a clinical criteria tool " CliEndomet". This study was conducted in Hospital Raja Perempuan Zainab II, Kota Bharu and Hospital Universiti Sains Malaysia (HUSM) for 18 months duration, from 1st November 2011 until 31st April 2013. This study consisted of 176 patients who presented with pelvic pain.

4.2 REFERENCE POPULATION

Patient with pelvic pain (dysmenorrhea, dyspareunia, ovulation pain, dyschezia and any chronic non-specific pelvic pain) in Kelantan.

4.3 SOURCE POPULATION AND SAMPLING FRAME

Patient with pelvic pain (dysmenorrhea, dyspareunia, ovulation pain, dyschezia and any chronic non-specific pelvic pain), presented at gynaecology clinic, Hospital Raja Perempuan Zainab II and Hospital Universiti Sains Malaysia, Kelantan.

4.4 SAMPLE SIZE CALCULATION

The sample size was calculated using the two proportion formula as below:

$$n = \frac{p1(1 - p1) + p0(1 - p0) \times (z\alpha + z\beta)^2}{(p1 - p0)^2}$$

P0 = estimated proportion of endometriosis in women without chronic pelvic pain 35.0% (Chapron et.al., 2005 : Endometriosis is detected in 2-50% of women with no symptoms)

P1 = estimated proportion of endometriosis in women with chronic pelvic pain 62% (Robert Z. et.al., 2003 : Endometriosis is diagnosed among women with pelvic pain with prevalence ranging from 15-70%)

Zα and Zβ = study reference (in Pocock's table)

n = 66 + 13 (20% drop out) for each group

A minimum of 158 patients are required to be recruited. However, in this study 176 patients were recruited.

4.5 INCLUSION AND EXCLUSION CRITERIAS

Patients with the below criteria were included into the study :

a. Age between 18 to 45 years old
b. Regular menstrual cycle
c. Have at least one of the symptoms suggestive of endometriosis:
    i. Dysmenorrhoea
    ii. Deep dyspareunia
    iii. Ovulation pain
    iv. Pelvic pain
    v. Dyschezia

However, those with any of the below criteria were excluded:

a) Patients with known case of endometriosis prior to recruitment.
b) Patients who had pelvic pain which were already confirmed to be caused by other disorders such as pelvic inflammatory disease, varices or genital malformation
c) Patients with psychiatric problems

4.6 ETHICS AND CONSENT

This study was approved by the Medical Research and Ethics Committee of Ministry of Health and Human Medical Research and Ethics Committee of USM. Written consents were obtained from patients after they fulfilled the inclusion and exclusion criteria.

4.7 SAMPLING METHOD

All patients who came to seek treatment at Gynaecology clinic of Hospital Raja Perempuan Zainab II and Hospital Universiti Sains Malaysia, fulfilling the inclusion and exclusion criteria were recruited into the study.

4.8 STUDY METHOD

Each patient was evaluated for the pain intensity, menstrual pattern, parity and subfertility. The dysmenorrhea and non-menstrual pain (including pelvic pain and ovulation pain) were evaluated using a modified version of Andersch and Milsom's multidimensional verbal rating scale (Konincky PR, 1996), which defines pain according to the limitation of ability to work (unaffected = 0, rarely affected = 1, moderately affected=2, clearly affected =3), co-existing of systemic symptoms (absent=0, present=1), the systemic symptoms including nausea, vomiting, fatigue/weariness, intestinal complaints such as periodic bloating, diarrhea/constipation, referred pain to back or legs (ESHRE, 2013), and the need for analgesia (no=0, yes=1) and rank the total sum in three groups (1-2=mild, 3-4=moderate, 5=severe). The severity of deep dyspareunia and dyschezia was evaluated using a 10-point linear analogue scale, in which scoring 0 indicates no pain and scoring 10 indicates unbearable pain.

On physical examination, which was performed by a trained gynaecologist, body mass index (BMI) of each patient was calculated. It was followed by abdominal examination to look for any abdominal mass. If any abdominal mass was noted, further details of

the mass were evaluated (size, site, margin, surface, consistency, mobility and tenderness). For patients who have had sexual exposure, pelvic examination was done, to look for size, position and mobility of uterus, presence of vaginal nodule including size, site and tenderness, any adnexal mass or thickening and tenderness of uterosacral ligaments, any obliteration of Pouch of Douglas (POD). All the information was documented in the research forms and was entered into a computerized database.

An ultrasound scanning of the pelvis (either trans-abdominal or trans-vaginal) was performed to all patients. It was done by a same examiner who was blinded to patient's clinical data. The ultrasound machine which was used in this study was CAPASEE II (Toshiba Otawara, Japan) connected to a 3.75MHz transducer. Findings regarding the uterus size, endometrial thickness, flexion and presence of any abnormality were documented. If there was any ovarian or adnexal mass present, the details including the size, site, locule, presence of septum or papillary projection, the nature and content of the mass were recorded.

As suggested by Koninckx et al (1996), blood sample for Ca-125 was collected via venepuncture technique, it was performed during the late luteal phase or during menstruating as the test is more reliable when it is done during this time than in follicular phase. 2mls of blood was taken and was transported to Immunology Lab of HRPZ II or HUSM respectively in plain container for analysis.

The concentration of Ca-125 in serum samples were determined by means of a one-step-sandwich radioimmunoassay (Fujirebio America Inc.). 100µL of undiluted serum samples were incubated overnight in duplicate with polystyrene beads coated with anti-CA 125 mAbs (capture antibody). Unbound molecules in the serum was removed by washing the beads. The bound radioactivity was proportional to the Ca-125

concentration in serum samples. Serum Ca-125 was expressed in u/mL serum and was calculated by comparison to a standard curve that ranges from 0 to 500U/mL. The sensitivity of this method was established at 0.4U/mL. Interassay and intra-assay variations were less than 5% (Daniele Gagne et al, 2003). This Ca-125 level was unknown to the surgeon performing the operation later, and the decision to perform operation (either laparoscopy or laparotomy) did not depend on the serum Ca-125 concentration.

A laparoscopy or laparotomy operation was performed on each patient to confirm the presence or absence of endometriosis. The diagnosis of endometriosis required the presence of typical bluish or blackish lesions, with or without tissue biopsy was taken for histopathology examination. The staging of endometriosis was determined according to the revised classification of the American Society for Reproductive Medicine (R-ASRM).

The clinical criteria which were strongly associated with the diagnosis of endometriosis from this study subjects were extracted from statistical model, and were transformed for development of the clinical criteria scoring system, the Cli-Endomet.

4.9 STATISTICAL ANALYSIS

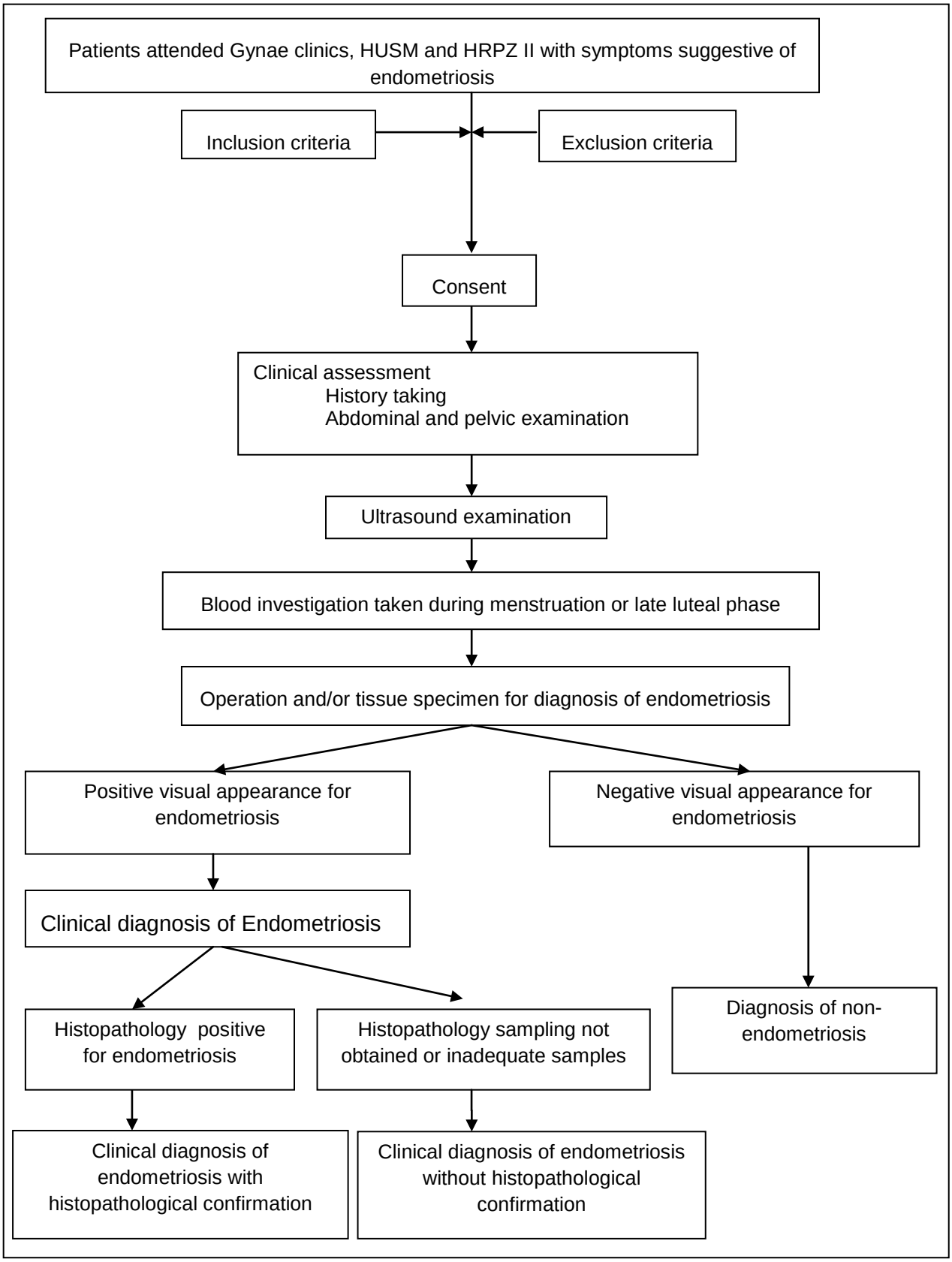
All the data collected were entered, cleaned and analyzed using SPSS version 19.0. The mean and standard deviations for numerical variables and frequency and proportion for categorical variables were reported along with histogram or bar chart. For univariable analysis the simple logistic regression was used.

For multivariable analysis, multiple logistic regression was used for analysis to adjust for confounding variables, to look for association between the clinical manifestation,

biochemical marker (Ca 125), surgical staging and histopathology results. Level of significance was set at 5% and results were presented with 95% confidence intervals.

Area under curve (AUR) was used to determine the sensitivity and specificity of each variable in production of criteria for Cli-Endomet . Generalized likelihood ratio test statistics were used and P value of < 0.05 was considered to indicate statistical significance

4.10 FLOW CHART OF STUDY



5.0 RESULTS

A total of 176 patients were recruited into the study, out of which 103 patients (58.5 %) were diagnosed to have endometriosis during operation (Figure 1). Out of these 103 patients who were noted to have endometriosis intraoperatively, 92 patients (89.3%) were confirmed to have endometriosis with tissue diagnosis.

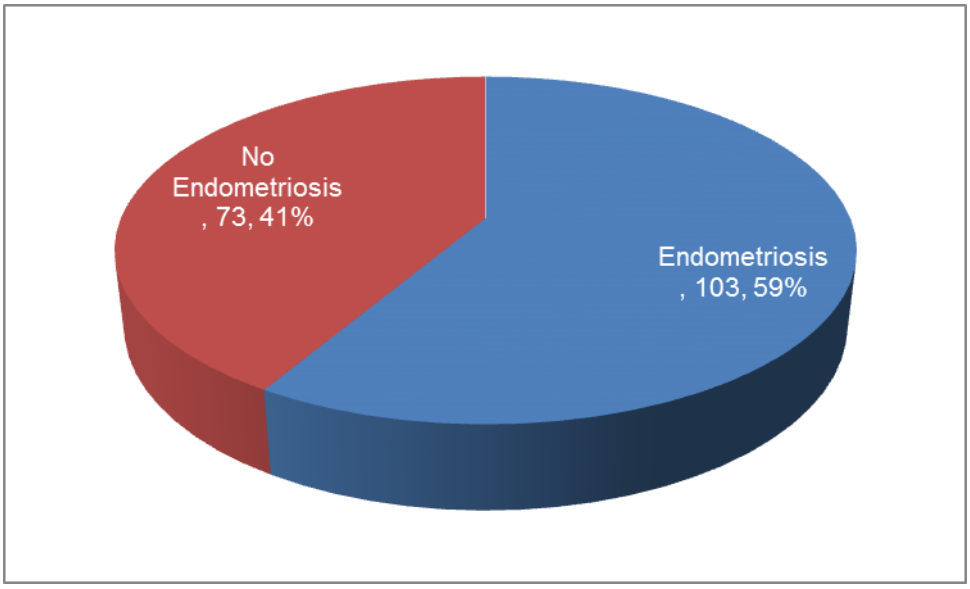


Figure 1: Distribution of endometriosis diagnosis among the participants

5.1 Demographic data

5.1.1 Age

The age of the patients recruited ranges from 23 to 43 years old. The mean age was 35.41± 6.90 years.

5.1.2 Parity

Endometriosis is one of the causes for infertility. Therefore, the parity of the subjects was looked into. All subjects are married. 66 (37.5%) of them remained nulliparous. 39 subjects (22.2%) have one or two children (Para 1 or Para 2), while the rest (n=71, 40.3%) have more than 2 children, as shown in Table 1.

Among the 66 subjects who were nulliparous, 48 (27.3%) of them were confirmed to have endometriosis. 22 subjects (12.5%) in the Para 1 and 2 and 33 (18.8%) of the more than Para 2 were confirmed to have endometriosis (Figure 2).

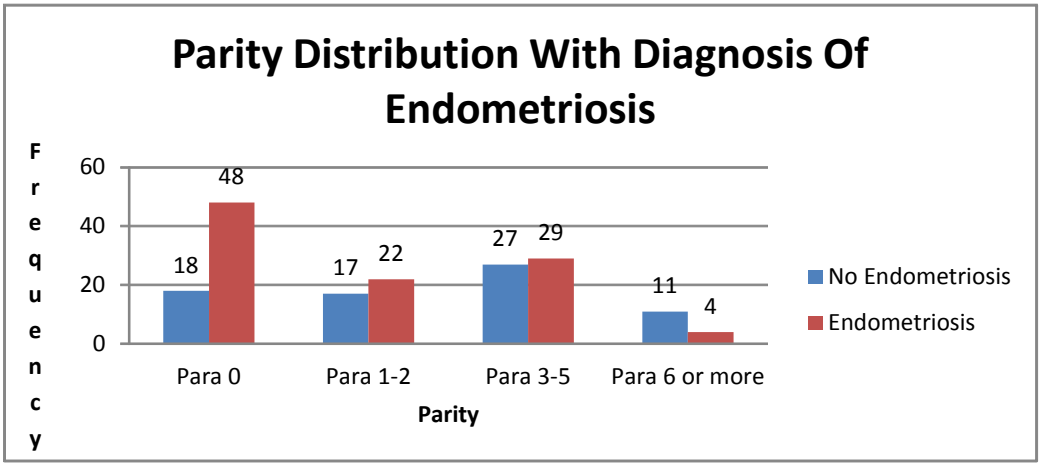


Figure 2: Parity distribution with endometriosis

5.1.3 Body mass index

There is a wide range of body mass index (BMI) of the subjects in this study. Their BMI ranges from less than 18kg/m^2 to more than 40kg/m^2. Majority of them have normal and overweight BMI. The distribution of the subjects' BMI is as shown in Figure 3.

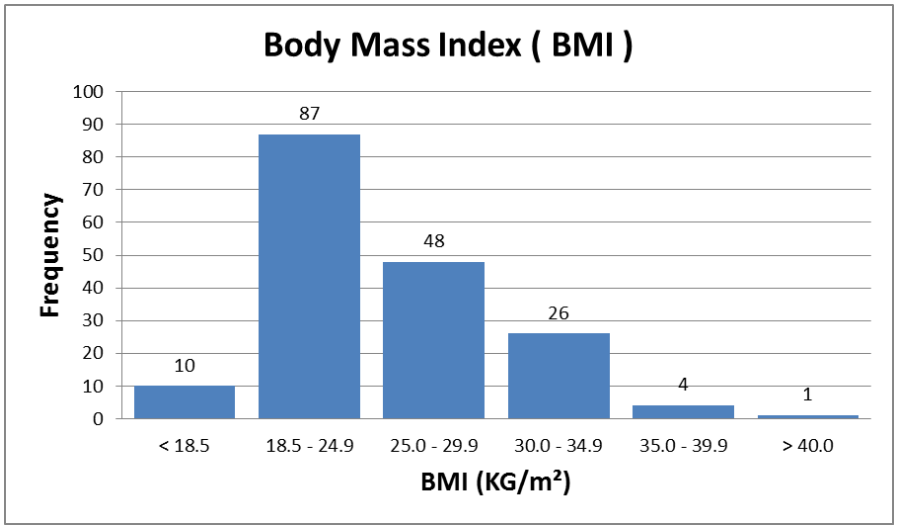


Figure 3: Distribution of the BMI of the subjects

The mean BMI of the subjects was 25.10±4.79kg/m^2, which was overweight.

Table 1: Demographic data of subjects

Variables	Frequency (n)	Percentage (%)	Mean	Standard deviation (SD)	P value
Age (years)			35.41	6.90	
Parity:					
▪ **Nulliparous**	66	37.5			
▪ **Para 1-2**	39	22.2			
▪ **Para 3-5**	56	31.8			
▪ **Para 6 and above**	15	8.5			
BMI (kg/m^2):			25.10	4.79	
▪ **≤ 18.5**	10	5.7			
▪ **18.5- 24.9**	87	49.4			
▪ **25.0- 29.9**	48	27.3			
▪ **30.0- 34.9**	26	14.7			
▪ **35.0- 39.9**	4	2.3			
▪ **≥ 40.0**	1	0.6			
Mean BMI (kg/m^2):					
▪ **With endometriosis**			24.96	4.82	
▪ **No endometriosis**			25.19	4.78	
History of sub-fertility:					
▪ **Present**	106	60.2			
• **With endometriosis**	63	59.4			
• **Without endometriosis**	43	40.6			
▪ **Absent**	70	39.8			
• **With endometriosis**	40	57.1			
• **Without endometriosis**	30	42.9			
Duration of sub-fertility (years, n= 106):			4.12	5.41	
▪ **2-4**	32	30.2			
▪ **5-7**	23	21.7			
▪ **≥ 8**	51	48.1			

Mean duration of subfertility (years):		
▪ **With endometriosis**	4.69	5.62
▪ **Without endometriosis**	3.38	5.05

5.1.4 History of subfertility

As stated above, endometriosis is one of the causes for infertility. Therefore, this parameter is looked into in this study. Only those with involuntary subfertility are considered as being sub-fertile in this study.

Among the 176 subjects, 106 subjects (60.2%) have history of subfertility (Table 1). The mean duration of subfertility was 4.12 ± 5.41 years.

Out of those with history of subfertility, 63 subjects (59.4%) were confirmed to have endometriosis, while the rest (n=43, 40.6%) did not have endometriosis. The mean duration of subfertility for those with endometriosis was 4.69 ± 5.62 years as compared to 3.38 ± 5.05 years in those without endometriosis. Seventy subjects (39.8%) have no history of sub-fertility. Forty of them (57.1%) were confirmed to have endometriosis and another 30 did not have one (Table 1).

When comparing the frequency of those subjects who were diagnosed to have endometriosis (n = 103, 100%), 63 subjects (61.2%) had history of subfertility, and 40 subjects (38.8%) did not have subfertility, which was statistically significant (p value < 0.05).

5.2 Clinical features

5.2.1 Clinical manifestation

As shown in Table 2, 169 (96.0%) subjects presented with dysmenorrhea, while 7 of them (4.0%) did not have such symptom. The distribution of the severity of dysmenorrhoea was noted to be equal among all the 169 subjects. 60 subjects (35.5%) experienced mild dysmenorrhoea, 73 (43.2%) moderate and the rest (n=36, 21.3%) have severe dysmenorrhoea, which caused them to take work leave and regular analgesia.

Only 26 subjects (14.8%) of these subjects experienced deep dyspareunia, 3 subjects (1.7%) were certain they have ovulation pain and 4 subjects (2.2%) experienced dyschezia.

The relationship of each clinical presentation (together with the demographic data) with the presence of endometriosis was looked into.

Among the 169 subjects who had dysmenorrhoea, 100 subjects (56.8%) were noted to have endometriosis. Even though its presence indicated a high possibility to be caused by endometriosis, it was not shown to be statistically significant (crude OR 2.90 95% CI 0.52-16.27; p value 0.227). However, when comparing the severity of dysmenorrhoea experienced by the subjects, the presence of severe dysmenorrhea was significantly associated with the presence of endometriosis (crude OR 14.67, 95% CI 2.18-98.78, p value 0.006).

Table 2: The frequency and distribution of clinical features

Variables	Frequency (N)	Percentage (%)
Dysmenorrhoea (n=176)		
▪ **Present**	169	96.0
▪ **Absent**	7	4.0
Severity of dysmenorrhoea (n=169)		
▪ **Mild**	60	35.5
▪ **Moderate**	73	43.2
▪ **Severe**	36	21.3
Deep dyspareunia (n=176)		
▪ **Present**	26	14.8
▪ **Absent**	150	85.2
Ovulation pain (n=176)		
▪ **Present**	3	1.7
▪ **Absent**	173	98.3
Dyschezia (n=176)		
▪ **Present**	4	2.3
▪ **Absent**	172	97.7

On the other hand, 19 out of the 26 subjects (73.1%) who experienced deep dyspareunia were found to have endometriosis. Similarly, the presence of deep

dyspareunia was associated with the presence of endometriosis but not statistically significant (crude OR 1.61, 95% CI 0.68-3.79, p value 0.277).

Two of the three subjects (66.7%) who were certain to have ovulation pain and two subjects with dyschezia (50.0%) were diagnosed to have endometriosis. The same analysis on those clinical presentations and their association with endometriosis was found.

5.2.2 Physical Examination findings

Out of the 176 subjects, 97 subjects (55.1%) were found to have abdominal mass during abdominal examination. 91 subjects (93.8%) in whom the abdominal masses were noted had regular and well defined margin, while the rest (n=6, 6.2%) had irregular margin. In consistence with that, 94 masses (96.9%) had smooth surface. 87 masses (89.7%) were found to have cystic consistency while the rest (n=10, 10.3%) were firm in consistency. None of the masses was hard in consistency. The mobility of the masses was rather equally distributed. 49 masses (50.4%) were found to be mobile and 45 masses (46.4%) had restricted mobility. Three masses (3.2%) were found to be fixed. Most of these masses were non-tender (n=92, 94.8%).

Only five subjects (2.8%) were found to have bluish vaginal nodule, which represent the endometriotic nodule.

Majority of the subjects (n=160, 90.9%) had anteverted uterus. The uteruses of most of the subjects regardless of their position were found to be mobile (n=111, 63.1%). Only 65 subjects had either restricted mobility or fixed uterus (n= 65, 36.9%).

In consistent with the small percentage of the presence of deep dyspareunia in the subjects, 27 subjects (15.3%) were found to have thickened uterosacral ligaments. However, only eight of them had tender uterosacral ligaments.

48 subjects (27.3%) were noted to have obliterated POD. Table 4 shows the summary of the distribution of the clinical findings.

Table 3: Clinical presentation in relation with endometriosis

Variable	b	Crude OR (95% CI)	Wald statistic (df)	p value
Age (year)	-0.03	0.97 (0.93, 1.02)	1.49 (1)	0.222‡
Parity	-0.23	0.80 (0.69, 0.92)	10.14 (1)	0.001†
BMI	-0.01	0.99 (0.93,1.05)	0.09 (1)	0.752
History of subfertility	0.79	2.20 (1.19,4.06)	6.41(1)	0.011‡
Duration of subfertility (years)	0.05	1.05 (0.99, 1.11)	2.59 (1)	0.108‡
Dysmenorrhoea				
▪ **Absent**			1.00	
▪ **Present**	1.06	2.90 (0.52, 16.27)	1.46 (2)	0.227‡
Severity of dysmenorrhoea				
▪ **No pain**			1.00	
▪ **Mild**	-0.90	0.91 (0.91,4.46)	0.01 (1)	0.912
▪ **Moderate**	0.62	1.85 (0.39,8.86)	0.59 (1)	0.492
▪ **Severe**	2.68	14.67 (2.18,98.78)	7,62 (1)	0.006†
Deep Dyspareunia				
▪ **Absent**			1.00	
▪ **Present**	0.48	1.61 (0.68,3.79)	1.18 (1)	0.277
Deep Dyspareunia pain score	0.28	1.33 (1.00, 1.76)	3.87 (1)	0.049†
Ovulation pain				
▪ **Absent**			1.00	
▪ **Present**	0.77	2.16 (0.22, 21.19)	0.44 (1)	0.509
Dyschezia				
▪ **Absent**			1.00	
▪ **Present**	-0.35	0.70 (0.09,5.11)	0.12 (1)	0.728
Pelvic pain				
▪ **Absent**			1.00	
▪ **Present**	0.23	1.26 (0.65,2.43)	0.48 (1)	0.490

Table 4: Distribution of physical examination findings

Variables	Endometriosis N (percentage)	No Endometriosis N (percentage)	Total N (percentage)
Abdominal mass (n = 176)			
• **Present**	55 (31.2%)	42 (23.9%)	97 (55.1%)
• **Absent**	48 (27.3%)	31 (17.6%)	79 (44.9%)
Margin of the mass (n = 97)			
• **Regular**	50 (51.6%)	41 (42.2%)	91 (93.8%)
• **Irregular**	5 (5.2%)	1 (1.0%)	6 (6.2%)
Surface of the mass (n = 97)			
• **Smooth**	55 (56.7%)	39 (40.2%)	94 (96.9%)
• **Irregular**	0 (0.0%)	3 (3.1%)	3 (3.1%)
Consistency of the mass (n =97)			
• **Cystic**	53 (54.6%)	34 (35.1%)	87 (89.7%)
• **Firm**	2 (2.1%)	8 (8.2%)	10 (10.3%)
• **Hard**	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mobility of the mass (n = 97)			
• **Mobile**	23 (23.6%)	26 (26.8%)	49 (50.4%)
• **Restricted mobility**	30 (30.9%)	15 (15.5%)	45 (46.4%)
• **Fixed**	2 (2.1%)	1 (1.1%)	3 (3.2%)
Mass tenderness (n = 97)			
• **Tender**	2 (2.1%)	3 (3.1%)	5 (5.2%)
• **Non – tender**	53 (54.6%)	39 (40.2%)	92 (94.8%)

Presence of vaginal nodule (n = 176)			
• **Present**	3 (1.7%)	2 (1.1%)	5 (2.8%)
• **Absent**	100 (56.8%)	71 (40.4%)	171 (97.2%)
Position of uterus (n = 176)			
• **Anteverted**	90 (51.1%)	70 (39.8%)	160 (90.9%)
• **Retroverted**	13 (7.4%)	3 (1.7%)	16 (9.1%)
Uterine Mobility (n = 176)			
• **Mobile**	40 (63.1%)	71 (40.3%)	111 (63.1%)
• **Restricted mobility**	52 (29.5%)	1 (0.6%)	53 (30.1%)
• **Fixed**	11 (6.2%)	1 (0.6%)	12 (6.8%)
Uterosacral ligament (n = 176)			
• **Normal**	77 (43.8%)	72 (40.9%)	149 (84.7%)
• **Thickened**	26 (14.8%)	1 (0.5%)	27 (15.3%)
Uterosacral ligament Tenderness (n = 176)			
• **Tender**	8 (4.5%)	0 (0.0%)	8 (4.5%)
• **Non-tender**	95 (54.0%)	73 (41.5%)	168 (95.5%)
Pouch of Douglas (POD) (n = 176)			
• **Normal**	65 (36.9%)	63 (35.8)	128 (72.7%)
• **Obliterated**	38 (21.6%)	10 (5.7%)	48 (27.3%)

Upon comparing the physical examination findings with the presence of endometriosis, 55 subjects (31.2%) who were found to have abdominal masses were confirmed to have endometriosis. Among these 55 subjects (n=55, 100%), most of the abdominal masses were found to have regular and well defined margins (n=50, 90.9%), smooth surface (n=55, 100%) and cystic in nature (n=53, 96.4%). However, there was no specific characteristic in the mobility of the masses which was associated with endometriosis (Table 4).

The association of the physical examination findings and the diagnosis of endometriosis were looked into (Table 5). Despite more than 50% of the patients were found to have abdominal masses, its presence could not predict the diagnosis of endometriosis, with crude ratio of 0.81 (95% CI 0.45-1.49) and p value of 0.503. The rest of the characteristic of the abdominal mass could not specifically associated with the diagnosis of endometriosis (Table 5).

The presence of endometriotic vaginal nodule made the diagnosis of endometriosis more likely (crude ratio 1.07, 95% CI 0.17-6.54). However, it was not statistically significant (p value 0.946). The presence of retroverted uterus, with restricted mobility and obliterated POD were found to be significantly associated with the diagnosis of endometriosis (crude ratio 3.37 (95% CI 0.92-12.29), p value 0.066; crude ratio 7.17 (95% CI 2.07-24.86), p value 0.002; crude ratio 3.68 (95%CI 1.69-8.02), p value 0.001 respectively) (Table 5).

Table 5: The correlation of physical examination findings with the diagnosis of endometriosis

Variable	b	Crude OR (95% CI)	Wald statistic (df)	p value
Abdominal mass				
Absent			1.00	
Present	-0.21	0.81 (0.45,1.49)	0.49 (1)	0.503
Margin of abdominal mass				
▪ **No cyst**		1.00	1.97 (2)	0.373
▪ **Regular**	-0.24	0.79 (0.43,1.45)	0.58 (1)	0.444
▪ **Irregular**	1.17	3.23 (0.36,28.97)	1.09 (1)	0.295
Surface of abdominal mass				
▪ **No cyst**		1.00	0.09 (2)	0.950
▪ **Smooth**	-0.09	0.91(0.49,1.67)	0.09 (2)	0.760
▪ **Irregular**	-21.64	0.00 (0.00)	0.00 (1)	0.999
Consistency of abdominal mass				
▪ **No cyst**		1.00	0.81 (3)	0.846
▪ **Cystic**	-0.31	0.73 (0.35, 1.52)	0.69 (1)	0.406
▪ **Firm**	-0.05	0.95 (0.45, 1.99)	0.02 (1)	0.895
▪ **Hard**	0.26	1.29 (0.11, 14.86)	0.04 (1)	0.837
Mobility of abdominal mass				
▪ **No cyst**		1.00	4.12 (3)	0.249‡
▪ **Mobile**	-0.56	0.57 (0.28, 1.17)	2.32 (1)	0.128‡
▪ **Restricted**	0.25	1.29 (0.60, 2.78)	0.43 (1)	0.513
▪ **Fixed**	0.25	1.29 (0.11, 14.86)	0.04 (1)	0.837
Tenderness of abdominal mass				
▪ **No cyst**		1.00	0.87 (2)	0.648
▪ **Tender**	-0.84	0.43 (0.07, 2.73)	0.80 (1)	0.371
▪ **Non-tender**	-0.13	0.88 (0.47, 1.62)	0.17 (1)	0.676
Vaginal nodule				
▪ **Absent**			1.00	
▪ **Present**	0.06	1.07 (0.17, 6.54)	0.01 (1)	0.946
Uterine position				
▪ **Anteverted**			1.00	
▪ **Retroverted**	1.22	3.37 (0.92, 12.29)	3.39 (1)	0.066‡

Uterus mobility				
▪ **Mobile**		1.00	9.77 (2)	0.008†
▪ **Restricted**	1.97	7.17 (2.07,24.86)	9.64 (1)	0.002†
▪ **Fixed**	0.58	19.53 (2.43,156.83)	0.22 (1)	0.637
Adnexae mass				
▪ **Absent**			1.00	
▪ **Present**	0.59	1.81 (0.80,4.08)	2.05 (1)	0.152‡
Uterus Ligaments				
▪ **Thickened**			1.00	
▪ **Not thickened**	-3.19	0.04 (0.01,0.31)	9.56 (1)	0.002†
POD				
▪ **Normal**			1.00	
▪ **Obliterate**	1.30	3.68 (1.69,8.02)	10.78 (1)	0.001†

5.2.3 Ultrasound findings

Table 6 shows the ultrasound findings of the subjects in this study. Although from physical examination we found only 97 subjects with abdominal masses, a total of 158 subjects (89.8%) were found to have pelvic masses detected from the ultrasound. 99 of them (n=99, 100%) are diagnosed to have endometriosis, in which 42 subjects (42.4%) had uniloculated mass and the rest were multiloculated (n=57, 57.6%). Majority of the multiloculated pelvic masses in patients with endometriosis were thin septum (n=54, 94.7%). More than 95% of the pelvic masses found, did not have any papillary projection. In consistent with the examination finding, majority of the masses were cystic in nature (n=156, 98.7%). Majority of the subjects, who had endometriosis with presence of ovarian mass on ultrasound scan, noted to have thick sedimentation or ground glass appearance of the content of the mass (n=98, 98.9%)

When correlating the ultrasound findings with the diagnosis of endometriosis, cystic pelvic masses with thin septae but without papillary projections and with thick sedimentation or ground glass appearance were more common to be diagnosed to have endometriosis (Table 6).

Table 6: Ultrasound findings in relation to the diagnosis of endometriosis

Variables	Endometriosis N (percentage)	No Endometriosis N (percentage)	Total N (percentage)
Presence of ovarian mass (n = 176)			
• **Present**	99 (56.2%)	59 (33.5%)	158 (89.8%)
• **Absent**	4 (2.3%)	14 (8.0%)	18 (10.2%)
Locule of the mass (n = 158)			
• **Uniloculated**	42 (26.6%)	33 (20.9%)	75 (47.5%)
• **Multiloculated**	57 (36.0%)	26 (16.5%)	83 (52.5%)
Feature of the septum of the cysts (n = 83)			
• **Thin**	54 (65.0%)	22 (26.6%)	76 (91.6%)
• **Thick**	3 (3.6%)	4 (4.8%)	7 (8.4%)
Papillary projection (n = 158)			
• **Present**	0 (0.0%)	2 (1.3%)	2 (1.3%)
• **Absent**	99 (62.7%)	57 (36.0%)	156 (98.7%)
Nature of the mass (n =158)			
• **Cystic**	99 (62.7%)	57 (36.0%)	156 (98.7%)
• **Solid**	0 (0.0%)	2 (1.3%)	2 (1.3%)
Content of the ovarian cyst (n = 158)			
• **Clear**	1 (0.6%)	50 (31.7%)	51 (32.3%)
• **Thick with sediments /Ground-glass appearance**	98 (62.0%)	9 (5.7%)	107 (67.7%)

Subjects with ovarian mass found in ultrasonographic study had 5.87 risks of having endometriosis (Table 7). A multiloculated mass carried a higher risk as compared to uniloculated mass (crude ratio 7.67, 95% CI 2.30- 25.58, p value 0.001 and crude ratio 4.46, 95% CI 1.34- 14.06, p value 0.015 respectively). Similarly, a cystic mass with thick sedimentation or ground glass appearance made the diagnosis of endometriosis stronger (Table 7).

Table 7: The correlation between the ultrasound findings and Ca125 with the diagnosis of endometriosis

Variable	b	Crude OR (95% CI)	Wald statistic (df)	p value
Scan Ovarian Mass				
▪ **Absent**			1.00	
▪ **Present**	1.77	5.87 (1.85,18.68)	8.99 (1)	0.003†
Locule of ovarian mass				
▪ **No cyst**		1.00	11.57 (2)	0.003†
▪ **Uniloculated**	1.49	4.46 (1.34,14.06)	5.94 (1)	0.015†
▪ **Multiloculated**	2.04	7.67 (2.30,25.58)	11.00 (1)	0.001†
Septum of ovarian mass				
▪ **No cyst**		1.00	13.59 (3)	0.004†
▪ **Uniloculated**	1.41	4.08 (1.22,13.64)	5.94 (1)	0.015†
▪ **Multiloculated-thin**	2.13	8.45 (2.46,29.01)	12.00 (1)	0.001†
▪ **Multiloculated-thick**	0.97	2.63 *0.41,16.94)	1.03 (1)	0.310
Papillary projection				
▪ **No cyst**		1.00	9.33 (2)	0.009†
▪ **Absent**	1.81	6.08 (1.91,19.35)	9.33 (2)	0.002†
▪ **Present**	-19.95	0.00 (0.00)	0.00 (1)	0.999
Nature of mass by scan				
▪ **No cyst**		1.00	9.33 (2)	0.009†
▪ **Cystic**	1.81	6.08 (1.91,19.35)	9.33 (1)	0.002†
▪ **Solid**	-19.95	0.00 (0.00)	0.00 (1)	0.999
Content of ovarian mass				
▪ **No cyst**		1.00	55.31 (2)	<0.001†
▪ **Clear**	-2.65	0.07 (0.01,0.68)	5.27 (1)	0.022‡
▪ **Thick with sediments**	3.64	38.11(10.34,140.42)	29.93 (1)	<0.001†
Ca125	0.04	1.04 (1.03, 1.05)	37.24 (1)	<0.001†

5.3 Serum Ca125

The ROC (Receiver Operating Characteristic) curve was plotted to analyse the association in between the serum Ca 125 values with the diagnosis of endometriosis (Figure 4). The area under curve of the ROC curve was 0.8989 in correlation with the diagnosis of endometriosis, suggesting it as a good diagnostic tool for endometriosis. It was also noted that the value of serum Ca125 of ≥ 50u/ml had 80% sensitivity and 86% specificity to detect endometriosis. Further increment in the level was shown to be further increased the likelihood of endometriosis. However, levels of more than 200u/ml was shown to carry low sensitivity (7.7%) but high specificity (98.6%), which is not

suitable to be used for detection of endometriosis. Therefore, the cut off points of 50u/ml and 200u/ml was used for further analysis of association.

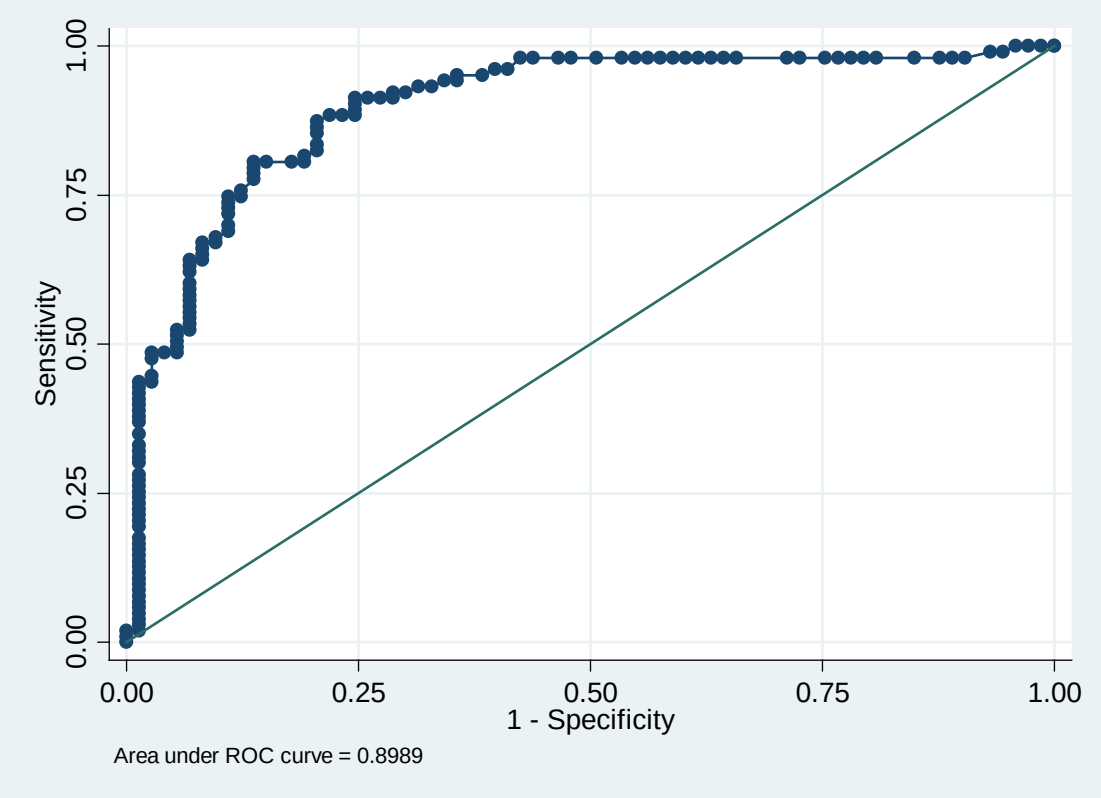


Figure 4: The association between the levels of serum Ca125 and the diagnosis of endometriosis

Using this cut off points, a correlation was made with the findings of endometriosis intraoperatively. As seen in Table 8, only 28 subjects (15.9%) were confirmed to have endometriosis with the serum level of <50u/ml or >200u/ml. In contrast, 75 subjects (42.6%) had endometriosis with the serum Ca125 levels was between 50 to 200u/ml. When a simple logistic regression test was performed, this level (50-200u/ml) was strongly associated with the presence of endometriosis (crude OR 19.05; 95% CI 8.38-43.32; p value <0.001) (Table 9).

Table 8: Serum Ca125 levels in relation with endometriosis

Serum Ca125 (u/ml)	Endometriosis N (%)	No Endometriosis N (%)	Total
< 50	12 (6.8 %)	53 (30.1%)	65 (36.9%)
50 - 200	75 (42.6%)	9 (5.1%)	84 (47.7%)
>200	16 (9.1%)	11 (6.3%)	27 (15.3%)
Total	103 (58.5%)	73 (41.5%)	176 (100%)

Table 9: Simple logistic regression test to associate the levels of serum Ca125 with endometriosis

Serum Ca 125 (u/ml)	b	Crude OR (95% CI)	Wald	p Value
< 50 or > 200			1.00	
50 - 200	2.95	19.05 (8.38, 43.32)	49.40	< 0.001

5.4 Correlation of clinical features, ultrasound findings and serum Ca125 with the diagnosis of endometriosis

From the previous simple logistic regression test performed on various clinical features and ultrasound findings, it was noted that the below features were found to be significantly associated with the presence of endometriosis:

1. Presence of subfertility
2. Dysmenorrhoea according to its severity
3. Dyspareunia according to its severity
4. Restricted mobility of the uterus
5. Obliterated POD

6. The presence of multiloculated, cystic ovarian mass with thick sedimentation in ultrasonographic study
7. Serum Ca125

To evaluate the combination of these features with the diagnosis of endometriosis, a multiple logistic regression test was performed (Table 10). It was noted that the presence of dysmenorrhoea, regardless of it severity, the presence of ovarian mass with thick sedimentation and the level of serum Ca125 between 50 to 200u/ml were significantly correlate with the diagnosis of endometriosis.

5.5 Staging of endometriosis

The staging of endometriosis was performed during the operation, based on the revised ASRM classification. It was found that out of the 103 subjects who were diagnosed to have endometriosis, 4 subjects (3.9%) had stage I endometriosis, 12 subjects (11.7%) were in stage II, 43 subjects (41.7%) and 44 subjects (42.7%) were in stage III and stage IV respectively (Table 11).

Table 10: The association between the significant variables with endometriosis

Variable	b	Adjusted OR (95% CI)	LR statistic (df)	p value
Ca125	0.03	1.03 (1.02, 1.05)	22.44 (1)	<0.001
Dysmenorrhoea Severity				
No pain		1.00	14.27 (3)	0.003
Mild	0.30	1.35 (0.13, 13.64)	0.06 (1)	0.800
Moderate	2.78	16.04 (4.41, 58.34)	1.34 (1)	0.248
Severe	3.33	27.89 (1.89, 411.95)	5.87 (1)	0.015
Content of ovarian mass				
No cyst			55.31 (2)	<0.001
Clear	-2.66	0.07 (0.007,0.678)	5.27 (1)	0.022
Thick with sediments	3.64	38.11 (10.34,140.42)	29.93 (1)	<0.001
Uterus Position				
Anteverted			1.00	
Retroverted	18.53	111693393 (0.00)	3688.70 (1)	0.996
Uterine Mobility				
Mobile			1.00	
Restricted mobility	19.15	20668373.30 (0.00)	0.00 (1)	0.996
Fixed	35.84	3.66 (0.00)	0.00 (1)	0.995
Pouch of Douglas				
Normal			1.00	
Obliterated	0.463	1.59 (0.25,10.07)	0.242 (1)	0.623
Locule of ovarian mass				
No cyst			0.65 (2)	0.722
Uniloculated	-1.83	0.16 (0.00,30.00)	0.47 (1)	0.493
Multiloculated	-0.38	0.68 (0.00,132.70)	0.02 (1)	0.888
Septum of ovarian mass				
No cyst			12.84 (3)	0.005
Uniloculated (no septum)	1.89	6.64 (1.59,27.65)	6.77 (1)	0.009
Multiloculated-thin septum	2.39	10.91 (2.58,46.05)	10.58 (1)	0.001
Multiloculated-thick septum	0.336	1.40 (0.14,13.69)	0.08 (1)	0.773

Table 11: Stages of endometriosis diagnosed intraoperatively

Stages of Endometriosis	Frequency (N)	Percentage (%)
Stage I (Minimal; score 1-5)	4	3.9
Stage II (Mild; score 6-15)	12	11.7
Stage III (Moderate; score 16-40)	43	41.7
Stage IV (Severe; score> 40)	44	42.7

Table 12 shows the distribution of the features strongly correlate with endometriosis according to the stages of disease found. The significant features were then tested to see their correlation with the stage of the disease, as shown in Table 13. Symptoms of severe dysmenorrhea were statistically significant in correlation with all the stages of endometriosis. It was found that the presence of serum Ca125 between 50 to 200u/ml has three times risk for stage III to IV endometriosis. The rest of the clinical manifestations did not correlate well with the stages of endometriosis.

Table 12: Distribution of various clinical features in relation to the stages of endometriosis

Variables	Stage of endometriosis			
	Stage I (N)	Stage II (N)	Stage III (N)	Stage IV (N)
Dysmenorrhoea (n=100)				
• **Mild**	0	1	14	9
• **Moderate**	2	8	16	17
• **Severe**	2	3	11	17
Ovarian cyst with thick sedimentation	1	12	43	44

Table 13: The correlation between dysmenorrhoea, cystic with thick sedimentation ovarian mass and serum Ca125 with stages of endometriosis

Variable	Stage of endometriosis	b	Crude OR (95% CI)	Wald statistic (df)	p value
Mild Dysmenorrhoea	**Stage I**	-21.12	0.00	0.00 (1)	0.999
	Stage II	-2.32	0.09 (0.01,0.80)	4.08 (1)	0.031†
	Stage III	-0.65	0.52 (0.24,1.15)	2.59 (1)	0.107‡
	Stage IV	-1.28	0.28 (0.12,0.66)	8.37 (1)	0.004†
Moderate dysmenorrhoea	**Stage I**	0.30	1.35 (0.18,10.15)	0.09 (1)	0.768
	Stage II	0.99	2.71 (0.75,9.81)	2.31 (1)	0.129‡
	Stage III	-0.22	0.80 (0.37,1.74)	0.31 (1)	0.578
	Stage IV	-0.16	0.85 (0.39,1.83)	0.17 (1)	0.683
Severe dysmenorrhoea	**Stage I**	3.65	23.33 (2.39,227.05)	7.36 (1)	0.007†
	Stage II	2.05	7.78 (1.36,44.51)	5.31 (1)	0.021†
	Stage III	2.08	8.02 (2.09,30.74)	9.23 (1)	0.002†
	Stage IV	2.69	14.69 (3.98,54.19)	16.28 (1)	<0.001†
Ovarian cyst with thick sedimentation	**Stage I**	0.86	2.37 (0.22,25.31)	0.51 (1)	0.475
	Stage II	23.17	>100 (0.00,)	0.00 (1)	0.998
	Stage III	23.17	>100 (0.00,)	0.00 (1)	0.997
	Stage IV	5.01	>100 (30.73,725.6)	38.52 (1)	<0.001†
Serum Ca125 50-200u/ml	**Stage I**	0.86	2.37 (0.22,25.31)	0.51 (1)	0.475
	Stage II	0.35	1.42 (0.87, 7.56)	0.17 (1)	0.679
	Stage III	3.44	31.11 (11.02,87.82)	42.16 (1)	<0.001↑
	Stage IV	3.63	37.59 (12.93,109.3)	44.34 (1)	<0.001↑

5.6 Histopathology examination

Whenever possible, tissue specimen from the subjects noted to have endometriosis, was taken from the subjects during the operation. Out of 103 patients who were diagnosed to have endometriosis, 92 patients were confirmed to have endometriosis histopathologically (Table 14).

Table 14: Histopathology diagnosis of endometriosis

Histopathology diagnosis of Endometriosis	Endometriosis (N, percentage)	No Endometriosis (N, percentage)
Positive	92 (52.3%)	0 (0.0%)
Negative	11 (6.2%)	73 (41.5%)

6.0 DISCUSSION

6.1 GENERAL

This cross sectional study evaluated the accuracy of clinical manifestation (including symptoms, physical examination, ultrasonography features) and serum Ca 125 levels to diagnose endometriosis, in comparison with laparoscopic or laparotomy findings with or without histopathological examination. This study aimed to create a scoring system named CliEndomet, which consists of various clinical manifestations and Ca 125 level which suggestive of endometriosis.

The gold standard for detecting endometriosis disease is direct visualization via laparoscopy or laparotomy with or without histopathology confirmation (Gerard A. et. al, 2012). Latest guideline by ESHRE on endometriosis (ESHRE, 2013) stated that the combination of laparoscopy and the histological verification of endometrial glands and/or stroma is considered for the diagnosis of endometriosis. The GDG (Guideline Development Group) recommends that endometriosis diagnosed by a positive laparoscopy with histology, even though negative histology does not exclude it. Thus, in this study, the clinical diagnosis of endometriosis was done according to positive laparoscopy (direct visualization) with or without histopathology confirmation. Ultimately, diagnosis of endometriosis requires a careful clinical evaluation in combination with judicious use and critical interpretation of laboratory tests, imaging techniques and, in most instances, surgical staging combined with histological examination of excised lesions (Robert Z. et.at, 2003). Many international studies had been done and published in effort to diagnose endometriosis without surgical intervention. However, none of the presenting symptoms or signs was pathognomonic towards endometriosis. The predictive value of any one symptom or set of symptoms remains uncertain, and

establishing the diagnosis of endometriosis on the basis of symptoms alone can be difficult (RCOG, 2006).

Serum Ca 125 level has been evaluated in many previous studies in order to diagnose endometriosis. Moderate elevations of serum Ca 125 has been observed in patients with moderate to severe disease, but the specificity and sensitivity of this biomarker alone have not been proven adequate for clinical diagnosis (Pratibha A. et.al, 2006). The sensitivity of serum Ca 125 is too low for it to be used alone as a screening or diagnostic test for endometriosis.

This study aimed to investigate whether the diagnosis of endometriosis might be improved by compilation of symptoms, physical examinations, ultrasound features and serum CA 125 level, comparing with surgical staging and/or histopathology examination. Few and limited studies had been done internationally for the same objective, suggested combination use of clinical indexes may be a reliable non-surgical diagnostic method for endometriosis, but none of those studies has come out with a scoring system, which correlate the history, clinical examination, ultrasound findings and serum CA 125 level.

6.2 DEMOGRAPHIC DATA

There were 176 patients involved in this study, out of which 103 of them were diagnosed to have endometriosis and 73 patients with no surgical evidence of the disease. Endometriosis is almost always detected in women of reproductive age (Robert Z.et.al 2003). The mean age of the women in this study was 35.41 ± 6.90 years. The majority being between 30 and 40 years of age for both cases and control. This is nearly the same as previous study by Daniele G.et.al., published by ASRM Elsevier in 2003, with mean age 37.30 ± 6.40 years. Possible reason for these women seek treatment late at their 30's could be due to reduce in ability to cope with the

symptoms related to endometriosis when the disease progress (Houston, 1984; Hadfield et.al., 1996).

According to study done by Robert Z.et.al, 2003, the protective effect of pregnancy appears to wane gradually and an increased risk of endometriosis has been observed with an increase in the number of years since the last child birth. However, there was not much difference in the mean duration of last child birth among patients with endometriosis compared with those without endometriosis (4.42 ± 5.53 years versus 4.81 ± 4.39 years respectively) noted in this study.

The present study found that majority of the subjects with endometriosis were nulliparous or low parity (para 1 or 2), comprised of 68.0%, and most of them have history of sub-fertility (61.2%).

The mean duration of subfertility for patients with endometriosis was 4.69 ± 5.62 years, which was longer than mean duration of subfertility for patients without endometriosis, i.e. 3.38 ± 5.05 years. This finding is in tandem with the fact that endometriosis is associated with reduced fertility. Robert Z et. al and Sangi H. P. et. al. also found similar findings in their studies (Robert Z et. al, 2003; Sangi H.P. et. al., 1995).

6.3 CLINICAL ASSESSMENT

6.3.1 Clinical presentation

Although women with endometriosis may be asymptomatic, symptoms are common and typically include pelvic pain. In this study, the clinical symptoms of dysmenorrhea, dyspareunia, ovulation pain, dyschezia and non-specific pelvic pain were evaluated.

Among the 176 subjects, 169 subjects (96.0%) presented with dysmenorrhea in this study. 56.8% out of patients with dysmenorrhea were diagnosed to have endometriosis,

whereas only 3 patients (1.7%) with endometriosis did not presented with dysmenorrhea. Most of the patients with endometriosis were categorized in moderate (43.0%) and severe (33.0%) group of severity of dysmenorrhea. This finding was similar with the study by Eskenazi et al in 2001, where there were higher prevalence of endometriosis among patients with moderate to severe degree of dysmenorrhea (Eskenazi et al, 2001). Cramer and his associates (1986) demonstrated a positive correlation between the severity of dysmenorrhea and the risk of endometriosis.

However, the current revised American Society for Reproductive Medicine (rASRM) classification of endometriosis poorly predicts symptoms (Dietmar H.et.al, 2012). Women with extensive disease (stage IV) may have mild symptoms, whereas those with minimal disease (stage I) may presented with significant pain. This trend was seen in my study, which 9 patients who presented with mild dysmenorrhea were diagnosed to have stage IV endometriosis, whereas 5 patients who presented with severe dysmenorrhea had stage I and II endometriosis. Many researches have been published, revealing no association between the stage of endometriosis and the severity of dysmenorrhea as well as non-menstrual pelvic pain (Robert Z.et.al, 2003). Evidence regarding the association between the intensity of pain and morphologic features of the endometriotic implant was inconclusive and contradictory (Robert Z et. al, 2003). In a multicentre cross-sectional observational study, found no significant correlation between stage and site of endometriosis and severity of dysmenorrhea, non-menstrual pain and dyspareunia.

Endometriosis-related dyspareunia is usually positional and most intense upon deep penetration, it is usually associated with endometriosis of cul-de-sac and rectovaginal septum (Robert Z.et.al, 2003). Endometriosis-related dyspareunia is suspected if pain developed after years of pain-free intercourse (Ferrero, 2005). This study had

demonstrated only 19 out of 26 subjects (18.4%) who presented with dyspareunia were confirmed to have endometriosis. Though the simple logistic regression test had shown that dyspareunia was associated with high prevalence of endometriosis, this finding was found not to be statistically significant, perhaps due to the small number of subjects. Because of this, its association with the stage of disease was not analysed. In contrast to this finding, Prathiba et. al. in 2006 had found a higher prevalence of dyspareunia in endometriotic patients (25-40%), which could be caused by a higher number of studied subjects.

Ovulation pain may represent an extension of dysmenorrhea, in severe cases, patients may suffer from pain throughout the menstrual cycle. The ovulation pain has been reported in 57-68% of women with endometriosis and pain (Gruppo et.al, 2001). The number of subjects with ovulation pain in this study was too small (N=2) to be commented or concluded.

Dyschezia, or painful defecation, is less common to occur than other clinical manifestation in endometriosis. This was evidenced by only 2 patients with endometriosis in my study complaint of dyschezia, with pain score 2/10 and 4/10 respectively. This symptom typically reflects rectosigmoid involvement with endometriotic implants (Azzena, 1998).

6.3.2 Physical Examination

Physical examination may provide a broad range of findings. In mild endometriosis, the gynaecologic examination may be unremarkable. Abdominal examination is usually not significant unless patient presented with abdominal mass or in rare instances of scar endometriomas, painful swelling or focal tenderness (Robert Z et al, 2003). In this study, 97 subjects were noted to have abdominal mass and out of this number, 55 of them (31.2%) were confirmed to have endometriosis. This finding was consistent with

the prevalence of endometrioma, which was reported to be between 17 to 44% of all women with endometriosis (Patreli et.al, 2011). Endometrioma will typically cystic in nature, with uni or multiloculated surface, regular margin and can be tender if palpated during menses. The finding of the endometrioma in this study was consistent with those features, in which more than 90% of the masses were found to have regular margin, smooth surface and cystic in consistency. Usually endometrioma was tender on palpation but in this study, 96.4% of the masses were non- tender. Although endometrioma typically associated with restricted mobility due to the presence of adhesion, only 32 out of 55 patients with endometrioma were found to be restricted mobility.

Ideally the gynaecologic examination should be performed while the patient experiences at least some symptoms, preferable during menstruation, when it may be easiest to detect and localize areas suspected of harbouring endometriosis (Robert Z et.al, 2003). However, almost all the vaginal examinations were done when the subjects were not menstruating, as the cultural practised by the patients here refused for vaginal examination during having menses. According to Chapron et al in 2002, lesions were visible during speculum examination in only 14.4% and a classic, painful, spheric nodule was palpable during manual examination in 43.1% of patients. Speculum inspection may reveal bluish implants typical of endometriosis or red, hypertrophic lesions bleeding on contact, usually in the posterior fornix. Only 5 subjects were noted to have vaginal nodule in this study, and only 3 of them were confirmed to have endometriosis, although this showed high sensitivity (60%) with low specificity in detecting endometriosis, but was not statistically significant in view of small number of subjects.

Positive physical signs are found on bimanual and rectovaginal examination of pelvic structures. Palpation of the uterus in patient with endometriosis may reveal retroversion, decreased or absent mobility, and tenderness (Robert Z.et.al, 2003). This study however demonstrated majority of the subjects with endometriosis (n=90, 87.3%) have anteverted uterus. 63 subjects (61.2%) had restricted mobility. The position of the uterus was not found to correlate well with the presence of endometriosis (p value 0.066). On the other hand, a restricted mobility uterus was highly and significantly correlate with endometriosis (crude OR 7.17; 95% CI 2.07- 24.86; p value 0.002). But when this feature was tested using the multiple logistic regression test, the correlation was cancelled and found not to be significant. Retroverted with restricted mobility of uterus are more common in severe endometriosis (Chapron et.al, 2002). This trend was seen in my study. There were 26 subjects (25.2%) out of 103 patients with endometriosis, had thickened uterosacral ligament, 2 of them (7.69%) were classified as stage 2 endometriosis, 10 subjects (38.5%) in stage III and 14 subjects (53.8%) in stage IV. Only 8 patients (7.8%) had tenderness over the uterosacral ligament, which were not sensitive nor specific findings in diagnosing endometriosis. Uterosacral ligament nodularity or thickening and tenderness may reflect active disease or scarring along the ligament (Chapron et.al, 2002). 38 patients with endometriosis (36.9%) had obliterated Pouch of Douglas (POD). This figure was similar to the percentage reported by Reid S. et.al in 2013, which there was nearly 30% of endometriosis patients had obliterated POD. Majority of them had more severe stage of endometriosis (stage III and stage IV).

Although pelvic organ palpation may assist in diagnosis, the sensitivity and specificity of focal pelvic tenderness in detecting endometriosis displays wide variation and ranges from 36 to 90 per cent and 32 to 92 per cent, respectively (Chapron, 2002; Eskenazi, 2001; Koninckx, 1996). According to Robert Z.et.al in 2003, a normal clinical

examination does not rule out the diagnosis of endometriosis, and pelvic examination showed poor sensitivity, specificity and predictive values. A prospective study validating non-surgical approaches to diagnosis of endometriosis found that pelvic examination was a reliable predictor of ovarian endometriomas but was not helpful in prediction of non-ovarian lesions (Robert Z. et.al, 2003).

6.4 Ultrasonographic findings

Ultrasonographic examination is particularly helpful in the evaluation of endometriotic cysts but has a limited role in the diagnosis of adhesions or superficial peritoneal implants (Friedman H.et.al, 1985). Small endometriotic plaques or nodules may occasionally be seen, but these findings are inconsistent (Carbognin, 2007). Transvaginal sonographic (TVS) approach was done in most of the patients in this study as it is more sensitive to detect small pelvic masses than transabdominal ultrasound. Endometriomas can be diagnosed by TVS with adequate sensitivity if they are 20mm or greater in diameter (Chapron et.al, 2002). According to Moore.et.al in 2002, the sensitivity and specificity of TVS to diagnose endometriomas range from 64 - 90% and from 22-100%, respectively. This study had demonstrated that ultrasonographic examination carried a high sensitivity (96.1%) but low specificity (19.2%) in diagnosing endometriomas. 99 out of 103 subjects with endometriosis were noted to have ovarian mass during ultrasound scan. Their presence was found to correlate well with endometriosis (crude OR 5.87, 95% CI 1.85-18.68; p value 0.003). Majority of the cases that were confirmed to have endometriomas, when ovarian mass were detected during ultrasound, had features of multiloculated mass (55.3%), with thin septation (94.7%), cystic in nature (100%), and ground-glass appearance or thick with sediments (98.9%), without papillary projection.

Among the features of ovarian mass, the presence of cystic mass with thick sedimentation was found to be more than 38 times associated with endometriosis (crude OR 38.11; 95% CI 10.34- 140.42; p value < 0.001). These finding, were consistent with the statement by Athey et.al in 1989 that endometriomas often present as cystic structures, with low-level internal echoes (95%). Patel M.et.al in 1999 also found that an adnexal mass with diffuse low-level internal echoes and absence of particular neoplastic features is very likely to be an endometrioma if multilocularity or hyperechoic wall foci are present. According to Nezhat et.al in 1992, the endometriomas may be unilocular, but are often multilocular when more than 3cm in diameter. Occasionally endometriomas may have thick septation and thickened walls. Diagnostic accuracy of ultrasound may be enhanced by colour Doppler flow studies which demonstrate pericystic flow (Kurjak, 1994).

6.5 BIOCHEMICAL MARKER Ca 125

Elevated Ca 125 levels has been shown to positively correlate with the severity of endometriosis (Hornstein, 1995). This study analysed the performance of serum Ca 125 measurement in women with endometriosis. Timing of blood collection for Ca 125 in relation to the menstrual cycle significantly affects this test. As suggested by Koninckx et.al, 1996, almost all the blood samples in this study were taken during menstruation, as this test would be more reliable and clearly elevated than testing in follicular phase.

23 studies have investigated serum Ca 125 in women with surgically confirmed endometriosis. Those studies have shown only 28% sensitivity and 98% specificity to detect endometriosis. Similarly, this study had also shown a low sensitivity (30%) but high specificity (98%). Could the low sensitivity alter the different level of serum Ca125. Therefore, a ROC analysis was performed for the subjects. The ROC analysis had

shown that the AUC for serum Ca125 was 90%, indicating 90% accuracy in predicting the presence of endometriosis. From the curve, it was noted the levels between 50 to 200u/ml carried 80% sensitivity and 86% specificity, with a corresponding likelihood ratio of 5.8. It was found that the sensitivity of the serum Ca125 reduces for the levels above 200u/ml, even though the specificity increases. Therefore, the levels between 50 to 200u/ml were taken as the reference values for the correlation. Using this reference value, it was found that 75 out of 103 subjects with endometriosis has serum Ca125 levels at this levels (50 to 200u/ml), with crude OR of 19.05 (95% CI 8.38 – 43.32; p value < 0.001).

6.6 Formation of the CliEndomet

The most important aim of this study is to find a non-surgical way that is highly suggestive of endometriosis. Any single use of clinical indexes achieved poor sensitivity in diagnosing endometriosis (J.Leng et.al, 2006). In women with endometriosis, a normal CA 125 neither confirms the absence of endometriosis nor predicts recurrence (Ozaksit et.al, 1995). Therefore, the use of CA 125 levels alone to diagnose endometriosis is not warranted. There are few studies have been done to evaluate mutual dependency between a medical history, physical examination, imaging and serum CA 125 measurement, to arrive at a diagnosis without surgery, but none come out with a proper conclusion yet nor proven clinically useful on their own. Therefore, a multiple logistic regression test to evaluate the significant features to diagnose endometriosis was performed. It was found that dysmenorrhoea, ultrasonographic findings of cystic ovarian mass with thick sedimentation and serum Ca125 between 50 to 200u/ml significantly associated with endometriosis. A combination of these features may be able to help in diagnosing endometriosis. Therefore, a scoring system that is highly suggestive of endometriosis using these features, named CliEndomet, was formed (Figure 5). From the total score which was

obtained using the CliEndomet scoring system, the risk of a patient to have endometriosis could be assessed.

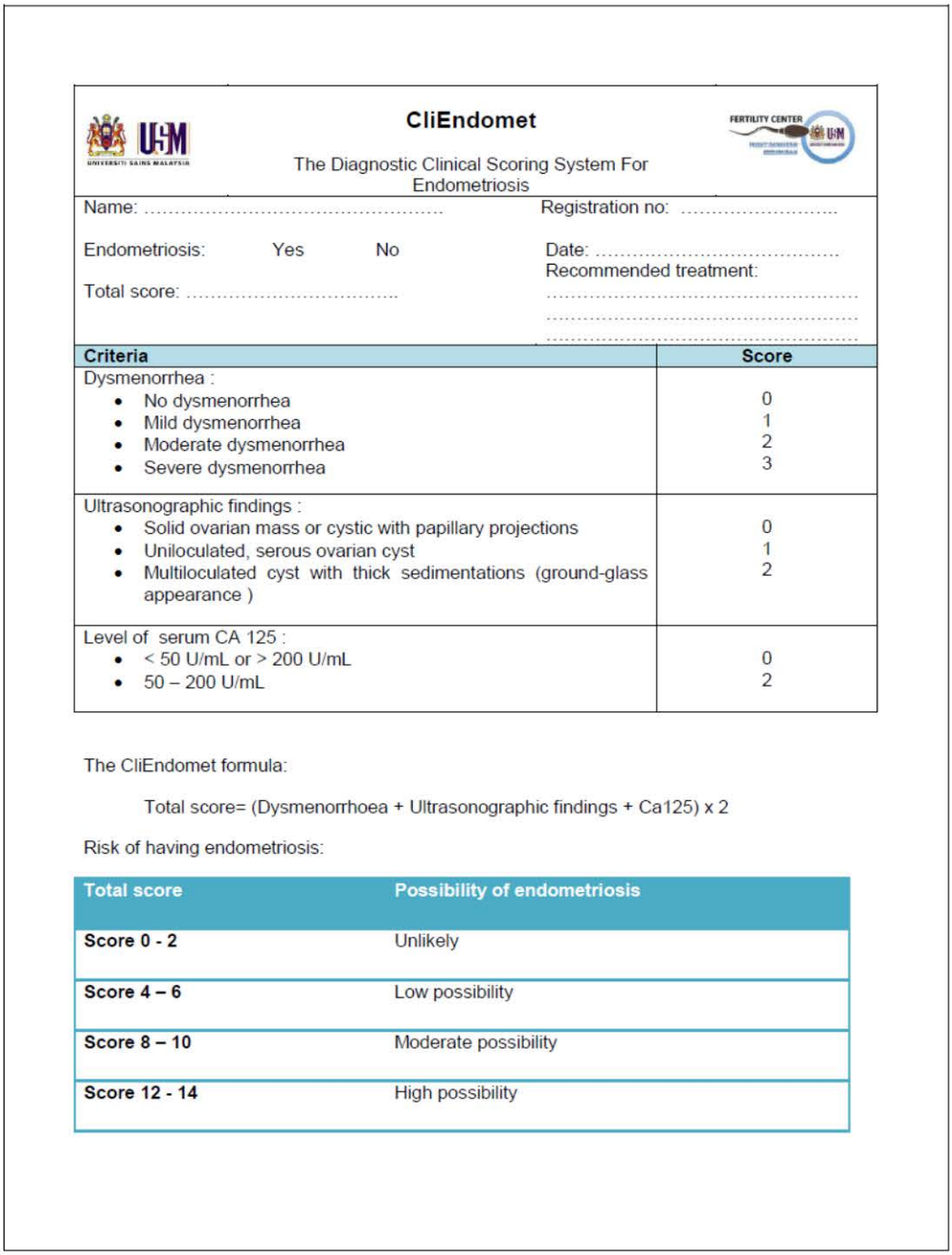
6.7 Surgical findings versus histopathological results

Laparoscopy with or without histopathology confirmation is considered to be the 'gold standard' for the diagnosis of endometriosis (Gerard A.et.al, 2012). Several articles, however, reported that laparoscopy diagnosis is often an inaccurate determination. This is mainly due to variable appearance of the endometriotic lesions with different colours and morphology visualized during laparoscopic examinations. American Society for Reproductive Medicine (ASRM, 1997) suggested that relying solely on laparoscopic findings without histologic confirmation often results in overdiagnosis. Therefore, Tommaso et.al in 2003 concluded that a diagnostic laparoscopy without histologic confirmation of the disease may lead to incorrect assignment of the diagnosis, and very subtle or minimal lesions may be more difficult to diagnose during operation and this may lead to an underestimate of the prevalence of disease.

Laparoscopic visualization of ovarian endometriomas has a sensitivity and specificity of 97% and 95%, respectively (Vercellini, 1991). Due to this, ovarian biopsy is rarely required for diagnosis.

The current guideline on endometriosis by ESHRE, 2013 recommends that positive laparoscopy with histology is used for diagnosis of endometriosis. However, this guideline also stated that negative histology does not exclude the diagnosis. Thus, in this study, the clinical diagnosis of endometriosis were based on positive laparoscopy with direct visualization with or without histopathological confirmation.

Figure 5: CliEndomet; The Clinical Scoring System that help in diagnosis of Endometriosis



CliEndomet

The Diagnostic Clinical Scoring System For Endometriosis

Name: ..... Registration no: .....

Endometriosis: Yes No Date: .....

Recommended treatment:

Total score: .....

.....

.....

Criteria	Score
Dysmenorrhea : • No dysmenorrhea • Mild dysmenorrhea • Moderate dysmenorrhea • Severe dysmenorrhea	 0 1 2 3
Ultrasonographic findings : • Solid ovarian mass or cystic with papillary projections • Uniloculated, serous ovarian cyst • Multiloculated cyst with thick sedimentations (ground-glass appearance)	 0 1 2
Level of serum CA 125 : • < 50 U/mL or > 200 U/mL • 50 – 200 U/mL	 0 2

The CliEndomet formula:

Total score= (Dysmenorrhoea + Ultrasonographic findings + Ca125) x 2

Risk of having endometriosis:

Total score	Possibility of endometriosis
Score 0 - 2	Unlikely
Score 4 – 6	Low possibility
Score 8 – 10	Moderate possibility
Score 12 - 14	High possibility

In a prospective study by Walter et.al in 2001, correlated visual diagnosis of endometriosis at laparoscopy with final histological confirmation in 44 patients. Walter et.al concluded that, with the use of strict histological criteria resulted in lower rates of confirmed endometriosis as visually detected endometriosis was observed in 36% of cases but confirmed histologically in only 18% of cases. The finding was different in our study, where 103 patients (58.5%) were diagnosed to have endometriosis either via direct visualization during laparoscopic examination with or without histopathological confirmation. 92 patients in this study (52.3%) were confirmed histopathologically. The residual 11 patients (6.3%) either no specimen taken (eg. ablative method used intraoperatively and no specimen taken for HPE) or inadequate samples for histopathological examination, but diagnosis via direct visualization without biopsy still considered as a reliable method to diagnose endometriosis, regardless of the stages of disease.

7.0 VALIDATION OF CLIENDOMET

7.1 VALIDATION OF CLIENDOMET SCORING SYSTEM

Table 15: The frequency and distribution of total score by CliEndomet

Total Score	Frequency (N)	Percentage (%)
0	0	0
2	14	8.0
4	25	14.2
6	40	22.7
8	28	15.9
10	29	16.5
12	26	14.7
14	14	8.0

Table 16: The correlation between the possibility of endometriosis (from CliEndomet) with diagnosis of endometriosis

Possibility of endometriosis	Endometriosis (N, percentage)	No Endometriosis (N, percentage)
Unlikely (score 0-2)	1 (0.5%)	13 (7.4%)
Low possibility (score 4-6)	12 (6.8%)	53 (30.1%)
Moderate possibility (score 8-10)	51 (29.0%)	6 (3.5%)
High possibility (score 12-14)	39 (22.2%)	1 (0.5%)

Table 17: Distribution of possibility of endometriosis (from CliEndomet) in relation to the stages of endometriosis

Possibility of endometriosis	Stage of endometriosis			
	Stage I (N,%)	Stage II (N,%)	Stage III (N,%)	Stage IV (N,%)
Unlikely	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Low possibility	3 (2.9%)	3 (2.9%)	4 (3.9%)	2 (1.9%)
Moderate possibility	1 (0.9%)	6 (5.9%)	26 (25.3%)	18 (17.5%)
High possibility	0 (0%)	2 (1.9%)	13 (12.6%)	24 (23.4%)

Table 18: Categories of possibility of endometriosis (from CliEndomet) in relation with diagnosis of endometriosis

Category of possibility of endometriosis	Endometriosis (N, %)	No Endometriosis (N, %)	Total (N, %)
Unlikely and low possibility	13 (7.4%)	66 (37.5%)	79 (44.9%)
Moderate and high possibility	90 (51.1%)	7 (4.0%)	97 (55.1%)
Total (N, %)	103 (58.5%)	73 (41.5%)	176 (100%)

7.2 SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF CLIENDOMET

Sensitivity of CliEndomet :

$$\frac{90}{103} \times 100\% = 87.4\%$$

Specificity of CliEndomet :

$$\frac{66}{73} \times 100\% = 90.4\%$$

Positive Predictive Value :

$$\frac{90}{97} \times 100\% = 92.8\%$$

Negative Predictive Value :

$$\frac{66}{79} \times 100\% = 83.5\%$$

From the scoring system CliEndomet, we have calculated retrospectively the score of possibility of endometriosis on the same sample of patients (N = 176), noted there was high sensitivity 87.4%, high specificity 90.4% with positive predictive values 92.8% and negative predictive value 83.5%.

Subjects who fall into moderate or high possibility of endometriosis (N = 97), 90 of them (92.8%) had been diagnosed endometriosis (either via direct visualization from laparoscopy or laparotomy, with or without histopathology confirmation). Another 79 subjects fall into unlikely or low possibility category, 66 of them (83.5%) did not have endometriosis.

However, the accuracy of this CliEndomet scoring system is better to be validated in another samples of patients, to test the sensitivity and specificity of this scoring system.

8.0 CONCLUSION AND SUGGESTIONS

The clinical presentation of endometriosis varies in terms of clinical symptoms, signs found during physical examination, ultrasonographic findings of ovarian mass and elevation of serum Ca125. Standing alone, each of these features fails to detect endometriosis accurately.

This study has demonstrated a few significant clinical menifestations of endometriosis, i.e. the presence of dysmenorrhoea, an ultrasonographic finding of a cystic ovarian mass, which contains thick sedimentation and an elevated serum Ca125 in the range between 50 to 200u/ml. Using the combination of these features, a clinical suggestive scoring system, named as CliEndomet, was formulated.

Endometriosis is highly suggestive by using the CliEndomet scoring system, which takes into consideration of several significant clinical parameters. This scoring system was designed to detect all stages of the disease and thus could be used to all patients suspected of having endometriosis. However, the accuracy of the CliEndomet is better to be validated in another sample of patients.

9.0 LIMITATION AND RECOMMENDATION

The findings in the present study may be limited by a few factors, and recommendation for the betterment of the study was made as below:

- This study was done in 2 hospitals in Kelantan, the presentation and outcomes might differ in other places. Ideally multi-centered study with collaboration with other centre, will give more variations in the results. Although the CliEndomet scoring system is formed based on data obtained from a carefully characterized study population, it remains necessary to validate these results on a different study population.

- There was difference in the numbers of patients in different stages of endometriosis, which was not equally distributed. Therefore we would suggest for balancing the numbers of cases for each stages of endometriosis in future research and to minimize bias on the results.

- The usage of CliEndomet scoring system could be used and extended to non-sexually active patients with pelvic pain.

- The accuracy of Cli-Endomet scoring system is not yet validated. Thus, a further validation study (on different sample of patients) is required to test the sensitivity and specificity of this scoring system in helping the diagnosis of endometriosis. We recommend another study with this objective to be done on a new group of patients in near future.

- This scoring system is helpful in diagnosis of endometriosis but have limitation in further division into the stages of the disease. Should it proven to be accurate,

its usage could also be extended to determine the severity of the disease in order to predict its prognosis.

- This scoring system aimed in selecting patient who is moderately or highly suggestive to have endometriosis, however, if this test has been validated in future study, the further treatment of patient will be individualized, either medical or surgical treatment. However, if associated with huge pelvic mass (endometrioma), surgery may be needed, which is beyond the scope of this study.

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APPENDIX 1 : USM HUMAN ETHICAL APPROVAL CERTIFICATE

Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

Our. Ref. : USMKK/PPP/JEPeM [243.3.(7)]
Date : 3rd November 2011

Universiti Sains Malaysia
Kampus Kesihatan,
16150 Kubang Kerian,
Kelantan. Malaysia.
T: 609 - 767 3000 *samb.* 2350 / 2352
F: 609 - 767 2351
E: jepem@kk.usm.my
www.crp.kk.usm.my

Assoc. Prof. Dr. Adibah Ibrahim
Department of Obstetrics and Gynecology
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

The Human Research Ethics Committee, Universiti Sains Malaysia (FWA Reg. No: 00007718; IRB Reg. No: 00004494) has approved in principle the study mentioned below:

Protocol No	N/A	**Principle Investigator**	Assoc. Prof. Dr. Adibah Ibrahim
Date of approval Protocol received Reviewed by Committee Received Amended Protocol	3rd November 2011 5th September 2011 20th October 2011 -	**Co-Investigator(s)**	Prof. Dr. Mohd Shukri Othman Assoc. Prof. Dr. Nor Aliza Abd. Ghaffar Dr. Nurul Khaiza Yahya Dr. Wan Mohd Zahiruddin Wan Mohamad Dr. Mohd Pazudin Ismail
Title	The Diagnostic Factors (Combination of Clinical Presentation, Ultrasonography Findings and Ca 125) for Endometriosis.		
Research Center	Hospital Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II, Kota Bharu.	**Date of study start**	November 2011 – October 2013
Financial Support	Short Term Grant, USM	**Number of Samples**	200 subjects

The following item (✓) have been received and reviewed:-

(✓) **Ethical Approval Application Form**
(✓) **Study Protocol**
(✓) **Patients Information Sheet and Consent Form**
(✓) **Clinical Research Form**

Investigator(s) are required to:
a) follow instructions, guidelines and requirements of the Human Research Ethics Committee, Universiti Sains Malaysia (JEPeM)
b) report any protocol deviations/violations to Human Research Ethics Committee (JEPeM)
c) comply with International Conference on Harmonization – Guidelines for Good Clinical Practice (ICH-GCP)
d) note that Human Research Ethics Committee (JEPeM) may audit the approved study.

PROFESSOR DR. HANS AMIN VAN ROSTENBERGHE
Chairman
Human Research Ethics Committee

APPENDIX 2 : CLINICAL RESEARCH FORM

CLINICAL RESEARCH FORM

The association between clinical manifestation, biochemical markers (Ca125), and diagnostic laparoscopy or laparotomy findings, with or without histopathological confirmation for the diagnosis of endometriosis.

Reg. No :		Age :	
Parity :		LCB :	

HISTORY TAKING

<table>
<tr><td>Dysmenorrhoea</td><td>
Present ☐ Absent ☐

If dysmenorrhoea is present, please score the severity of pain according to the below criteria and take the sum to rank the severity:

<table>
<tr><td>Score</td><td>0</td><td>1</td><td>2</td><td>3</td></tr>
<tr><td>Limitation of ability to work</td><td>Unaffected</td><td>Rarely affected</td><td>Moderately affected</td><td>Clearly affected</td></tr>
<tr><td>Co-existing of systemic symptoms</td><td>Absent</td><td>Present</td><td></td><td></td></tr>
<tr><td>Need for analgesia</td><td>No</td><td>Yes</td><td></td><td></td></tr>
<tr><td>Total score</td><td colspan="4"></td></tr>
<tr><td>Rank of severity of pain</td><td>Mild
(1-2)</td><td>Moderate
(3-4)</td><td>Severe
(5)</td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Deep dyspareunia</td><td>

Present ☐ **Absent** ☐

If deep dyspareunia is present, please score the severity of pain according to the below 10- point linear analogue scale:

<table>
<tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr>
<tr><td colspan="11">No pain ⟷ Unbearable pain</td></tr>
</table>

</td></tr>
<tr><td>Pelvic pain</td><td>

Present ☐ **Absent** ☐

If pelvic pain is present, please score the severity of pain according to the below criteria and take the sum to rank the severity:

<table>
<tr><td>Score</td><td>0</td><td>1</td><td>2</td><td>3</td></tr>
<tr><td>Limitation of ability to work</td><td>Unaffected</td><td>Rarely affected</td><td>Moderately affected</td><td>Clearly affected</td></tr>
<tr><td>Co-existing of systemic symptoms</td><td>Absent</td><td>Present</td><td></td><td></td></tr>
<tr><td>Need for analgesia</td><td>No</td><td>Yes</td><td></td><td></td></tr>
<tr><td>Total score</td><td colspan="4"></td></tr>
<tr><td>Rank of severity of pain</td><td>Mild
(1-2)</td><td>Moderate
(3-4)</td><td>Severe
(5)</td><td></td></tr>
</table>

</td></tr>
<tr><td>Ovulation Pain</td><td>

Present ☐ **Absent** ☐

If ovulation pain is present, please score the severity of pain according to the below criteria and take the sum to rank the severity:

<table>
<tr><td>Score</td><td>0</td><td>1</td><td>2</td><td>3</td></tr>
<tr><td>Limitation of ability to work</td><td>Unaffected</td><td>Rarely affected</td><td>Moderately affected</td><td>Clearly affected</td></tr>
</table>

</td></tr>
</table>

	Co-existing of systemic symptoms	Absent	Present		
	Need for analgesia	No	Yes		
	Total score				
	Rank of severity of pain	**Mild (1-2)**	**Moderate (3-4)**	**Severe (5)**	

Non-menstrual Pain

Present ☐ **Absent** ☐

If non-menstrual pain is present, please score the severity of pain according to the below criteria and take the sum to rank the severity:

Score	**0**	**1**	**2**	**3**
Limitation of ability to work	Unaffected	Rarely affected	Moderately affected	Clearly affected
Co-existing of systemic symptoms	Absent	Present		
Need for analgesia	No	Yes		
Total score				
Rank of severity of pain	**Mild (1-2)**	**Moderate (3-4)**	**Severe (5)**	

Dyschezia

Present ☐ **Absent** ☐

If dyschezia is present, please score the severity of pain according to the below 10- point linear analogue scale:

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
No pain ◄										► Unbearable pain

Sub- fertility

Present ☐ **Absent** ☐

Duration: ……. years

PHYSICAL EXAMINATION

Height: ……. cm Weight: ……..kg

Body mass index (BMI): ……kg/m^2

Abdominal examination:

Abdominal mass	**Present** ☐		**Absent** ☐	
	If abdominal mass is present, please evaluate the details of the mass as below:			
	Size			
	Site			
	Margin	Regular	Irregular	
		☐	☐	
	Surface	Smooth	Irregular	
		☐	☐	
	Consistency	Cystic	Firm	Hard
		☐	☐	☐
	Mobility	Horizontal	Mobile	Restricted mobility / Fixed
		Vertical	Mobile	Restricted mobility / Fixed
	Tenderness	Tender ☐		Non- tender ☐

Pelvic examination:

Vaginal nodule	**Present** ☐		**Absent** ☐	
	If abdominal mass is present, please evaluate the details of the mass as below:			
	Site			
	Size			
	Colour			
	Tenderness	Present ☐		Absent ☐
Uterus	Size			
	Flexion	Anteverted		Retroverted
	Mobility	Mobile	Restricted	Fixed

Adnexae		Right	Left
	Cyst	Present ☐ Absent ☐ If cyst is present, kindly evaluate as follows: Size Tenderness Margin Surface Consistency Mobility	Present ☐ Absent ☐ If cyst is present, kindly evaluate as follows: Size Tenderness Margin Surface Consistency Mobility
	Ovary	Size Tenderness Mobility	Size Tenderness Mobility
	Uterosacral ligaments	Thickened / Not thickened Tender / Non- tender	Thickened / Not thickened Tender / Non- tender
	POD	Normal Obliterated	Normal Obliterated

INVESTIGATIONS

Ultrasound examination:

Please circle the method of ultrasound used: TAS TVS

Ultrasound findings:

Uterus:	
Size	
Endometrial thickness	
Flexion	
Abnormality	

Ovaries:				
Right ovary			**Left ovary**	
Size			Size	
Cyst		Present Absent	Cyst	Present Absent
	Size		Size	
	Locule	Uniloculated/ Multiloculated	Locule	Uniloculated/ Multiloculated
	Septum	Thin Thick	Septum	Thin Thick
	Papillary projection	Present Absent	Papillary projection	Present Absent
	Nature	Cystic Solid cystic Solid	Nature	Cystic Solid cystic Solid
	Content	Clear Thick with sediments	Content	Clear Thick with sediments

Ca 125 :	
Date taken :	
Level :	

OPERATIVE FINDINGS

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
_____
Prognosis _____

PERITONEUM	**ENDOMETRIOSIS**	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

	POSTERIOR CULDESAC OBLITERATION	Partial	Complete
		4	40

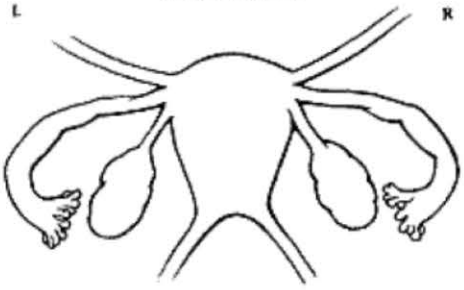
OVARY	**ADHESIONS**	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

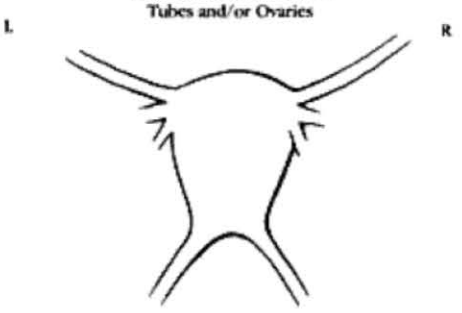
Additional Endometriosis: _____

Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries

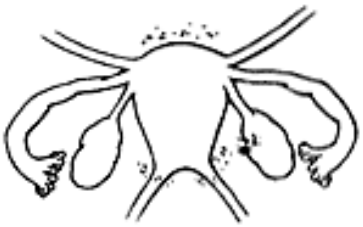


To Be Used with Abnormal Tubes and/or Ovaries



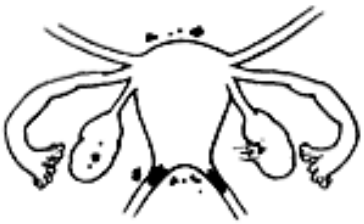
EXAMPLES & GUIDELINES

STAGE I (MINIMAL)



PERITONEUM		
Superficial Endo	– 1-3cm	· 2
R. OVARY		
Superficial Endo	– < 1cm	· 1
Filmy Adhesions	– < 1/3	· 1
TOTAL POINTS		4

STAGE II (MILD)

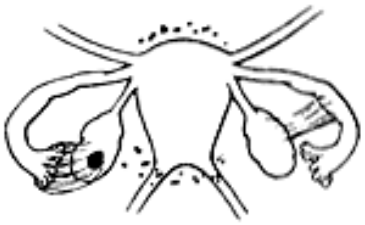


PERITONEUM		
Deep Endo	– > 3cm	· 6
R. OVARY		
Superficial Endo	– < 1cm	· 1
Filmy Adhesions	– < 1/3	· 1
L. OVARY		
Superficial Endo	– < 1cm	· 1
TOTAL POINTS		9

STAGE III (MODERATE)

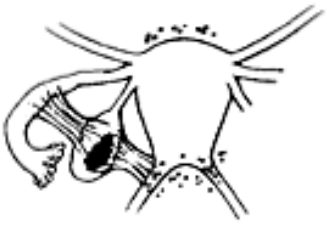
PERITONEUM		
Deep Endo	– > 3cm	· 6
CULDESAC		
Partial Obliteration		· 4
L. OVARY		
Deep Endo	– 1-3cm	· 16
TOTAL POINTS		26

STAGE III (MODERATE)



PERITONEUM		
Superficial Endo	– > 3cm	· 3
R. TUBE		
Filmy Adhesions	– < 1/3	· 1
R. OVARY		
Filmy Adhesions	– < 1/3	· 1
L. TUBE		
Dense Adhesions	– < 1/3	· 16*
L. OVARY		
Deep Endo	– < 1 cm	·4
Dense Adhesions	– < 1/3	·4
TOTAL POINTS		29

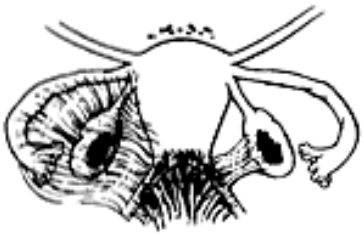
STAGE IV (SEVERE)



PERITONEUM		
Superficial Endo	– > 3cm	· 3
L. OVARY		
Deep Endo	– 1-3cm	· 32**
Dense Adhesions	– < 1/3	· 8**
L. TUBE		
Dense Adhesions	– < 1/3	·8**
TOTAL POINTS		51

*Point assignment changed to 16
**Point assignment doubled

STAGE IV (SEVERE)



PERITONEUM		
Deep Endo	– > 3cm	· 6
CULDESAC		
Complete Obliteration		· 40
R. OVARY		
Deep Endo	– 1-3cm	· 16
Dense Adhesions	– < 1/3	· 4
L. TUBE		
Dense Adhesions	– > 2/3	· 16
L. OVARY		
Deep Endo	– 1-3cm	· 16
Dense Adhesions	– > 2/3	· 16
TOTAL POINTS		114

Determination of the stage or degree of endometrial involvement is based on a weighted point system. Distribution of points has been arbitrarily determined and may require further revision or refinement as knowledge of the disease increases.

To ensure complete evaluation, inspection of the pelvis in a clockwise or counterclockwise fashion is encouraged. Number, size and location of endometrial implants, plaques, endometriomas and/or adhesions are noted. For example, five separate 0.5cm superficial implants on the peritoneum (2.5 cm total) would be assigned 2 points. (The surface of the uterus should be considered peritoneum.) The severity of the endometriosis or adhesions should be assigned the highest score only for peritoneum, ovary, tube or culdesac. For example, a 4cm superficial and a 2cm deep implant of the peritoneum should be given a score of 6 (not 7). A 4cm deep endometrioma of the ovary associated with more than 3cm of superficial disease should be scored 20 (not 24).

In those patients with only one adnexa, points applied to disease of the remaining tube and ovary should be multipled by two. **Points assigned may be circled and totaled. Aggregation of points indicates stage of disease (minimal, mild, moderate, or severe).

The presence of endometriosis of the bowel, urinary tract, fallopian tube, vagina, cervix, skin etc., should be documented under "additional endometriosis." Other pathology such as tubal occlusion, leiomyomata, uterine anomaly, etc., should be documented under "associated pathology." All pathology should be depicted as specifically as possible on the sketch of pelvic organs, and means of observation (laparoscopy or laparotomy) should be noted.

STAGE OF ENDOMETRIOSIS: STAGE I / II/ III / IV

HISTOPATHOLOGICAL EXAMINATION (Please tick)

CONFIRMED ENDOMETRIOSIS	
NO ENDOMETRIOSIS	

APPENDIX 3 : CONSENT FORM

PATIENT INFORMATION AND CONSENT FORM

The association between clinical manifestation, biochemical marker (Ca125), and diagnostic laparoscopy or laparotomy findings with or without histopathological confirmation for the diagnosis of endometriosis.

Name of Priciple Researcher : Dr Pang Suk Chin

Name of Supervisor : Assoc. Prof Dr Adibah Ibrahim

Name of co-supervisor (HUSM) : Prof Dr Mohd Shukri Othman

Dr Mohd. Pazudin Ismail

Dr. Wan Mohd. Zahiruddin Wan Mohd

Name of Co-supervisor (KKM supervisor) : Dr Haji Abdul Rahman

Dr Nik Ahmad Nik Abdullah

Introduction

You are invited to take part voluntarily in a research study involving patient with the symptoms that suggestive of endometriosis. Before agreeing to participate in this research study, it is important that you read and understand this form. It describes the purpose, procedures, benefits, risks, discomforts, and precautions of the study. It also describes the alternative procedures available to you and your right to withdraw from the study at anytime. If you participate, you will receive a copy of this form to keep for your records.

Your participation in this study is expected to last for six months. 200 patients will be participating in this study.

Purpose of the Study

The purpose of this study is to develop the Cli-Endomet as a reliable tool in the diagnosis of endometriosis

Qualification to Participate

The doctor in charge of this study or a member of the study staff will discuss with you the requirements for participation in this study. It is important that you are completely

truthful with the doctor and staff about your health history. You should not participate in this study if you do not meet all the qualification criteria.

To participate in this study you must be:

- Consented to participate in the study
- Age between 18 to 45 years
- Having symptoms like chronic pelvic pain, dysmenorrhea, dyspareunia or infertility

You cannot participate in this study if you are

- known case of endometriosis which confirmed by tissue examination
- diagnosed to have endometriosis and on treatment
- refuse for operation for confirmation of the disease

Study Procedures

You will only be invited to participate in this study if you fulfilled the above criteria.

You will be first seen in the Gynaecology Clinic, whereby a few questions will be asked. You will be examined by the doctor and an ultrasound will be performed. Blood investigations will be taken, if you are having menses, blood investigation will be taken stat, if you are not having menses yet, you will be asked to come again for blood taking during menses.

You will be given the date for ward admission to undergo operation (which is not more than 3 months from your first day of follow up),the operation will be done by the specialists who are involved in this research. You may be allowed to be discharged after 3-5 days post-operatively if there are no complication.

Risks

There are general risks of operation. You might have minor side effect such as nausea, headache (3-5%), or major risks such as bleeding, internal organ injury (less than 3%).

Participation in the Study

Your participation in this study is entirely voluntary. You may refuse to take part in the study or you may stop participating in the study at any time, without a penalty or loss of benefits to which you are otherwise entitled.

Your participation also may be stopped by the study doctor without your consent.

If you stop being part of this study, the study doctor or one of the staff members will talk to you about medical issues regarding the stopping of your participation.

Possible Benefits

Procedures will be provided at no cost to you. You may receive information about your health from any physical examinations to be done in this study. In addition you will have your disease confirmed and appropriate treatment will be given to you.

Information obtained from this study will benefit Ministry of Health and future clinical approach of such problem.

Questions
If you have any question about this study or your rights, please contact**:**

Dr Pang Suk Chin
Jabatan Obstetrik & Ginekologi
Hospital Raja Perempuan Zainab II
Tel: 012-5114622

If you have any questions Regarding the Ethical Approval, please contact:

Puan Mazlita Zainal Abidin
Setiausaha Jawatankuasa Etila Penyelidikan (Manusia) USM
Pelantar Penyelidikan Sains Klinikal, USM Kampus Kesihatan
Tel : 09-7672355 / 09-7672352

Confidentiality
Your medical information will be kept confidential by the study doctor and staff and will not be made publicly available unless disclosure is required by law.

By signing this consent form, you authorize the record review, information storage and data transfer described above.

Signatures
To be entered into the study, you or a legal representative must sign the signature page.

Research Title : The association between clinical manifestation, biochemical marker (Ca125), and diagnostic laparoscopy or laparotomy findings with or without histopathological confirmation for the diagnosis of endometriosis.

Name of Principle Researcher: Dr Pang Suk Chin

To become a part of this study, you or your legal representative must sign this page.

By signing this page, I am confirming the followngs :

I. I have read all of the information in this Patient Information and Consent Form including **any information regarding the risks in this study** and I have had time to think about it.

II. All of my questions have been answered to my satisfaction.

III. I voluntarily agree to be part of this research study to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.

IV. I may freely choose to stop being a part of this study at anytime.

V. I have received a copy of this Patient Information and Consent Form to keep for myself.

…… Patient's name	…… Patient's signature and contact no.
…… Patient's signature or legal representative	…… Date (DD/MM/YY)
…… Witness name and signature	…… Date (DD/MM/YY)

**All subjects / participants who are involved in this study will not be covered by insurance