VALIDATION OF CLIENDOMET AS A DIAGNOSTIC TOOL FOR ENDOMETRIOSIS

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LISTS OF ABBREVIATIONS

BMI	Body mass index
CA-125	Cancer antigen 125
CI	Confidence interval
CT SCAN	Computer topography scan
Hospital USM	Hospital Universiti Sains Malaysia
HPE	Histopathological examination
MRI	Magnetic resonance imaging
POD	Pouch of Douglas
SPSS	Statistical package for social sciences
TRUS	Transrectal ultrasonography
TVUS	Transvaginal ultrasonography

ABSTRAK (BAHASA MALAYSIA)

Latar belakang: Endometriosis adalah salah satu penyakit ginekologi yang paling lazim dialami oleh kaum wanita dalam lingkungan umur produktif. Sehingga kini, pendiagnosaan penyakit ini dibuat melalui pembedahan, dengan melihat rupa bentuk tisu, serta dipastikan melalui ujian histopatologi tisu terlibat. Memandangkan ramai pesakit yang tidak mahu menjalani pembedahan untuk pendiagnosaan penyakit ini, diagnosa yang tepat dan rawatan yang sewajarnya tidak dapat dibuat. Baru baru ini, sekumpulan penyelidik dari Hospital Universiti Sains Malaysia telah membuat satu sistem skor yang diberi nama CliEndomet, yang tidak memerlukan pembedahan untuk pendiagnosaan endometriosis. Sistem skor ini didapati setanding dengan diagnosa endometriosis yang dibuat melalui pembedahan. Walau bagaimanapun, perbandingan tersebut dibuat tanpa pengesahan ujian histopatologi. Kesahihan sistem skor tersebut akan menjadi lebih jitu jika perbandingan dengan histopatologi dapat dilakukan.

Objektif: Kajian ini adalah bertujuan untuk mengkaji ketepatan CliEndomet sebagai alat diagnosa endometriosis berbanding dengan pendiagnosaan secara pembedahan dan histologi tisu.

Metodologi: Seramai 94 pesakit yang mempunyai tanda penyakit endometriosis seperti sakit sengugut, dan sakit pada ruang pelvis telah menyertai kajian ini. Mereka telah menjalani pemeriksaan abdomen dan pelvis, ujian ultrasound dan darah mereka telah diambil untuk ujian CA-125. Data-data mereka telah dimasukkan ke dalam sistem skor CliEndomet dan kemungkinan setiap pesakit untuk menghidap endometriosis telah diambilkira. Pesakit-pesakit kemudiannya menjalani pembedahan di mana tisu mereka telah diambil untuk ujian histologi. Seandainya

mereka dijangkakan mempunyai endometriosis semasa dalam pembedahan, mereka akan digolongkan kepada peringkat penyakit berdasarkan revised American Society for Reproductive Medicine (ASRM) system. Pesakit hanya disahkan mempunyai endometriosis sekiranya ujian histologi mengesahkan diagnosa tersebut. Kesahihan skor diagnosis CliEndomet dikenalpasti dengan mengambil kira sensitiviti, spesifisiti, positive predictive ratio (PPV), negative predictive ratio (NPV), likelihood ratio positive (LR +), likelihood ratio negative (LR-) dan ujian Kappa coefficient, yang dibandingkan dengan diagnosa melalui histologi.

Keputusan: Seramai 94 pesakit telah menyertai kajian ini. Seramai 56 pesakit telah disahkan mempunyai endometriosis melalui kaedah ujian histologi, manakala 50 pesakit didapati berisiko tinggi mempunyai endometriosis melalui kaedah penskoran CliEndomet. Kepekaan, kekhususan, PPV, NPV, LR + dan LR - of CliEndomet adalah 69.6%, 71.1%, 78.0%, 61.4%, 2.41 dan 0.43. Mereka juga bersetuju adil antara CliEndomet dan diagnosis endometriosis berdasarkan pengesahan histologi, $\kappa = 0.397$ (95% CI, 0,21-0,58), $p < 0.005$. Melalui kaedah pemerhatian semasa pembedahan, 62 orang pesakit telah didapati mempunyai endometriosis. Dengan menggunakan penskoran CliEndomet, lima orang pesakit di dalam kumpulan endometriosis peringkat awal telah didapati berisiko rendah dan 12 orang pesakit berisiko tinggi mempunyai endometriosis. Di kalangan mereka yang mempunyai risiko tinggi melalui kaedah CliEndomet, hanya dua orang pesakit mempunyai endometriosis peringkat awal dan 43 orang pesakit mempunyai endometriosis peringkat tinggi. CliEndomet telah didapati berkesan untuk diagnosa endometriosis peringkat tinggi berbanding peringkat awal, dengan spesifikasi 78% dan negative predictive value 96%, berbanding peringkat awal yang hanya mempunyai sensitiviti 71% dan positive predictive value 29%.

Kesimpulan: CliEndomet didapati boleh membantu dalam mendiagnosis endometriosis, bagi pesakit-pesakit yang tidak mahu menjalani pembedahan untuk pendiagnosaan yang lebih tepat. Keupayaan CliEndomet untuk berbuat demikian adalah lebih ketara untuk mereka yang mempunyai endometriosis peringkat tinggi.

ABSTRACT (ENGLISH)

Background: Endometriosis is one of the most common gynaecological disorders affecting the reproductive age group of women. The current gold standard in diagnosing this disease is via direct visualisation of endometriosis lesion intraoperatively and followed histological confirmation. Detection of non-invasive test is one of the priorities in endometriosis research. CliEndomet which was formulated by a group of researchers in Hospital Universiti Sains Malaysia using clinical manifestations, ultrasound findings and serum CA-125 had shown to be in substantial agreement with the intraoperative findings of endometriosis, but there is a need to validate the accuracy and reliability of CliEndomet using a more objective method i.e. histology confirmation.

Objectives: The main objective of this study is to assess the accuracy of CliEndomet in the diagnosis of endometriosis with histopathology as the confirmation. It also serves to determine the accuracy of CliEndomet in staging the severity of endometriosis.

Methodology: This was a cross sectional study that involving 94 patients who presented with symptoms of dysmenorrhea and chronic pelvic pain suggestive of endometriosis. Data regarding the symptoms, physical examination, scan findings and serum CA-125 were obtained preoperatively and scoring done according to CliEndomet into high possibility and low possibility group. Patients were then subjected to operation accordingly and the intraoperative findings were obtained regarding presence of endometriotic lesion. If endometriosis was clinically diagnosed, the disease was staged according to the revised American Society for Reproductive Medicine (ASRM) staging system. Regardless of the presence of

typical endometriotic lesion, tissue biopsy was taken during the operation for histopathology confirmation. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio (PPV) , negative likelihood ratio (NPV), likelihood ratio positive (LR +) and likelihood ratio negative (LR-). The reliability for the diagnosis of endometriosis using CliEndomet was tested using Kappa coefficient.

Results: A total of 94 patients were recruited into this study. Of the 94 patients, 56 were confirmed to have endometriosis by histology examination, and 50 were noted to have high risk for endometriosis using the CliEndomet scoring system. CliEndomet was shown to be 69.6% sensitive to diagnose endometriosis with positive predictive value of 78%. It has 71.1% of specificity and 61.4% negative predictive value. Its positive likelihood ratio was 2.41 and negative likelihood ratio of 0.43. CliEndomet was shown to have a fair agreement in diagnosing endometriosis (κ = 0,397 (95% CI, 0,21-0,58), p <0.005). During the surgery, 62 patients were found to have endometriosis. These patients were classified into having early stage endometriosis (AFS scoring system: minimal and mild endometriosis), and advanced stage disease (AFS scoring system: moderate and severe endometriosis). Of those who have early stage endometriosis, 5 patients had low risk and 2 had high risk of endometriosis according to the CliEndomet scoring system. Among those in the advanced stage disease, 12 patients were scored as low risk and 43 were scored as high risk. The sensitivity of CliEndomet to detect early stage endometriosis was 42% with positive predictive value of 29%. It is more capable to detect advanced stage disease (specificity 78%, negative predictive value of 96%).

Conclusions: CliEndomet has a role to diagnose endometriosis in patients who refuse invasive diagnostic method. It is more accurate to predict the existence of advanced disease then early stage disease.

1.0 INTRODUCTION

Endometriosis is a common gynaecological condition affecting about 6-10% of women of reproductive age and can be a debilitating disease. It is the second most common reason for surgery in premenopausal women. It is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory like reaction (S *et al.*, 2005). The presentation of endometriosis varies, being abdominal or pelvic pain remains as the commonest presentation. However, the severity of the pain does not correlate well with the extent of the disease. On the other hand, these symptoms mimic a lot of other diseases such as pelvic inflammatory disease and irritable bowel syndrome. Because of the non-specific presentation and clinical findings, diagnosis of endometriosis remains a challenge to clinicians over the centuries.

The use of blood investigations for various tumour markers and various imaging techniques has been evaluated to diagnose endometriosis. However, to date, no individual serum marker has been found to be specific to endometriosis (Hsu *et al.*, 2010). Combination of six biomarkers has been reported with good sensitivity and acceptable specificity even for minimal to mild disease (Mihalyi et al., 2010). Unfortunately, the exorbitant cost of these tumour markers prohibits its usage in our community.

In 2014, the European Society of Human Reproduction and Embryology (ESHRE) has stated that combination of laparoscopy and histological verification of endometrial glands and/ or stroma is considered the gold standard for diagnosis of the disease (Dunselman *et al.*, 2014). Despite this guideline, it was found that there was a wide variety in the inter observer accuracy in the visual diagnosis of endometriosis in the same patient (Buchweitz *et al.*, 2005). As at present there is no

other better diagnostic tool for endometriosis, this method remains to be the gold standard diagnostic tool for endometriosis. It means that for every patient in whom endometriosis is suspected clinically, an operation either by laparotomy or laparoscopic surgery for direct visualization of the lesion appearance, with histopathologic confirmation is required. At the current worldwide economic downturn, this management will cause an escalation to the medical cost and be a burden to many patients. In addition, many patients will be reluctant to undergo such an invasive procedure.

Because of the above problems, a consensus workshop, convened following the tenth world congress of endometriosis, had recommended that detection of a non-invasive diagnostic test is one of the priorities in endometriosis research (Rogers *et al.*, 2013). The development of a non-invasive diagnostic test for endometriosis would have a ground breaking impact on the patients' quality of life, on the efficacy of available treatment as well as on the cost of endometriosis (Mihalyi *et al.*, 2010). By having endometriosis to be diagnosed early, this will indirectly improve the outcome of infertility treatment which is associated with endometriosis.

1.1 THE CLIENDOMET

In 2014, a non-invasive diagnostic tool for endometriosis, named as CliEndomet, was created by a group of USM researchers. The objective of this yet to be published study was to find a non-invasive diagnostic tool for endometriosis, which include the combination of clinical presentation (chronic pelvic pain), pelvic assessment, ultrasonic assessment and the level of serum CA-125 (Pang SC et al, 2014).

In that study, all patients who presented to the Gynaecology Clinic of Hospital USM (Hospital USM), with any form of pelvic pain were recruited. A thorough history and physical examination which include pelvic examination was performed. The serum

CA-125 was taken and all patients had to undergo diagnostic operation either by laparoscopy or laparotomy to visualize the presence of endometriotic lesion. In the presence of endometriotic lesion, the stage of the disease was done in accordance to the revised America's Fertility Staging System.

A simple logistic regression test was then performed to evaluate the significant parameters which present among the patients diagnosed with endometriosis during the operation. From the analysis, significant variables were identified and later analysed using the multiple logistic regression test, which could predict the presence of endometriosis. It was noted that the presence of dysmenorrhoea, ovarian mass and serum CA-125 between 50 to 200u/ml were significantly associated with endometriosis. With those findings, a scoring system, which was named as CliEndomet (as shown in Figure 1), was formulated and was tested for its reliability to diagnose endometriosis. In that study, it was noted that CliEndomet carried a substantial agreement with direct visualisation of lesion for the diagnosis of endometriosis (kappa 0.77).

Even though direct visualisation of endometriotic tissue is considered as the gold standard diagnostic tool for endometriosis, when it comes to the development of a new diagnostic tool, the comparison should be made with an objective diagnostic tool, that is the histology of the biopsied tissue, thus the main aim of this study.

CliEndomet

The Diagnostic Clinical Scoring System For Endometriosis

Registration no: …… Date: ……

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

Total score = (dysmenorrhoea + ultrasonographic findings + CA-125) 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

Figure 1: The CliEndomet Scoring System

1.2 STUDY JUSTIFICATION

The diagnosis of endometriosis in the previous study had led into the formulation of CliEndomet (Pang et al, 2014) Even though this new non-invasive scoring system was proved to be reliable to predict the presence of endometriosis, the comparison was made with the intraoperative findings, which was surgeon's dependant. It is very important to be certain of the accuracy of this diagnostic tool, as when wrong diagnosis is made, the management given for the patient will be affected.

To further analyse the accuracy of the CliEndomet, an objective method of diagnostic tool, i.e. by histopathology examination of the lesion found during the operation, is needed. As tissue biosy was not taken in all patients in the previous study, comparison with this objective method could not be done in the same cohort of patients, thus the need of this study to be performed.

The methodology of the current study was same as in the previous study, except that tissue biopsy was done for all patients, regardless of the presence of typical endometriotic lesion.

2.0 LITERATURE REVIEW

A long delay in diagnosis of endometriosis has been reported in several studies due to the non-specific presentation of the disease: an overall diagnostic delay of 10 years in Germany and Austria, 8 years in the UK and Spain, 7 years in Norway, 7-10 years in Italy and 4-5 years in Ireland and Belgium (Ballard *et al.*, 2006; Nnoaham *et al.*, 2011) Considerable diagnostic delay of up to 8 years from presenting symptoms often confers a heavy economic and social price (Ballard *et al.*, 2006).

Traditionally, patients with endometriosis usually presented with cyclical pain and infertility although chronic pelvic pain, deep dyspareunia, cyclical intestinal complaints and fatigue are also common presentation. The ESHRE recommended that clinicians should consider the diagnosis of endometriosis in the presence of gynaecological symptoms, which include dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, infertility and fatigue, and non-gynaecological symptoms like dyschezia, dysuria, hematuria and rectal bleeding and shoulder pain in women of reproductive age (Dunselman *et al.*, 2014).

Specific symptoms have been reported to occur more frequently in women with endometriosis when compared to the control group (Ballard *et al.*, 2008). In a cohort study of women with chronic pelvic pain, women with endometriosis are more likely to report their pain as throbbing and experience dyschezia, in comparison with women with an apparently normal pelvis (Ballard *et al.*, 2010). However, the severity of endometriosis does not always correspond to the pain intensity. In a study conducted in Indonesia, the most frequent symptoms in patient with endometriosis was infertility (77.8%), which was followed by dysmenorrhea (62.5%), dyspareunia (35%) and chronic pelvic pain, which only consist of 27.5% (Hadisaputra, 2013). These symptoms could predict the stage III and stage IV endometriosis with good

accuracy, but very poor in diagnosing the early staged disease (Nnoaham *et al.*, 2012).

The presence of thickening of the uterosacral ligaments, and nodularity of the vagina, rectovaginal space and Pouch of Douglas found during the pelvic examination may indicate the presence of endometriosis (Bazot *et al.*, 2009; Hudelist *et al.*, 2009).

Several imaging methods, such as transvaginal ultrasonography (TVUS), transrectal ultrasonography (TRUS), computed topography scan (CT scan) and magnetic resonance imaging (MRI) have been used in an attempt to improve the non-invasive diagnosis of endometriosis. However, due to its inadequate resolution to identify adhesions or superficial peritoneal implants of endometriosis, its usage is rather limited (Hsu *et al.*, 2010).

TVUS has been proposed as the first line-line imaging technique because it allows extensive exploration of the pelvis. It is well accepted and widely available (Bazot *et al.*, 2009; Exacoustos *et al.*, 2014). Few literatures have supported that endometrioma can be diagnosed accurately by TVUS (Hsu *et al.*, 2010; Somigliana *et al.*, 2010; Van Holsbeke *et al.*, 2010). However, its value for the assessment of superficial peritoneal lesions, ovarian foci, and deeply infiltrating endometriosis is questionable (Lo Monte *et al.*, 2014) The inclusion of TVUS-based soft markers in women with symptoms suggestive of endometriosis improves the ability to predict or exclude the presence of endometriosis (Said and Azzam, 2013). Investigations on the use of three dimensional (3D) ultrasonography in area of rectovaginal septum, rectosigmoid and deep infiltrating disease have shown promising results (Abrao *et*

al., 2007; Grasso *et al.*, 2010; Pascual *et al.*, 2010). However, its accuracy is not well established (Dunselman *et al.*, 2014).

MRI is mostly used as a second line imaging modality for endometriosis. Although the accuracy is proven to be more superior to TVUS (Abdel Maboud Ibrahim and Elsaeed, 2012; Bazot *et al.*, 2009), the significant cost differential between MRI and TVUS makes MRI more useful only for ultrasonographically-indeterminate pelvic mass (Hsu *et al.*, 2010).

A considerable effort has been invested in searching for non-invasive methods of diagnosis of endometriosis. Various serum, peritoneal fluid and tissue markers are reported to be associated with endometriosis. Among those biomarkers that received more research attention than others are Cancer antigen 125 (CA-125), vascular endothelial growth factor (VEGF) and several interleukins such as IL-6 and IL-8 (Bedaiwy and Falcone, 2004; Elgafor El Sharkwy, 2013; Foda and Aal, 2012; Hirata *et al.*, 2011; Kitawaki *et al.*, 2005; Ozhan *et al.*, 2014; Ramos *et al.*, 2012; Socolov *et al.*, 2011). Unfortunately, until now the proposed markers have not shown to be effective in their diagnostic value due to their inconsistency that change with age, menstrual cycle and the fluctuant level in early stage of the disease (Socolov *et al.*, 2011). Combined use of potential biomarkers has been proposed to increase the sensitivity and specificity of the tumour markers in diagnosing endometriosis even in mild to moderate stage of the disease (May, Conduit-Hulbert et al, 2010; Mihalyi, Gevaert et al., 2010; Vodolazkaia, El-Aalamat et al, 2012; Ozhan, Kokcu et al., 2014). However, its accuracy and reliability is yet to be proven clinically.

Endometrial nerve fibers in the endometrium of women with endometriosis were analysed and being explored for diagnosis. Using endometrial biopsy for the

diagnosis was possible on the basis of the fact that multiple small unmyelinated sensory nerve fibers have found in the functional layer of ectopic endometrium in all women with endometriosis (Tokushige *et al.*, 2007). However some evidences suggest that endometriosis patients on hormonal treatment also have fewer nerve fibers compared to endometriosis patients who are not on hormones. Therefore this method was not useful unless combined use with other non-invasive method such as IL-6 (Elgafor El Sharkwy, 2013).

The gold standard for diagnosis of endometriosis remains inspection of the abdominal cavity and histological demonstration of lesions using laparoscopy or laparotomy (Dunselman *et al.*, 2014). However, performing any surgery is not without risk. There are also personal and institutional financial consequences attached to any surgery as well as the potential anxiety for women undergoing the procedure. Furthermore laparoscopic visualisation of endometriosis does not always correlate with the histopathologic diagnosis, especially for deep seated endometriosis (Wanyonyi *et al.*, 2011).

3.0 GENERAL OBJECTIVE

To assess the accuracy of CliEndomet as a reliable tool in the diagnosis of endometriosis

3.1 SPECIFIC OBJECTIVES:

1. To determine the reliability of CliEndomet in the diagnosis of endometriosis, with histopathology diagnosis as the comparison

2. To determine the accuracy or validity of CliEndomet in staging the severity of endometriosis

3.2 RESEARCH HYPOTHESIS

The CliEndomet is a reliable and accurate non-invasive diagnostic tool to diagnose any stage of endometriosis.

4.0 METHODOLOGY

4.1 STUDY DESIGN, LOCATION AND PERIOD OF STUDY

This is a cross sectional study with a goal to validate the accuracy of CliEndomet to diagnose endometriosis. The study was conducted in Hospital USM, for 12 months, from 1st October 2015 until 30th September 2016. This study consisted of patients who presented with pelvic pain.

4.2 REFERENCE POPULATION

Patients who have dysmenorrhea and chronic pelvic pain in Kelantan.

4.3 SOURCE POPULATION AND SAMPLING FRAME

Patients with chronic pelvic pain presented at Gynaecology clinic Hospital USM, Kelantan.

4.4 INCLUSION AND EXCLUSION CRITERIA

4.4.1 Inclusion criteria

1. Age between 18 to 45 years old, as endometriosis is common to occur in this reproductive age group.
2. Presented with any form of chronic pelvic pain, such as dysmenorrhoea, dyspareunia or dyschezia.
3. Ever have sexual intercourse, as pelvic examination which comprises of bimanual vaginal examination is part of the patient's assessment.

4.4.2 Exclusion criteria

1. Patients who have been confirmed to have endometriosis prior to study recruitment
2. Patients who have been 'empirically' treated as endometriosis prior to study recruitment

3. Patients who had pelvic pain which were already confirmed to be caused by other disorders such as pelvic inflammatory disease, varices or genital malformation
4. Patients with psychiatric problems

4.5 SAMPLE SIZE CALCULATION

The sample size was calculated using single proportion formula as below:

n= $(\frac{z}{\Delta})^2$ p (1-p)

Anticipated population proportion (p) = 59% (Pang SC et al , 2014)

Level of significance = 0.05

Absolute precision = 0.1

n = $\left(\frac{1.96}{0.1}\right)^2$ $0.59x\ (1-0.59)$

= 93

For the sample size of sensitivity and specificity is as below based on the calculation by Dr. Lin Naing @ Mohd. Ayub Sadiq from the website http://www.kck.usm.my/ppsg/statistical_resources/samplesize_forsensitivity_specificitystudiesLinNaing.xls and previous phase I study by Pang SC et al, 2014.

Expected sensitivity of 87.4%

Expected specificity of 90.4%

Expected prevalence of 47%

With desired precision of 0.1 at 95% confidence level, 94 subjects were recruited into the study.

As 10% drop out rate was anticipated therefore, a total of 103 (94 + 9) patients were required at the analysis stage.

4.6 STUDY METHOD

Patients presented with dysmenorrhea and chronic pelvic pain, who attended the Gynaecology Clinic of Hospital USM, fulfilled the inclusion and exclusion criteria, were recruited, using the convenience sampling. The consent to participate in the study was obtained from the selected patients. The study was not blinded to any parties.

In accordance to the standard procedure, all patients with any type of abdominal or pelvic pain were clinically assessed (via history taking and pelvic examination), had a transvaginal ultrasound performed, blood for Ca125 level taken and be subjected to operation (either laparoscopic or laparotomy), to obtain tissue for histology examination.

Dysmenorrhoea is defined as having cyclical abdominal pain one or two days prior to the onset of menses, lasted at any time during or throughout the menses.

Chronic pelvic pain refers to any form of pelvic pain (dyspareunia/ ovulation pain/ dyschezia/ non-specific pelvic pain) of more than 6 months' duration that has significant effect on daily function and quality of life.

A questionnaire was developed to determine the intensity of pain and severity of the disease The dysmenorrhoea and pelvic pain were evaluated using a modified version of Andersch and Milsom's multidimensional verbal rating scale (Koninckx PR , 1996), which defines pain according to the limitation of the ability to work (unaffected=0; rarely affected=1; moderately affected=2; clearly inhibited=3), co-existing of systemic symptoms (absent=0; present=1) and the need for analgesics (no=0; rarely=1; regularly=2; inefficacious=3). The score for each symptom was summed up and ranked into three groups as

mild, moderate and severe. Score 1-3 was considered as mild, 4 and 5 as moderate and 6 and 7 were ranked as severe.

The severity of deep dyspareunia and non- specific pelvic pain was evaluated using a 10- point linear analogue scale in which 0 indicated no pain and 10 as unbearable pain.

In clinical examination, the abdominal and bimanual examination were performed to determine the presence of abdominal or adnexa mass. The characteristic of the mass was evaluated for tenderness, mobility, margin, surface, consistency and the presence of ascites. The size and position of the uterus was also being evaluated.

Ultrasound of the pelvis was performed as transvaginal scan using CAPASEE II (Toshiba Otawara, Japan) connected to a 7MHz transducer. The size and position of the uterus were evaluated. In the presence of an adnexal mass, its size, site, nodularity, natre, content, the presence of septum and papillary projection were determined.

CA-125 is a high molecular weight glycoprotein of epithelial origin found in normal cells and which is produced in the celomic epithelium during embryonic development. Pang et al (2014) had demonstrated that serum CA-125 at the level of 50 to 200u/ml was strongly associated with endometriosis. Similarly in this study, blood for CA-125 level was taken prior to the time patient was going for operation.

The data of the patients were entered in the Clinical research Forms, which is only assessable to the research team members.

At the end of the clinical assessment, the data were collated and the risk of endometriosis for the patient will be scored using the CliEndomet scoring system, before subjecting the patient for operation.

Patients then subjected to operation, either by laparoscopic or laparotomy. Cystectomy was performed and the cyst wall was sent for histology examination should it was noted to be present during the operation. In the absence of ovarian tissue or endometriotic lesion, a random tissue biopsy was taken for that purpose. Should a typical endometriotic lesion was observed during operation, the disease was staged using the revised American Society for Reproductive Medicine (ASRM) staging system.

The reference diagnosis of endometriosis was made based on the findings of endometriotic tissue (defined as the presence of ectopic endometrial tissue, i.e. glandular and stromal structures) in the histopathology examination.

4.7 STATISTICAL ANALYSIS

Data was entered and analysed using SPSS version 22. Descriptive statistics were used to summarise the socio demographic characteristics of subjects. Numerical data will be presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data will be presented as frequency (percentage).

Level of significance is set as 5% and result was presented with 95% confidence intervals. The accuracy or validity of CliEndomet was tested by determining the sensitivity and specificity of the score, as well as the positive predictive and negative predictive value were determined.

The reliability for the diagnosis of endometriosis using CliEndomet was tested using Kappa coefficient.

4.8 TERMINOLOGY

Chronic pelvic pain :

Any form of pelvic pain (dyspareunia/ ovulation pain/ dyschezia/ non-specific pelvic pain) of more than 6 months duration that has significant effect on daily function and quality of life.

Dyschezia

Difficult or painful evacuation of feces from the rectum.

Dysmenorrhea

Cyclical abdominal pain one or two days prior to the onset of menses, lasted at any time during or throughout the menses

Dyspareunia

Persistent or recurrent genital pain that occurs just before, during or after intercourse.

Histopathology

It is the microscopic study of abnormal tissue and organs at the cellular level.

Nonspecific pelvic pain

Abdominal or pelvic pain of less than 7 days duration for which the diagnosis remain uncertain after clinical examination and baseline investigations.

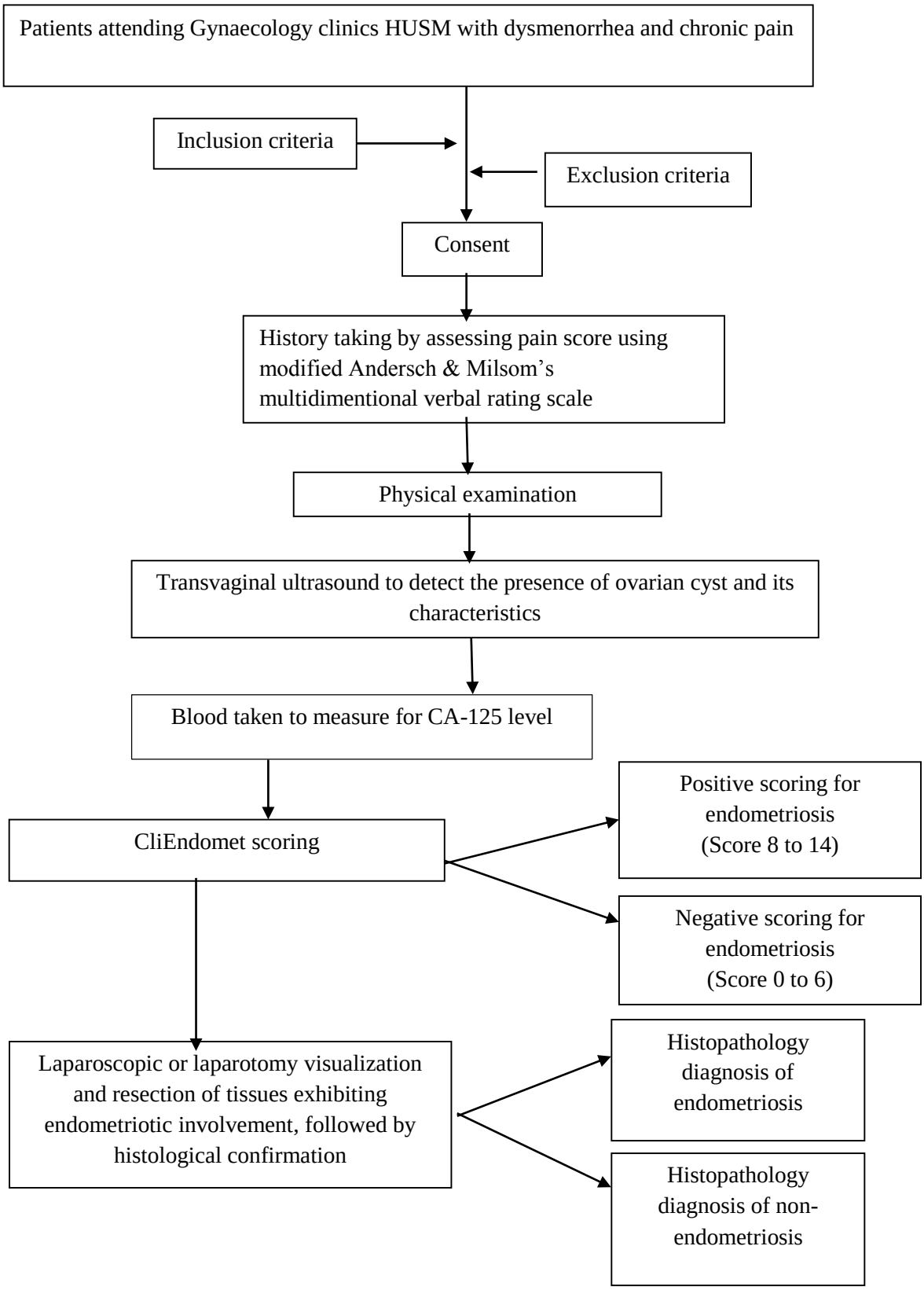
Ovulation pain

Lower abdominal pain associated with ovulation, about 14 days prior to next menstruation

Sexual intercourse

Any penetration of the female sex organ by the male sex organ

4.9 FLOW CHART OF STUDY



RESULTS

5.0 RESULTS

5.1 DEMOGRAPHIC DATA

A total of 94 patients were recruited into the study, 56 patients (59.6%) was confirmed to have endometriosis by histology examination (Figure 2).

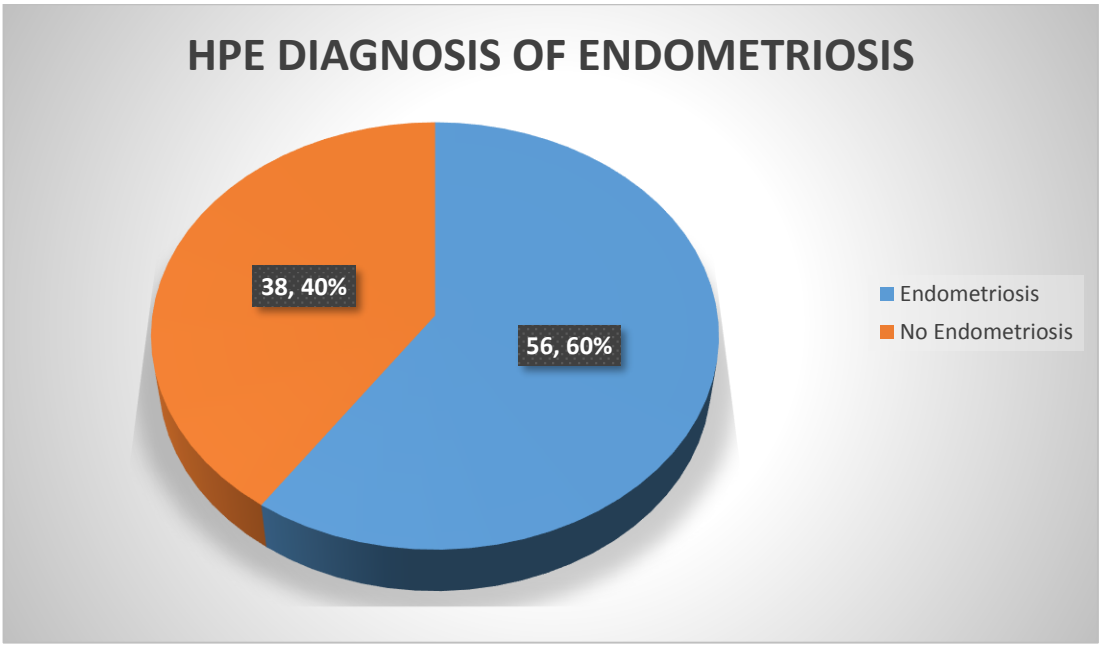


Figure 2: Diagnosis of endometriosis by histology examination

The age of the patients ranged from 19 to 45 years old, with mean age of 32.87 ± 7.25 years (Table 1).

Majority of the patients were Malay (96.8%).

Majority of the patients fell in the category of overweight and obese, contributing 34.04% (n= 32) and 22.34% (n=21) respectively. Only 30.85% (n=29) of them had normal BMI. Eight patients (8.51%) were noted to be underweight and one (1.06%) was noted to be morbidly obese. The mean BMI of the patients was 26.33 ± 5.61 kg/m^2.

More than half of the patients (n=55, 58.5%) had subfertility. The mean duration of subfertility was 8.12 ± 6.00 years. The mean parity for those with a child or children was 1.07 ± 1.72.

The demographic data of the patients was summarised as in Table 1.

The demographic data of the patients was compared between endometriotic patients and non-endometriotic patients. The demographic data were noted to be well distributed among the two groups, as shown in Table 2.

Table 1: Demographic data

Variables	Frequency (n)	Percentage (%)	Mean	Standard deviation (SD)
Age (years):			32.87	7.25
- **≤ 19.9**	2	2.10		
- **20.0-29.9**	35	37.20		
- **30.0-39.9**	32	34.0		
- **40.0-49.9**	25	26.6		
Ethnic group:				
- **Malay**	91	96.81		
- **Chinese**	1	1.06		
- **Indian**	0	0.00		
- **Others**	2	2.13		
BMI (kg/m^2)			26.33	5.61
- **< 18.5**	8	8.51		
- **18.5-24.9**	29	30.85		
- **25.0-29.9**	32	34.04		
- **30.0-34.9**	21	22.34		
- **35.0-39.9**	3	3.19		
- **≥ 40**	1	1.06		
Subfertility				
- **Present**	55	58.51		
- **Absent**	39	41.49		
Duration of subfertility (years), n=55			8.12	1.72
- **2.0-4.9**	20	36.36		
- **5.0-7.9**	11	20.00		
- **8.0-10.9**	24	43.64		
- **≥ 11**	0	0.00		
Parity			1.07	6.00
- **0**	57	60.64		
- **1-2**	20	21.28		
- **3-4**	13	13.83		
- **5-6**	4	4.25		
- **≥7**	0	0.00		

Table 2: Comparison of demographic data between endometriotic and non-endometriotic patients

VARIABLES	MEAN		b	Crude OR (95% CI)	P Value
	Endometriosis (n= 56)	No endometriosis (n=38)			
Mean age (years)	32.98 (7.293)	32.71 (7.00)	0.01	1.01 (0.95-1.06)	0.863
BMI (kg/m^2)	25.67 (6.07)	27.30 (4.89)	-0.052	0.95 (0.88-1.02)	0.741
Parity	0.96 (1.80)	1.24 (1.58)	-0.09	0.91 (0.72-1.16)	0.835
Subfertility					
• **Present**	36 (64.3%)	19 (50%)	0.59	1.80 (0.78-4.16)	0.169
• **Absent**	20 (35.7%)	19 (50%)			
Last child birth	3.36 (5.92)	4.21 (5.92)	-0.02	0.98 (0.91-1.05)	0.491
Years of subfertility	8.13 (6.30)	8.11 (5.56)	0.01	1.00 (0.91-1.10)	0.987

5.2 DIAGNOSIS OF ENDOMETRIOSIS USING CLIENDOMET

Using the CliEndomet scoring system, the patients were categorised to be either unlikely to have endometriosis, low possibility, moderate possibility, or high likely to have endometriosis. Only patients who were in the moderate and high possibility to have endometriosis were considered to be positive endometriosis using the CliEndomet criteria.

Table 3 shows the distribution of total score of the patients using the CliEndomet scoring system. Most of the subjects fall into the total score of 6 and 8, with 18 persons in each group, followed by 17 persons with total score of 10.

Table 3: Distribution of total score using CliEndomet scoring system

Total Score	Frequency (n)	Percentage (%)
0	1	1.1
2	10	10.6
4	14	14.9
6	18	19.1
8	18	19.1
10	17	18.1
12	14	14.9
14	2	2.1
Total	94	100.0

The total scores of the patients were grouped into unlikely to have endometriosis (0-2), low possibility (4-6), moderate (8-10) and high possibility (12-14) to have endometriosis, and these possibilities were compared with the histology diagnosis as shown in Table 4.