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**Objectifying acute effects of Acupuncture for pelvic pain due to endometriosis:
A clinical research protocol using a novel pain assessment system - study design
and case report.**

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Dedication

To my Dear Mother Rahma Ahmed, and my lovely brother Abdullahi Ibar,
for the love and support.

Acknowledgments

First of all I would like to thank Allah for giving me everything in my life.

To my Family for being always on my side emotionally and physically.

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Abstract

Background:

Endometriosis (EM) is a common health problem affecting women worldwide and often undiagnosed. It is estimated that 7% -10% of women in the general population suffer from EM. According to conventional medicine, treatment of EM needs life-long management including medical or surgical treatments, hormonal therapy being mostly used. However, prolonged administration of these therapies remains challenging due to the plethora of serious adverse effects.

Acupuncture has been studied in Gynecological disorders but its effectiveness for pain in endometriosis remains uncertain. Few studies have been published on acupuncture for "Endometrialgia". Current data suggests that acupuncture may be helpful in relieving the chronic pelvic pain which in turn may improve EM patient's quality of life.

Objectives:

To develop a clinical research protocol for a randomized, sham-controlled preliminary study that evaluates the acute effects of acupuncture for endometriosis-related pain.

To objectively measure the effect of acupuncture in pain, by using a new pressure sensitive sensor device.

To assess feasibility of the study protocol, and collect preliminary data, for a larger study.

To evaluate whether acupuncture can significantly improve pelvic pain in patients with pelvic endometriosis.

Methods:

Study type: a clinical protocol of a preliminary, prospective, randomized, controlled, single- blinded clinical trial in a cross over design.

Inclusion Criteria: women from 18-55 yrs. with pelvic pain due to EM beyond the time of menstrual bleeding at Sao Joao Hospital EM clinic, mentally fit and co-operative with the study. Patients are naïve to acupuncture.

Exclusion criteria: women with menses (to exclude dysmenorrhea), chronic pelvic pain due to non-endometriosis causes, active infectious disease, congenital diseases or any other severe disease.

Intervention: The verum acupuncture consists of leopard spot technique on Gb 41 and Sp6, sham acupuncture, however in non-acupoints 1Cun distant from the Acupoints of the verum group.

Setting: Endometriosis outpatient consultation office, Service of Gynecology and Obstetrics of Hospital Center São João.

Ethics Committee: The protocol was approved by the institutional local Ethics Committee.

Sample: 30 patients, diagnosed with pelvic Endometriosis, and have pelvic pain secondary to EM.

Randomization: patients are assigned into two groups by coin flip into Experiment and Control group. All patients' consents are obtained before the beginning of the intervention. Crossover of the two groups will be performed after one week of wash out.

- **Experiment group:** patients will undergo verum acupuncture in points chosen according to the Heidelberg model of Traditional Chinese Medicine (Gb 41 and Sp6).
- **Control group:** patients will undergo sham acupuncture in non-acupoints 1 *cun* distant from the verum acupoints, outside the conduits.

Experimental procedure: The first step is pain assessment by VAS and by using specially designed sensor for this study while applying deep pressure on the pelvic region until the maximum pain intensity. The second step consists of one type of Intervention as defined above (verum or sham). Needling consists of applying the bloodletting "leopard spot" technique in both groups-

Expected Results:

The effect of acupuncture as analgesic is demonstrated extensively in the literature. Recruitment for this study has recently started at Hospital São João, a major central university hospital in Porto. The study may reveal that a significant relief could be achieved after the application of acupuncture in patients with chronic pelvic pain due to endometriosis in the specific point according to Heidelberg model and this decrease of the pain intensity can be detected by the pain scales and tools such as VAS and the pain sensor machine.

Discussion:

This study is currently in course. We have introduced a novel pressure sensitive device in order to measure the objective effect of acupuncture in pain. Results from this study may in the future grant a larger prospective, controlled, multi-blinded, randomized protocol with longer follow-up period. This may add more evidence to the growing number of evidences and prove that Acupuncture is another interesting tool to manage this condition responsible for a great discomfort and reduced quality of life for affected women and their partners and could be included in the guidelines for the management of chronic pain due to endometriosis guidelines.

Keywords: Endometriosis, Chronic Pain, Acupuncture, Traditional Chinese Medicine.

Resumo

Enquadramento:

A endometriose (EM) é um problema de saúde comum que afecta as mulheres mundialmente e com frequência subdiagnosticado. Estima-se que 7-10% das mulheres na população geral padecem de EM. De acordo com a medicina convencional, o tratamento da EM necessita de uma abordagem para toda a vida, incluindo tratamento médico ou cirúrgico, sendo a hormonoterapia a mais usada. Contudo, a administração prolongada dos tratamentos convencionais permanece um desafio devido à pleora de efeitos adversos sérios potencialmente associados.

A acupunctura tem sido aplicada no tratamento de distúrbios ginecológicos mas a sua eficácia no tratamento da dor na endometriose permanece incerta. Poucos estudos foram publicados sobre acupunctura para “Endometrialgia. Os dados actuais sugerem que a acupunctura poderá ser útil no alívio da dor pélvica crónica, o que por sua vez poderá melhorar a qualidade de vida das doentes com EM.

Objectivos:

- 1) Desenvolver um protocolo de investigação clínica para um estudo preliminar, randomizado, controlado com acupunctura falsa, que avalie os efeitos da acupunctura na dor relacionada com a endometriose.
- 2) Medir objectivamente o efeito da acupunctura na dor, usando um novo sensor sensível à pressão.
- 3) Avaliar a viabilidade do protocolo de estudo, recolher dados preliminares para um suportar um estudo posterior de maior escala.
- 4) Avaliar se a acupunctura pode melhorar significativamente a dor pélvica em doentes com endometrioses.

Métodos:

Tipo de estudo: ensaio clínico preliminar, prospectivo, randomizado, controlado, cego, com desenho tipo “*cross-over*”.

Crítérios de inclusão: mulheres entre 18-55 anos de idade, com dor pélvica devida a EM fora do cataménio; doentes da consulta de Endometriose no Hospital São João, sem doenças psiquiátricas ou neurológicas que impeçam acupuncturam; pacientes que nunca tenham realizado acupuncturam previamente; assinam consentimento informado.

Crítérios de exclusão: mulheres na altura da menstruação (para excluir dismenorrea primária), com dor crónica por causas diversas. Doença infecciosa activa; doenças congénitas ou outras doenças graves

Intervenção: A acupunctura verdadeira consiste de técnica “*leopard spot*” nos pontos Gb41 e SP6; acupunctura falsa consiste de não-acupontos 1 *cun* distantes dos pontos verdadeiros.

Local: Consulta de Endometriose, Serviço de Ginecologia e Obstetrícia do Centro Hospitalar de São João.

Comissão de Ética: O protocolo foi aprovado pela Comissão de Ética local.

Amostra: 30 pacientes, com diagnóstico de Endometriose pélvica, e com dor pélvica secundária a EM.

Randomização: pacientes são alocados em 2 grupos através do método de moeda ao ar, para o grupo Experimental e grupo controlo. O cruzamento dos doentes entre os grupos realiza-se após uma semana de “*wash-out*”

- **Grupo Experimental:** submetidos a acupunctura verdadeira em pontos seleccionados de acordo com o modelo de Heidelberg de Medicina Tradicional Chinesa (Gb 41 and Sp6).
- **Grupo Controlo:** submetidos a acupunctura falsa em não-acupontos 1 *cun* distantes dos pontos verdadeiros, fora dos condutos.

Procedimento experimental: 1º passo: avaliação da dor pela escala visual analógica e por um sensor especialmente elaborado para este estudo enquanto se aplica pressão profunda na região pélvica até atingir a intensidade máxima da dor. 2º Passo: intervenção (acupunctura verdadeira ou falsa). A punctura consiste da aplicação da técnica de sangria “*leopard spot*” em ambos os grupos.

Resultados esperados:

O efeito analgésico da acupunctura tem vindo a ser demonstrado extensivamente na literatura. O recrutamento para este estudo iniciou-se recentemente no Centro Hospitalar São João. O estudo poderá revelar que a acupunctura em pontos específicos de acordo com o Modelo de Heidelberg de MTC poderá provocar um alívio significativo da dor crónica pélvica devida a endometrioses e que esta redução da intensidade da dor possa ser detectada em escalas da dor bem como através de um dispositivo de medição da pressão que induz a dor máxima tolerada por forma a obter uma avaliação objectiva do efeito da acupunctura.

Discussão:

Este estudo encontra-se em curso. Introduzimos a novidade de um dispositivo criado de novo que consiste de um sensor de mediação de pressão e que pode objectivar a alteração da intensidade da dor provocada pela acupunctura.

Os seus resultados poderão suportar no futuro um estudo de maior dimensão, prospectivo, randomizado, controlado, e duplamente cego com um período de seguimento de longo prazo.

Isto pode adicionar mais evidência à evidência atual que prove que a acupuntura possa ser uma ferramenta adicional na abordagem desta condição clínica que provoca um grande desconforto e reduzida qualidade de vida às mulheres bem como aos seus parceiros. Se demonstrada o seu benefício, então a acupuntura poderá vir a ser incluída nas linhas de orientação da abordagem da dor crónica secundária a endometriose

.
Palavras-chave: Endometriose, dor crónica, Acupuntura; Medicina Tradicional Chinesa

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List of abbreviations

EM	Endometriosis
TCM	Traditional Chinese Medicine
HM	Heidelberg Model
CPP	Chronic Pelvic Pain
VAS	Visual Analogue Scale
CAM	Complementary & Alternative Medicine
CHM	Chinese Herbal Medicine
TENS	Transcutaneous Electrical Nerve stimulation
EA	Electrical Acupuncture
GB	Gallbladder Meridian
SP	Spleen Meridian
ST	Stomach Meridian
BL	Bladder Meridian
LI	Liver Meridian
HT	Heart Meridian
GV	Governor Vessel Meridian
KI	Kidney Meridian
CV	Conception Vessel Meridian
TE	Triple Energizer Meridian
PG	Prostaglandins
MA	Manual acupuncture
ASRM	American Society of Reproductive medicine
MMP-2	MATRIXMETALLOPROTIENASE-2
CA125	Cancer Antigen 125
NSAID	Non-Steroidal Anti Inflammatory Drugs

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I. Introduction

1.1. Definition and epidemiology

Endometriosis is a disorder in which abnormal growths of tissue, histologically resembling the endometrium are present in locations other than uterine lining[1]. Although Endometriosis can occur very rarely in post-menopausal women, it is found almost exclusively in women of reproductive age and it is divided according to the site of implementation, the lesions are usually found on the peritoneal surfaces of the reproductive organs and adjacent structures of the pelvis, but they can occur anywhere in the body. The size of the individual lesions varies from microscopic to large invasive masses that erode into the underlying organs and cause extensive adhesion formation. The most common symptom is chronic pain, notably dysmenorrhea, dyspareunia, and infertility, which all may lead to a reduction in the patient's quality of life[2].

Endometriosis is a common and important health problem of women. It is estimated that 7% to 10%[1] of women in the general population have endometriosis. Pelvic endometriosis is present in 6% to 43% of women undergoing sterilization, 12% to 32% of women undergoing laparoscopy for pelvic pain, and 21% to 48% of women undergoing laparoscopy for infertility. Endometriosis occurs more often in women who have never had children[3].

Some evidence suggests that endometriosis may have a genetic component. Women with first degree relatives with endometriosis have nearly a 10-fold increased risk of developing endometriosis. The proposed mechanism of inheritance is polygenic multifactorial [4].

1.2. Pathogenesis

The cause of endometriosis is unknown. However, there are Three major theories by which Endometriosis may develop.[1, 5]

- 1.** Direct implantation of endometrial cells, typically by means of retrograde menstruation. This mechanism is consistent with the occurrence of pelvic endometriosis and its predilection for the ovaries and pelvic peritoneum, as well as for sites such as an incision or episiotomy scar. Direct implantation is commonly referred to as Sampson's theory because of his experimental work in 1920s that showed the possibility of such a mechanism.
- 2.** Vascular and Lymphatic dissemination of endometrial cells (Halban's theory). Distant sites of endometriosis can be explained by this process (i.e., endometriosis in locations such as lymph nodes, the pleural cavity, and kidney).

3. Coelomic theory of multi potential cells in the peritoneal cavity (Meyer's theory) states that, under certain conditions, these cells can develop into functional endometrial tissue. This could even occur in response to the irritation caused by retrograde menstruation. The early development of endometriosis in some adolescents before the onset of menstruation lends credence to this theory.

It is probable that more than one theory is necessary to explain the diverse nature and locations of endometriosis. Underlying all these possibilities is a yet undiscovered immunological factor that would explain why some women develop endometriosis whereas others with similar characteristics do not.

1.3. Diagnosis and classification of Endometriosis

Endometriosis is a chronic, multifactorial disease, and has significant impact on a women's quality of life. Pelvic pain, infertility, dyspareunia, dysmenorrhea and intestinal disorders, are the most common clinical manifestations.

The diagnosis of EM is often strongly suspected from the initial history of the patient, most patients complaining from constant pelvic pain, infertility, dysmenorrhea and dyspareunia, in those patients EM have to be excluded. Cancer Antigen (CA-125) is often elevated in women with endometriosis.

However, it has been shown that this marker is elevated in many other pelvic diseases and therefore has little specificity in the diagnosis of endometriosis. After medical or surgical treatment CA-125 return to normal value and in this case it can be helpful to evaluate recurrence.[6]

Laparoscopy is considered the primary diagnostic modality for endometriosis. Histologic demonstration of a combination of endometrial glands and stroma in biopsy specimens obtained from outside the uterine cavity is required to make the diagnosis of endometriosis [7].

The following in descending order are the most common sites of involvement found during laparoscopy [1, 7, 8]:

- Ovaries (almost have of the cases)
- Posterior cul-de-sac
- Broad ligament
- Uterosacral ligament
- Recto-sigmoid colon
- Bladder
- Distal ureter

There are some staging systems to assist in describing the anatomic location and severity of endometriosis at operation, although they are not entirely satisfactory, these scoring systems are useful for reporting operative findings and for comparing the results of various treatment protocols. One of the reliable tools is the American society for reproductive medicine revised classification of endometriosis.



AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____
 Stage I (Minimal) - 1-5 Laparoscopy _____ Laparotomy _____ Photography _____
 Stage II (Mild) - 6-15 Recommended Treatment _____
 Stage III (Moderate) - 16-40 Prognosis _____
 Stage IV (Severe) - >40
 Total _____

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	4		40	
	Complete				
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.
 Denote appearance of superficial implant types as red (R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white (W), opacifications, peritoneal defects, yellow-brown], or black (B) black, hemosiderin deposits, blue]. Denote percent of total described as R___%, W___% and B___%. Total should equal 100%.

Additional Endometriosis: _____

 Associated Pathology: _____

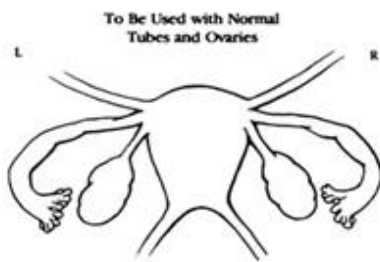


Figure1: Revised ASRM classification of Endometriosis.

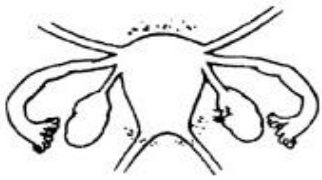
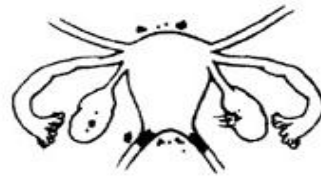

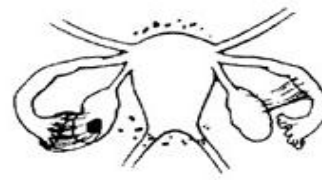
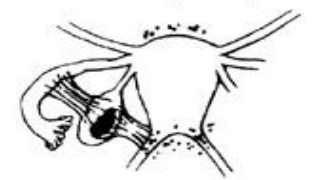

STAGE I (MINIMAL)			STAGE II (MILD)			STAGE III (MODERATE)		
								
PERITONEUM	Superficial Endo	- 1-3cm - 2	PERITONEUM	Deep Endo	- > 3cm - 6	PERITONEUM	Deep Endo	- > 3cm - 6
R. OVARY	Superficial Endo	- < 1cm - 1	R. OVARY	Superficial Endo	- < 1cm - 1	CULDESAC	Partial Obliteration	- 4
	Filmy Adhesions	- < 1/3 - 1		Filmy Adhesions	- < 1/3 - 1	L. OVARY	Deep Endo	- 1-3cm - 16
	TOTAL POINTS	4	L. OVARY	Superficial Endo	- < 1cm - 1		TOTAL POINTS	26
								
PERITONEUM	Superficial Endo	- > 3cm - 3	PERITONEUM	Superficial Endo	- > 3cm - 3	PERITONEUM	Deep Endo	- > 3cm - 6
R. TUBE	Filmy Adhesions	- < 1/3 - 1	L. OVARY	Deep Endo	- 1-3cm - 32**	CULDESAC	Complete Obliteration	- 40
R. OVARY	Filmy Adhesions	- < 1/3 - 1		Dense Adhesions	- < 1/3 - 8**	R. OVARY	Deep Endo	- 1-3cm - 16
L. TUBE	Dense Adhesions	- < 1/3 - 16*	L. TUBE	Dense Adhesions	- < 1/3 - 8**		Dense Adhesions	- < 1/3 - 4
L. OVARY	Deep Endo	- < 1 cm - 4		TOTAL POINTS	51	L. TUBE	Dense Adhesions	- > 2/3 - 16
	Dense Adhesions	- < 1/3 - 4				L. OVARY	Deep Endo	- 1-3cm - 16
	TOTAL POINTS	29					Dense Adhesions	- > 2/3 - 16
							TOTAL POINTS	114
			*Point assignment changed to 16					
			**Point assignment doubled					

Figure 2: Endometriosis Stages

1.4. Chronic pelvic pain

Chronic pelvic pain (CPP) could be defined as the presence of non-cyclic pain of 6 months duration or longer, that localizes to the anatomic pelvis and is severe enough to cause functional disability and require medical or surgical treatment. That means we can make diagnosis of CPP when the pain started from the pelvic area and remain for at least 3-6 months.

CPP etiology could be related to different situations. It is well evidenced by Howard[9] and Vercellini et al [10] that pain may be due to nociceptive, inflammatory, or neuropathic mechanisms and probably all three of these mechanisms are relevant to endometriosis-associated pelvic pain. Chronic pelvic pain in Endometriosis patients is mostly related to the adhesions and pelvic scarring found in association with pelvic endometriosis. The severe pain is associated with deeply infiltrating lesions, and it is thought that the degree of pain is perhaps determined by the depth of invasion. Pelvic EM is present in 6% to 43% of women undergoing sterilization, and up to 12% to 32% of women undergoing laparoscopy for pelvic pain.

In an effort to describe the mechanisms of the pain in endometriosis three theories are drawn to explain the pain and they are as follow

- production of substances such as growth factors and cytokines by activated macrophage and other cells associated with the functioning endometriosis implant
- Direct and indirect effect of acute bleeding from endometriosis implant
- irritation of the pelvic or direct invasion of these nerves by infiltrating endometriosis implants specially in cul-de-sac[9]

Another important element to consider is that pathophysiology in one organ can influence physiology and responses to pathophysiology in other organs because CNS is organized by intensive cross-system and viscerovisceral interaction this means that CPP could arise and be exacerbated also by other organ's condition and often it derived from more than one of the following [11, 12]:

1) Gynecological and obstetric: post-surgical pain due to the presence of adhesions that can involve pelvic organs and walls; chronic cervical infection for cervical stenosis; post-surgical complication after cryo/laser/diathermy surgery; pelvic inflammatory disease (PID) and adenomyosis.

2) Urologic: recurrent and/or interstitial cystitis; complication after urologic surgery; nephrolithiasis; urolithiasis.

3) Gastrointestinal: irritable bowel syndrome; chronic inflammatory bowel disease, diverticulosis, polyposis.

4) Vascular disease: pain is thought to arise from dilated pelvic veins in which blood flow is markedly reduced (pelvic congestion syndrome).

5) Musculoskeletal diseases

6) Neurological: altered spinal cord and brain processing of stimuli in women with chronic pelvic pain.

7) Psychological: it is widely reported that psychological diseases, such as depression and/or anxiety disorder could vent on the pelvic area.

The treatment of chronic pelvic pain may consist of two approaches. On one hand it is important to treat chronic pain considering itself as a diagnosis and on the other hand to treat diseases or disorders that might be a cause of or a contributor to chronic pelvic pain as mentioned earlier[11].

1.5 Conventional Therapy of EM

Treatment options are dictated by the patient's desire for future fertility, her symptoms, and the stage of her disease and to some extent her age.

We will briefly state the management in both western medicine and in the complementary and alternative medical (CAM)[12]

Treatment for EM in western medicine can be medical and/or surgical. In this field hormone replacement therapy is commonly used and involves oral contraceptives, progestogenics, gestrinone, Danazol (androgen derivate), and gonadotropin-releasing hormone(GnRH) agonists. Current investigations are also evaluating the role of GnRH antagonists, estrogen receptor beta ($ER\beta$) agonist, progesterone receptor modulators, angiogenesis inhibitors, aromatase inhibitors, COX-2 (Cyclooxygenase 2) selective inhibitors, and immune modulators. However, long-term administration with these therapies remains challenging due to the plethora of serious adverse effects involved, such as massive hemorrhage, premenopausal stage symptoms, masculinizing manifestations, and liver dysfunction.

On the other hand in the recent years, the complementary and alternative medical (CAM) treatment for EM has become popular due to the few adverse reactions reported. The CAM therapy for EM includes several different treatments such as herbs (herbal prescription, extract, and patent), acupuncture, microwave physiotherapy, and Chinese herb medicine enema (CHM enema). [12]

These CAM therapies are effective at relieving dysmenorrhea, shrinking adnexal masses, and promoting pregnancy, with less unpleasant side effects when compared to hormonal and surgical treatments.

Although it has been known for long time the uses of CAM especially in pain management the Guideline development group (GDG) assigned by the European Society of human Reproduction and Embryology for developing guideline for the management of women with endometriosis based on the best available evidence in the literature has retrieved and evaluated existing evidence on complementary and alternative treatment options for pain in women with endometriosis, and concluded that the effectiveness of high-frequency transcutaneous electrical nerve stimulation, dietary supplements, acupuncture and traditional Chinese medicine are not well established for pain management in endometriosis (Astin et al., 1998; Eisenberg et al., 1998; Proctor et al., 2002; Sesti et al., 2007; Flower et al., 2009; Zhu et al.,2011). The GDG also does not recommend the use of nutritional supplements, complementary or alternative medicine in the treatment of endometriosis-associated pain, because the potential benefits and/or

harms are unclear. This should be considered in light of the methodological restriction to papers written in English and of the inherent difference between the holistic Chinese approach and the scientific approach of the Western world. However, the GDG acknowledges that some women who seek complementary and alternative medicine may feel benefit from CAM.[13]

Complementary medicine Approaches for treatment of Endometriosis

Table 1: General view of all therapeutic approaches.

Therapeutic approaches	Clinical indication	Specifications	Efficacy	Precautions
Herbal products	EM with chronic pelvic pain, dysmenorrhea, and infertility	According to TCM practitioners' judgment of the disease, propose appropriate TCM prescriptions	Alleviate dysmenorrhoea Shrink endometriotic lesion Promote pregnancy Reduce recurrence rate	Patients who are allergic to some foods and pollen should take the herbal products with caution
Acupuncture and Moxibustion	EM with chronic pelvic pain, dysmenorrhoea, and infertility	Take the appropriate acupoints and choose needling, auricular point, or moxa-moxibustion therapy, according to the disease status of patient. 30 min is a course of treatment for acupuncture (needling, auricular point); 40–50 min is a course of treatment for moxibustion	Alleviate dysmenorrhoea Promote pregnancy	Some patients may occur fainting condition
CHM enema	EM with chronic pelvic pain, dysmenorrhoea, and infertility	Ask the patient to take the left lateral decubitus position. Put the boiled TCM herbal liquid into 20 mL syringe, with the temperature of 38~40°C. With a disposable catheter connection, slowly push TCM herbal liquid into the rectum. Tell the patient to relax and keep the TCM herbal liquid more than 2 hours	Alleviate dysmenorrhoea Shrink endometriotic lesion	Unfit for predominant irritable bowel syndrome patients
Microwave physiotherapy	nonacute phase of EM	Ask the patient to take supine position. Put the microwave physiotherapy instrument facing patient's lower abdomen, with the distance of 35–45 cm. 30 min is a course of treatment	Alleviate dysmenorrhoea Shrink endometriotic lesion	Attention to operating time, adjusting the distance of microwave physiotherapy equipment, so as not to scald patients

Figure 3: General view of all CAM therapeutic approaches.

2. Acupuncture History and overview

The origin of Acupuncture can be traced back to age of clan communities during the period of primitive Chinese Society.

Acupuncture needles were developed from ancient Bian-stone needles. A Bian Stone needles is kind of Medical instrument made of special stone which was ground into different shapes. Bian-stone needles with sharp ends were most commonly used for bloodletting and removing pus, while the lancet-shaped Bian-stones were used to create incisions. The club or round shaped Bian-stones were used for message and heat application. It is believed that treating diseases with Bian-stone needles was first used by the Chinese ethnic people who lived in fishing areas on the eastern coastline. In addition Bian-stone needles were found in the Neolithic sites in inner Mangolia autonomous region and in the city of Rizhao located in Shandong province. All these findings provided strong evidence that the origin of acupuncture can be traced back to the Neolithic age. Therefore Bian-stone needling is the predecessor of acupuncture. With the development of metallurgy, metal needles subsequently replaced stone needles as therapeutic tool.[14]

Acupuncture as academic discipline has experienced an interrupted long course of development. The rapid progress in politics, economy and culture all provided a conducive milieu for the development of TCM. As early as the 6th century A.D., TCM was also introduced to other countries such as Korea, Japan. And with more and more cultural exchanges, Acupuncture become known worldwide with appropriate categories such as definition of name, location and techniques of needling of 349 points.[15] International academic exchange became a frequent event while more academic associations were established, especially after acupuncture and moxibustion were introduced to Europe in the late 16th Century A.D. In 1950s, medical staff from the pre-Soviet Union and Eastern Europe begun to learn acupuncture in China. In 1997, WHO listed 43 diseases that suitable indications for acupuncture and moxibustion therapy. According to available statics, more than 300 kinds of disease in different specialist areas of Internal Medicine, Surgery, Gynaecology, Paediatrics, five sense organs and Dermatology can be treated by acupuncture and moxibustion. 1997, it was clearly stated in the specialists' hearing of the National Institute of Health (NIH) of the United States of America that acupuncture can be effectively used for a wide range of diseases because of it is significant therapeutic effects and few side effects.[16]

Officially, Chinese medicine starts with a book called The Yellow Emperor's classic on internal medicine. [17]

Body Measurements of Acupuncture

In Chinese Medicine Acupuncture Measurements are taken individually using the thumb measurement known as *cun* of the person being treated, therefore measuring distances in the body surface must be adjusted to the patient size. See the figure below.[18]

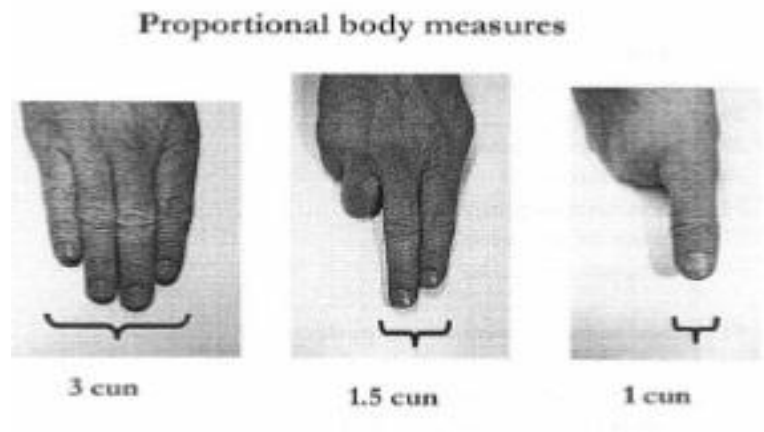


Figure 4: Proportional body measurement for acupuncture.

3. Heidelberg Model of TCM “TCM as a novel Vegetative Medicine”

TCM is a system of findings and sensations designed to establish the functional vegetative state of the body; this state may be treated by i.e. Chinese pharmacology, acupuncture, Chinese manual therapy (Tuina), Qigong, or dietetics. A study published in 1989 by Kroenke and Mangelsdorf demonstrated that 85% of patients complaints in the out-patient clinic cannot be correlated to a measurable lab finding.[19]

This large number of unexplainable complaints is suggested to derive from psychosomatic disorders. As much as 60-80% of chronic ill patients with unexplainable symptoms search for help in complementary medicine.[20]

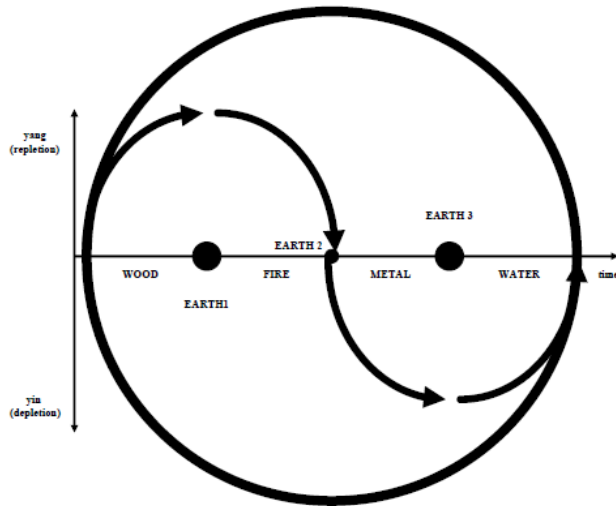
The integration of Chinese medicine into the western world has three important steps:

- 1- A rational concept of TCM Model
- 2- Scientific proof of efficacy and safety.
- 3- Quality control.

In order to reach the rational approach of Chinese medicine, Professor Greten developed the Heidelberg Model of TCM as scientific model with precise Latin terminology based on Professor Porkert previous sino-studies (Porkert 1983, Porkert, M. 1974, Porkert M. a. 1995) relying on primary Chinese literature.

Based on the first book of mankind (the *I Ging*), Leibniz Developed the binary numbering system which enables to describe the circular process. Even before the yellow emperor's classic, there is evidence that in classical china, these regulatory fluctuations where described by circulatory function in a simple manner resembling a sinus wave. This wave is part of the so-called monad (Leibniz) or Taiji sign.

fou qi emblem: a symbol for the regulatory meaning of yin, yang, and the phases



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Figure 5: Fou qi emblem

Most of the regulatory processes describe periodical fluctuations of the actual value around a target value. Accordingly as vegetative system is a regulatory process; the symptoms are categorized leading to ORB "Group of diagnostically relevant signs that indicate the functional state of a body region, which correlates the functional properties of a conduit.

The technical and regulatory dimension of Yin/Yang and the evolutionary phases (EP), i.e., Wood, Fire, Earth, Metal, Water, can be seen in an analogous example of the regulation of temperature in a water basin by a thermostat system. Due to the inherent fluctuations, the actual temperature value moves around the set point approximately in a sinus wave.

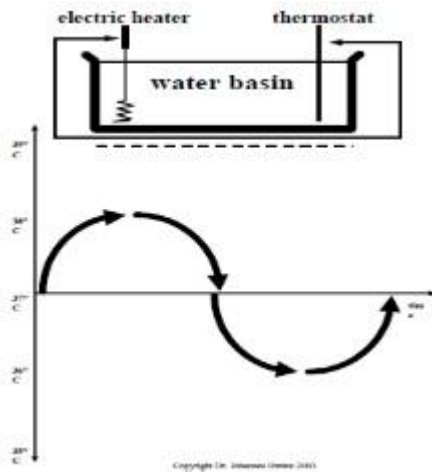


Figure 6 Regulation in sinusoidal curve. Regulation as a technical process. The temperature profile of the pool is not constant (straight line), but rather sinusoidal. Temperature is on the y-axis and time plotted on the x-axis, which corresponds to the desired temperature

Heidelberg Model of TCM hypothesizes a relation between this sinusoidal-pattern and the autonomic nervous system activities and its major molecular effects (hormones, neurotransmitters).

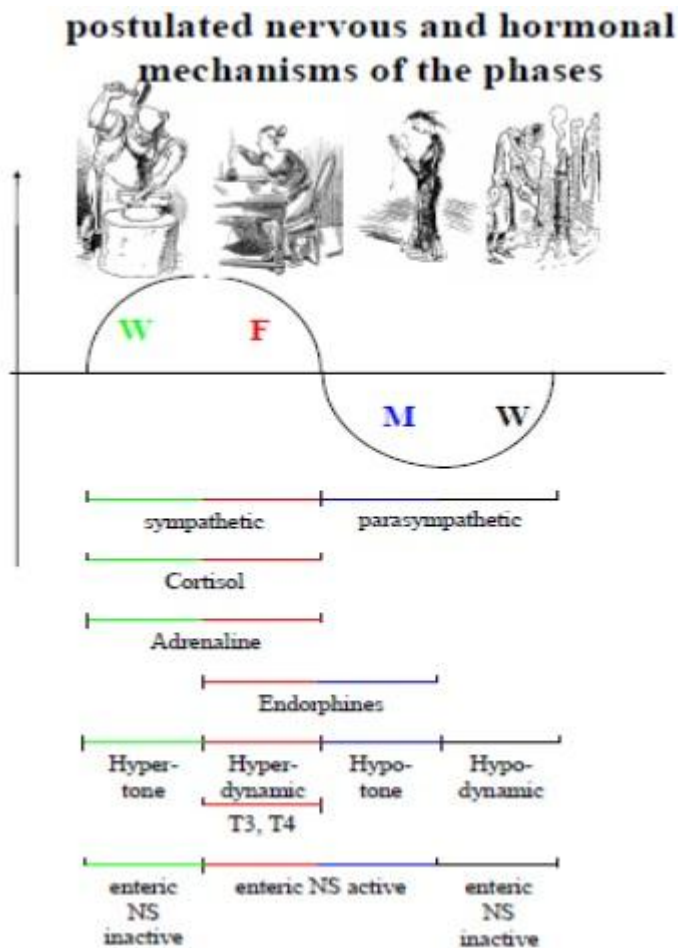


Figure 7 Postulated assignment of phases of Chinese medicine into the autonomic nervous system with respective analogies between the phases and the neuro-hormonal mechanisms.

W – Wood phase. F – Fire phase.

M – Metal phase. W- Water phase.

This theory is supported by several scientifically proofed studies all using the Heidelberg Model as backbone and common ground to draw conclusions regarding their respective objectives. Some of these studies are; pain following tonsillectomy (Sertel, et al., 2009), Gait improvement (Hauer K. 2011), Qigong effects (Sousa, et al., 2012), polyneuropathy (Schroeder, Lieper, Remppis, & Greten, 2007), walking distance in peripheral occlusive disease (Forschungsgemeinschaft, 2006).

Mechanisms to become sick in Heidelberg Model of TCM

- 1- Excess of an Agent
- 2- Problem of transition from one phase to the next
- 3- Imbalance of antagonist between phases
- 4- Yin deficiency (in our example of water Basin Yin deficiency means less water causing high variation of the temperature)

Chinese Medicine: complex network-regulation

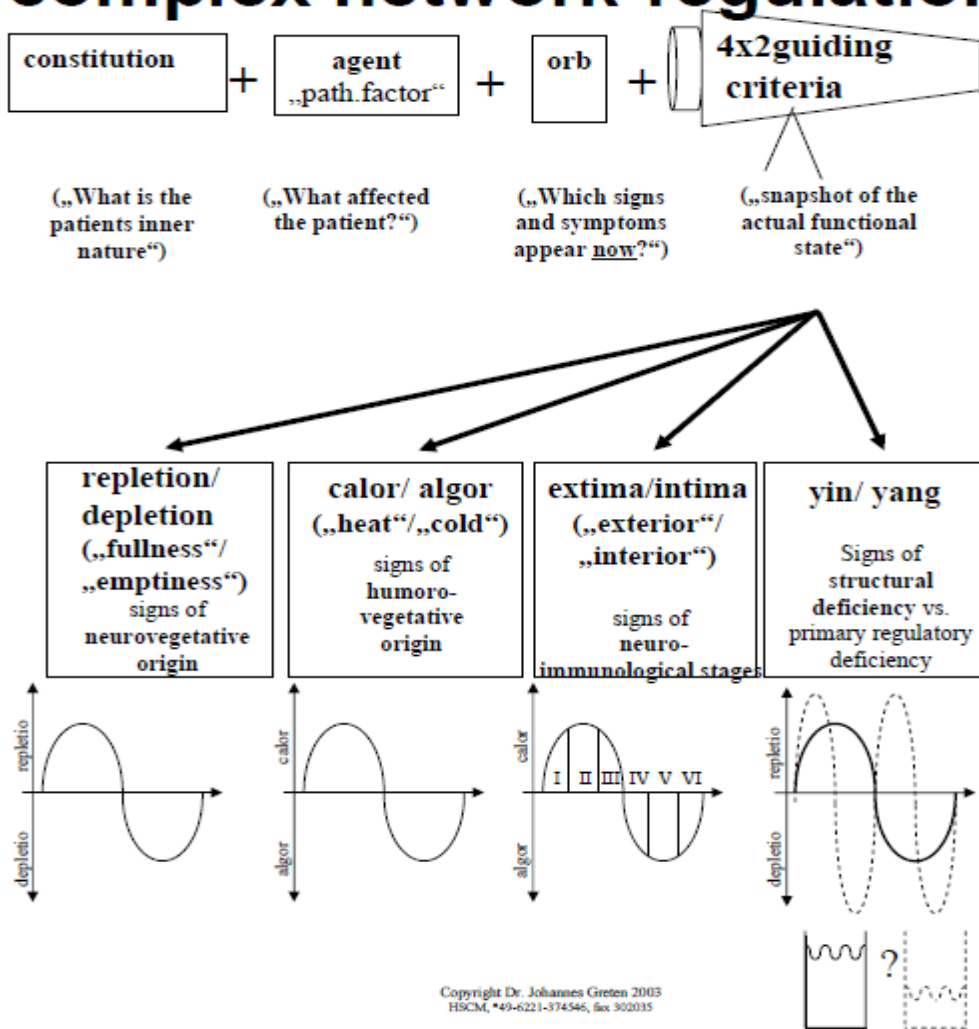


Figure 8: Chinese medicine complex network regulation

The functional TCM diagnosis has 4 components:

- 1- **Constitution:** a tendency to express the signs of one orb predominantly so that they show in the physical phenotype.
- 2- **Agent:** a pathogenic factor eliciting specific signs and symptoms. These may resemble and therefore promote orb patterns. There are external; internal and natural agents.

Table 1: Agents in HM of TCM

External Agents	Internal Agents	Neutral Agents
Ventus('wind'),algor ('cold'), humour ('humidity'), ariditas ('dryness'),aestus ('summer heat'), ardour ('glow')	Ira('anger'),voluptas ('lust'), cogitatio('excessive thinking'),maeror ('grief'), sollicitudo('worriedness'), timor('anxiety'),pavor ('shock')	Overwork, malnutrition, trauma, infections.

- 3- **Orb:** a group of diagnostically relevant signs indicating the functional state of body island (body region) which correlates with the functional properties of a conduit.

- 1st GC – Repletion (fullness)/ depletion (emptiness) describes Qi content of the body by terms of orbs, Qi, Phases. In western medical view this describes symptoms predominantly originating from Neuro-vegetative system.
- 2nd GC - Calor(heat)/ Algor (cold) this describes the activity of Xue (blood), as western medical view this describes the clinical signs predominantly originating from Humoro-vegetative system, including the regional and systemic effects of microcirculation.
- 3rd GC – Extima (exterior)/Intima (interior) describes the course of a disease caused by an exterior agent invading the body. Most important model within TCM is the model of the six stages (Shan Han Lun). In western medical view this is interpretation of clinical signs predominantly induced by Neuro-immunological mechanism.
- 4th GC - Yin/Yang- this is to distinguish the origin of signs and symptoms, yin (structural deficiency). Yang (primary deregulation). Diseases described by guiding criterion Yin, there symptoms are due to deficiency of functional tissue (body substance). diseases described as yang, however symptoms are primary due to dysregulation described by the first three guiding criteria.[20]

4. TCM approach to Endometriosis

According to a survey of TCM treatment for endometriosis, TCM strategies may include[21]:

1. TCM internal treatment, including:

- 1.1. Syndrome-differentiation treatment
- 1.2. The periodic therapy (application of different prescriptions and treating principles at different periods of the menstrual cycle.)
- 1.3. The special-prescription treatment (prescription specially formulated for this disease based on the differential theory and clinical experience)

2. TCM external treatment, including:

- 2.1. Chinese herbal enemas
- 2.2. Medicinal plaster therapy
- 2.3. Acupuncture treatment**

Acupuncture is a type of treatment that stimulates certain locations or points of the body, by manipulating needles. All the methods in acupuncture treat diseases by exerting a certain stimulation on the body especially in the acupoints by which to free the conduits in order to move Qi and activate Xue (blood) so as to regulate the balance between Yin and Yang to coordinate the Function of Zang Fu; and to support the health of Qi and eliminate the Evil Qi.[22]

Acupuncture therapy has been known as a practice associated with oriental and complementary medicine, and it has been recently identified in the field of complementary medicine as a potential therapeutic procedure for which there is good scientific evidence.[12] Based on TCM acupuncture is used widely around the world, but other methods of acupuncture exist, and numerous variation of acupuncture therapy has been developed.[23] Scientific research into the mechanism of action of acupuncture began around 1950 when an important pharmacological study was published by a group at Peking University. They demonstrated that an induction time of 15 to 20 minutes is required for the development of an analgesic effect and proposed the participation of chemical substances in the analgesic actions of acupuncture [4]. Before the 1990s, most experts agreed on the concept that in normal animal models, lower frequency electro-acupuncture (EA) stimulates the release of beta-endorphin, enkephalin and endomorphin, which in turn activates the mu- and delta-opioid receptors, and that higher frequency EA stimulates dynorphin which activates the kappa-opioid receptor.[24]

Acupuncture in endometriosis – literature review:

Acupuncture has been studied in gynecological disorders but its effectiveness for pain in endometriosis is uncertain (Figure 10).[25]

However the use of acupuncture for chronic pelvic pain is suggested to be helpful in relieving the pain and in turn improving patient’s quality of life.[26] More than 50% among women with chronic pelvic pain used at least one complementary health approach in the past year, including acupuncture 8%, special food or diet 22%, herbs 27%, and Vitamins and minerals 29%.[27]

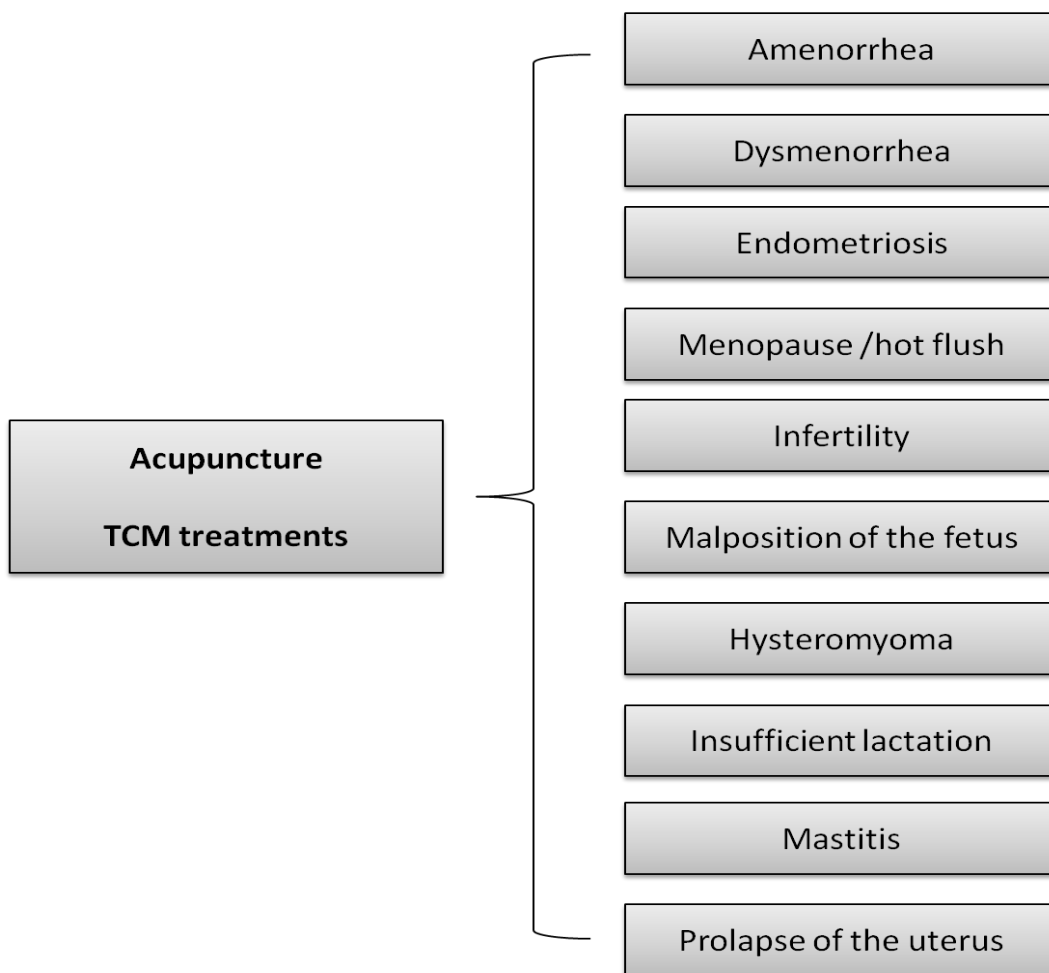


Figure 10: Acupuncture traditional use in Gynecological disorders[28].

Acupuncture has satisfactory results of relieving dysmenorrhea, especially the primary type, but also in secondary dysmenorrhea.[28].

Lewers et al. applied acupuncture-like transcutaneous electrical nerve stimulation (TENS) in treating 21 cases of primary dysmenorrhea and found an average pain relief of at least 50% immediately post-treatment[28].

Helms investigated the effectiveness of acupuncture in primary dysmenorrhea pain in a randomized controlled trial, with 43 women for one year and allocated to 4 groups. The verum acupuncture group was given random point acupuncture on weekly basis for 3 menstrual cycles. In the Verum group, 10/11 (90.9%) women showed improvement that was much higher than the placebo group or in other 2 control groups. There was 41% reduction of analgesic medication used by the women in the real acupuncture group after their treatment series and no change or increased use of medication seen in the other groups[28].

A study by Maric applied acupuncture in 32 patients with primary dysmenorrhea, showing a relief of the pain already after the first menstruation; one year after the completed therapy, there was a full disappearance of dysmenorrhea pain in 93% and a partial one in 75 of the cases[28].

A study by Tsenov included 48 women in reproductive age, 24 with primary dysmenorrhea in the first group and 24 women with secondary dysmenorrhea in the second group. The results were that in the first group effect was very good after one course of 2-4 acupuncture sessions before menstruation. In the second group, effect was satisfactory in 50% of the cases after two courses of acupuncture treatment [29].

LI Yuan-feng [21] used auricular seed-embedding and herbal prescription for dysmenorrhea due to EM with “quite good” results. The auricular seed-embedding with vaccaria seeds was applied starting from 5 days before the menstrual period on the auricular points of Sub cortex, Endocrine, Sympathetic Nerve, Ear-Shenmen, Liver, Kidney, Internal Genitalia, and Tingzhong. The embedded seeds were pressed 3–5 times a day, lasting 30 min each time. The seed-embedding was done every 2 days alternately on both ears, altogether 5 times, with two menstrual cycles forming one therapeutic course.

DING Zhe [21] applied vaccaria seed-embedding on the auricular points of Internal Genitalia, Endocrine, Liver, Kidney, Ear-Shenmen, and Sympathetic Nerve. The treatment began 3–5 days before the menstrual period, and lasted 3–5 menstrual cycles. The total effective rate was 97%.

RUAN Ji-yuan [21] defend that point-injection therapy with Chinese phytotherapy can improve the ectopic endometrial adhesion and fibrosis. For that purpose, they applied point-injection with salvia injection at Zusanli (ST 36) and Xuehai (SP 10), or at Ciliao (BL 32) and Sanyinjiao (SP 6), with the two groups of points alternately used every other day, during 2 months, achieving good symptom relief.

CHANG [21], based on TCM syndrome-differentiation, applied acupuncture treatment for EM. For the excessive heat syndrome, Baihui (GV 20), Ququan (LR 8), Shenmai (BL 62), Shenmen (HT 7), Xuehai (SP 10), Yinbai (SP 1), Zhongji (CV 3), and Zhaohai (KI 6) were selected; and for *qi*-insufficiency, Baihui (GV 20), Sanyinjiao (SP 6), Yangchi (TE 4), Yinbai (SP 1), and Zusanli (ST 36) were selected. Sometimes, auricular points of Ear-Shenmen, Uterus and Ovary were also used, with herbal prescription given in combination for better therapeutic effects.

XIONG Yun-bim, et al. [21] adopted electro-acupuncture 4 days before the menstrual period at the points of Guanyuan (CV 4), Zhongji (CV 3), and Sanyinjiao (SP 6) with an effective rate of 95,71%. The treatment was given twice daily, each lasting 30 min. Each month, a 5-days treatment formed one therapeutic course. After 5 treatment courses, of the 70 cases treated, marked effects found in 37 cases, 30 cases were improved and 3 cases failed. WANG Hui-min²⁰ made a powder with Fu Zi (Radix Aconiti Preparata), Lu Jiao Shuang (Cornu Cervi Degelatinatum), Rou Gui (Cortex Cinnamomi), Ru Xiang (Resina Olibani) and Wu Ling Zhi (Faeces Troglodyteris) in the ratio of 5:2:1:1: 1, and then mixed the powder with 20% alcohol to make the medicinal cakes, 0.5cm in thickness and 3 cm in diameter. Along with the rising of temperature, the pungent, warm and aromatic medicinal action of the herbs would enter the lower abdomen, uterus, and channels and collaterals to produce the therapeutic effect [21].

LIU Ya-xin, et al.[21] Obtained marked therapeutic effects for dysmenorrhea in EM cases treated by medicinal moxibustion.

A 2011 Cochrane review on acupuncture for pain in endometriosis retrieved data from 24 studies. Only one trial defined pain scores and cure rates according to the Guideline for Clinical Research on New Chinese Medicine. Dysmenorrhea scores were lower in the acupuncture group (mean difference -4.81 points, 95% confidence interval -6.25 to -3.37, $P < 0.00001$) using the 15-point Guideline for Clinical Research on New Chinese Medicine for Treatment of Pelvic Endometriosis scale. The total effective rate ('cured', 'significantly effective' or 'effective') for auricular acupuncture and Chinese herbal medicine was 91.9% and 60%, respectively (risk ratio 3.04, 95% confidence interval 1.65 to 5.62, $P = 0.0004$). The improvement rate did not differ significantly between auricular acupuncture and Chinese herbal medicine for cases of mild to moderate dysmenorrhea, whereas auricular acupuncture did significantly reduce pain in cases of severe dysmenorrhea. Data were not available for secondary outcomes measures. In this study, acupuncture was more effective and safer for treating mild and moderate dysmenorrhea than other alternative Chinese medicines based on the use of herbs. Among the 67 female participants, the

dysmenorrhea scores were significantly lower in the group that was treated with acupuncture. However, a single study cannot define the evidence relating to the effectiveness and safety of acupuncture for treating dysmenorrhea in cases of Endometriosis. The authors underlined that more studies are needed for developing future studies that are well-designed, double-blinded, randomized controlled trials that assess various types of acupuncture in comparison to conventional therapies[30].

Jin YB et al in Randomized controlled study on ear-electro acupuncture treatment of endometriosis-induced dysmenorrhea in 80 patients with endometriosis concluded that both ear and body electro-acupuncture can effectively relieve endometriosis-induced dysmenorrhea, and that the former seems to be superior to the latter in reducing pain severity, which may be closely related to their effects in reducing plasma PGE2 and raising 6-Keto-PGF1alpha level.

Yan H et al in Observation on therapeutic effect of acupuncture and moxibustion on disorders of myometrial gland performed a randomized controlled trial to explore the therapeutic effect of acupuncture on endometrial disorders. Sixty-six women were allocated to an acupuncture group or a medication group (Danazol). They concluded that acupuncture has obvious therapeutic effect, which is better than that of simple western medicine.

TCM treatments frequently combine acupuncture and Chinese herbs in endometriosis and secondary dysmenorrhea in order to promote the curative effect. A study by Wang that included 37 cases of mild and severe endometriosis treated with point-injection of Fu-Fang-Danshen (main ingredient is *Radix salvia miltiorrhizae*) solution and moxibustion for 3-5 courses of treatment, showed an effective rate of 85.91% for dysmenorrhea.

In sum, to the present date, few studies have been published on acupuncture for chronic pelvic pain related to Endometriosis. All these studies using different acupuncture techniques suggested acupuncture in combination with medical therapy as a better option for reducing pelvic pain related to EM, for reducing serum levels of CA125, for primary and secondary dysmenorrhea also reduction of ectopic tissue, hence treating the Endometriosis.[11, 23, 31-34], see Annex-6.

5. Endometriosis according to the Heidelberg Model of Traditional Chinese Medicine

Endometriosis according to Heidelberg Model of Chinese medicine has three main causes;

1-Qi stasis that reflects in changes on vegetative patterns, which in turn will cause stagnation of the functional capacity of the female reproductive tract.

2-Xue stasis which will reflect a change in the microcirculation and body fluids, particularly the interstitial fluids.

3-The third cause involved in endometriosis is a uncontrollable in Qi Constructivum that can be understood by the ability of somatic body construction.[35]

These 3 main causes arise from a lack of mechanisms of body regulation that Chinese medicine translates as a lack of transition between phases in the cycle of "fou qi", which is described by the Heidelberg Model of Chinese medicine as a mathematical form of a sinus curve. And the stagnation is in the first phase of the curve.

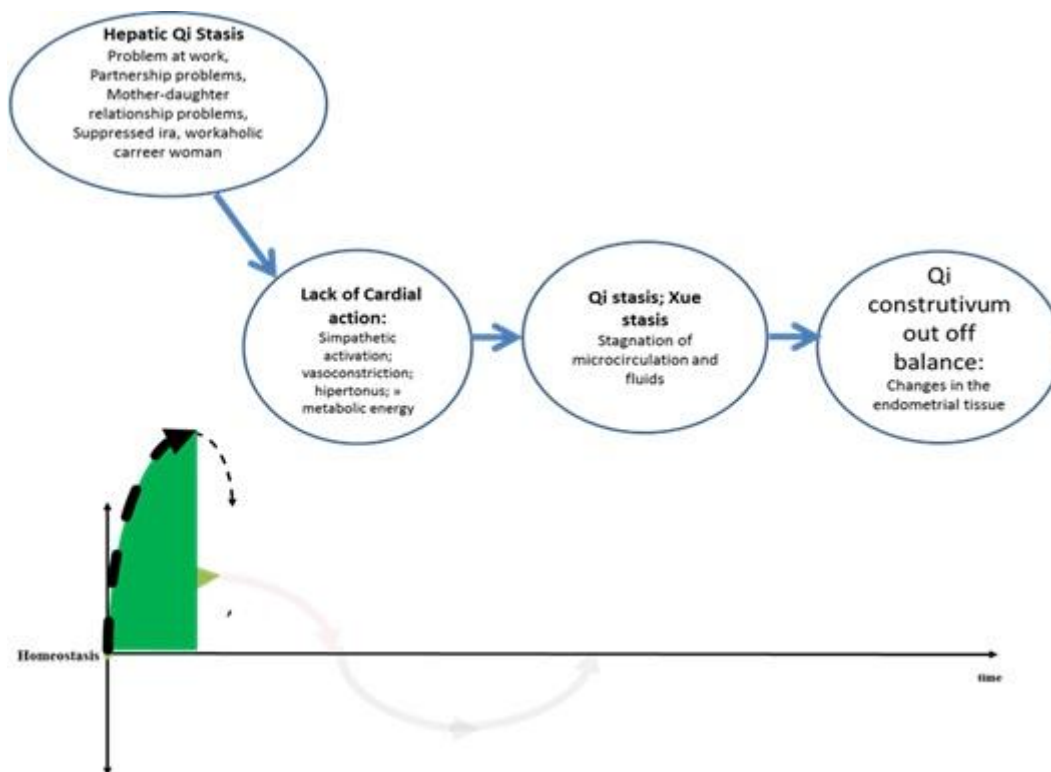


Figure 11: Development of EM in HM

In HM of Chinese Medicine the pathogenesis of Endometriosis is due to stagnation of Qi and Xue in the hepatic orb due to lack of transformation of potential created by the wood phase (hepatic orb) into function by the fire phase (cardiac orb). The trigger stimuli for the stagnation such as problems at work, problems of partnership, mother-daughter relationship problems, suppressed anger in career workaholic women, cause sympathetic activation, increased muscle tone, metabolic energy increase, and stagnation of Qi and Xue by the lack of Cardial function which transforming Potential to Function, and this will be a trigger of uncontrollable somatic construction causing a change of endometrial tissue.[35]

According to Heidelberg Model chronic pelvic pain in Endometriosis is due to the Qi and Xue Stasis, and this protocol we will use only two points distant from the pelvic region but have effects on the pelvic region, by a Leopard Spot technique (blood-letting technique) this Technique is mostly used for Blood stasis situations and it restores the normal microcirculation of target area.[35]

Following the HM and Prof. Greten experience, chosen points for our research protocol are:

- GB41 (Felleal 41) - it is wood point and takes part the harmonisation of phase wood (harmonises the Hepatic and Felleal orbs. It activates the Sinarteria Zonalis (daimai), one of the eight extraordinary conduits which are originated from the renal Orb; Sinarteria Zonalis originates from Renal Orbs like other extraordinary conduits and feeds the uterus and the whole lower Abdomen in order to prepare for fertility. So Leopard Technique in this point is highly recommended to be effective in treatment of Endometriosis it is self and also for the chronic pelvic pain related to endometriosis.[18, 36]

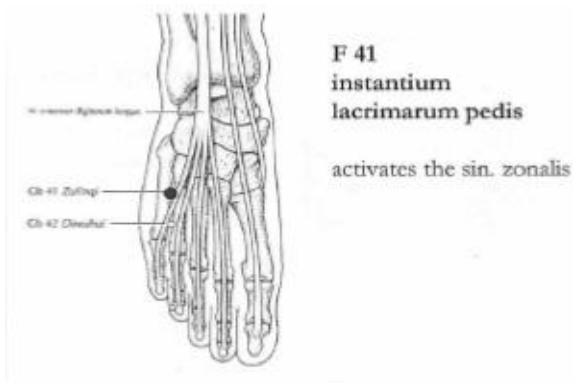


Figure 12: GB 41 Acupoint

- Sp6 (Lienal 6)- Copulatio trium yin- it is the junction point of the three yin Conduits; Liver (Hepatic), Spleen (Lienal), and Kidney (Renal). It is the Master Point of the Lower Abdomen, the three conduits each one has specific influence on the lower abdomen and pelvic Region. Hepatic conduit reduces cramps of the Intestines and Uterus, and controls the bleeding processes (Menses); this is main point for gynaecological problems. Lienal has good influence in the tension of pelvic floor, holds the flesh, and mucous membrane swellings. Renal orb and yin are associated with many complaints that Western Medicine interprets as hormonally induced. (e.g.; Endometriosis, chronic pelvic pain related to Endometriosis). So using L6 Leopard Technique affects all these three conduits at the same time.

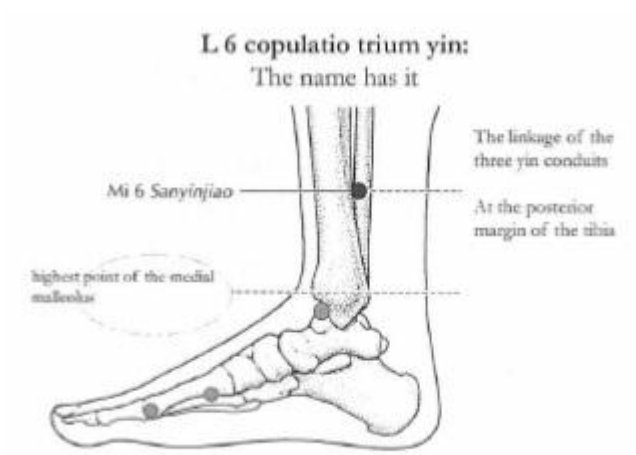


Figure 13: SP 6 Acupoint

II. CLINICAL RESEARCH PROTOCOL

Title: Objectifying acute effects of Acupuncture for pelvic pain due to endometriosis. A clinical research protocol using a novel pain assessment system

1. Background:

Endometriosis (EM) is a common health problem affecting women worldwide and often underdiagnosed. It is estimated that 7% -10% of women in the general population suffer from EM. Pelvic endometriosis is present in 6% to 43% of women undergoing sterilization, 12% to 32% of women undergoing laparoscopy for pelvic pain, and 21% to 48% of women undergoing laparoscopy for infertility.

According to conventional medicine, treatment of EM needs life-long management including medical or surgical treatments, hormonal therapy being mostly used. However, long administration of these therapies remains challenging due to the plethora of serious adverse effects.

Acupuncture has been studied in Gynecological disorders with few studies have been published on acupuncture for Endometriosis induced pain but its effectiveness for pain in endometriosis remains uncertain. The use of acupuncture is suggested to be helpful in relieving the chronic pelvic pain which in turn improves patient's quality of life.

2. Research team

2.1.1 Main investigator: Khadija Bashir Ibar

- Physician graduated from Faculty of Medicine Benadir University Mogadishu – Somalia.
- Resident house officer in Obstetrics and Gynecology department Benadir Teaching Hospital.
- Master student of Traditional Chinese Medicine at the Instituto de Ciências Biomédicas Abel Salazar (ICBAS)

2.2 Research supervisors:

2.2.1 Main supervisor: Prof. Dr. Henry Johannes Greten

- Invited Associated Professor; Director of the Specialization and Master Program in Traditional Chinese Medicine; Department of Aquatic Production; Abel Salazar Institute for Biomedical Sciences, University of Porto, Portugal.
- Head of the Heidelberg School of Traditional Chinese Medicine
- President of the German Society of Traditional Chinese Medicine (DGTCM), Heidelberg, Germany
- President of the German-Chinese Research Foundation for TCM, Heidelberg, Germany

2.2.2 Supervisor: Dr. Nuno Cândido Maia Correia

- Assistant in Internal Medicine, Service of Emergency, Hospital Center São João, Porto
- Invited Assistant Professor of General Pathology – Nursing School of Porto
- Master in Traditional Chinese Medicine - ICBAS / UP
- Heidelberg School of Health and Sciences

2.2.3 Co-supervisor: Dra. Ana Rosa Costa.

- Hospital Assistant of the Service of Gynecology and Obstetrics, Hospital Center São João. Responsible for the outpatient consultations of Endometriosis, Family Planning and Climateric.

2.2.4 Co-supervisor: Dra. Maria João Santos.

- Teacher at TCM Master Program ICBAS/UP
- Heidelberg School of Health and Sciences

3. Objectives:

3.1 General objectives:

- ✓ To develop a clinical research protocol for a randomized, sham-controlled preliminary study that evaluates the acute effects of acupuncture for endometriosis-related pain.
- ✓ To assess feasibility of the study protocol, and collect preliminary data, for a larger study.

3.2. Specific objectives:

- ✓ To assess if acupuncture can improve pelvic pain in patients with endometriosis.
- ✓ To objectively measure the effect of acupuncture in pain, by using a pressure sensitive sensor device.

4. Methods:

4.1. Setting

Local: Hospital Center São João, Service of Gynecology and Obstetrics, Consultation of Endometriosis.

4.2. Ethics assessment: The study protocol was approved by the Ethical Committee of Hospital Center São João (See Annex 1). Data recruitment already started.

4.3. Study sample:

30 patients, diagnosed with pelvic endometriosis and having chronic pelvic pain secondary to EM.

4.4. Informed consent.

All patients' consents were obtained before the beginning of the intervention.(see annex 2)

4.2 Study design

The study is designed has preliminary, prospective, randomized, controlled, single-blinded clinical trial in a cross-over methodology.

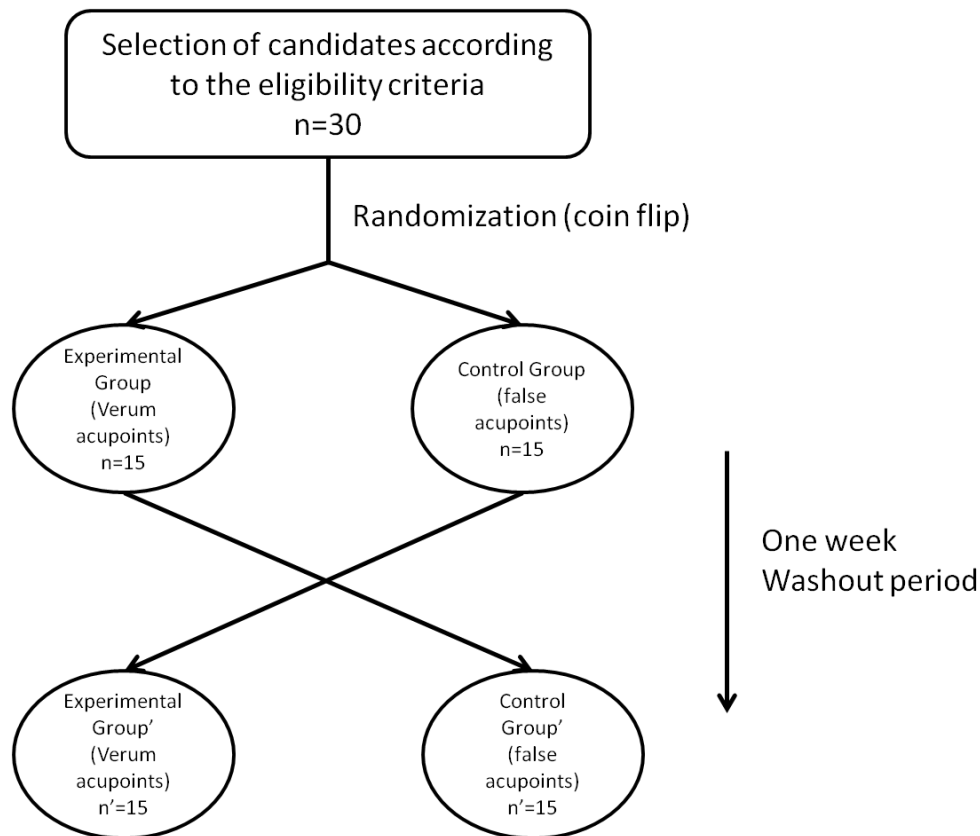


Figure 14: cross over design. A cross-over design is defined in order to avoid possible carry over effects.

Experimental group: verum acupoints. Control group: false acupoints.

- ✓ **Experiment group:** 15 patients will first undergo true acupuncture in points chosen according to HM of TCM followed by sham acupuncture
- ✓ **Control group:** 15 patients will undergo sham acupuncture first and then verum acupuncture.

4.3. Eligibility Criteria

Inclusion Criteria: women from 18-55 yr .with pelvic pain due to EM beyond the time of menstrual bleeding at Sao Joao Hospital EM clinic, mentally fit and co-operative with the study; naïve to acupuncture.

Exclusion criteria: women with menses (to exclude dysmenorrhea), chronic pelvic pain due to non-endometriosis causes, active infectious disease, congenital diseases or any other severe disease.

4.4. Blinding methodology

This study follows a single blinded methodology:

- Patients are blinded to acupuncture since they are naïve to acupuncture. As such they cannot distinguish between true or false acupoints during needling.
- The acupuncturist is not blinded. A trained acupuncturist will do the acupuncture and the palpation of the pelvic with the sensor measuring the pressure.
- The VAS will be measured by another researcher, before and 5 min after the treatment, which is also not blinded.

4.5. Randomization

Coin flip will divide the patients into the verum (true) and sham (control) acupuncture groups. Patient's document sheet is marked with different colors according to which group the patient belongs to.

4.6 Experimental protocol

Step1: Before the Intervention, data recruitment using clinical questionnaire (see annex 3), VAS will be measured baseline (see annex 4), and pelvic palpation with pressure application in a region two fingers above the superior anterior iliac spine and three fingers from the midline. This location was selected on the basis that it is common to have pain in this region on palpation specially women with endometriosis (Greten H., Understand TCM Scientific Chinese Medicine- the Heidelberg Model, 2013, 6th edition).

Step 2: acupuncture intervention with leopard spot technique on GB41 and Sp6.

Step3: 5 minutes after the treatment the measurements with the VAS and pressure sensitive device will be done to be compared and analyzed.

Step 4: Cross-over of the two groups: after one week of washout period for the previous acupuncture intervention the two groups will be exchanged.

Step 5: Experimental group will become control group and will undergo the same process of VAS measurement and Pelvic palpation and measuring the pressure with the pressure sensor, and in the intervention step the points will be

Sham points with leopard spot technique. The Control Group will become experimental group and subject to same evaluation process.

4.6.1 Intervention:

The **verum acupuncture** consists of needling following the leopard spot technique on Gb 41 and Sp6.

Table 2: Acupoints locations and areas of innervation. D – Dermatome, M – myotome, S - sclerotome

Acupoints	Location and target	Neurotomes
Sp6	3 cun superior to the most prominent part of the medial malleolus on the medial border of the tibia Target: flexor digitorum longus	D L4 /S1/S2 M L2/L3/L4 S L3
Gb41	In the depression distal to the junction of the 4th and 5 th metatarsals, lateral to the tendon of extensor digitorum longus that passes to the 5 th toe Target: 4 th dorsal interosseus	D L5/S1 M S1/S2 S S2



Figure 15: Verum acupuncture group

The **false acupuncture** consists of needling following the leopard spot technique in non-acupoints 1 *cun* distant from the true acupoints (see figure 16). Needles are inserted according to the leopard spot technique (same stimulation as verum-group), using the same number of needles at skin points outside the conduits.

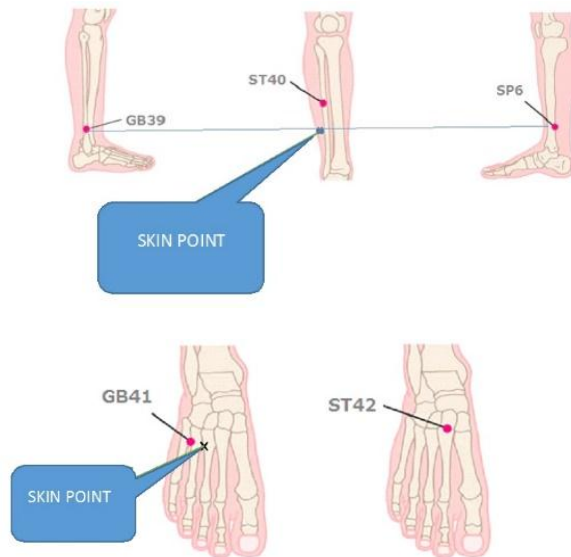


Figure 16: Sham acupuncture group

Table 3: Location of Skin point (sham group)

Skin Points	Location
Skin Point 1	1 cun medial to GB 39 in between GB and ST conduit in the same level with GB39 and SP6
Skin Point 2	1 cun medial to GB 41 in between GB and ST conduit in the same level with GB 41 lateral side

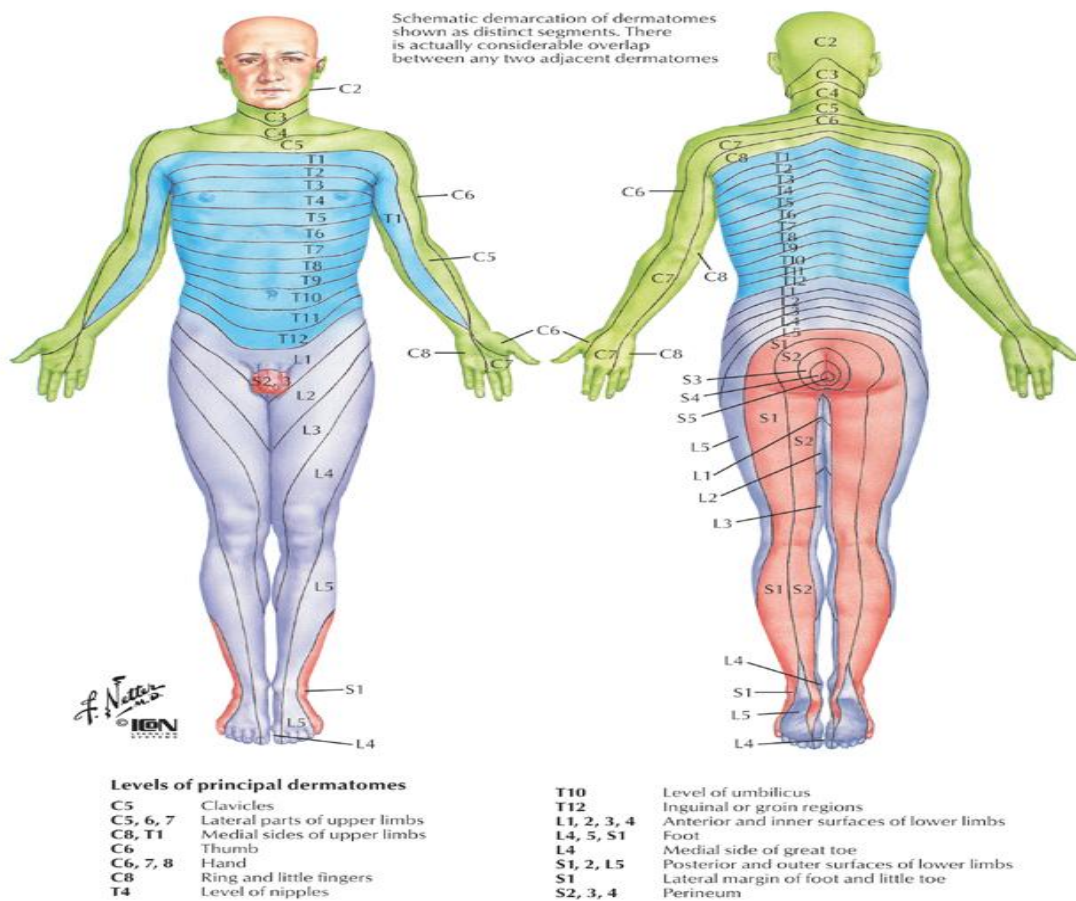


Figure 17: schematic demarcation of dermatomes .The dermatomes map allows understanding the segmental effect of acupuncture needling stimuli.

(in http://www.backpain-guide.com/Chapter_Fig_folders/Ch06_Path_Folder/Ch06_Images/06-4%20Radiculopathy.jpg, consultation on the 2014/09/3)

The **leopard spot technique** consists of 5 rapid in-and-out bloodletting strokes with acupuncture needles over the point's skin area.

Patients are subject to 2 session of acupuncture with one week of interval (verum or false acupuncture)

VAS pelvic pain is assessed at baseline (before acupuncture) and 5minutes after the acupuncture.

Pain is elicited by pelvic palpation with pressure on region above the anterior superior iliac spine and measurement of the pressure needed to reach the maximum pain by a pressure sensitive sensor specially designed to do this study.

Acupuncture treatments:

Verum group (experimental group): “real” acupuncture- based on a concept of acupuncture according to Heidelberg Model of Chinese Medicine, aiming to relief the Qi and Blood (xue) stagnation which are the main causes of Endometriosis it is self and also the Chronic Pelvic Pain. . (Greten H., Understand TCM Scientific Chinese Medicine- the Heidelberg Model, 2013 6th Ed).

- GB41, *instantium lacrimarum pedis*, *Zu lin qi*.
- Sp6, *copulatio trium yin*, *San yin jiao*.

False group (control group): an invasive control using acupoints outside the conduits, 1 cun distant from the acupoints used in the verum group.

Both treatments will be performed using the same number of needles, applied on the leg on the same side as the pelvic side with more pain as assessed at baseline (ipsilateral needling).

Insulin needles are used for leopard spot technique in a calm room located at the Outpatient office of Gynecology. Sterile Single use needles will be used in both groups.



Figure 18: Insulin needle. To perform the “leopard spot” needling technique insulin needles were used measuring X mm of length.

4.7 Main parameters:

4.7.1. Pain subjective assessment

Visual Analog Scale (VAS) for pain (fig X under):

Patient is asked to indicate the pain between 0(no pain) to (10 maximum pain) in 4 moments according to the following schema (figure 19 under):

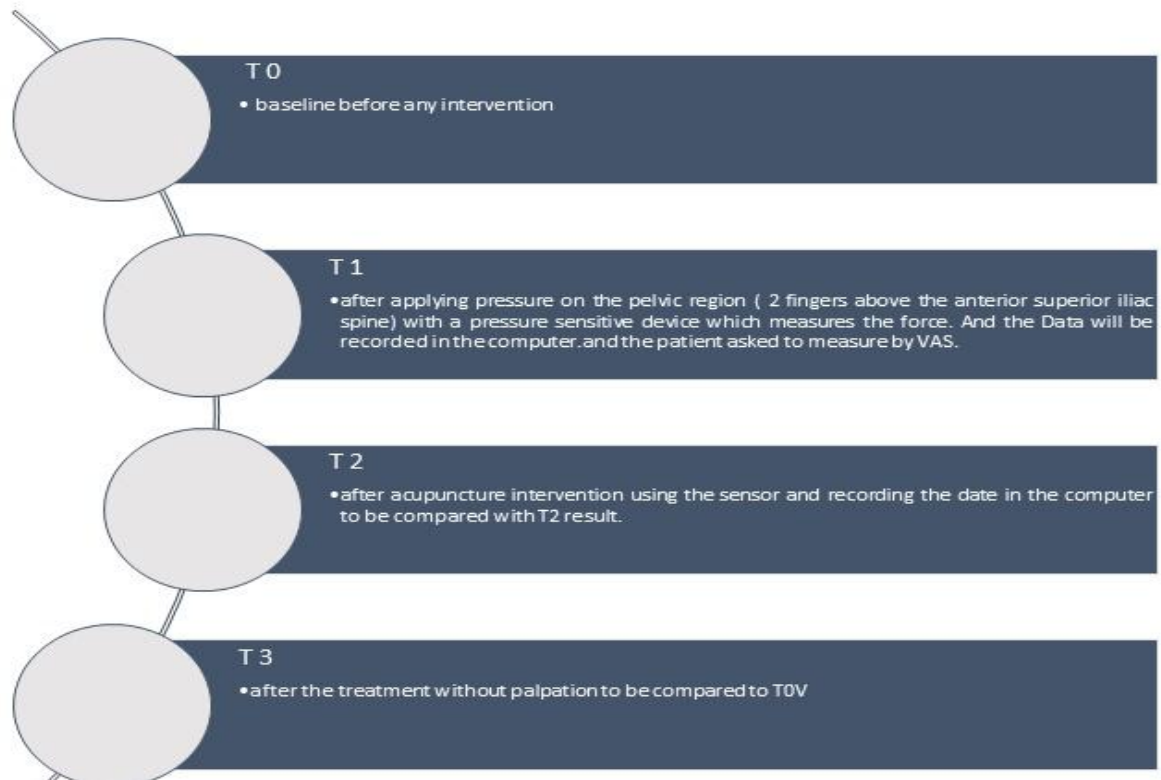


Figure 19: Subjective pain assessment VAS. Subjective pain assessment. Visual analogue scales are used in 4 moments during the protocol.

4.7.2. Objective pain assessment

A special pressure sensitive device was designed for this study in cooperation with the Biomedical Engineer department of the Engineer Faculty of the University of Porto.

By measuring the maximum pressure that elicits pain, an objective measure of pain is assessed.

Maximum Pressure-induced pain was measured in two moments:

- T1- before acupuncture (true or sham)
- T2- after acupuncture (true or sham)

4.7.2.1. Details of this pressure sensitive device are presented:

Objectives

Acquire force sensor signals using Arduino resources in order to measure the force applied.

Develop an integrated LabVIEW application to obtain data and store information for further analysis.

Application – Interface

Software: LabVIEW 2013 SP1

Modules:

- LabVIEW Interface for Arduino vs. 2.2.0.79
- LabVIEW Run-Time Engine
- LabVIEW Application Builder

Hardware

Arduino Uno Rev3

USB A-B cable to connect Arduino serial port to PC USB port

A201 Flexiforce sensor with 25 lb/sqi range

Electric circuit for force sensor signal conditioning

Push button to record pain events

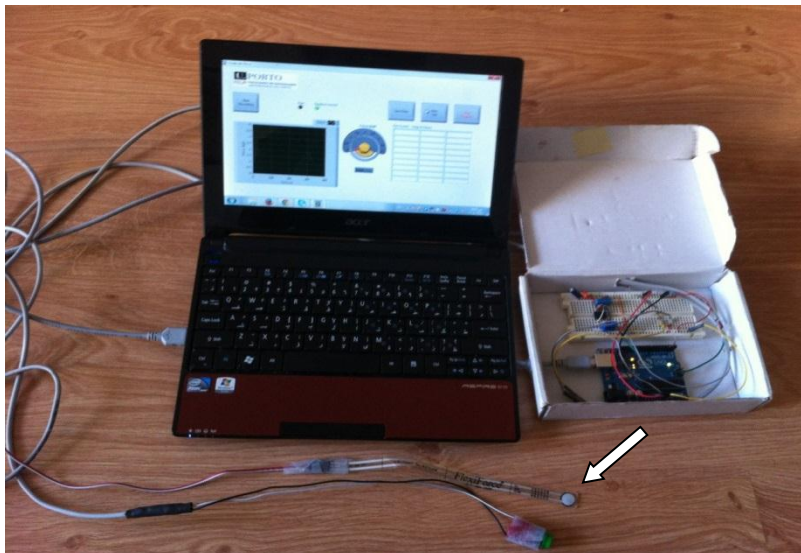


Figure 20: Pressure sensitive sensor (white arrow) connected to a laptop with special software to analyze the acquired data.

Development – Software

All the software development was carried on LabVIEW 2013 environment, in order to obtain an application to communicate with the Arduino Uno Board and acquire signals from both sensor circuit and push button.

The developed application has the following flowchart:

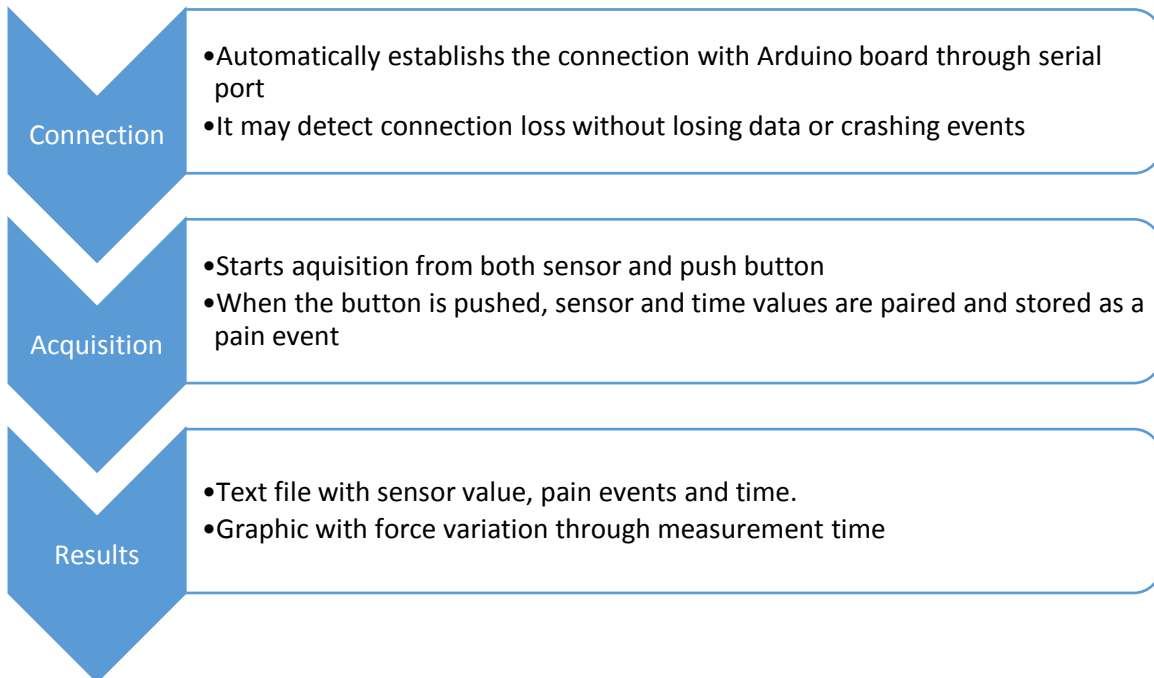


Figure 21: schematic of software development

Development – Hardware

All the hardware development was carried on Flexiforce sensors signal conditioning. In order to use these force sensors, it is needed to apply a signal amplification to establish the proper measuring range.

The following electric circuit and integrated components are used in the amplification process:

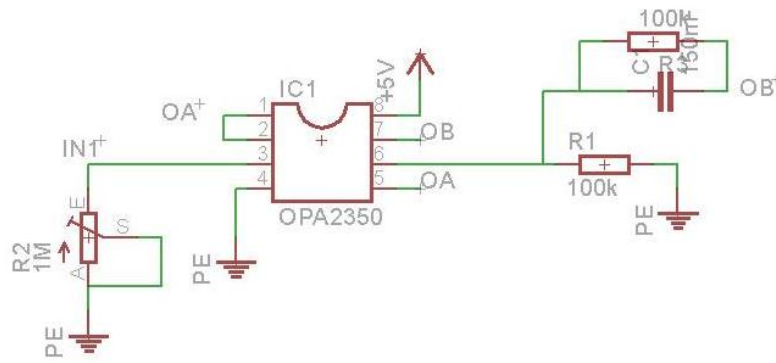


Figure 22: schematic of hardware development

To set the measuring range, a potentiometer is used in order to establish the measuring range. In fact, this electric circuit acts as a voltage divider. Considering that the highest possible value read to be obtained is 5V, as it is the supply voltage, adjusting both the applied force in sensor and the resistance in the potentiometer (R2) makes it possible to adjust the used range. In this work, measuring range was set to a maximum of 4kgf applied in the sensor.

Application – How to use

- 1 – Open LabVIEW application.
- 2 – Connect Arduino USB cable to computer USB port.
- 3 – Start application.

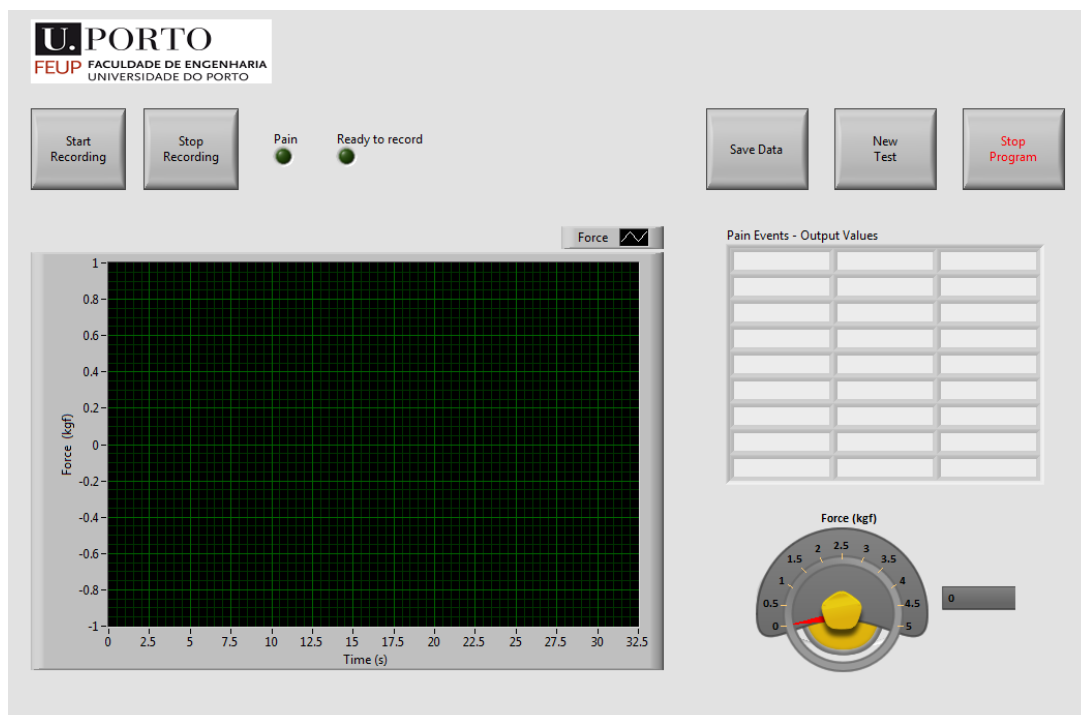
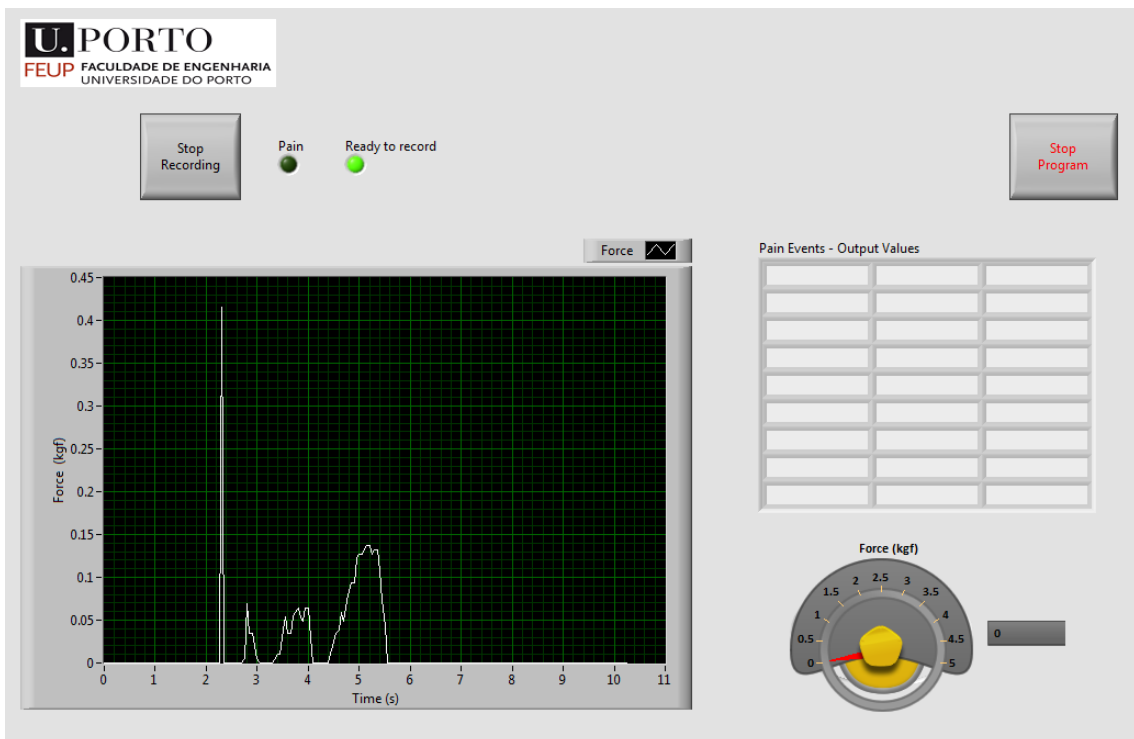
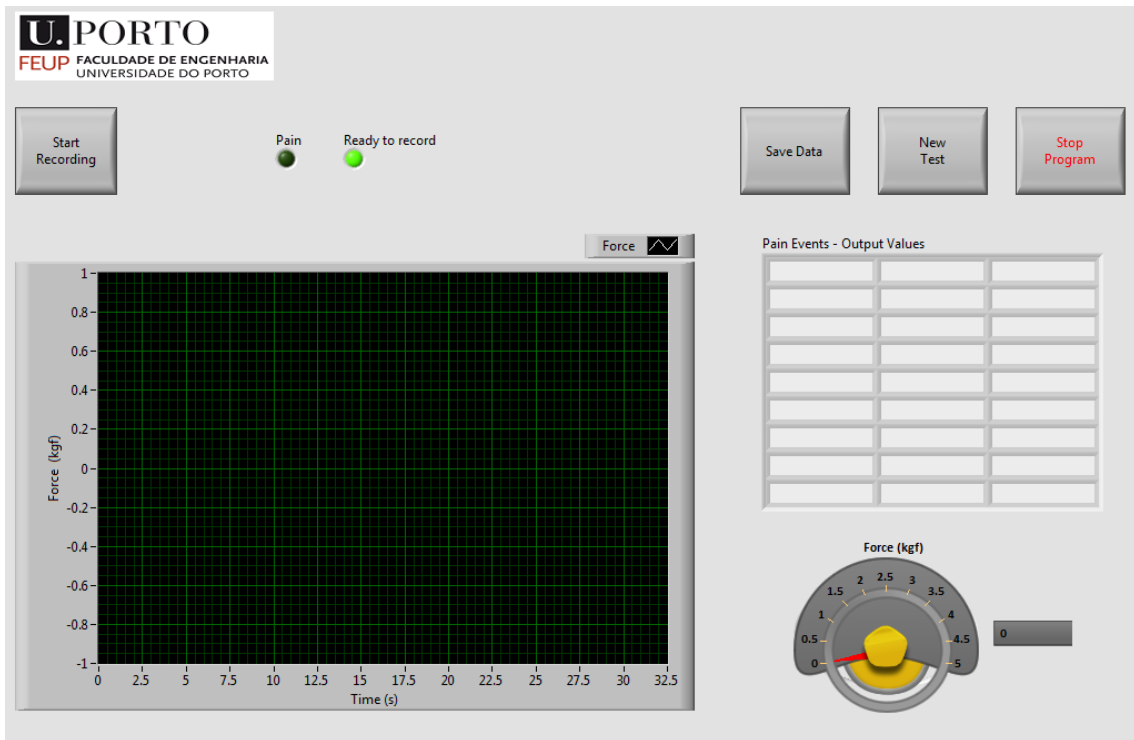


Figure 23: Sensor start up screen

4 – When **Ready to record** indicator turns on, acquisition is ready, so **Start Recording** button becomes visible.



Figures 24, 25: Sensor recording pressure screen

5 – Pressing **Start Recording** button, data is stored and it is possible to add values to the **Pain Events – Output Values** table. When record is under way, it is only possible to

press **Stop Recording** or **Stop Program**

6 – Press **Stop Recording** to immediately stop the acquisition. To save the data, press **Save Data** button, to open a prompt windows to select a file name. All obtained values and graph plot are stored, respectively, on a .txt file and a .bmp file.

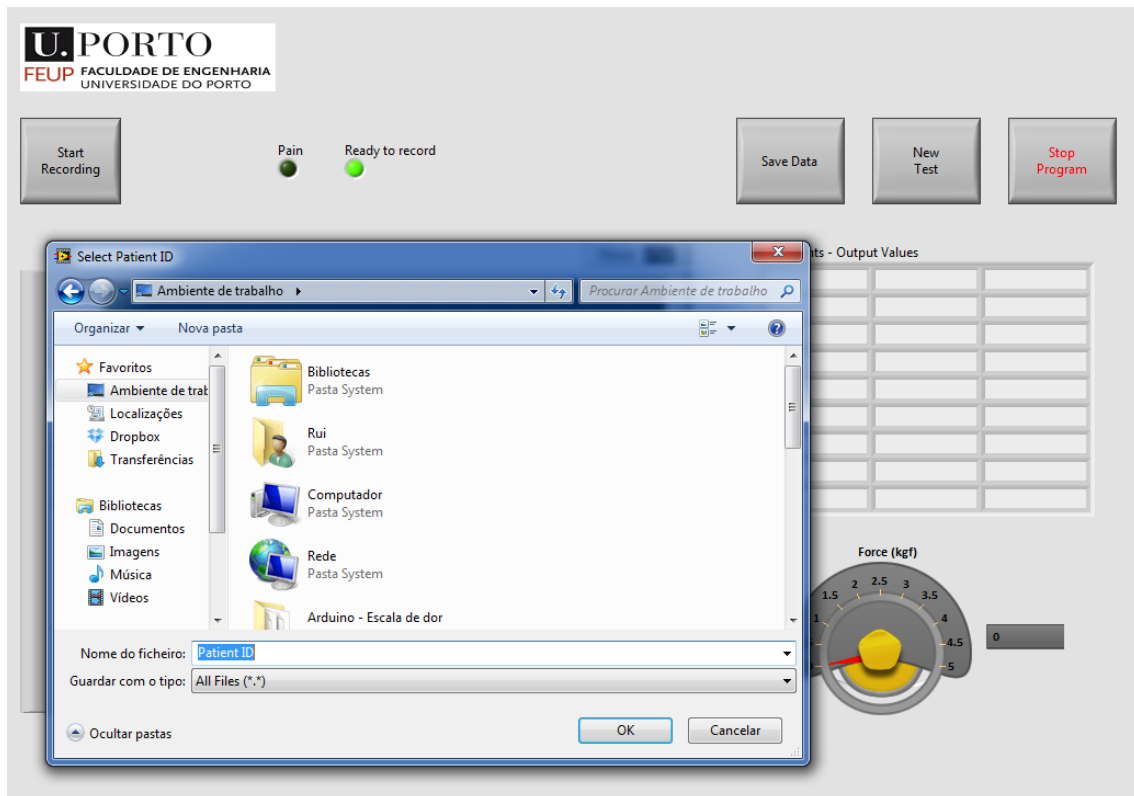


Figure 26: Sensor data saving and reporting

7 – On file saving screen, add patient ID to file name.

8 – Press **New Test** to reset application for new measurement.

9 – Press **Stop Program** to stop the application. If there is data to be saved, it is also possible to select from three different options: **Continue data recording**, **Save Data** or **Close Program**. The first option redirects to previous window. Save data opens a prompt window to select the file to which data will be stored and the last option completely closes the application.

Data to be analyzed:

1. VAS before and after the acupuncture with-out applying pressure on the pelvic. T0 and T3.
2. VAS before and after the intervention with pressure application on the pelvic.T1 and T2
3. Analysis of the data recorded in the computer with the pain events and the force needed to induce the maximum pain before and after the treatment.
4. Analysis of both VAS and the saved data from the Sensor and comparison after the cross-over between the groups.

4.8 Study Chronogram:

Table 4: Study Chronogram

Time period	Main tasks and goals
September 2013 to January 2014	Literature research; preparation of the research protocol.
February to May 2014	Submission of the research project to Hospital Centre São João for Ethics Committee assessment (already approved see Annex 1).
May – June 2014:	Patient selection according to the inclusion criteria of this study, and data recruitment recently started at the Hospital.
Since June	Study protocol practical work and continuous patient recruitment and enrolments.
October	Master thesis delivery
December 2014	Predicted end of the study
January 2015	Data analysis and article writing
February-March 2015	Submission and publication of results

5. Research partnership:

Cooperation between ICBAS TCM Master Program and the Service of Gynecology and Obstetrics of Hospital Center São João was established. Agreement for the research project was obtained from the Director of the Service of Gynecology and Obstetrics, Prof. Doctor Nuno Montenegro.

6. Expected Results:

This proposed clinical protocol has been submitted for approval by the Ethics Committee of São João Hospital (appendix 1), the authorization to work on the Endometriosis clinic has been granted (appendix 3), and steps towards its completion are being accomplished.

Enrollment of the patients is currently in course.

Until the present date, 20 patients were contacted. Only 6 could be selected due to the eligibility criteria.

Main reasons for exclusion:

- Not interested in acupuncture
- Patients underwent surgical treatment for endometriosis
- No pain under medication
- Patients had other medical conditions and treatment that did not allow for visits to the hospital or participation in acupuncture treatments.
- Professional reasons not allowing their coming for a research study.

In addition, summer time traditional Portuguese holidays (July-August-September) limited the voluntary adherence of the patients to the study until the thesis delivery deadline.

From 6 patients that were selected, we had 5 drop outs generally due to:

- No pain with pressure at baseline on the first visit assessment in office or at the second session of acupuncture.
- Missed 2nd session of acupuncture after 1 week (some could only come 2 weeks after which did not follow the protocol).

So far we have one case report which showed clinical improvement with verum acupuncture that we describe.

6.1. Case report

A 44 years-old woman diagnosed with pelvic endometriosis two years ago. She developed chronic pelvic pain with dysmenorrhea secondary to endometriosis and was taking NSAIDs plus analgesics Paracetamol 1000 mg 3 times daily and Tramadol 50 mg two times daily since 7 months with limited improvement.

After randomization, the patient was firstly enrolled to the verum acupuncture group.

After one week, she was subjected to the sham acupuncture in her second session. During the pain assessment (VAS baseline T0) she reported that she didn't feel the pain during the week and so did not use the drugs.

The results of the VAS and Pressure maximum-induced pain measurements are shown in table 5 (VAS) and table 6 (sensor).

Table 5: Pain evaluation VAS results

Type of pain measurement VAS	Stages of the pain measurement				
	T0	T1	T2	$\Delta T2-T1$	T3
Verum acupuncture	0	7	3	4	0
Sham acupuncture	1	4	3	1	0

Table 5.1 Pain evaluated by VAS. T0: baseline and patient reported taking Paracetamol 1000mg and Tamadol 50mg 3hr attending the session; T1: after pressure to maximum pain at pelvic point before acupuncture; T2: after acupuncture; T3: after treatment, at rest. $\Delta T2-T1$: magnitude of VAS before and after acupuncture.

The above table is showing the result of VAS both before and after intervention.

Table 6: Pressure sensor device results

Pressure induced maximal pain	Stages of the pain measurement		
	T1	T2	$\Delta (T2-T1)$
Verum acupuncture	1.740 kg	2.501 kg	0.761
Sham acupuncture	1.027 kg	1.576 kg	0,549

Table 2 –Maximum pain after pressure as measured by a pressure-sensitive sensor. T1: before: after pressure to maximum pain at pelvic point before acupuncture; T2: after acupuncture; $\Delta (T2-T1)$: magnitude of pressure maximum-induced pain before and after acupuncture.

7. Discussion

The scientific approach is the best way to increase knowledge and understanding of acupuncture in the future, because it is self-critical by its very nature. Only through a scientific approach, acupuncture and TCM may be validated as a therapeutic option for patients.

Acupuncture analgesic effects are widely described in literature, mainly for musculoskeletal conditions (upper limb pain, neck pain, back pain, osteoarthritis of the knee or hip), headache (migraine, tension-type), myofascial pain, fibromyalgia, pelvic pain in pregnancy, dental pain, or postoperative pain.

These neurophysiologic effects have been described by acting at 5 levels[37]:

- Local effects in the tissue
 - o Acupuncture promotes local healing
- Segmental effects at a particular level in the spinal cord (depression of the dorsal horn activity, thereby reducing the painful stimuli)
 - o Acupuncture reduces pain in the segment where the needles are inserted
- Extra-segmental effects by stimulating pain-suppressing endogenous mechanisms on the brainstem pathways thereby promoting a systemic pain reduction response.
 - o Acupuncture reduces pain on the whole body
- Central regulatory effects at the cortex, hypothalamus and limbic system, thereby exerting regulatory effects
 - o Acupuncture promotes a general wellbeing and relaxing sensation

Unfortunately, pharmacological approaches often render limited effects and also provoke potentially serious side effects. Hence, many patients try complementary medicine treatments. Amongst the non-pharmacological approaches, the use of acupuncture has increased consistently during the past few decades.

Regarding dysmenorrhea, from which 90% is primary, acupuncture seems to have satisfactory results according the present literature[28].

However, for dysmenorrhea secondary to endometriosis few studies have been performed.

There is preliminary evidence to support acupuncture as an effective treatment for endometriosis, with one small sham controlled trial ([23]) and a few comparative studies against Western medication ([38], [39], [6]).

Currently, it is thought that acupuncture treatment may improve pain due to endometriosis by:

1. providing pain relief - by stimulating nerves located in muscles and other tissues, acupuncture leads to release of endorphins and other neuro humoral factors, and changes the processing of pain in the brain and spinal cord ([40], [41], [42], [43]).
2. reducing inflammation - by promoting release of vascular and immune modulatory factors [44], [42]).
3. rregulating levels of prostaglandins ([45])· combining acupuncture with Chinese herbal medicine for endometriosis has been shown in animal studies to down regulate the abnormal increase of matrixmetalloproteinase-2 (MMP-2) levels that is associated with ectopic activity of endometrial cells. The treated rats had reduced areas of ectopic tissue (Chen 2008). MMP-2 is required for the anchoring of the placenta to the uterine wall in pregnancy but over-production can lead to endometriosis.

Further research is needed to confirm these observations.

In common to all acupuncture studies, we found methodological flaws in these studies of acupuncture for endometriosis including:

- lack of an adequate control for acupuncture
- absence of a double-blinding methodology
- lack of objective measurements of the acupuncture effect in pain modulation

We defined the needling of skin non-acupoints as the control acupuncture. Some researchers prefer to compare true acupuncture to a waiting list. However, by comparing true acupoints with non-acupoints, we wanted to assess whether true acupuncture effects are specific since it is known that needling any point on the skin elicits unspecific body responses. Interestingly, our selected control points share same segmental nerve roots with verum acupoints. If we observe specific effects of verum acupoints, then we must raise the hypothesis of an additional mechanism beside the neurological theory of “western medical acupuncture”.

Our case report suggests that the effect of true acupuncture is superior to sham, indicating possibly a specific effect of verum acupoint needling. However, this observation must be skeptically considered, since we need more cases, more data, to exclude that this particular clinical case observation was not merely due to chance.

Due to lack of time, financial and human resources, we could not develop a double-blinded methodology.

For this, we believe we could follow the Heidelberg double-blind assay, in which the individual inserting needles would be a non-acupuncturist, and therefore could not distinguish from true or sham acupoints that were marked on the skin with different alternating colors[46].

It is widely discussed, proved and recommended in the literature to use pain measurement tools like VAS to measure overall pain in clinical practice.

However, problems exist in *objective* measuring the effect of acupuncture in pain.

All studies in acupuncture for endometriosis have only applied VAS to measure pain. This tool has been criticized because it is highly subjective and therefore may not represent real effects of acupuncture.

We wanted to introduce in our protocol a new method to objectively evaluate the effect of acupuncture in pain.

In strict cooperation with the Engineer Faculty colleagues, we develop a novel pressure-sensitive sensor device which allows objective measurement of acupuncture's effect in pain in endometriosis patients.

By measuring how much pressure the patient can tolerate by abdomeno-pelvic palpation until maximum pain, we can achieve results of pressure in kg units that could indicate changes in pain by acupuncture.

By analysing the resulted data from the sensor and the VAS we could get more accurate, reproducible measurement of the extent of the reduction induced by the treatment.

We have seen in some cases, that VAS changes not always follow the same direction of change as with pressure-sensitive sensor assessment. Therefore, pain perception and real pain are different phenomena for patients. Our study could add information regarding these differences. Most importantly, the pressure maximum induced pain methodology allows an objective measurement of acupuncture effects, which in turn will contribute to the demystification of acupuncture.

Since the study is in the beginning and there is not enough data yet available at the time of this thesis submission in order to take out conclusion regarding acupuncture effect in endometriosis.

It is expected that the real acupuncture could show decrease in pain even after one treatment and this effect could be assessed with the visual pain scale and the sensor measurement before and after each session.

It is foreseen that the real acupuncture could demonstrate a significant reduction in pelvic pain sensation, compared to the sham group keeping in mind that the both groups should be with no statistically significant differences regarding age, gender, and use of medication (this last factor may be difficult to control).

Limitations

Our study protocol has some limitations that we want to dissect.

In a practical level some problems were detected.

Since we are inviting patient out of their scheduled consultations, it was almost impossible to get the patient at the right time for the 2nd session one week after the 1st session. Availability of a room in the Gynecology outpatient sector in the hospital was limited to two days per week only in the afternoon 3hrs per day (6hrs per week) which also restricted the researcher's availability for patient's participation bearing in mind their own time-table availability to participate.

As we mentioned in the results section, the recruitment of the patient already started and we faced several problems. So far we had 6 cases included into the study that signed the consent. From these, recruitment data and the first session were done, but only one of these six patients completed the second session in the right time (1 week apart from the first assessment), due lack of right timing between patients availability and the availability of the rooms in the hospital, some technical problems with the sensor that were meanwhile improved, and some patients just disappeared and did not come to the second session.

In addition, most of the contacted patients did not have spontaneous pelvic pain, because they were controlled with pain killers. Ethically, we are not allowed to ask them to stop their medication in order to try acupuncture instead.

Because it is a short time study, action of external factors such as change in medicaments, change of lifestyle, diet, alcohol intake, smoking status are less likely to happen and influence results.

Also, crossover designs are prone to carry-over effects. Although it is generally accepted that the effect of one acupuncture session has vanished one week later, we cannot rule out residual carry-over effects based on an empirically notion. Statistically analyses may help to clear this doubt.

We cannot also exclude that baseline pain may be different in the two sessions (1st or 2nd). However, comparison of the magnitude of the effects of acupuncture (true or false)

between the 1st and 2nd session will serve as the index to avoid possible baseline differences.

Although we include patients with chronic pain, the pain due to endometriosis may fluctuate in relation to its hormonal influences. This may limit the cross-over method. In order to overcome this limitation, a parallel two group study (verum vs. false acupuncture) with at least 8 to 12 sessions of acupuncture would be needed.

This study protocol was conceived to evaluate acute effects of acupuncture in endometriosis pelvic pain in order to have a preliminary study to support a further larger study.

As such, we are unable to infer the long-term or cumulative effects of repeated applications. A long-term study evaluating the chronic impact of acupuncture for endometriosis would then be needed and it can be done using the Endometriosis health profile (EHP-30, EHP-5) (Annex 5) which recognized to be the best questionnaire to evaluate the pain in endometriosis and patient's quality of life.

We did not blind the acupuncturists for the reasons expressed previously.

For a subsequent study evaluating long-term effects of acupuncture in endometriosis, we believe it would be important to blind the acupuncturist following the Heidelberg double-blinded assay [46]

Finally, the controversy over acupuncture extends to the issue of the most effective method of acupuncture. Some practitioners favor a “modern medical /western acupuncture”, treating patients according to a standardized set of points based on the areas of innervation. Other practitioners adhere to an individualized “classical acupuncture”, which selects acupuncture points based on assessment of disease patterns (syndrome differentiation) and a physical examination, including Chinese tongue and pulse diagnosis and the localization of par aesthetic pressure points. While the data support the notion that the choice of needling points matters, the relevant aspects of the Chinese diagnosis still remain to be elucidated[46]. This, however, cannot be addressed in this work.

In this context, we opted to choose acupoints and the leopard spot technique on the basis of a general common treatment within the TCM Heidelberg model approach considering the need to treat qi and xue stasis which is present in all endometriosis patients according to TCM theory. As such, it is an open question to study an

individualized acupuncture treatment based on neuro vegetative pattern differentiation, i.e., following an individual functional diagnosis.

Hypothetically, acupuncture treatment based on an individualized selection of acupoints may be superior to a general standardized acupuncture treatment approach as we need which was not the goal of this study protocol. This study should, therefore, be considered a proof of concept study.

- Blinding the patients to avoid the effects of their beliefs and expectations because these can influence the response to the therapy. . (Kaptchuk, 2002)(Flaten, Simonsen, & Olsen, 1999). DISCUSSION

8. Future perspectives:

This study may reveal that acupuncture may significantly decrease chronic pain due to endometriosis in comparison to the sham group, therefore possibly indicating specific physiological effects of acupuncture.

The introduction of a novel pressure sensor to evaluate pain is a pioneer methodology that we want to further explore. Preliminary experience showed that this device is working successfully by objectifying pressure tolerance as a measure of pain reduction.

Therefore, at the conclusion of this study protocol we may show that this device can be used as step towards objective research on acupuncture and of EM induced pelvic pain, thus validating the effects of acupuncture.

This assessment could then be useful for additional research with larger sample and longer acupuncture treatment and follow up periods to assess the real effect of acupuncture.

This study can be used as step toward the inclusion of acupuncture in the future guidelines for the management of EM induced pelvic pain.

Results from this study may in the future grant a larger prospective, controlled, double-blinded, and randomized protocol with longer follow-up period.

Acupuncture may prove to be another interesting tool to manage this condition responsible for a great discomfort and reduced quality of life for affected women and their partners.

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45. Jin, Y.B., Z.L. Sun, and H.F. Jin, [*Randomized controlled study on ear-electroacupuncture treatment of endometriosis-induced dysmenorrhea in patients*]. Zhen Ci Yan Jiu, 2009. **34**(3): p. 188-92.

46. Karner, M., et al., *Objectifying specific and nonspecific effects of acupuncture: a double-blinded randomised trial in osteoarthritis of the knee*. Evid Based Complement Alternat Med. **2013**: p. 427265.

Annexes

Annex 1: Approval Letter from The Hospital Ethical committee

Direcção Clínica
10/4/14

CES 47/14



Exmo. Senhor

Presidente do Conselho de Administração do
Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Khadija Ibar

Título do projecto de investigação: EFEITO DA ACUPUNTURA NA DOR PELVICA NA
ENDOMETRIOSE - ESTUDO DE VIABILIDADE
/ The effect of acupuncture on pelvic pain due

Pretendendo realizar no(s) Serviço(s) de Ginecologia do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 8 / Janeiro / 2013

O INVESTIGADOR/PROMOTOR



Comissão de Ética para a Saúde – Centro Hospitalar São João/FMUP

Parecer

Título do Projecto: Efeito da Acupunctura na Dor Pélvica na Endometriose – estudo de viabilidade.

Nome do Investigador Principal: Dr^a. Khadija Ibar

Local onde sera realizado o estudo: Serviço de Ginecologia e Obstetrícia – CHSJ havendo autorização do respectivo Director de Serviço. Apresenta como Elo de Ligação, a Dr^a Ana Rosa Costa, e apresenta a respectiva Declaração.

Mestrado em Medicina Tradicional Chinesa - ICBAS

Objectivo do estudo:

Avaliar os efeitos da acupunctura na dor pélvica em doentes com endometriose.

Período previsto de conclusão: 30.Junho.2014

Benefícios: Está referido como possíveis benefícios, uma melhoria da analgesia com controlo de sintomas associados a endometriose, e consequente melhoria da qualidade de vida.

Riscos: Como riscos estão referidos ligeira dor e equimose local, associado à acupunctura.





3.3.14
os esclarecimentos
prestados estão de acordo com
os princípios éticos, pelo que
proponho a sua aprovação pela
CES.

John
John Rodrigues Preto
Cirurgião Geral
35084

Respeito pela liberdade e autonomia do sujeito do ensaio: Prevê-se a obtenção de consentimento informado, complementado por uma informação escrita que é esclarecedora dos objetivos, dos riscos e benefícios potenciais do estudo, bem como a garantia de confidencialidade dos dados e a liberdade em participar. Inclui, igualmente, um consentimento informado para os Responsáveis Legais dos participantes menores, uma vez que o estudo prevê a inclusão de jovens a partir dos 13 anos.

Confidencialidade dos dados: está garantida a confidencialidade dos dados e esta informação será restrita aos Investigadores.

A Investigadora Principal dispõe de competência técnica e científica para a realização do estudo.

O estudo prevê a realização de questionário, mas não foi incluído um exemplar.

Custos: O estudo não prevê custos acrescidos para a instituição.

Parecer: Em face da análise do protocolo de estudo, proponho a sua aprovação pela CES do CHSJ/FMUP, que ficará dependente da resposta da investigadora às questões em itálico.

Porto, CHSJ, 24 de fevereiro de 2014

O Relator

John
Dr. John Preto

28.02.14:
Foi incluído um exemplar de
cada questionário. No entanto, o
EHP-30, EHP-5 e da UCLA,
estão em língua inglesa. Caso
seja para serem preenchidos pelas
participantes, deverá ser entregue
exemplares em português. Por outro
lado, o questionário da UCLA deve
ser anonimizado.
John

CES

COMISSÃO DE ÉTICA PARA A SAÚDE

7. SEGURO

a. Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?

SIM (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)

NÃO

NÃO APLICÁVEL

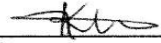
8. TERMO DE RESPONSABILIDADE

Eu, Khadija Ibar,

abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 8 / Janeiro / 2013

A Comissão de Ética para a Saúde tendo aprovado o parecer do Relator, aguarda que o Investigador/Promotor esclareça as questões nele enunciadas para que possa emitir parecer definitivo.


O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

*Considerado por forma a ser aceite
o esclarecimento prestado pelo investigador*

A Comissão de Ética para a Saúde
APROVA por unanimidade o parecer do
Relator, pelo que nada tem a opor à
realização deste projecto de investigação.


Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

2014.03.10

emitido na reunião plenária da CES

de



Efeito da Acupuntura na dor pélvica na endometriose – um estudo de viabilidade

**PROJECTO DE INVESTIGAÇÃO CLÍNICA
CONSULTA DE ENDOMETRIOSE - SERVIÇO DE GINECOLOGIA
CENTRO HOSPITALAR DE SÃO JOÃO**

CONVITE

Hospital de São João, 20 de Março de 2014

Exma. Sra.

Vimos por este meio convidá-la a participar num estudo clínico que será promovido pelo Serviço de Ginecologia do Hospital São João.

Trata-se de um projecto de investigação clínica que pretende avaliar o efeito da acupuntura na dor associada à endometriose.

Este estudo está a ser conduzido pela Dra. Khadija Ibar (médica, investigadora principal) sob orientação da Dra. Ana Rosa Machado Costa, responsável pela consulta de Endometriose do Hospital de São João, no âmbito de uma tese de mestrado em Medicina Tradicional Chinesa do Instituto de Ciências Biomédicas de Abel Salazar da Universidade do Porto.

Este estudo foi aprovado em Fevereiro de 2014 pela Comissão de Ética do Centro Hospitalar de São João, Porto.

Os participantes neste estudo serão submetidos a tratamento de acupuntura com a periodicidade de 1 vez por semana durante 1 mês (4 sessões de acupuntura no total). Cada sessão de tratamento terá a duração de 30 minutos. Todas as respostas a questionários serão tratadas de forma confidencial e os participantes individuais nunca serão identificados. Todos os dados serão agregados e publicados de forma conjunta.



SÃO JOÃO

A acupuntura é uma técnica terapêutica que consiste na inserção de agulhas esterilizadas e de fino calibre em pontos específicos da pele e tecido muscular. Trata-se de uma técnica geralmente segura. Os efeitos secundários graves são muito raros - menos de 1 por 10.000 tratamentos.

A sua participação é voluntária e a recusa em cooperar com este estudo não trará consequências nem perda de benefícios. Os participantes poderão sair do estudo em qualquer altura, sem consequências nem perda de benefícios a que de outra forma tenham direito.

A sua participação contribuirá para esclarecer se a acupuntura constitui uma arma terapêutica adicional no tratamento da endometriose.

Nos próximos 3 a 5 dias iremos entrar em contacto consigo para avaliar da sua disponibilidade em participar neste estudo clínico.

Com os melhores cumprimentos,

A Investigadora Principal

Dra. Khadija Ibar

DECLARAÇÃO DE CONSENTIMENTO

*Considerando a “Declaração de Helsínquia” da Associação Médica Mundial
(Helsínquia 1964; Tóquio 1975; Veneza 1983; Hong Kong 1989; Somerset West 1996 e Edimburgo 2000)*

Designação do Estudo (em português):

Eu, abaixo-assinado, (nome completo do doente ou voluntário são)

declaro não ter participado em nenhum outro projecto de investigação durante este internamento, tendo compreendido a explicação que me foi fornecida acerca do meu caso clínico e da investigação que se tenciona realizar. Foi-me ainda dada oportunidade de fazer as perguntas que julguei necessárias, e de todas obtive resposta satisfatória.

Tomei conhecimento de que, de acordo com as recomendações da Declaração de Helsínquia, a informação ou explicação que me foi prestada versou os objectivos, os métodos, os benefícios previstos, os riscos potenciais e o eventual desconforto. Além disso, foi-me afirmado que tenho o direito de recusar a todo o tempo a minha participação no estudo, sem que isso possa ter como efeito qualquer prejuízo na assistência que me é prestada.

Por isso, consinto que me seja aplicado o método, o tratamento ou o inquérito proposto pelo investigador.

Data: ____ / _____ / 201__

Assinatura do doente ou voluntário são: _____

O Investigador responsável:

Nome:

Assinatura:

Comissão de Ética do Centro Hospitalar de S. João – Modelo CE 01

Annex 3: Clinical Questionnaire

Projecto de Investigação

Efeito da acupunctura na dor pélvica na endometriose – estudo de viabilidade

Questionário Clínico

Nota: Os questionários serão mantidos sob confidencialidade

Questionário nº _____

A. Identificação:

1. Nome (iniciais): _____
2. Nº processo clínico: _____
3. Data de nascimento: ___ / ___ / _____
4. Estado Civil
 - a. Solteira
 - b. Casada
 - c. Divorciada
 - d. Viúva
 - e. União de facto
5. Profissão: _____
6. Contacto telefónico: _____

B. História clínica da Endometriose

- a. Data do diagnóstico: ___ / ___ / ___
- b. Tipo de endometriose
 - i. Pélvica: S ___ N ___
 - ii. Extra-pélvica S ___ N ___
- c. Dor pélvica
 - i. Intensidade (0-10)
 - ii. Nº agudizações / semana
 - iii. Predomínio diário: Manhã ___ Tarde ___ Noite ___
 - iv. Uso de analgésicos /AINEs: _____
- d. Outros sintomas /problemas associados
 - i. Dispareunia S ___ N ___
 - ii. Disuria S ___ N ___
 - iii. Fadiga S ___ N ___
 - iv. Dor abdominal S ___ N ___
 - v. Diarreia S ___ N ___
 - vi. Obstipação S ___ N ___
 - vii. Infertilidade S ___ N ___
- e. CA -125

Data	Resultado

C. História Ginecológica e Obstétrica

- a. Menarca: _____ (anos)
- b. Cataménios
 - i. regulares: _____ dias
 - ii. irregulares: _____ a _____ (ex: 12 a 50 dias)
 - iii. duração: _____ dias
- c. Menorragias: S__ N__
- d. Metrorragias: S__ N__
- e. Primerio dia da última menstruação: ____/____/____
- f. Dor associada à menstruação? S__ N__
 - i. Se sim: antes da menstruação S__ N__; Durante S__ N__; Antes e durante S__ N__
- g. Nunca esteve grávida: _____
- h. Gravidez:

Ano	Abortamento S/N	Tipo Parto Eutócito (E) Cesarina (C)	Duração da gestação (semanas)	Nados vivos	Nados mortos	Complicações do parto

D. História de contraceção

- a. Método: _____

E. História sexual

- a. Tem parceiro sexual: S__ N__ (Homem ____; Mulher ____)

F. História médica passada:

- a. VIH _____
- b. VHB _____
- c. VHC _____
- d. Sífilis _____
- e. Gonorreia _____
- f. Clamidia _____
- g. Infecções vaginais _____

- h. Verrugas venéreas____
- i. Herpes genital____
- j. Doença inflamatória pélvica____
- k. Diabetes tipo 1 _____ tipo 2____
- l. Doença tiroideia_____
- m. Doença cardíaca_____
- n. Doença respiratória_____
- o. HTA_____
- p. Doença hepática____
- q. Doença renal_____
- r. Doença psiquiátrica_____
- s. Doença neurológica_____

G. História passada cirúrgica

Cirurgias	Ano
_____	_____
_____	_____
_____	_____

H. Hábitos de vida:

- a. Alimentares:
- b. Tabágicos:
- c. Alcoólicos:
- d. Consumo de drogas ilícitas:

I. Rastreios

- a. Mamografia: S___ N___
 - i. Anos:_____
 - ii. Resultados:_____
- b. Citologia Papanicolau: S___ N___
 - i. Anos:_____
 - ii. Resultados:_____
- c. Tratamentos para citologias anormais?
 - i. Crioterapia: S___ N___ Ano___
 - ii. Laser : S___ N___ Ano___
 - iii. Biópsia de cone: S___ N___ Ano___
 - iv. Excisão : S___ N___ Ano___

I. História medicamentosa

Medicação	Dose	Posologia

Reacções adversas ou alérgicas a fármacos:

S__ N__

Quais: _____

J. Terapêuticas não convencionais

a. Acupunctura: S____ N____

b. Yoga: S____ N____

c. Reiki: S____ N____

d. Outros: _____

J. História familiar

Diabetes _____

Neoplasia do ovário _____

Neoplasia do endométrio _____

Neoplasia mamária _____

Neoplasia do cólon _____


Outros: _____


Elementos afectados: _____


Annex 4: Visual Analogue Scale:


Date: _____

P Name: _____ ID: _____

T0: 

T1: 

T2: 

T3: 

ENDOMETRIOSIS

HEALTH

PROFILE QUESTIONNAIRE

(EHP-5)

PART 1: CORE QUESTIONNAIRE

DURING THE LAST 4 WEEKS,
HOW OFTEN, BECAUSE OF YOUR ENDOMETRIOSIS, HAVE YOU...

	Never	Rarely	Sometimes	Often	Always
1. Found it difficult to walk because of the pain?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Felt as though your symptoms are ruling your life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Had mood swings?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Felt others do not understand what you are going through?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Felt your appearance has been affected?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please check that you have *ticked one box for each question.*

SAMPLE COPY - DO NOT USE

ENDOMETRIOSIS QUESTIONNAIRE

HEALTH

PROFILE

(EHP-30)

PART 1: CORE QUESTIONNAIRE

DURING THE LAST 4 WEEKS,
HOW OFTEN, BECAUSE OF YOUR ENDOMETRIOSIS, HAVE YOU...

	Never	Rarely	Sometimes	Often	Always
1. Been unable to go to social events because of the pain?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Been unable to do jobs around the home because of the pain?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Found it difficult to stand because of the pain?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Found it difficult to sit because of the pain?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Found it difficult to walk because of the pain?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Found it difficult to exercise or do the leisure activities you would like to do because of the pain?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Lost your appetite and/or been unable to eat because of the pain?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please check that you have ***ticked one box for each question***
before moving onto the next page.

ENDOMETRIOSIS,

8 Been unable to sleep properly because of the pain?

9 Had to go to bed/lie down because of the pain?

10. Been unable to do the things you want to do because of the pain?

11. Felt unable to cope with the pain?

12. Generally felt unwell?

13. Felt frustrated because your symptoms are not getting better?

14. Felt frustrated because you are not able to control your symptoms?

Please check that you have ***ticked one box for each question*** before moving onto the next page.

ENDOMETRIOSIS,

15. Felt unable to forget your symptoms?

16. Felt as though your symptoms are ruling your life?

17. Felt your symptoms are taking away your life?

18. Felt depressed?

19. Felt weepy/tearful?

20. Felt miserable?

21. Had mood swings?

22. Felt bad tempered or short tempered?

Please check that you have ***ticked one box for each question*** before moving onto the next page.

ENDOMETRIOSIS,

23. Felt violent or aggressive?

24. Felt unable to tell people how you feel?

25. Felt others do not understand what you are going through?

26. Felt as though others think you are moaning?

27. Felt alone?

Felt frustrated as you cannot
28. always wear the clothes you would choose?

29. Felt your appearance has been affected?

30. Lacked confidence?

Please check that you have ***ticked one box for each question.***

nex 6: Summary of Studies done about Acupuncture in Endometriosis

Authors	Title	Study type	Conclusions	Ref.
Zhu X, Hamilton KD,McNicol ED.	Acupuncture for pain in endometriosis.	Review	The evidence to support the effectiveness of acupuncture for pain in endometriosis is limited, based on the results of only a single study that was included in this review. This review highlights the necessity for developing future studies that are well-designed, double-blinded, randomised controlled trials that assess various types of acupuncture in comparison to conventional therapies.	Cochrane Database Syst Rev. 2011 Sep 7;(9):CD00786 4. doi: 10.1002/1465 1858.CD00786 4.pub2.
Xiang DF, Sun QZ, Liang XF.	Effect of abdominal acupuncture on pain of pelvic cavity in patients with endometriosis	Clinical study (acupuncture vs CM herbs)	Effect of abdominal acupuncture on relieving pain of pelvic cavity caused by endometriosis, reducing the level of serum CA125 is superior than Tianqi Tongjing Capsule (radix notoginseng capsule for dysmenorrhea). However, the effects on reducing the size of the ovarian endometrial cyst and the size of uterus with adenomyosis are not significant. Therefore, it is concluded that abdominal acupuncture is a better choice for endometriosis with pain as the chief complaints.	Zhongguo Zhen Jiu. 2011 Feb;31(2):113- 6.
Chen M, Zhang H, Li J, Dong GR.	Clinical observation on acupuncture combined with acupoint sticking therapy for treatment of dysmenorrhea caused by endometriosis	Clinical s. Acup. vs medication group	The therapeutic effect of acupuncture combined with acupoint sticking therapy is very significant for dysmenorrhea caused by endometriosis, and it is a good therapy for this kind of disease.	Zhongguo Zhen Jiu. 2010 Sep;30(9):725- 8
Rubi-Klein K, Kucera- Sliutz E, Nissel H,	Is acupuncture in addition to conventional medicine	Clinical s. RCT, cross-over N=101 Acup (n=47) vs	Acupuncture treatment on specific acupuncture points appears to be an effective pain treatment for endometriosis, but this has to be confirmed in further study.	Eur J Obstet Gynecol Reprod Biol. 2010

Bijak M, Stockenhuber D, Fink M, Wolkenstein E	effective as pain treatment for endometriosis? A randomised controlled cross-over trial.	Non-specific acup (n=54)		Nov;153(1):90-3. doi: 10.1016/j.ejogrb.2010.06.023. Epub 2010 Aug 21
Ahn AC, Schnyer R, Conboy L, Laufer MR, Wayne PM.	Electrodermal measures of Jing-Well points and their clinical relevance in endometriosis-related chronic pelvic pain.	RCT	Electrodermal measures may be significantly associated with clinical outcome and acupuncture treatments in adolescent women with chronic pelvic pain.	Altern Complement Med. 2009 Dec;15(12):1293-305. doi: 10.1089/acm.2008.0597
Chen YF, et al	Effects of acupuncture combined with medicine on expression of matrix metalloproteinase-2 in the rat of endometriosis]	Rat EMs model	Combination of acupuncture with medicine has a better therapeutic effect on endometriosis and down-regulates the abnormal increase of MMP-2 level to inhibit the invasion of ectopic tissue to extracellular matrix, so as to reduce the ectopic tissue, hence cure of endometriosis.	Zhongguo Zhen Jiu. 2008 Sep;28(9):675-80.
Wayne PM, et. All..	Japanese-style acupuncture for endometriosis-related pelvic pain in adolescents and young	RCT; feasibility study	Preliminary estimates indicate that Japanese-style acupuncture may be an effective, safe, and well-tolerated adjunct therapy for endometriosis-related pelvic pain in adolescents. A more definitive trial evaluating Japanese-style acupuncture in this population is both feasible and warranted.	J Pediatr Adolesc Gynecol. 2008 Oct;21(5):247-57. doi: 10.1016/j.jpaga.2007.07.008.

	women: results of a randomized sham-controlled trial.			
Lundeberg T, Lund I.	Is there a role for acupuncture in endometriosis pain, or 'endometrialgia'?	Review	Management of pain in women with endometriosis is currently inadequate for many. Possibly acupuncture and cognitive therapy may be used as an adjunct.	Acupunct Med. 2008 Jun;26(2):94-110.
Sun YZ, Chen HL	Controlled study on Shu-Mu point combination for treatment of endometriosis	RCT N=30 vs n=30 Acup vs Danazol	Shu-Mu point combination needling method has an obvious therapeutic effect on endometriosis, with lower adverse effect than that of the western medicine group. Reduction of pain and CA125 levels	Zhongguo Zhen Jiu. 2006 Dec;26(12):863-5.
Highfield ES, et al.	Adolescent endometriosis-related pelvic pain treated with acupuncture: two case reports.	Case report N=2	These case reports provide preliminary evidence that acupuncture may be an acceptable and safe adjunct treatment therapy for some adolescents with endometriosis-related pelvic pain refractory to standard antiendometriosis therapies. These observations suggest that a prospective, randomized controlled trial of the safety and efficacy of acupuncture for this population may be warranted.	J Altern Complement Med. 2006 Apr;12(3):317-22.
Xiang D et al.	Ear acupuncture therapy for 37 cases of dysmenorrhea due to endometriosis.	Case report N=37	Not available	J Tradit Chin Med. 2002 Dec;22(4):282-5.

Tsenov D	The effect of acupuncture in dysmenorrhea	N=48 Primary (1 st Group) vs secondary dysmenorrhoea (2 nd group)	In the 1st group effect was very well after one course of 2-4 acupuncture procedures before menstruation. In the 2nd group effect was satisfactory in 50% of the cases after two courses acupuncture treatment. In conclusion effect of acupuncture treatment on dysmenorrhoea depend on its kind--primary dysmenorrhoea is influenced very well, while secondary dysmenorrhoea is influenced satisfactory.	Akush Ginekol (Sofia). 1996;35(3):24-5.
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