Effectiveness of the osteopathic treatment of women with uterine fibroids: Development of a study protocol of a randomized controlled trial

by

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A Thesis Submitted to the
Post-graduate School of
Osteopathic Clinical Research
in Partial Fulfillment of the Requirements for the
Degree of Master of Science in Osteopathic Clinical Research

A.T. Still University
2010

Approval Page

This Thesis Proposal was submitted by Joachim Salomon, whose committee was composed of the persons indicated below. It was submitted to the Dean of the Post-graduate School of Osteopathic Clinical Research and approved in partial fulfillment of the requirements for the degree of Master of Science in Osteopathic Clinical Research at A.T. Still University of Health Sciences.

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Abstract

Effectiveness of the osteopathic treatment of women with uterine fibroids: Development of a study protocol of a randomized controlled trial. Joachim Salomon, 2010: Thesis, Post-graduate School of Osteopathic Clinical Research, A.T. Still University of Health Sciences./M.Sc./Osteopathic Clinical Research.

Background: Uterine fibroids are the most common benign pelvic tumors affecting women at reproductive age. They are estrogen-dependent tumors and occur more frequently as age increases. About 25-30% of women affected have symptoms such as menstrual bleeding disturbances, pain, compression syndromes and reproductive dysfunctions.

Objective: The purpose of the study was to provide a description of the actual level of medical knowledge on the clinical problem and to analyze interventional trials on uterine fibroids in terms of methodological aspects. As a result of this work a study protocol of a randomized controlled trial on the effectiveness of osteopathic treatment of patients with uterine fibroids should be developed.

Methods: In order to research the clinical problem, a systematic review of the literature was undertaken in the databases, Medline, Embase, Cochrane Library and Science Direct. The second part of the research of literature was conducted with the aim of collecting information on the methodological structure of studies and with regard to evaluating the development of my own study protocol. The examined databases were Cochrane Library, Medline, a number of osteopathic databases and the Physiotherapy Evidence database. Relevant, non-Medline-listed trade journals, congress reports, e.g. ICAOR, directories of master and PhD theses and current study projects from different universities for osteopathic clinical studies on uterine leiomyoma have been perused. To ensure that the design decisions are consistent with the trial's stated purpose, PRECIS - the Pragmatic-Explanatory Continuum Indicator Summary - was used.

Results: As well as a comprehensive presentation of the actual medical level of knowledge on the clinical problem, a complete study protocol, ready for use, has been

developed in order to carry out a pragmatic trial. This concerns a randomized, controlled study to test the effectiveness of usual care plus osteopathic treatment in comparison with only usual care.

Conclusion: The examination with PRECIS results has determined that the study protocol is very close to the pragmatic trial maximum and therefore fulfills its stated purpose.

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List of Abbreviations

ÄZQ	Ärztliches Zentrum für Qualität in der Medizin (Germany) [Medical Center for Quality of Medicine (Germany)]
BMI	Body Mass Index
CAM	Complementary and Alternative Medicine
CM	Conventional Medicine
FDA	Food and Drug Administration
FU	Follow Up
GnRH	Gonadotropin Releasing Hormone
HRQL	Health Related Quality of Life
Medline	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Heading
MRI	Magnetic Resonance Imaging
MRgFUS	Magnetic Resonance guided Focused Ultrasound Surgery
OVID	Database (Medical Information Service)
QOL	Quality of Life
RFA	Transvaginal Radiofrequency Thermal Ablation
SERMs	Selective Estrogen Receptor Modulators
TVS	Transvaginal Sonography
UAE	Uterine Artery Embolization
UFS-QOL	Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire
US	United States
USD	United States Dollar
VAS	Visual Analog Scale

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Chapter 1: Effectiveness of the osteopathic treatment of women with uterine fibroids: Development of a study protocol of a randomized controlled trial

1.1. Background

Uterine myoma has always represented an important topic in all the gynecological teaching that I have had in the context of different training courses. I, and most of my fellow students, were quite horrified at the image communicated of a myoma the size of a child's head. And yet, for a long time, things remained at this rather onomatopoeic stage until I discovered a tumor of this terrible size in a patient during a visceral palpation. The gynecological examination, which I subsequently asked to have done, confirmed my suspicions: A uterine myoma roughly the size of a child's head. From this moment on, the idea of treating the growth of uterine myomas with osteopathic treatments persisted. In actual fact, afterwards, I was able to bring about a halt in the growth or even a reduction in the size of the existing myoma within 4-5 osteopathic treatments in a number of patients. And in some cases, a decline in symptoms was also noted. This happened in patients who were all seeking osteopathic treatment for other reasons, not because of their myomas. These were discovered more as an aside. In conversations with colleagues at osteopathic congresses and teachers from different schools of osteopathy, these results were confirmed. Reading through literature on the subject, it became clearer and clearer how interesting a clinical study on the effectiveness of osteopathic treatment on uterine myomas could be. On the one hand, it can determine that even small reductions in size of the myoma, e.g. of about 13.5 % can bring about a significant improvement in symptoms (Hindley et al., 2004b). On the other, it is emphasized time and again that there is no treatment for the early stages of uterine myomas (Myers et al., 2002a; Stewart et al., 2003). As more and more women are postponing pregnancies to later ages, in future, doctors will be increasingly confronted with women who have symptomatic myomas on the one hand and who, on the other, do not want to lose their fertility (Dixon et al., 2006; Hindley et al., 2004a; Myers et al., 2002b). This means that more and more women will

be looking for minimally invasive alternatives to hysterectomies in order to reduce any post-operative periods and to retain their fertility. Alongside minimally invasive uterine artery embolization (UAE), and Magnetic Resonance Guided Focused Ultrasound Surgery (MRgFUS), in the event of evidence of effectiveness, osteopathic treatment could become increasingly important in the future. However, it is obvious that a critical first step in generating new treatments today is to ensure a strong scientific foundation. The fact that numerous studies have evaluated the hormonal dependency, epidemiology, molecular biology, pathology, and genetics of fibroids and that still many questions remain unanswered related to their etiology and the role of genetic or environmental influences on their pathogenesis (Flake, Andersen, & Dixon, 2003a; Stewart, 2001a; Walker & Stewart, 2005a) makes it clear that my work cannot be about conducting basic research. Bearing in mind the high prevalence and limited non-invasive therapies for myomas as well as the lack of early intervention strategies, it has become my task to develop a methodologically rigorous clinical study.

1.2. Objective

The objective of this study is to develop a protocol for a clinical study in order to question whether a positive effect on the growth and the symptomatic of uterine myomas can be achieved with osteopathic treatments. The study protocol should correspond with the current scientific quality standards.

Chapter 2: Review of literature

2.1. Systematic review of the literature on uterine fibroids

2.1.1. Objective

The aim of this literature review is to outline the current knowledge on uterine myomas has comprehensively as possible.

2.1.2. Methods

To ensure a systematic search of literature, the National Library of Medicine Medical Subject Headings (MeSH) key word nomenclature with regard to the search term leiomyoma was used, as well as further terms applied in specialist literature, in order to develop the search strategy. Here it can be seen that by linking search results from different synonymous terms for uterine myoma with or brought about a clear increase in hits. In the process, both the use of different terms and word combinations as well as different endings played a role. For example, leiomyomata resulted in only 793 hits, whereas the combination of uterine leiomyata resulted in 15980 hits. And yet the combination of uterine and leiomyoma with 15940 hits is less than the amount of hits for the term leiomyoma alone. In addition, the use of different endings and links, by way of the word or, increased the number of hits. For example: fibroid = 16609 hits; fibroids = 16680 hits and by linking both options, 17268 hits were achieved. As linking fibroid* and uterine fibroid with or resulted in exactly the same amount of hits as linking fibroid*, fibroid and fibroids, the final search strategy utilized fibroid* and uterine fibroid. See table 1.

Table 1: Example of developing the search strategy in Medline

#1 Search **fibroid***	3025
#2 Search **uterine fibroid***	1350
#3 Search **uterine fibroid**	16147
#4 Search **uterine fibroids**	16501
#5 Search **(fibroid*) OR (uterine fibroid)**	17270
#6 Search **((fibroid*) OR (uterine fibroid)) OR (uterine fibroids)**	17270
#7 Search **(uterine fibroid) OR (uterine fibroids)**	16639
#8 Search **((uterine fibroid) OR (uterine fibroids)) OR (uterine fibroid*)**	16639
#9 Search **fibroid**	16609
#10 Search **fibroids**	16680
#11 Search **(fibroid) OR (fibroids)**	17268
#12 Search **((fibroid) OR (fibroids)) OR (fibroid*)**	17270
#13 Search **(((fibroid) OR (fibroids)) OR (fibroid*))) OR ((fibroid*) OR (uterine fibroid))**	17270

The use of fibroid tumor incl. the possible variations does not produce any additional hits to search 3 in table 1. Linking the search results from Fibroid and Fibromyom did not result in increased hits, which is the same as adding the forms of the term, Leiomyom to the results. The word order proposed in the MeSH catalog, e.g. uterus, fibroid and fibroid uterus makes no difference to the number of hits. Upper or lower case of the initial letter also does not appear to make a difference (see leiomyoma and Leiomyoma or Fibroma and fibroma).

In light of these results, it was decided to include all synonyms as well as the use of different endings in the search strategy. The search results produced by the individual terms were linked by the word or. In order to filter out the different aspects of the clinical problem, the existing search result and the corresponding terms (definition, therapy, symptomatology, etiology, etc.) were linked by the word and. The results have been confirmed by a variety of limits. In order to narrow the search down to articles that are relevant to the subject of the study, a limit was set in MeSH to major topics. To concentrate the hits on current information, the search was limited to publications from 1980 and also to female and, with the exception of etiology, to humans. Of the available reviews, first the headlines were viewed with the purpose of removing any unsuitable reviews. The abstracts of the remaining titles were read and full-text copies of the articles of the relevant ones were taken to be read in more detail. This method was tested in Medline and the subsequently developed strategy was applied to other databases. The following search terms were used: uterine fibroids, hysteromyoma, uterine leiomyomata, fibromyoma, myoma. The detailed search strategy is listed in table 2.

Table 2: Example for detailed search strategy MEDLINE

#1	Search uterine fibroma	16165
#2	Search fibroma*	14635
#3	Search leiomyom*	16678
#4	Search uterine leiomyoma	15955
#5	Search fibromyom*	680
#6	Search fibromyoma	16127
#7	Search fibroid*	3026
#8	Search uterine fibroid	16150
#9	Search hysteromyom*	40
#10	Search OR/1-9	32215
#11	Search #10 Limits: Female, Publication Date from 1990 to 2010/05 Field: MeSH Major Topic	12779
#12	Search diagnosis	6831355
#13	Search diagnoses	5952593
#14	Search examination	1209202
#15	Search OR/12-14	6959611
#16	Search (#10) AND #15 Limits: Female, Publication Date from 1990 to 2010 Field: MeSH Major Topic	10682
#17	Search (#10) AND #15 Limits: Female, Publication Date from 2000 to 2010 Field: MeSH Major Topic	6533
#18	Search epidemiology	1280380
#19	Search Incidence	1535674
#20	Search Frequency	1691987
#21	Search Prevalence	1400821
#22	Search OR/18-21	2031810
#23	Search (#22) AND #10	2657
#24	Search (#22) AND #10 Limits: Humans, Female, Publication Date from 1990 to 2010 Field: MeSH Major Topic	1574

Once the results from the Medline research had been evaluated, the results from other databases (Cochrane Library, Science Direct) were examined. It became apparent that no different hits were made here. The results from the Medline research had already provided a large amount of extremely top quality hits (HTA reports, ACOG practice bulletins, reports for and by the National Institute of Health, etc.), and therefore it was decided not to evaluate and research further into the other databases.

2.1.3. Results

Definitions/classifications

Uterine fibroids are benign (non-cancerous) tumors of the uterus. Fibroids are tumors of the smooth muscle cells of the uterus. The collagen content of the tumor gives it a hard, fibrous texture, thus the name fibroid. These tumors are also called leiomyomata or myomas. The cause of uterine fibroids is unknown (Hildreth, Lynm, & Glass, 2009). The MeSH-definition from Medline describes the fibroid tumor as follows: A benign tumor derived from smooth muscle tissue, also known as a fibroid tumor. They rarely occur outside of the Uterus and the Gastrointestinal Tract but can occur in the skin and subcutaneous tissue, probably arising from the smooth muscle of small blood vessels in these tissues. The size of these benign tumors varies from that of a pinhead to larger than a melon (American Accreditation HealthCare Commission., 2003).

A common problem among investigators conducting clinical or translational leiomyoma research is the current lack of a standardized, clinical system for classification of these tumors. Uterine leiomyomas by nature are difficult to classify because they can be single or multiple, of different sizes and located within different regions of the uterus. But because fibroids generate from the diseased wall of the uterine they can be classified in three ways, depending on their location (See figure 1).

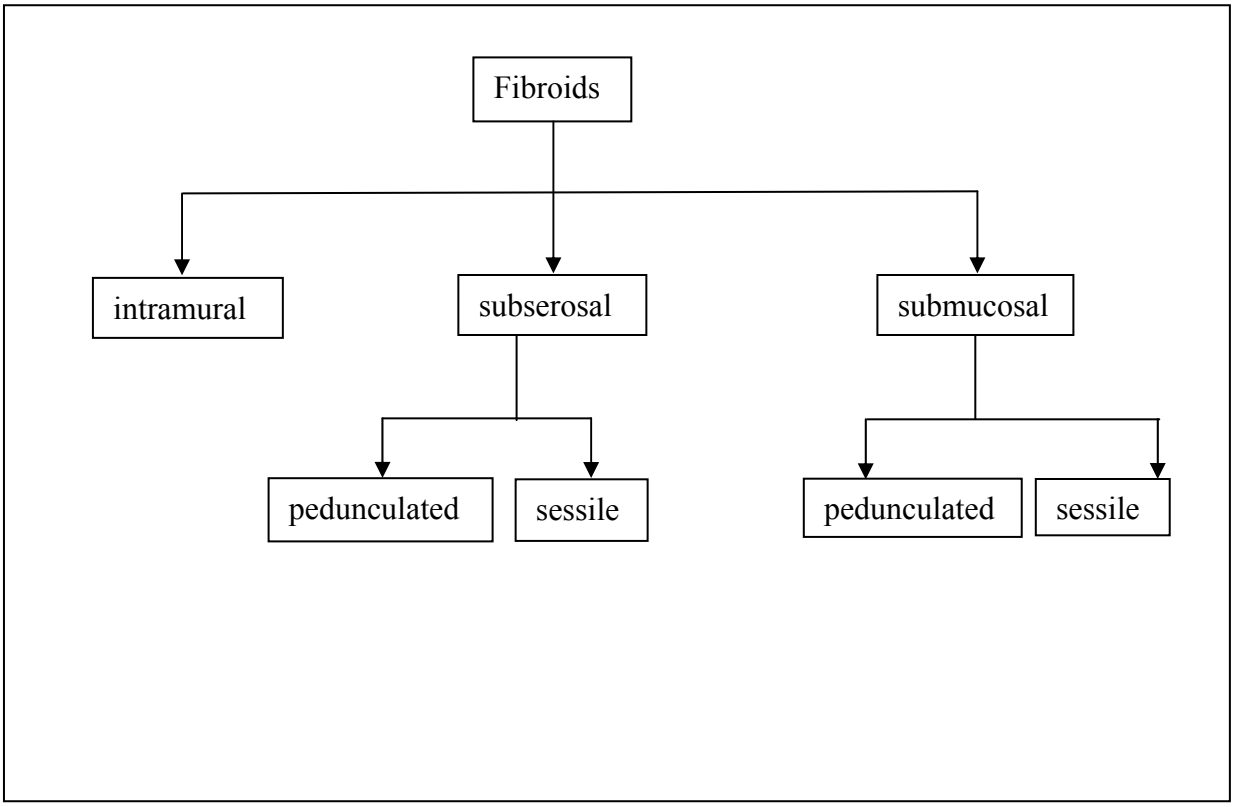


Figure 1: Characterization of fibroids

Intramural fibroids are the most common. They grow within the myometrium. Subserosal fibroids are the second most common. They grow from the serosa and can be either pedunculated (stalk-like) or sessile (broad-based). Submucous fibroids grow from the endometrium. They can also be pedunculated or sessile. Only about 5% of fibroids are submucous (Vollenhoven, 1998).

Epidemiology

Uterine fibroids are one of the most common conditions affecting women at reproductive age. They are also the most common tumors in women and the most frequent pelvic tumors. Statements about prevalence are not always consistent. They vary in particular depending on the surveyed population, whether asymptomatic women are included or excluded and on sensitivity, or more specifically, specification of the applied diagnostic methods. In a Scandinavian study, which concentrated solely on

asymptomatic women aged between 25 and 40, a prevalence of only was 5.4% was determined by way of ultrasonic diagnostic; prevalence increases with the age of the test persons (3.3% in women between 25-32 in comparison with 7.8% in women between the age of 33 and 40) (Borgfeldt & Andolf, 2000a). This represents a very low prevalence, especially in light of the fact that most US American and European authors of clinical studies mention a prevalence of between 30 and 50% in their background information. In newer, dedicated epidemiological studies, the very different figures are accounted for by the populations under investigation.

Prevalence in different racial and ethnic groups

In a study published in 2003 in which 1364 women aged between 35 and 49 took part, a cumulative incidence of 60% was established in women aged 35 and more than 80% in African-American women aged 50. A cumulative incidence of 40% was noted in Caucasian women aged 35 and almost 70% by the age of 50. However, these figures also include the 19% for which no clear "focal" myoma findings were discovered by ultrasound examination, which was the examination method used in this study. In these women, a diffuse heterogeneous echo pattern was noticed, which indicates a myoma. This means that not all of them necessarily had a myoma, but possible an adenomyosis, simple myometrium contractions, or similar. Even if these subgroups are excluded, we can still establish that the majority of US American women have myomas at menopausal age. This therefore more likely represents the standard rather than the exception (Baird D., Dunson, Hill, Cousins, & Schectman, 2003). Donna Baird, one of the authors of this study, concluded at the congress on advances in uterine leiomyoma research 2005, that after adjusting for all the risk factors she had examined, an unresolved difference exists in the prevalence between African-American women and white women, and that the risk for African American women is equivalent to a 10-year increase in fibroid development than in comparable white women (Dixon et al., 2006). Many studies confirm this higher prevalence among African-American women (Chen, Buck, Courey, Perez, & Wactawski-Wende, 2001; Baird D. et al., 2003; Wise, Palmer, Stewart, & Rosenberg, 2005; Faerstein, Szklo, & Rosenshein, 2001). This difference in occurrence of the illness can be seen in the high percentage rate (75%) of myoma-induced hysterectomies carried out

on African-American women (Farquhar & Steiner, 2002). Similarly, the two to three times higher incidence rate – a 3% year-on-year probability of being diagnosed with myoma during the reproductive years (Wise et al., 2005). This even involves an increased tendency at a young age of developing multiple, larger myomas (Baird D. et al., 2003). Unfortunately, a lot of studies do not detail the different incidence rates within different ethnic groups. One study, however, concentrated on investigating different prevalence rates of myomas detected by ultrasound examination or hysterectomies, occurring across different racial groups right from the start. An increased risk was only noted here in African-American women. The risk among Latin Americans, women of an Asian origin and Caucasian women appears to be similar (Marshall et al., 1997a).

Prevalence in different populations

A number of studies from different European countries indicate that myoma prevalence is slightly less among European populations. A German cohort study, which began in 1998, examined 10241 women with the help of a health questionnaire tailored to women. Among other things, it asked about existing diagnoses of uterine myomas. Surprisingly, evaluations of responses have indicated a prevalence of only 5%. However, a similar number of women stated that they had been diagnosed with a "benign tumor of the uterus", which is very likely to be the same as a diagnosis of uterine myoma. If this group of women is included, the prevalence rate amounts to 10.7%. These figures indicate a group of women with an average age of 39.6 years who have reported being diagnosed with myoma. This is a constellation that certainly does not account sufficiently for asymptomatic and non-diagnosed myomas. Despite the clear methodological limitations of the study, the results suggest that myoma rates are less frequent in Central Europe than in the USA. One of the best estimates with the respect to prevalence rates in Europe comes from Italy, as here the absence or presence of a myoma is determined independently of the symptomatic. In the Seveso Women's Health Study, a myoma was discovered in 21.4% of 341 women who underwent ultrasound examination aged between 30 and 60 (Marino et al., 2004).. The very low rate of prevalence in the already mentioned Scandinavian/Swedish study, of about 5.4% is almost certainly due essentially to the methodological limitations of the study. Particularly worthy of mention

here is the limited age distribution of the test persons (25-40 years) as well as the limitation to asymptomatic women.

Etiology

Although some progress has been made in the last few years in understanding the hormonal, genetic and growth factors and molecular biology of these benign tumors, the precise causes of myomas are still unknown. This also applies to the most important aspect of the etiology of myomas - their initiators. When trying to understand the current insights into the development of uterine myomas, it helps to divide the factors involved in tumor growth into 4 groups: initiators, promoters, effectors and predisposing or risk factors, in the sound knowledge that these factors frequently cannot be separated from each other with regard to their mechanisms of action.

Initiators

Acquired genetic changes in the tissue of the myomas appear to play an important role. Once established, they are influenced by effectors (growth factors) and promoters (hormones) (Parker, 2007a). According to current theories, three possible situations are held responsible for the initiation of genetic changes in myoma tissue. These can be summarized according to the following key words:

a) hormonal changes
b) intrinsic abnormalities of the myometrium i.e. elevated estrogen receptors
c) unfavorable response to ischemic injury at the time of menses

Ad a): One hypothesis states that increased estrogen and progesterone levels can cause increased mitotic activity, which could contribute to the development of a myoma in that the likelihood of somatic mutation is increased (Rein, 2000).

Ad b): Richards and Tiltman put forward an abnormality of the myometrium itself for discussion, based on a clearly increased occurrence of estrogen receptors in uteri affected by myoma (Richards & Tiltman, 1996).

Ad c): Another interesting theory discusses the similarity of myoma pathogenesis with keloid development (hypertrophic scarring) as a reaction to injury to tissue, as can happen after operations, for example (Stewart & Nowak, 1998). The myometrium could be injured by ischemia accompanied by an increased release of vasoconstrictive substances during menstruation. Increased prostaglandin and vasopressin secretion has been found in women with dysmenorrhea, which, after all, occurs in up to 70% of all women 5 years after menarche (Coupey S, 2000). The question to be answered now is whether the cells in the smooth muscle of the myometrium react in an analog way to injuries as the smooth muscle cells in blood vessels. This would suggest a transformation from a contractile to a proliferative-synthetic type. As determined by Dixon et al., a morphological similarity has to exist, as there, myomas exhibit an increased proliferation rate as well as the capacity for the synthesis of an extra-cellular fibrous matrix (Dixon et al., 2002). After a vascular injury, the basic fibroblast growth factor (bFGF) plays an essential role in the proliferation of smooth muscle. It is precisely this that is over-represented in uterine myomas (Lindner & Reidy, 1991; Mangrulkar et al., 1995). These successive findings have not so far led to a clear understanding of myoma development, but the subject is worthy of continued research, particularly with respect to the universality of menstruation and the frequency of uterine myoma.

The same degree of uncertainty exists with regard to the role of hereditary genetic predispositions. Findings from epidemiological studies have seeded the idea that there could be a genetic connection. The approach to this subject has been conducted according to 4 perspectives: studies on twins, studies on frequency in families, on ethnic predispositions and in connection with the rare hereditary Reed Syndrome, which involves multiple leiomyomas in the skin and/or uterus. However, no clear evidence has been found for a hereditary source. Some studies have also had considerable problems with reporting and detection bias (Flake, Andersen, & Dixon, 2003b). Recently numerous studies and reviews on clonality and cytogenetics with respect to uterine leiomyomas have been carried out (Gross & Morton, 2001; Ligon & Morton, 2000; Ligon & Morton, 2001; Quade et al., 2004; Walker & Stewart, 2005b; Hashimoto et al., 1995). Their very comprehensive results can only be reported roughly here, as their role as initiators of the uterine myoma remain unclear to this very day.

The most frequent chromosomal abnormalities in myoma tissue affect translocations between chromosomes 12 and 14, trisomy of chromosome 12 and deletions of chromosome 7. However, these modifications have only been found in about 40% of uterine myomas. What cannot be ruled out is that there might be other, previously undetected, mutations in the remaining 60%. Otherwise, over 100 genes have been discovered that were either over- or under-represented in myoma cells, including the sex-steroid associated genes, estrogen receptor alpha, estrogen receptor beta, progesterone receptor A, progesterone receptor B, collagen and extracellular matrix genes, prolactin receptors and growth hormone receptors. Many of these genes seem to influence mitogenesis, differentiation, cell growth and proliferation (Parker, 2007b).

Effectors

It is undisputed that the hormones, estrogen and progesterone have a growth-stimulating influence not only on the myometrium but also on the uterine myoma. This effect is most likely conveyed, however, by the mitogenic effects of growth factors. What is understood by these effectors, or, growth factors, are proteins and polypeptides that control the proliferation of cells and can stimulate the growth of myomas. These substances are produced locally by smooth muscle cells. They can influence these cells in many ways, and, depending on whether they occur singly or multiply, can have very different effects. Many of these growth factors have been identified and can be located physiologically in the myometrium, however, in myoma tissue, they are over-represented (Parker, 2007b). (See table 3.)

Table 3: Growth factors and their areas of activity (Flake et al., 2003b)

Growth factors	Abbreviation	Probable effect
Transforming growth factor-β	TGF- β	Increase smooth muscle proliferation, stimulate synthesis of extracellular matrix, promote mitogenesis
Basic fibroblast growth factor	bFGF	Increase smooth muscle proliferation, promote angiogenesis
Vascular endothelial growth factor	VEGF	Promote angiogenesis
Epidermal growth factor	EGF	Increase DNA synthesis, promote mitogenesis
Prolactin		Promote mitogenesis
Insulin-like growth factor	IGF	Promote mitogenesis
Platelet-derived growth factor	PDGF	Increase DNA synthesis

It is very likely that further substances important to myoma growth will be discovered and it is merely a question of time as to which will be classed as the most important.

Promoters

Female sexual hormones are counted among them. Diverse clinical, biochemical and pharmacological observations speak clearly for the myoma-promoting role of estrogen and progesterone.

Clinical observations:

- Myomas seldom appear before puberty
- Highest prevalence during reproductive years
- Decline during menopause
- Increase in incidence due to a rise in overall life estrogen exposition, e.g. in obesity or early menarche
- Lower incidence when life estrogen exposition is decreased, e.g. multiple births, regular sport, etc.
- Accelerated myoma growth in women with hormonal replacement therapy

- Myoma volume reduction due to GnRH agonist treatment which produces a decrease in estrogen levels (Parazzini et al., 1996; Romieu, Walker, & Jick, 1991; Ross et al., 1986; Cramer, 1992).

It has proven very difficult to clarify the difference between the significance of estrogen and that of progesterone, as progesterone increases regularly during the reproductive years and is considerably increased during pregnancy and lowered in menopause. In addition, a decrease in leiomyomas was observed under the influence of the antiprogesterone drug, RU 486; at the same time it was noticed that only the number of progesterone receptors was reduced, but not the number of estrogen receptors in the tumor tissue (Murphy, Kettel, Morales, Roberts, & Yen, 1993).

Biochemical observations

In laboratory studies, indications as to an influence of ovarian hormones on myoma development have also been found. Significant, quantitative differences in tissue concentrations of sexual hormones and their receptors have been found in the myometrium and in leiomyomas. Although the serum concentration of estrogen and progesterone in women with and without diagnosed myomas is similar, in normal myometrium and in myomas, different estradiol and aromatase concentrations have been found. On the one hand, many authors make this increased concentration of aromatase responsible for the raised concentration of estradiol, an enzyme which converts androgens into estrogen, and on the other, many researchers consider a low concentration of enzymes to be the trigger for the transformation of estradiol into estrogen. The increased concentration of female sexual hormones also brings about an increase of estrogen and progesterone receptors, initiating over-reactivity to this hormone, which, as some authors conclude, promotes myoma growth. Commensurate with this idea is the fact that during the complete menstruation cycle, the myomas have a higher proliferative index than the normal myometrium (Cook & Walker, 2004). The proposition behind the significance of progesterone is also supported by the increased number of progesterone receptors A and B found in myoma tissue, in comparison with the normal myometrium.

The interactions between the two hormones and their respective receptors are numerous and have not been conclusively researched in their entirety (Flake et al., 2003b).

Pharmacological observations

These findings with respect to hormone concentration in myoma tissue have subsequently led to the idea of therapeutic hormone manipulation, in the belief that a reduction in estrogen levels will also trigger a reduction in the growth or even cause the myomas to decrease in size. Research on the effects of gonadotrophin-releasing hormone (GnRH) agonists - which produce a decrease in estrogen concentrations (Lumsden, West, Bramley, Rumgay, & Baird, 1988; Rein, Friedman, Pandian, & Heffner, 1990) – has shown a decrease in size of myomas. However when progestin is taken simultaneously (synthetic progesterone), the effect is restrained. They have even been able to indicate that the taking of contraceptives that are only composed based on progestin, is associated with an increased risk of developing a myoma (Wise et al., 2004a). With the help of progesterone receptor modulators, e.g. Mifepristone, myomas could be shrunk (Murphy, Morales, Kettel, & Yen, 1995).

Risk factors

Interpretation of epidemiological data in connection with risk factors should be prudent, as they are still subject to considerable limitations. Problems are incurred here by the limited number of studies that exist, selected study populations, possible detection bias by either different medical care or the application of self-reported diagnosis and the usually unclear point in time at which the myoma has started to develop, which could have been before exposition to a possible risk factor. In addition, the mechanisms of action that underlie the observed risk factors cannot be clearly clarified. They could involve being participated in either the initiation or promotion phases. Even though their effect appears to play an important level on estrogen and progesterone levels, other mechanisms should not be forgotten. For example, early menarche leads to an increased life exposition to estrogen and also to more menstruations, which, in turn, also means an increased likelihood of damage being caused to the tissue of the myometrium. The following list of risk factors has been put together without taking their mechanisms of

action into consideration, but is more a list of current opinions, taken from available literature.

African-American Ethnicity

There is a general consensus in literature on the increased prevalence of uterine myomas in African-American women. Witherspoon and Butler already determined this fact in 1934 (Witherspoon & Butler, 1934). In the meantime, a number of studies have been carried out that confirm this thesis (Vollenhoven, Lawrence, & Healy, 1990; Buttram, 1986). Kjerullf et al. in 1996 determined that black women are not only affected more frequently (89% to 59%) than white women, but also tend to have larger, more numerous myomas, and incur more symptoms. They are also affected at a younger age (Kjerulff, Langenberg, Seidman, Guzinski, & Stolley, 1996). In a very widespread study, 95061 nurses who had not been diagnosed with myoma were accompanied prospectively. The incidence rate among black women was almost twice if not three times higher than in white women. This result persevered, even when the higher presence of other risk factors in black women were taken into account such as higher BMI (Marshall et al., 1997b).

Age

Several studies have shown that prevalence increases with age during the reproductive years (Ross et al., 1986; Marshall et al., 1997a; Velebil, Wingo, Xia, Wilcox, & Peterson, 1995; Wilcox et al., 1994). A clear increase in myoma diagnosis is noted around the age of forty, i.e. in the premenopausal phase of life (Ross et al., 1986).

Obesity

Results from several studies have given rise to the assumption of a connection between obesity and myoma development. For example, in their study carried out in 1986, in Great Britain, Ross et al. discovered that risk of myoma development increases by 21% for every 10 kg of extra body weight (Ross et al., 1986). Similar results have been produced by Marshall et al. in their prospective study of nurses carried out in the USA. An increased risk of myoma was also noted in relation to a rising BMI (Marshall

et al., 1998c). These results are not limited to the industrial nations of the western world. A case-control study in Japan reported a significantly increased risk of myoma in women with occult obesity (BMI < 24.0 and percent body fat ≥ 30%) or women with upper-body fat distribution (> 0.80 waist-to hip ratio) (Sato, Nishi, Kudo, & Miyake, 1998) and a study in Thailand observed a rise in myoma risk in relation to an increased BMI (Lumbiganon et al., 1996).

One possible explanation for the connections between obesity and myoma risk could be given by obesity-associated hormonal changes. A high number of such metabolic changes are known. The following 3 items are of particular interest in our context:

- Increased conversion of circulating adrenal androgens to estrone by excess adipose tissue
- Decreased hepatic production of sex hormone–binding globulin
- Decreased metabolism of estradiol by the 2- hydroxylation route (Schneider et al., 1983)

The consequence of these changes is a rise in biologically-available estrogen, which could explain an increase in prevalence or growth. However, two studies at least exist that have not found a link between obesity and myoma prevalence. These differences in study results are probably due to differences in how the studies have been designed. The significance of the definition of obesity rate, measuring methods and differences in study design with regard to the comparative, or control groups has been named as an important characteristic (Troiano & Flegal, 1999).

Family history

There are different indications pertaining to hereditary components involved in myoma development. First-degree relatives to women who have been diagnosed with a myoma are at double the risk (Schwartz, Marshall, & Baird, 2000; Vikhlyaeva, Khodzhaeva, & Fantschenko, 1995). Identical twins are much more likely to receive inpatient treatment for myomas as nondientical twins. These observations are allegedly

not entirely free of reporting bias (Treloar, Martin, Dennerstein, Raphael, & Heath, 1992).

Nulliparity

Several studies have discovered a link between the number of births and risk of myoma whereby risk of myoma decreases in proportion to an increase in births. Relative risk declines progressively as number of births increases. Women who have given birth carry a relative risk of only 0.5 in comparison to nulliparas (Parazzini et al., 1996; Ross et al., 1986; Lumbiganon et al., 1996; Marshall et al., 1998a).

Hypertension

According to a relatively new study, women with high blood pressure have an increased myoma rate. This impact becomes more significant as the duration increases and as the level of blood pressure rises. Every time the systolic blood pressure reading increases by 10 mm Hg, myoma risk increases by 8-10% (Boynton-Jarrett, Rich-Edwards, Malspeis, Missmer, & Wright, 2005).

Protective factors

While they were looking for risk factors, some authors have come across a number of possible protective factors. The most important are listed below:

- Exercise: Former college athletes exhibit a myoma prevalence reduced by about 40%. However, it is not entirely clear whether this value is actually due to physical training or maybe more to do with associated changes in their styles of life, e.g. eating habits, etc. (Wyshak, Frisch, Albright, Albright, & Schiff, 1986).
- Increasing parity (see above)
- Smoking: Some changes in hormone metabolism due to nicotine could be responsible here (Daniel, Martin, & Drinkwater, 1992; Michnovicz, Hershcopf, Naganuma, Bradlow, & Fishman, 1986; Barbieri, McShane, & Ryan, 1986).

- Menopause

There is still a large number of other factors, such as eating habits, hormone replacement therapy during menopause, the taking of oral contraceptives, xenoestrogen etc. for example, under discussion as to whether they are more likely to be risk factors or protectors (Flake et al., 2003b; Marshall et al., 1998a; Saxena et al., 1987; Chiaffarino et al., 1999).

Symptomatology

Even though leiomyomas are not related to a higher mortality rate, they can cause considerable health problems and therefore significantly reduce quality of life. Myomas often do not cause any problems. This is particularly the case with regard to very small tumors. All in all, about 25% of all women with myomas suffer symptoms of illness (Boynton-Jarrett et al., 2005). The type and intensity of complaints depends heavily on the localization, number and size of the myomas. The symptoms can be divided into 4 groups.

- Menstrual disorders
- Pain
- Compression syndrome
- Reproductive dysfunction

Ad a): What occurs most frequently are irregularities of the menstrual cycle (menorrhagia) featuring a prolonged and heavy menstrual period (hypermenorrhea) and dysmenorrhea. These menstrual problems occur most frequently in the event of submucous myomas (Jolley, 2009; Stewart, 2001b). Other authors have suggested that the relation with abnormal menstruation is more to do with the size of the myoma and less to do with its location (submucous) (Wegienka et al., 2003). If these symptoms persist over a longer period, women can develop anemia and the corresponding symptoms of abnormal fatigue, vertigo, headache, dyspnea and tachycardia, etc.

Ad b): Different types and locations of pain are described, for example, acute lower abdominal pain, back pain (ischialgic pain), dyspareunia, pain in the pelvic area

and legs. The causes for the acute occurrence of pain could be due to the torsion of peduncular myomas or to the very seldom occurring tissue degeneration (Stewart, 2001b). In addition, pain development is certainly related to tissue compression and therefore cannot be clearly separated from C.

Ad c): Depending on where the myomas are located, different symptoms are caused because of neighboring organs being compressed. For example, anterior located myomas can cause urinary symptoms such as pollakiuria, stress incontinence or urge symptomatic, while cranial to posterior located myomas are more likely to trigger problems in the intestines, such as constipation, bloating and indigestion (Pron et al., 2003a; Jolley, 2009; Stewart, 2001b).

Ad d) With regard to reproductive dysfunction, problems with fertility and complications during pregnancy and birth can occur. In a diverse number of examinations, the particular role of submucous myomas has been substantiated. In her review as early as 2001, Pritts described how fertility rates in women can be reduced by myomas and increased after resection of submucous myomas. Neither subserosal nor intramural myomas appear to be of influence here - once removed, fertility rates did not improve (Pritts, 2001). In the reprint of her review in 2009, the authors Pritts et al. reached a similar conclusion. It was confirmed that subserosal myomas do not influence reproductive functions. However, women with both intramural and submucous myomas exhibited a significantly reduced clinical pregnancy rate, implantation rate and ongoing pregnancy/live birth rate and a significantly higher spontaneous abortion rate (Pritts, Parker, & Olive, 2009). This new insight into the participation of intramural myomas, as well, is argued by the authors with the existence of newer and often improved studies. However they do not consider this argumentation to be final, which would consequently recommend the removal of intramural myomas, especially in light of the risks and possible unwanted side effects of this operation method. It was not possible in this study to assign a significantly increased risk of premature birth to any myoma type. Other studies, however, have published different results. Qidway et al., for example, found amongst other things an increased risk of premature births, placenta praevia, postpartum hemorrhage and Cesarean section (Qidwai, Caughey, & Jacoby, 2006). In contrast, in

their study, Vergani et al. discovered no increased incidence of preterm delivery, premature rupture of membranes, fetal growth restriction, placenta praevia, placenta abruption, postpartum hemorrhage, or retained placenta, merely an increased rate of Cesarean section in women with myomas of 23% in comparison to 12% among women without myomas (Vergani et al., 1994).

Diagnosis

The diagnosis is largely based on manual examination, transvaginal ultrasound, hysteroscopy and MRI. However, the applied diagnostic method depends on a number of different factors. A clinically prominent subserosal or intramural myoma can initially be detected via a manual pelvic examination. Diagnosis of a myoma includes discovery of a distended, irregularly shaped uterus, which is not soft and can be even hard to touch. Myoma size can be very reliably estimated by a bimanual examination, as a retrospective study established, which was based on postoperative uteri (Cantuaria, Angioli, Frost, Duncan, & Penalver, 1998; 2001). However, in order to determine the optimal choice of therapy, more precise examinations are necessary to ascertain the exact size, number and most importantly, the position of the myomas. To this purpose, imaging procedures, ultrasound, saline infusion sonography, as well as hysteroscopy and MRI can be applied.

Transvaginal ultrasound

This is the most economic method that provides the best access. Large myomas are detected most easily by a combination of transvaginal and abdominal ultrasound. Transvaginal sonography (TVS) can be helpful in providing a differential diagnosis. In some cases, however, it can happen that the precise number and position of myomas cannot be detected via TS. TVS is most reliable in uteri of a volume of up to 375 ml and with up to four myomas (Dueholm, Lundorf, Hansen, Ledertoug, & Olesen, 2002a).

Saline-Infusion Sonography

Saline-Infusion Sonography (SIS) means that saline is injected into the uterine cavity by a small catheter immediately prior to a vaginal probe ultrasound examination. The liquid helps create an interface with the lining of the uterus and abnormal structures

can be seen on imaging. The technique is not that new, having started in 1981, but it has only become more frequently used in the middle 90's since scientific reports have confirmed its effectiveness. In the meantime, a number of indications have been established for the application of SIS. These include:

- Any abnormal uterine bleeding refractory to medical therapy
- (usually in women under the age of 40 in which hormonal therapy has been initially tried)
- Women with postmenopausal bleeding in which the uterine lining is greater than 5 mm
- Irregular bleeding in women on menopausal hormone replacement therapy
- (usually after the first 3 months of starting therapy)
- A thickened or bizarre appearance of the endometrium in women receiving tamoxifen therapy for breast cancer

The additional differential diagnostic possibilities in comparison to normal TS refer to

- Endometrial cancer
- Endometrial hyperplasia (possibly premalignant)
- Endometrial polyps
- Fibroids-intraluminal, submucosal
- Tamoxifen induced changes
- Intrauterine scarring (synechiae) (Widrich, Bradley, Mitchinson, & Collins, 1996; Bradley & Andrews, 1998; Dueholm, Forman, Jensen, Laursen, & Kracht, 2001a)

Hysteroscopy

Hysteroscopy is a reliable method for examining the intra-uterine cavity. It is a minor safe surgery that is usually done under general anesthesia and it may be used for diagnosis, treatment or both. The diagnostic hysteroscopy can be carried out without anesthetics and on an outpatient basis. The shaft, which provides the examiner with the

insight, is only three to five millimeters in width. This is also probably the reason why the complication rate is a lot less in comparison with operative hysteroscopy - although the complication rate depends on the objective of the surgical intervention. A study involving 925 operative hysteroscopic surgical procedures showed that the polypectomies and endometrial ablations count the least and the myomectomies and resections of uterine septa involve the highest rates. The overall complication rate amounted to 2.7% (Propst, Liberman, Harlow, & Ginsburg, 2000). The considerably more extensive study by Jansen et al. has confirmed these results. Of the operative procedures carried out, these involved the greatest complication risks:

- Adhesiolysis (4.48%)
- Endometrial resection(0.81%)
- Myomectomy (0.75%)
- Polypectomy (0.38%) (Jansen et al., 2000)

At a rate of about 1.42%, uterus perforation remains the most frequently mentioned complication in systematic reviews. More risks are involved in the necessary insertion of liquid (irrigation with glycine 1.5%, sorbitol 2.7% with mannitol 0.54% solution mixture, 5% mannitol, or Ringer's lactate solution for example) or gas (carbon dioxide) into the uterine cavity. Furthermore, infection can be incurred after the operation (in 0.3±1.6% of cases), e.g. urinary tract infections, endometritis, pyometritis and rarely tubo-ovarian abscess (Bradley, 2002).

As these reviews only list either overall complication rates or those from operative hysteroscopes, it is not possible to identify the complication rate of diagnostic hysteroscopy precisely. In all events, it is a very low figure, but can have very unpleasant consequences for those affected.

MRI

Magnetic resonance imaging is an excellent method to detect the size, position and number of myomas. It represents the best way of precisely assessing the penetration

of the myometrium by submucous myomas (Dueholm, Lundorf, Hansen, Ledertoug, & Olesen, 2001a).

Dueholm M. et al. studied 106 pre-menopausal women who wanted to have a hysterectomy and tested the reliability of different diagnostic methods. A sensitivity for the identification of submucous myomas was demonstrated by the MRI of 1.0, TVS 0.83, HSE (hysterosonographic examination) 0.90 and hysteroscopy 0.82; specificity was MRI 0.91, TVS 0.90, HSE 0.89 and hysteroscopy 0.87 (MRI vs. TVS, and MRI vs. hysteroscopy). MRI and HSE were most accurate for the evaluation of submucous myomas, and magnetic resonance imaging was significantly more precise than TVS, HSE, and hysteroscopy in determining submucous myoma in-growth (Dueholm et al., 2001a).

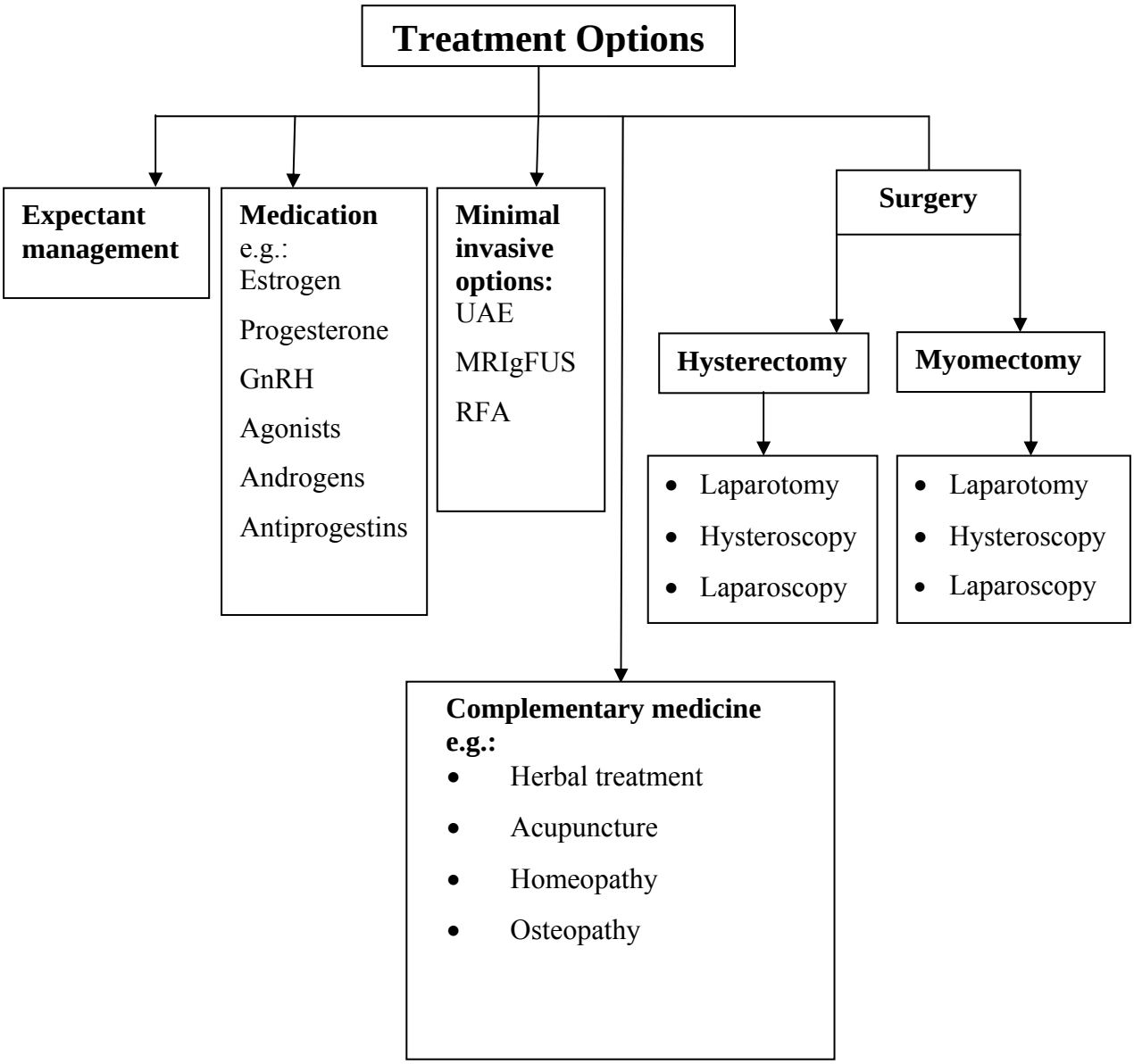
These comparative studies show on the one hand the superiority of MRI for the diagnosis of myomas and on the other, the very high hit rate of TVS, which is a diagnostic method that is generally readily available and also relatively economical.

Therapy

As the majority of myomas do not cause any symptoms, the most common practice is to watch and wait. While surgical methods were often chosen to treat symptomatic myomas in the form of either hysterectomy or myomectomy, in more recent times, the various forms of treatment have increased in number. This started in the 80s as a result of the development of laparoscopic methods and has been continued in the last few years with the rise in further minimally-invasive and non-invasive as well as medicinal methods. The treatment options vary depending on the size, location, number of tumors and whether the woman wishes to retain fertility. The current approaches to uterine leiomyoma treatment are categorized in five groups:

- Expectant management
- Medical treatments which are not causal but could reduce volume and relieve symptoms

- Minimally invasive or noninvasive approach causing damage to cellular viability for example the uterine artery embolization, the magnetic resonance guided focused ultra-sound, the radiofrequency ablation
- Surgical removal of either the myoma or the whole uterus,
- Complementary medicine



UAE	Uterine Artery Embolization
MRIgFUS	MRI-guided focused ultrasound surgery
RFA	Transvaginal Radiofrequency Thermal Ablation
GnRH	Gonadotropin Releasing hormone

Figure 2: Main Treatment Options for Uterine Fibroids

Expectant management

Watchful waiting is, on the one hand, not a form of treatment, and yet these women often resort to medication as required, for example, pain medication, i.e. many

untreated women are not completely without symptoms but exhibit simply few symptoms. It should be noted that the boundary here is movable and is subject to large individual fluctuations. If a woman has mild symptoms, such as pain, either the health care provider may suggest non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or naproxen sodium for symptomatic treatment, or the women supply themselves with the relevant medication (Falcone & Bedaiwy, 2002). However, there is very little research data on how watchful waiting proceeds. There are no studies whose primary task is to research symptoms such as anemia, abnormal bleeding, pain, health-related quality of life or modifiers of outcomes of watchful waiting. We are therefore reliant on examining available RCTs with untreated or placebo or minimally-treated control groups (some used iron, calcium or multivitamin tablets). In a report prepared in 2007 for the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services, this attempt was made. The authors reached the conclusion that the symptoms and volumes of uterine myomas do not change essentially in pre-menopausal women. Women were observed over two to three-month periods. Only one study included a follow-up after 6 months. Here, too, there were no noteworthy changes in symptoms. The size of myomas remained the same in 72% of the test persons; 23% exhibited an increase in size and 3% a decrease. The authors came to the following concluding evaluation: "The total picture provided is insufficient to project what the course of watchful waiting might be for an individual woman with fibroids. As these studies were not designed for this purpose, the overall quality of the research is too poor to inform the choice of expectant management over other intervention options." (Viswanathan et al., 2007).

Medicinal therapy

Many patients and doctors, too, prefer conservative management forms of treatment of non-life-threatening illnesses. As uterine myomas clearly belong to this category, first-line therapy is frequently the application of medication, whereby currently a number of different pharmacological approaches are being used.

Contraceptive steroids

Contraceptive steroids are often used to treat menstrual problems such as dysmenorrhea, abnormal bleeding or painful menstruation in women with and without myomas. Usually oral contraceptives are used which are composed either of a combination of estrogen and progesterone or solely of progesterone. On the other hand, systematic reviews have indicated that the effects only last for a short period and the women treated with medication often end up being operated on (Marjoribanks J, 2006). Oral contraceptives are definitely able to control bleeding symptoms, however, current studies show contentious results with regard to their effect on myoma size. And yet while some studies have been published stating that myomas have been reduced in size under progestin therapy (Wallach & Vlahos, 2004; Venkatachalam, Bagratee, & Moodley, 2004), others have produced results indicating that volume increases (Harrison-Woolrych & Robinson, 1995; MIXSON & HAMMOND, 1961; Carr et al., 1993; Friedman & Haas, 1993; Friedman, Daly, Juneau-Norcross, Fine, & Rein, 1992). These data have shown that it is of absolute necessity that myoma size and uterus size should be tightly monitored in women who are treated with contraceptives. In addition, epidemiological studies have shown that the taking of both combined oral contraceptives and progestin-only contraceptives reduces the risk of developing symptomatic myomas (Marshall et al., 1998b; Wise et al., 2004b). There is another contraceptive option: the levonorgestrel-releasing intrauterine system (LNG-IUS). Levonorgestrel intrauterine system is a plastic device that contains the hormone levonorgestrel. This device is placed in the uterus where it slowly releases the hormone to prevent pregnancy for up to 5 years. In addition to preventing pregnancies, LNG-IUS also brings about amenorrhea in many patients. These - in this case - useful side effects have encouraged researchers to test the usefulness of LNG-IUS in the treatment of menorrhagia and other symptoms caused by myomas. Generally speaking, studies have produced mixed data on the subject. The majority of studies appear to indicate a reduction in size of myomas and a decline in menstrual-related symptoms (Grigorieva, Chen-Mok, Tarasova, & Mikhailov, 2003; Mercorio et al., 2003; Magalhaes, Aldrighi, & de Lima, 2007; Stein K & Ascher-Walsh C., 2009). This uncertainty is surely the reason why the use of LNG-IUS is not recommended, particularly in publications for consumers or patients when abnormal

bleeding is already in existence. The list of absolute and relative contraindications is often very long, with the result that LNG-IUS is not considered as an option for many women. See here, an example of an excerpt from a website for consumers published by CIGNA, a global health service company:

"You should not use this medication if you are allergic to levonorgestrel, silicone, or polyethylene, or if you have:

- Abnormal vaginal bleeding;
- An untreated or uncontrolled pelvic infection (vaginal, uterine, or bladder);
- A serious pelvic infection following a pregnancy or abortion within the past 3 months;
- A history of pelvic inflammatory disease (PID), unless you have had a normal pregnancy after the infection was treated and cleared;
- Uterine fibroid tumors or other conditions that affect the shape of the uterus;
- Past or present breast cancer;
- Liver disease or liver tumor (benign or malignant);
- Known or suspected cervical or uterine cancer;
- A recent abnormal Pap smear that has not yet been diagnosed or treated;
- A disease or condition that weakens your immune system, such as AIDS, leukemia, or IV drug abuse;
- If you have another intrauterine device (IUD) in place; or
- If you do not have an exclusive sexual partner.

You may need special tests to safely use a levonorgestrel intrauterine device if you have:

- Diabetes;
- A bleeding or blood-clotting disorder;
- A vaginal infection, pelvic infection, or sexually transmitted disease; or
- High blood pressure, heart disease or a heart valve disorder." (CIGNA, 2010)

Aromatase Inhibitors

In a number of smaller studies, a decline in symptoms and reduction in myoma size was ascertained. The aromatase inhibitors cause a block to ovarian and peripheral estrogen production and decrease estradiol levels after 1 day of treatment. This has the advantage of a quick treatment effect and due to the mechanism of action there are probably less undesired side effects in comparison to GnRH agonists, for example. All in all, there is not much data and therefore the aromatase inhibitors have not yet been approved by the FDA for the treatment of leiomyomas (2008a).

Gonadotropin-Releasing Hormone (GnRH) Agonists

GnRH agonists represent a further form of treating myomas with medication. GnRH agonists are often used in the pre-operative treatment of myomas. They effect a down-regulation of estrogen receptors, which can result in a decrease in myoma growth to the tune of 35%-65% within the space of 3 months (Olive, Lindheim, & Pritts, 2004). This treatment also causes amenorrhea in most women. Unfortunately, the effects of GnRH agonists are only temporary. After termination of medication, the myomas start to grow again and within a few months are often back to their original size before therapy was started. The only medication approved by the FDA until the beginning of 2009 is Leuprolide in connection with taking iron supplements. It has its best effects in women with large myomas. In addition to the already described effects of GnRH agonists, what should also be taken into consideration are the undesired side effects as a result of the evoked pseudo-menopause, e.g. bone density atrophy and vasomotor symptoms due to the produced hypoestrogenism. This leads to a recommendation of only taking GnRH agonists for a period of about 6 months, providing no hormonal add-back therapy is prescribed. Low-dose preparations, equivalent to menopausal hormonal therapy, are recommended as additional therapies. Also, the additional application of raloxifene, a selective estrogen receptor modulator, which is also used as a therapy and prophylaxis against osteoporosis in post-menopausal women, has been reviewed in a number of studies. Here, an improvement in the undesirable effects on bone mineralization was established, while at the same time the uterus and myoma size continued to be reduced. With regard to other menopausal symptoms induced by treatment with GnRH agonists,

such as hot flushes or vaginal dryness, the application of raloxifene provided alleviation (2008b; Stein K & Ascher-Walsh C., 2009; Viswanathan et al., 2007).

Progesterone modulators

Progesterone receptors are found in increased concentrations in uteri containing myomas. Antiprogesterone agents have an effect on these progesterone receptors. A large number of studies concentrate on the active agent known as Mifepristone, a selective progesterone receptor modulator (SPRM), and have been able to show a clear reduction in myoma size with only a relatively small regrowth rate of the myomas after completion of the therapy. Amenorrhea and an improvement in symptoms related to pelvic pressure were also mentioned as additional effects. The bone de-mineralization induced by GnRH agonists was not observed in Mifepristone. But, taking Mifepristone is not completely free of undesirable side effects. The effects described are endometrial hyperplasia and the potential for antiglucocorticoid activity, which makes strict monitoring of the liver necessary (Eisinger, Bonfiglio, Fiscella, Meldrum, & Guzick, 2005; Fiscella et al., 2006; 2008b). Most recent research concentrates on optimal dosing of mifepristone (recommended is a 5 mg dosis (Carbonell Esteve et al., 2008)) and new selective progesterone modulators, such as CDB-2914 and asoprisnil for example. The smaller studies that have been carried out up to now in this area show a similar effect as mifepristone therapy, whereby myoma size is reduced, menstrual bleeding is cleared and there is an improvement in symptomatic quality of life scores. The leading researchers on this subject, such as Kevin Fiscella, M.D., University of Rochester, Rochester, New York, comment that these medications should only be taken for a limited period, due to their side effects, and that more research is required in order to determine long-term use and risk (Dixon et al., 2006).

Selective estrogen receptor modulators (SERMs)

Select estrogen receptor modulators (SERMs) are substances that have an effect in certain organs or tissues similar to estrogen, and in others block the effect of estrogen. Many studies have tried to examine the effect of different SERMs on uterus symptoms. However, their effectiveness has remained contentious up to now. In a systematic

Cochrane review, a tendency towards a reduction in myomas has been determined, however this has not been confirmed in all studies. And besides, there have also been reports of adverse reactions. The review authors concluded that no evidence can be deduced from the small number of positive studies that SERMs reduce myoma size or improve clinical parameters. Therefore, further clinical studies are required to research the effectiveness of SERMs in treating women with uterine myomas (Wu, Chen, & Xie, 2007).

Non- or minimally-invasive therapy

A number of new minimally-invasive methods to treat myomas have been developed in the last few years. The most important are Uterine Artery Embolization (UAE), MRI-guided focused ultrasound surgery (MRIgFUS) and Transvaginal Radiofrequency Thermal Ablation (RFA).

Uterine Artery Embolization (UAE)

Since the first description of UAE in 1995 by Ravina, this method has been used to treat symptomatic myomas in many centers all over the world (Ravina et al., 1995). UAE is generally carried out by interventional radiologists. To prepare for embolization, the patients are given an opioid or a combination of a short-acting benzodiazepine and opioid intravenously to avoid acute complaints during embolization. Pain therapy can also be given in the form of a pain pump, controlled by the patient whenever necessary, or in the form an epidural anaesthetic. Embolization subsequently takes place by way of a digital subtraction angiography (DSA). The application of embolization materials (polyvinyl alcohol particles of trisacryl gelatin microspheres and sometimes supplemental metal coils) is given via a transcutaneous femoral artery approach. This leads to uterine fibroid devascularization and involution.

Numerous studies have been carried out to determine the effectiveness and reliability of the methods. The short-term and long-term outcomes are both estimated to be very good. The effects range from volume reduction to an improvement of myoma-associated complaints and even improved values in quality of life surveys. The amount

in which volume is reduced is between 42% and 70% (Pron et al., 2003b; Worthington-Kirsch, Popky, & Hutchins, Jr., 1998). Positive results have been reported in both studies over a short period of observation, e.g. 3 months in the Ontario Uterine Fibroid Embolization Trial (Pron et al., 2003b; Pron et al., 2003c) and also in studies with follow-ups after 3 to 5 years (Hehenkamp et al., 2005a; Hehenkamp, Volkers, Birnie, Reekers, & Ankum, 2008). In comparative studies including hysterectomies and/or myomectomies, women treated with UAE were in considerably less pain in the first 24 hours after operation, stayed a shorter time in hospital and were able to return to activities and work more quickly afterwards. However, the complication rate was somewhat higher, e.g. in one study the rate of major complications after UAE amounted to 4.9% in comparison to 2.7% after hysterectomy and the rate of minor complications, such as vaginal discharge, leiomyoma expulsion, and hematoma 58% versus 40%. Also, the rate of come-back of uterine myomas after UAE amounts to 11.1% in comparison to the logical 0% after hysterectomy. In a case-control study, a higher reoperation rate was ascertained of 29% to 3% with respect to UAE in comparison to myomectomy (Goodwin et al., 2006; Gupta, Sinha, Lumsden, & Hickey, 2006; Hehenkamp et al., 2005b; Hehenkamp, Volkers, Birnie, Reekers, & Ankum, 2006; Spies et al., 2002b). A study published in 2006, which dealt mainly with assessing the outcomes of patients who underwent UAE and evaluating the factors associated with the failure of UAE, reported a failure rate of 9.4%. The authors stress, however, that the failure rate could be underestimated here, as it cannot be guaranteed whether or not patients underwent other interventions elsewhere. Failure is understood when symptoms persist or reoccur, such as bleeding, pain, or bulk symptoms requiring hysterectomy, myomectomy, or repeat UAE. Long-term failure included patients who required surgery or repeat procedure more than 6 months after UAE and short-term failure involved patients requiring surgery or repeat UAE within 6 months after UAE. Interestingly, in this examination, it was the women with a reduction in myoma size of 36% in the asymptomatic group and those with a reduction of 54.4% in the failure group. This implies that a reduction in volume of the uterus or dominant myoma does not necessarily bring about an improvement to symptoms. The ACOG Committee on Practice Bulletings Gynecology proposed the following final evaluation of UAE in its guidelines published in 2008: “Based on long- and short-term outcomes,

uterine artery embolization is a safe and effective option for appropriately selected women who wish to retain their uteri. Women who wish to undergo uterine artery embolization should have a thorough evaluation with an obstetrician–gynecologist to help facilitate optimal collaboration with the interventional radiologists and to ensure the appropriateness of therapy, taking into account the reproductive wishes of the patient." (2008b) "At the current time, knowledge about the influence of UAE on fertility and pregnancy cannot be said to be reliable, even though there are some case reports on pregnancies without complications after UAE. Considering the fact that fertility can theoretically be influenced and that insufficient facts are known in order to provide a concluding assessment of the situation, many centers only offer UAE to women who no longer want to have children. In the clinical management guidelines published in 2008 by ACOG, they recommended noting that because there is biologic plausibility of uterine artery embolization causing compromised endometrial perfusion resulting in abnormal placentation in women not otherwise at risk, this approach should be used with caution for women who are pursuing pregnancy. The effect of uterine artery embolization on pregnancy remains understudied." (2008b)

MRI-guided focused ultrasound surgery (MRIgFUS)

Another minimally-invasive treatment method is the MRIgFUS method, which has been approved by the FDA since 2004. MRI-guided, focused ultrasound surgery is one technique that provides real-time thermal mapping and precise anatomic visualization. In this procedure, the ultrasound beam penetrates soft tissues and focuses on target sites causing localized high temperatures. The resulting thermocoagulation results in protein denaturation, irreversible cell damage and necrosis of uterine leiomyomas. In order to assess the effectiveness and reliability, literature has, up to now, usually only cited from four studies, of which two were carried out in the USA and two smaller studies in Japan. In the control examinations taking place after 6 and 12 months, a persisting improvement to symptoms has been ascertained for initially about 70% and then for only about 50% of the test persons at a moderate reduction in volume of 13.5% and 9.5% respectively. The magnitude of symptomatic improvement in the U.S. studies, which involved three US centers, two European and one Israeli center, amounted to 39%

after 6 months and 36% after 12 months. The failure rate after 6 months amounted to 11%, and after 12 months 28% had undergone additional treatments that included hysterectomy, myomectomy or UAE (Hindley et al., 2004b; Stewart et al., 2006). The Japanese studies provoked the assumption that MRIgFUS might not be as useful in obese women or those whose fibroids demonstrate high signal intensity on T2 (Mikami et al., 2008; Morita et al., 2008). Certainly this modality shows capability, but more research is essential. Anyhow few short-term studies show safety and efficacy, long-term studies are required to perceive whether the effects of MRI-guided focused ultrasound surgery will persist beyond 12 months (2008b; Viswanathan et al., 2007).

Transvaginal Radiofrequency Thermal Ablation (RFA)

A number of studies on RFA already exist, but this very new method has not yet been approved by the FDA. In RFA, a radiofrequency needle is introduced into the myoma, either transvaginally through the cervical canal, or percutaneously (puncture of Douglas or vesicouterine fold). The needle, which is now located in the centre of the myoma, is heated at the tip. This procedure takes place under ultrasonic guidance. The duration of ablation is determined by the manufacturer's recommendations or by sonographic criteria (Stein K & Ascher-Walsh C., 2009). In accordance with the description by Cho, H.H. et al., the complete ablation of a 3-cm large myoma usually takes five minutes, while that of an approximately 5-cm large myoma takes almost ten minutes. The intervention is carried out under intravenous anesthesia. The results observed by Cho et al. of a group of 153 premenopausal women with symptomatic uterine leiomyoma who underwent transvaginal radiofrequency thermal ablation under ultrasound guidance are very promising with a final reduction rate of the volume of the dominant fibroid of 73% after 18 months and significant improvements in symptoms, ascertained via the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire. The failure rate in the form of reoperations after myolysis amounted to 4.3%. If the dominant symptomatic myoma measured more than 75 cm3, the women concerned showed higher reoperation rates and lower satisfaction rates (Cho, Kim, & Kim, 2008). Two further feasibility studies with 6 and 18 test persons produced very similar results (Ghezzi et al., 2007; Recaldini et al., 2007). These studies show the

feasibility and possible effectiveness of RFA, however a lot of study is still required in order to ascertain the actual potential of RFA, its reliability as well as any influences on fertility.

Surgical management

Surgical management includes hysterectomy, myomectomy or myomenucleation.

Hysterectomy

Removal of the uterus is carried out above all in the event of considerable symptoms, i.e. when the patients are suffering a lot of pain, heavy menstrual bleeding and consequential anemia, and/or are accompanied with particularly fast growing and large number of myomas. Hysterectomy is preferred over myomectomy, especially in the event of growths that have grown together with the uterus over a wide base. Here, it is often not possible to remove the individual lumps, as the wound that would result would be too big. The absolute prerequirement for hysterectomy is that women no longer wish to become pregnant. Depending on the size and mobility of the uterus, either an abdominal incision or vaginal or rectal access is selected. Possible complications of the operation include secondary hemorrhage, infections, adhesions and injuries to other organs such as the bladder, ureter and intestines. In operations involving an abdominal incision, a scar remains after the operation. As specific blood vessels that supply the ovaries are pinched off during the operation, which can stop hormone production, this operation can have hormonal consequences, even the ovaries remain in place after removal of the uterus. Usually there is no more monthly menstrual bleeding, but regular fluctuations of the female sexual hormones, estrogen and gestagen are still ascertained. Positive side effects are elimination of any risk of cancer of the uterus and for some women absence of menstruation (FUS-Center Klinikum Dachau, 2010).

Myomectomy or myomenucleation

Myomenucleation is the term for removal of the myoma by enucleation, while the uterus is kept. The failure rate for regrowth of a myoma after operative removal is about 10 to 30%. Submucous myomas can be removed as part of a hysteroscopy. Here, the

uterine cavity is stretched via a rinsing solution and the myoma is removed with a resection loop. The pieces of the myoma are removed by way of the access channel used by the instruments (hysteroscope). Possible complications can involve injury to neighboring organs and also hyperhydration syndrome in the event of longer rinsing. Patients have died of this. Submucous myomas are removed via laparoscopy. If the myoma is located intramurally, an abdominal incision (laparotomy) is usually applied. While the minimally-invasive interventions (hysteroscopy and laparoscopy) usually involve only slight risks (see above) such as an increase in the risk of bleeding and infection, as well as the stress incurred by the anesthetic, abdominal incisions are likely to involve greater risks. The operation involves greater loss of blood. Adhesions can develop and the return to good health is a lengthier process.

Independent of the methods themselves, remain the risks of an operation:

- Blood loss (particularly in a laparotomy)
- Muscle weakness in the uterus and ripping of the seam during a pregnancy
- Later development of scar tissue (particularly after a laparotomy)
- Infections
- Injury to the intestines or bladder (particularly after a laparotomy) (FUS-Center Klinikum Dachau, 2010)

Further undesirable side effects are the risk of leiomyoma recurrence, Cesarean delivery, and reduced fertility due to surgical complications arising from the removal of multiple leiomyomas according to a large study in which the authors retrospectively analyzed reproductive performance before and after abdominal myomectomy for intramural and subserosal leiomyomas (Marchionni, Fambrini, Zambelli, Scarselli, & Susini, 2004).

Complementary/Alternative medicine

Among other alternative therapies, herbal treatments for fibroids are used in several medical traditions and countries, (Fugh-Berman et al., 2004; Shobeiri, Sharei,

Heidari, & Kianbakht, 2009) for example, the application of traditional Chinese herbal Medicines. According to the theory of Chinese medicine, uterine fibroids are a condition of imbalance between yin and yang in the body (in allopathic terms: disturbances of the endocrine system and blood circulation). Therefore, herbal preparations are used based on the patients' symptoms and observation of the tongue and pulse. In 2009, a Cochrane review was published with the primary objective to assess or evaluate the benefits and risks of herbal preparations for treating uterine fibroids. It included only two randomized trials on two different herbal preparations for the treatment of uterine fibroids. The control groups were treated with GnRH or mifepristone. The phytotherapeutically treated groups exhibited similar effects in terms of shrinkage or disappearance as the control groups. However the authors discovered that due to the small sample of the trials and methodological flaws in one trial, any indicated benefit is not conclusive and further large and rigorous trials are needed (Liu, Yang, Xia, & Cardini, 2009). Another Cochrane review involved acupuncture as an alternative treatment. There are many types of acupuncture used to manage uterine leiomyomas, with body acupuncture being the most commonly used. Even though literature provides frequent reports of the benefits of acupuncture for the management of uterine leiomyomas, the authors were forced to finally reach the conclusion that no randomized double-blind controlled trials met the inclusion criteria and therefore the effectiveness of acupuncture for the management of uterine fibroids remains uncertain. In order to ascertain insight into evidence for the efficacy and safety of acupuncture for uterine fibroids, there is a continued need for well designed RCTs with long-term follow-up (Zhang, Peng, Clarke, & Liu, 2010).

Also combinations of TCM and other complementary medical measures are applied. A pilot study in the USA is attempting to approach the topic. 37 non-menopausal women at ages between 24 and 45 with palpated uterine myomas and their matched controls, who were enrolled for conventional treatment, were treated for a period of 6 months. The treatment program consisted of weekly traditional Chinese medicine, body therapy (somatic therapy, bodywork), and guided imagery. In 22 patients in the treatment group, a reduction in volume or stop in the growth of the myomas was achieved in comparison to 3 in the group that was treated conventionally. The authors' conclusion

is that there surely is the possibility of existing alternatives to pharmacological and surgical methods (Mehl-Madrona, 2002).

Unfortunately, to date, there is no extensive literature on the effectiveness of osteopathic treatment of uterine myomas. Relevant database research in Medline has not produced any hits. (See Appendix, "Search Strategy".) However an unpublished randomized clinical study does exist, which was presented to acquire the brand DO® at the Akademie für Osteopathie in Germany. Here, 37 test persons were treated by three osteopaths and the results were compared with 28 test persons from the waiting-list control group. The treatment group exhibited a significantly greater reduction in myomas (-18% against +1%) and relatively fewer menstrual symptoms.

Economic Burden

Uterine fibroids can cause serious health complications for the women concerned and can result in enormous expense for society. Uterine fibroids are the most frequent indication for hysterectomy in premenopausal women and, therefore, are a major public health issue. Of the 600,000 hysterectomies performed annually in the United States, one-third is due to fibroids (Society of Interventional Radiology., 2010). According to a current survey the direct health costs of an average patient between the ages of 25 and 54 suffering from uterine fibroids amount to approximately 8,000 US-Dollar, while the indirect costs can be as high as 3,000 US-Dollar (Lee et al., 2007). A further extensive study of women between 18 and 64 years diagnosed with uterine fibroids totaled an average cost of 4,624 US-Dollar per woman per year (Hartmann et al., 2006). Flynn M. et al estimated the total direct cost to treat uterine fibroid tumors as in excess of 2 billion dollars. Most of the cost was due to inpatient care, in particular, hysterectomy (Flynn, Jamison, Datta, & Myers, 2006).

Osteopathic Literature

There are hardly any descriptions of the direct treatment of uterine myomas in osteopathic literature. All the more interesting in this context, is the description of the impact of osteopathic manipulations in the area of the uterus and vagina by the well-

known osteopath, and generally-recognized researcher, Jean-Pierre Barral. In his book, "Visceral Osteopathy in Gynecology", he lists the following local effects:

- The tissue is relieved of adhesions and to a certain extent gains back its elasticity
- Physiology, mobility and movement of the organs renormalize
- Circulation and lymphatic flow improve
- Mechanical nerve compressions are removed
- Sphincter and muscle tone are strengthened
- …..
- Pelvic pain are relieved and
- the local secretion of hormones is stimulated (Barrall, 2004).

In addition, there is a remarkable association with A.T. Still´s approach to the problem. He found that the lymphatic drainage disorder e.g. due to congestion of the cysterna chyli as a result of restriction of the ductus thoracicus at the entrance to the diaphragm could be a possible cause for a hypertrophy of the uterus (Still, 1999).

2.1.4. Discussion

Methods

The methods used to research the background to uterine myoma can be described as practical and useful. The applied search strategy corresponds to search strategies found in Cochrane reviews (Zhang et al., 2010). The fact that no precise evaluation of research in other databases has not, with hindsight, left us with gaps in our knowledge.

Results

The literature research has provided very extensive and detailed information on all aspects of uterine myomas. The wealth of information has made it difficult to limit the individual chapters of this research to the measure necessary. Subsequently, more detailed information including more biochemical details would have been available to explain the genetic context. However, this would have exceeded the framework of this

thesis. Furthermore, any readers who are interested can find more detailed information in the specified literature.

2.2. Analysis of interventional trials on uterine fibroids, concerning methodological issues

2.2.1. Objectives

The objective of this research and analysis of literature was to gain an overview of the applied study methods from the existing research studies; to analyze them with respect to the writing of my own study protocol and therefore to avoid any errors.

2.2.2. Methods

The basic search strategy was developed using the National Library of Medicine Medical Subject Headings (MeSH) key word nomenclature developed for MEDLINE. The same strategy was used to search in MEDLINE, CDSR, Science Direct, and EMBASE. The foundation for the literature search is based on the strategy described in chapter 2.1.2. This basket of search terms, constituting synonyms for uterine myoma, was supplemented with the terms, Limit Clinical Trial and Randomized Clinical Trial. The hits were initially filtered according to topic, i.e. all studies that had nothing to do with the symptomatic and/or size of myomas as a target criterion were eliminated. The remaining studies were investigated according to the following criteria: study design, study target, assessment parameters, assessment instruments, inclusion and exclusion criteria, duration of treatment, observation period, patient recruitment, setting.

2.2.3. Results

Study design

A two-armed study model emerged as being the most suitable as an applicable study design for the planned clinical study, in which osteopathic treatment plus usual care is compared with usual care. In this context, usual care means expectant management, which is also referred to as watchful waiting.

Assessment instruments

The newly developed UFS-QOL questionnaire was identified as being the most suitable assessment instrument for our purposes, which were to check the symptoms of uterine myoma and the effects on the quality of life of patients. The UFS-QOL was designed as a uterine-fibroid specific questionnaire to evaluate the symptoms of uterine fibroids and their impact on health-related quality-of-life (HRQL). The UFS-QOL was constructed as two scales: an 8-item symptom severity scale (UFS) and a health-related quality-of-life scale (QOL) with 29 HRQL items comprising six dimensions (concern, activities, energy/mood, control, self-consciousness, and sexual function). All items are arranged on a 5-point Likert scale, varying from "not at all" to "a very great deal" for symptom severity items and "none of the time" to "all of the time" for the HRQL items. Symptom severity and HRQL subscale scores are summed and transformed into a 0–100 point scale, in a way that higher symptom severity scores indicate greater symptoms while higher HRQL subscale scores indicate better HRQL. (See Appendix.) The UFS-QOL questionnaire is a useful und validated option to detect symptom severity and HRQL score among patients with uterine leiomyomata. It is considered to be an excellent discriminative in distinguishing not only normal subjects from leiomyomata patients but also patients with varying self-rated and physician-rated symptom severities. Women with leiomyomata show significant decline in health-related quality of life scores, particularly when experiencing severe symptoms (Spies et al., 2002a; Cho et al., 2008; Adamis et al., 2004).

The myoma size serves as an objective target criterion. Ultrasonography (US) emerged as a suitable assessment method. US has a very reliable level of accuracy. For example, Dueholm et al. discovered in a double-blind study of 106 premenopausal women who underwent hysterectomy for benign reasons that the presence of myomas was detected with the same high level of precision by both methods (magnetic resonance imaging: sensitivity, 0.99; specificity, 0.86; transvaginal ultrasonography: sensitivity, 0.99; specificity, 0.91). Magnetic resonance imaging and transvaginal ultrasonography myoma diameter measurements still had equal and high accuracies in patients with 1 to 4 myomas. According to the judgment of these authors, transvaginal ultrasonography is as

efficient as magnetic resonance imaging in detecting myoma presence. The precise localization of myomas is very slightly weaker when using the US method in comparison to magnetic resonance imaging, especially in large (> 375 ml) multiple myoma (> 4) uteri, which is made clear in literature on this topic. MRI is more accurate in estimating myoma size and localization, which is of particular significance when preparing a surgical intervention. Ultrasonography (US), using transvaginal and transabdominal modalities, was finally selected as the suitable instrument after weighing up the its slight weaknesses in precision on the one hand and its accessibility and relatively low costs on the other.

2.2.4. Discussion

With the help of the literature that was found, important insights were able to be gained that would help to structure this study in a targeted manner. For example, a two-armed design turned out to be very suitable and fulfilled our requirements with respect to an RCT together with our questionnaire. As expectant management represents the medical treatment option for patients with uterine myoma who are exhibiting few or no symptoms, the two-armed design is almost predestined for a study in which usual care (expectant management) and osteopathic intervention plus usual care is tested. In order to fulfill the target of this research, namely, to review the effectiveness of osteopathic treatment on uterine myoma, we selected this two-armed design structure; an additional comparison with a different therapy option is not necessary here.

The applied method can be categorized as target-oriented and productive, as new insights were able to be gained and existing ideas of the design of the study were able to be confirmed. For example, the development and validation of the UFS-QOL was able to be proven as an assessment instrument.

Individual results from the evaluation of literature are presented and discussed in more detail in chapter 4.

2.3. A Systematic Literature Review of Trials on Osteopathic Treatment of Patients with Uterine Fibroids

2.3.1. Objective

The target of this search and analysis of literature was to gain additional information from existing osteopathic studies on the specific problems pertaining to the applied study details, which might emerge from the characteristics of therapy methods using complementary medication, and to analyze and learn thereof to avoid mistakes in the development of our own study protocol.

2.3.2. Methods

The same basic search strategy was applied here as described already in chapters 2.1.2 and 2.2.2. In addition, we looked for appropriate clinical studies in the CINAHL, OSTEMD DR, osteopathic research, AFO and PeDro databases. As other studies exist in the area of complementary medicine that have not been published in Medline-listed journals or have not been published at all, congress reports, e.g. from ICAOR, popular trade journals that are not listed in Medline, directories of master and PhD theses, e.g. the Victoria University in Melbourne, study projects from the Centre for Complementary Medicine Research at the University of Western Sydney, National Council for Osteopathic Research were researched to find osteopathic clinical studies on uterine myoma.

2.3.3. Results

Only one clinical study was found. It was conducted in Germany by three osteopaths, presented in 2003 and achieved the German mark DO®. In this study 37 patients were treated osteopathically. The results were compared with 28 test persons from the waiting list control group. The treatment group indicated a significantly greater reduction in myomas: -18% in comparison to +1% and fewer symptoms of bleeding relatively speaking. Following these results, an impact of osteopathic treatment plus usual care of 20% was taken as the sample size calculation.

2.3.4. Discussion

Despite extensive searches of literature, only this one study was found. The additional, unsuccessful manual search through congress reports, master theses and lists of dissertations, current study projects at osteopathic universities in USA and Australia indicates that the meager results are not due to an insufficient search strategy. Despite the fact that interest in this subject took hold at an early stage and this interest persists to this day, it took until 2003 before the first and sole osteopathic clinical study was presented.

Chapter 3: Study Protocol

3.1. Introduction

Uterine fibroids are the most common benign pelvic tumors affecting women at reproductive age. Fibroids are tumors of the smooth muscle cells of the uterus. Its collagen content gives it a hard, fibrous texture. In the majority of cases it originates in the uterus and sometimes in the gastrointestinal tract.

3.1.1. Etiology

Although some progress has been made in the last few years in understanding the hormonal, genetic and growth factors and molecular biology of these benign tumors, the precise causes of myomas are still unknown (Hildreth et al., 2009). It is undisputed that the hormones, estrogen and progesterone, play an important role. In interaction with several proteins and polypeptides they control the proliferation of cells and can stimulate myoma growth (Rein, 2000).

3.1.2. Epidemiology

Statements about prevalence are not always consistent. They vary in particular depending on the surveyed population, on whether asymptomatic women are included or excluded, and depending on the sensitivity, or more specifically, specificity of the applied diagnostic methods. Among females, prevalence is between 20-50% (Baird D. et al., 2003). However this number varies depending on the section of the population examined. For example, a cumulative incidence of 26% is found in white US women between the ages of 35 to 40, whereas for African-American women the figure is 53%. At the age of 50 the cumulative incidence increases among white women to about 70% and to over 80% among African-American women (Chen et al., 2001; Baird D. et al., 2003; Wise et al., 2005; Faerstein et al., 2001). A number of studies from different European countries indicate that myoma prevalence is slightly less among European populations (Borgfeldt & Andolf, 2000b; Marino et al., 2004; Marino et al., 2004).

3.1.3. Symptomatology

A total of roughly 25% of all women with myomas indicate symptoms of illness. The type and intensity of complaints depends heavily on the localization, number and size of the myomas. The symptoms can be divided into 4 groups: menstrual bleeding disturbances, pain, compression syndrome, and reproductive dysfunction.

3.1.4. Diagnosis

The diagnosis is largely based on manual examination, transvaginal ultrasound, hysteroscopy and MRI. The size of the myoma can be reliably estimated by way of a bi-manual examination, as has been proven by retrospective study based on post-operative uteri (Cantuaria et al., 1998; 2001). However, in order to determine the optimal choice of therapy, more precise examinations are necessary to determine the exact size, number and most importantly, the position of the myomas. To this purpose, the imaging procedures, ultrasound, which can also be conducted as a saline infusion sonography, and hysteroscopy and MRI can be applied (Bradley, 2002) (Dueholm et al., 2001a).

3.1.5. Therapy

The treatment options vary depending on the size, location, number of tumors and whether the woman wishes to maintain fertility. The current approaches to uterine leiomyoma treatment are categorized in these five groups:

- Expectant management: This means watchful waiting. Numerous types of medication are taken in this area already e.g. NSAIDs for pain relief or medication to reduce symptoms related to anemia (Viswanathan et al., 2007).
- Medical treatments: They are not causal but they can reduce volume and relieve symptoms. However their impacts are not long-standing. And some of them produce heavy undesirable side-effects. And of course these medications cannot be used on women wishing to conceive (Marjoribanks J, 2006).

- Minimally invasive or noninvasive approach: The aim of these procedures is to cause damage to the cellular viability of the myoma tissue. The success rate in reducing the myoma size is very high. Effects on fertility and pregnancies in the treated women are, according to clinical management guidelines defined by the ACOG, inconclusive and therefore, some medical centers only offer these treatments to women who have completed their family planning (Hehenkamp et al., 2005a; Hehenkamp et al., 2008).
- Surgical removal: The available surgical procedures are hysterectomy and myomectomy. They are applied when symptoms are considerable. Removal of the uterus is, naturally, the most effective treatment. Possible complications of the operation include secondary hemorrhage, infections, adhesions and injuries to other organs such as the bladder, ureter and intestines. As more and more women are postponing pregnancies to later ages, and trends show that more women want to keep this organ intact, in future, this radical treatment method will be an option that fewer and fewer women will take into consideration. A different surgical alternative is the myomectomy. The recurrence rate of regrowth is about 10 to 30% (Marchionni et al., 2004).
- Complementary/Alternative medicine: From the field of CAM, mainly herbal medications and acupuncture from traditional Chinese medicine are applied. Combinations with other CAM methods are also used, e.g. body therapies and guided imagery (Fugh-Berman et al., 2004; Shobeiri et al., 2009).

3.1.6. Economic burden

The clinical relevance of uterine fibroids is reflected in the 200,000 hysterectomies, performed annually in the USA due to fibroids. In an attempt to calculate the direct medical costs in the USA, different authors came to amounts somewhat shy of USD 5000 to 8000, while indirect costs are alleged to be around the USD 3000 mark per woman per year. One study conducted in 2006 arrived at a direct

overall expenditure of more than USD 2 billion per year. Most of the cost was due to inpatient care, in particular, hysterectomy (Lee et al., 2007).

3.1.7. Why conduct a trial with osteopathic treatment now?

On the one hand we have expectant management as the standard therapy for women without or with moderate symptoms, and on the other, we and many of our colleagues have observed that osteopathic treatment can be very helpful for patients with uterine fibroids. Additionally one RCT exists, which was conducted as a pilot study from Germany in which 37 patients were treated osteopathically. The results were compared with 28 test persons from the waiting list control group. The treatment group indicated a significantly greater reduction in myomas: -18% in comparison to +1% and fewer symptoms of bleeding relatively speaking. Therefore it is our request to verify our experiences by means of scientific methods.

3.2. Study hypothesis

A series of five osteopathic treatments during the phase of expectant management has a positive influence on the intensity of symptoms and on the condition-related quality of life of women with uterine fibroids.

3.3. Study model

The study model has been developed as a prospective, two-armed, randomized, controlled clinical study.

3.4. Intervention group/control group

This study is based on a two-armed design, whereby an intervention group with osteopathic treatment plus usual care was formed as well as a control group where only usual care was practiced.

3.5. Size of groups

The groups should comprise 100 test persons each.

As well as the calculated size of 82, a further 18 test persons are added to each group in order to reduce the risk of forfeiting statistical power should any of the test persons abandon the study. See also chapter 3.9.1, "Statistical Analysis".

3.6. Inclusion, exclusion and termination criteria

3.6.1. Inclusion criteria

- Specialist diagnosed submucous or subserosal uterine myoma
- Minimum diameter of the myoma or dominant myoma of 2 cm
- Test persons may not be in menopause
- Negative pregnancy test
- Test persons should be at least 18 years of age or should be of full age according to the respective national regulations of the country in which the study is being carried out
- Should understand English or the language of the country in which the study is being carried out
- Minimum score in the severity symptom score according to UFS-QOL of 34

3.6.2. Exclusion criteria

- Taking or application of contraceptives of all kinds
- If contraceptives were no longer taken less than two months before the initial gynecological examination
- Any complementary or classical medical treatments for uterine myoma (medication as needed against acute pain is permitted and is documented)
- Acute infection
- Malignant diseases
- Surgical intervention of urogenital organs (with the exception of conizations and curettage)
- Endometrial polyps
- Adenomyosis

3.6.3. Termination criteria

If criteria occur after the onset of the study that are listed under termination criteria, this must be documented. If possible, the reasons for a termination to participation in the study should be taken to protocol, also in terms of whether the termination is definitely/probably/maybe or probably not related to participation in the study. These aspects are taken into consideration in the event of a secondary analysis of the results, a so-called per-protocol analysis.

3.7. Target parameters

3.7.1. Primary target parameters

The intensity of symptoms and how they influence quality of life is the primary target parameter.

3.7.2. Secondary target parameters

Perimenstrual intensity of pain and myoma size have been defined as the secondary target parameters. In the eventuality of several myomas (uterine myomatosis), this is determined based on the dominant myoma. Osteopathic examination results and the development of osteopathic insights are documented as additional target parameters.

The occurrence of any undesirable side effects is documented in the respective questionnaire. (See Appendix.)

3.8. Conduction of study

3.8.1. Research staff

The study is conducted by osteopaths who are qualified in accordance with the statues either of the Verband der Osteopathen Deutschland (VOD) or the Akademie für Osteopathie in Deutschland (AfO), the European Federation of Osteopaths (EFO) or a comparable organization (e.g. Australian Osteopaths' Registration Boards (AORB), Australian Osteopathic Association (AOA), American Academy of Osteopathy (AAO) and similar). The treating osteopaths must have several years of experience in their professions and must have practiced manual osteopathic medicine to at least 80% during this time. In addition, they should be experienced in treating gynecological illnesses or in the evaluation and treatment of the pelvic area (both parietal and visceral). The osteopaths taking part in the study are required to sign a respective declaration.

3.8.2. Setting

This is a multi-center phase study. At least three different osteopaths must be active in providing treatment. As there are still only a few clinics in Europe, and particularly in Germany, in which osteopaths practice, the treatments here are conducted in the practices of the osteopaths taking part. At each study location, at least one gynecologist must be gained to participate in the study, who is responsible for the initial

examination in accordance with the inclusion and exclusion criteria and also for measuring myoma size as the study progresses.

3.8.3. Recruitment

Recruitment is organized in accordance with the healthcare that is in existence in the respective country. For example, here, recruitment is described in line with the regulations stipulated by the German health system.

As the test persons are women with relatively low-level complaints, they will not be great numbers of them in the clinics. It is therefore necessary to organize recruitment by way of other registered doctors and therapists.

Freelance midwives, physiotherapists, osteopaths, general practitioners and gynecologists will therefore be asked or approached personally. Potential test persons will also be sought and approached via public means. This will take place via contacts to self-help groups, internet forums (e.g. http://www.nuff.org/research.htm) and advertising in print media. The gynecologists participating in the study can also approach potential test persons. In this event, the evaluation of the myoma size may not be carried out by the same gynecologist. The variety of recruitment methods should minimize possible selection bias.

3.8.4. Information/Agreement/Safety of participants

Potentially interested women should be informed verbally about the significance and purpose of the study and its procedure and also about osteopathy. This is conducted either personally or by telephone depending on the contact. Afterwards the women are given written information and diverse internet addresses where they can find more information about osteopathy and relevant organizations. (See Appendix B) The osteopath conducting the study is available for any questions. Prerequirement for participation in the study is submission of a written declaration by the test person.

3.8.5. Data protection

Directly after inclusion in the study, personal data is pseudonymized - each participant is given a keycode. This is the only way to enable the data to be assigned to the respective person. It is stored in a safe place by the responsible osteopath. Everyone working for this study is subject to the regulations of data protection legislation.

3.8.6. Randomization

After reviewing all the inclusion and exclusion criteria and upon submission of the declaration of agreement, the test person is enrolled for the study. By way of the randomization method, the test person is allocated to either the control or treatment group. The local study leader, or a person authorized by him/her, contacts the external institute responsible for conducting the randomization by telephone and communicates the test person's initials and study location. Group assignment is handled by an employee at the institute by way of block randomization. The result is communicated to the caller. Randomization is therefore processed centrally and organized as block randomization.

3.8.7. Procedure/duration

After being enrolled in the study and once the randomization process has been completed, another appointment is made with the osteopath. This is called T1. First of all, the test person fills out a questionnaire pertaining to medical history and VAS-perimenstrual pain. The test person will already have submitted a filled-out UFS-QOL questionnaire, as this is part of the inclusion criteria for acceptance to the study. The next step is an initial osteopathic examination, the results of which are taken to protocol in the respective form. All test persons are given a medication diary. The procedure that subsequently follows differs according to the two groups.

The first osteopathic treatment is now conducted in the treatment group. At intervals of 3 weeks each, 4 additional osteopathic treatments are conducted. When the menstrual period takes place before the appointments for treatment, perimenstrual pain intensity is taken to protocol according to a VAS. About two weeks after the fifth treatment appointment, a concluding osteopathic diagnosis is prepared and the UFS-QOL

questionnaire is filled out. A TVS also has to be conducted in the same period to determine myoma size. The first follow-up takes place three months later. The UFS-QOL questionnaire is filled out again and another TVS is carried out. The second follow-up is carried out six months later. The gynecologists do not know to which group the test persons belong.

The participants in the waiting group are given 4 more VAS forms for T1, in order to record their perimenstrual pain intensity after each menstrual period.

An appointment for the second TVS should be made for three months later with the responsible gynecologist. Three months later, the women have an appointment with the osteopath. They take with them the VAS and the medication diary and fill out the UFS-QOL. Next, providing the TVS has taken place, the test persons are examined osteopathically and the first treatment can be conducted. These results are not relevant for the evaluation of the study.

Both groups keep a medication diary during this time. To make sure that entries are made in the diary and also in the VAS, the test persons are called weekly by people working for the study to remind them.

To ensure that the study runs smoothly, all the treatment and examination appointments with the osteopath and gynecologist are made after the randomization process. The sonographic measurements of myoma size have to be taken at the same time during the menstruation cycle in order to keep the measurement results free of any fluctuations in size that could be due to the menstruation cycle.

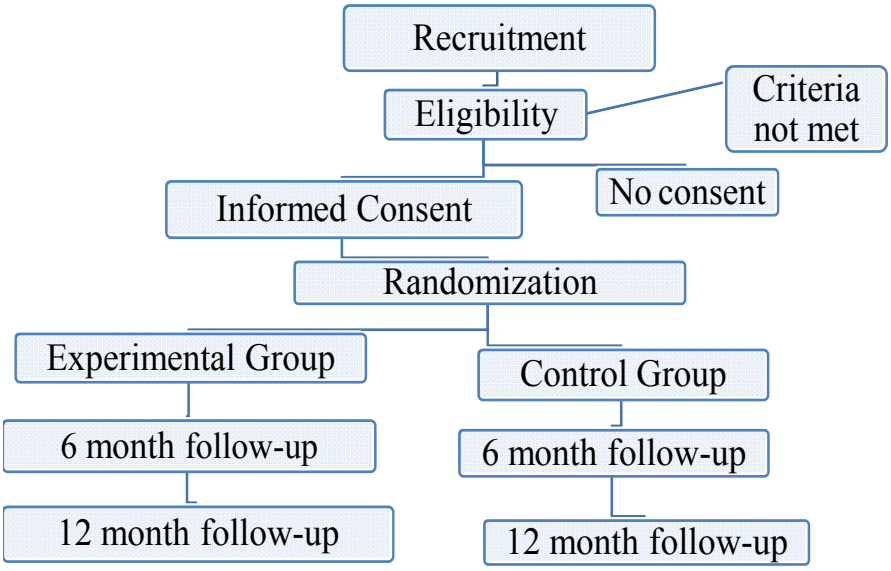


Figure 3: Flow chart of study timetable

The complete study process can be seen in the tables below.

Table 4: Timetable of study for the intervention group

TIME TABLE	Preparation Phase	Date 1	Date 2-5	Final date	1st Follow-up	2nd Follow-up
		week 0	week 3-12	week 14	after 6 months	after 1 year
Recruitment	**X**					
Screening	**X**					
Randomization	**X**					
History	**X**					
Assessment	**X**	**X**	**X**	**X**	**X**	**X**
Osteopathic Diagnosis		**X**	**X**	**X**	**X**	**X**
Osteopathic Treatment		**X**	**X**			

Table 5: Timetable of the study for the control group

TIME TABLE	Preparation Phase	Usual care	Final Date	1st Follow-up	2nd Follow-up
		week 0-12	12-14	13-25	week 27
Recruitment	**X**				
Screening	**X**				
Randomization	**X**				
History	**X**				
Assessment	**X**	**X**	**X**	**X**	**X**
Osteopathic Diagnosis	**X**		**X**	**X**	**X**
Osteopathic Treatment					

3.8.8. Assessment instruments

Assessment instruments for the primary target parameter

The UFS-QOL questionnaire is the assessment instrument for the primary target parameter.

Assessment instruments for the secondary target parameters

Myoma size is measured via transvaginal and/or transabdominal sonography (TVS). To assess the overall leiomyoma burden, the calculated leiomyoma volumes are added together to yield a total leiomyoma volume for each subject.

The perimenstrual pain intensity is recorded in a VAS (see Appendix).

The results of the osteopathic examinations are entered into the prepared report sheet.

3.8.9. Description of intervention

Osteopathic treatment is conducted after each osteopathic examination, which includes a report of all medical findings of the body as a whole. How to proceed can be decided by each osteopath individually. Usually all the regions of the body are examined globally and when findings are made, further localized testing is carried out. In this study, however, the pelvic area is always examined in more detail by the osteopaths. This examination includes an examination of the musculo-skeletal structures and the visceral structures. The manner of this examination can be decided by the osteopath him/herself, who acts in accordance with his/her qualifications, training and experience. The same applies for the osteopaths' decisions, as to which dysfunctions are dominant and require treatment. The therapy is therefore coordinated to suit each individual patient and corresponds to the situation in normal practice. Conduct of the study is very close to the everyday terms and conditions of healthcare as used by the respective patients.

The treated dominant dysfunctions are documented and at the next appointment, they are reexamined and their status is documented again. This means that the place

where treatment takes place and the development of the treated dysfunction can be traced at any time.

The interval between treatments of three weeks was selected in order to be able provide the treatments independently of the menstruation cycle.

3.9. Statistic

3.9.1. Statistical analysis

Statistical analysis is conducted with a program from the Institut für Medizinische Statistik Besondere Einrichtung für Medizinische Statistik und Informatik der Medizinischen Universität Wien. The size of the group is based on a statistical analysis with the following parameters:

- Alpha errors of 0.05
- 90% power
- Efficiency of 20% in the treatment group and
- 5% in the waiting group

3.9.2. Statistical method

First of all a check is made based on the baseline data to see if randomization was successful. Next, the two groups are checked to see if distribution is normal by applying the Kolgomorov-Smirnov test. If normal distribution is confirmed, the intra-group analysis is carried out with the t-Test for dependent random samples. To compare the inter-groups, the t-Test for independent random samples is applied. If distribution is not normal, an intra-group comparison takes place using the Wilcoxon test and an inter-group comparison is conducted using the Mann-Whitney-U test.

3.9.3. Intention to treat

To avoid reporting only good outcomes should patients drop out to undergo additional leiomyoma therapies and to handle missing data, we use the last observation

carried forward evaluation. Women are only removed from the statistical calculations when it is known that the reasons why they have terminated their participation in the study are not in any way related to the uterine myoma and the treatment. Change of residence or an accident are examples of such cases.

Basically, the intention-to-treat method is applied.

3.10. Ethics

Before any activities related to the study can develop, the study protocol has to be submitted to an ethics commission for review. Selection of the ethics commission is made in accordance with the respectively applicable national regulations.

Chapter 4: Discussion

4.1. General considerations

Discussion begins with general considerations about the topics that play an important role in the development of a clinical study.

4.1.1. Randomized controlled trial

The study design of a randomized clinical study nowadays enjoys the status of being the highest standard in assessments of clinical studies. In light of the very limited available resources to carry out osteopathic clinical studies, it would be very wasteful to select a different design. The interest of clinical research in the area of complementary medicine and osteopathy should be accepted widely among medical professionals and also among political decision-makers, and particularly in areas where it has shown its qualifications with positive research results.

4.1.2. Efficacy/Effectiveness

In creating a study protocol, the authors are faced with the question of whether they want to conduct a study on effectiveness or on the efficacy of an intervention. However, this is about an effectiveness trial for a study to examine the influence of an intervention under normal, everyday conditions and an efficacy trial that examines the influence of an intervention under ideal conditions. In this context, Schwartz and Lellouch introduced the terms, “explanatory” and “pragmatic” as early as 1967. The term “explanatory” is supposed to describe trials that test causal research hypotheses, while the term “pragmatic” pertains to trials that help practitioners choose between options for care (Schwartz & Lellouch, 1967). However this division should not be understood as an either/or dichotomy, but as a multidimensional continuum, as there are hardly any studies that can be categorized as solely explanatory or exclusively pragmatic. Nevertheless, it is still important that trialists ask themselves at the very beginning in which direction (explanatory or pragmatic) they want to focus their study, in order to develop the study design in accordance with the set target. Following the trial by

Gartlehner et al., to develop a tool to differentiate between the two study types, these criteria can be assigned to pragmatic trials (Gartlehner, Hansen, Nissman, Lohr, & Carey, 2006):

- Populations in primary care
- Less stringent eligible criteria
- Health outcomes
- Long study duration, clinical relevance of treatment modalities
- Assessment of adverse events
- Adequate sample size to assess a minimally important difference from patient's perspective
- ITT analysis

In one study, these 7 items were tested for their applicability as a tool to assess the study type based on 151 clinical studies from the area of apoplex rehabilitation. The authors came to the conclusion that the items lacked clear operational definitions (Zettler, Speechley, Foley, Salter, & Teasell, 2010). MacPherson described more differentiated, characteristic features of a pragmatic trial. And he added the following to the above-mentioned characteristics of a pragmatic trial: (MacPherson, 2004)

- More suitable for chronic conditions
- Not placebo controlled
- Patients unblinded to maximize synergy
- Aim to optimize non-specific effects
- Routine treatment, complex interventions
- Practitioner skilled in routine care- often long-term follow-up
- High external validity, lower internal
- High relevance/impact to practice
- Heterogenous

Basically, authors of pragmatic trials face the problem that the required study design is usually connected with losses in internal validity. The art of developing a

pragmatic trial in the area of CAM is to fulfill the requirements of external validity without completely losing sight of the internal validity of the study.

4.1.3. Clinical-ethical aspects of the development of a study design in CAM

The study path with respect to the introduction of new medication is clearly set: the explanatory trials have to be carried out first to check the efficacy of the substances, before they are made publicly available. The situation for CAM and especially for osteopathy is, however, completely different. CAM and osteopathic treatment have been known as established methods for decades. In the last few years they have been applied in everyday situations in more and more diagnoses, and increased numbers of consumers, or patients, are asking for them. Figures from Great Britain confirm this. They show that as early as 2000, over 50,000 complementary practitioners were working in the UK providing treatment to around 5 million patients a year (Budd & Mills, 2000). This automatically provides the argument that current research on the development of meaningful evidence should be aligned towards routine care. In light of the large number of patients, who would like to be treated osteopathically, it can even be considered an ethical challenge to conduct pragmatic trials at this point in time in order to establish whether and where there is a beneficial effect. Not until then would it be possible to determine the effect of the individual components of this treatment by means of explanatory trials.

4.2. Eligible Criteria

To justify the requirements of an effectiveness study, the eligibility criteria should not be drawn up to tightly, nevertheless, they should still guarantee that the patients actually suffers from the condition under examination. It is therefore interesting to discuss how suitable the individual criteria actually are.

Inclusion criteria:

- Uterine myoma diagnosed by specialist medic

Logically, this is the basic foundation for participation in the study and therefore is not a subject for discussion.

- Minimum diameter of the myoma or dominant myoma of 2 cm

This condition is owed to the measuring method. As a diverse number of studies have shown, TVS is not so sensitive in the event of small myomas.

- Test persons may not be in menopause

The probability that myomas reduce in volume during menopause is relatively high. For this reason care must be taken that the test persons are not in menopause and will not begin menopause during the course of the study.

- Negative pregnancy test

Myomas can change during pregnancy as a result of hormonal changes. In order to allocate the study results to the interventions, pregnancies must be excluded from the beginning and duration of the course.

- Test persons should be aged 18 at least or be of age in accordance with the stipulations of the country in which the study is being conducted.

This is a criterion that is not specifically to do with the basic subject, but represents a general requirement. The test persons must be in a position to decide for themselves, legally speaking, whether they want to have the respective treatments or not.

- Should understand English or the language of the country in which the study is being carried out

A conditio sine quo non, in order to understand the study information and be in the position to provide an informed consent. It is also of absolute necessity to fill out the questionnaire.

- Minimum score in the severity symptom score of the UFS-QOL of 34

The declared target of the study is test the osteopathic treatment of myoma patients with moderate symptoms. Therefore the existence of symptoms is a prerequirement. At a total score of 100 points, 34 points represents roughly one third, which can be termed as moderate symptoms. Additionally, 34 also represents a size that will be able to adapt to change among the targeted number of test persons and be documented statistically.

Exclusion criteria:

- The taking or using of hormonal contraceptives in any form

As myomas react to hormones, the taking of hormonal contraceptives could influence myoma size and symptoms, which would make interpretation of the results impossible.

- If contraceptives were no longer taken less than two months before the initial gynecological examination

See above.

- Any complementary medical treatment or conventional medical treatment of the uterine myoma (medication as needed for acute pain is permitted and documented).

In order to relate the results to the intervention or control, absolutely no other treatments may be permitted. Medication as needed in the event of acute pain, on the other hand, does not have a persisting influence and corresponds to a normal situation.

- Acute infection

This has to be excluded in order to ensure that the documentation of symptoms is not influenced by other illnesses. This does, however, mean a small limitation on how the results are interpreted, as they can only be applied to a patient group without infectious comorbidity.

- Malignant diseases

The same applies here as is described above. In addition, it would be problematic to include people with this kind of illness in a therapy study where the focus is not on the treatment of the malignant disease.

- Surgical intervention of urogenital organs (with the exception of conizations and curettage)
- Endometrial polyps
- Adenomyosis
- Both of these conditions have the same appearance as uterine myoma. According to guidelines set by the Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, status August 2008, the symptomatic is adenomyosis uteri, characterized by dysmenorrhea, menorrhagia and sterility (2008c). It is therefore imperative that these illnesses be taken to protocol in terms of a differentiated diagnosis with the required care, as the effectiveness of an osteopathic treatment is on uterine myoma and not on endometrial polyps or adenomyosis.

Termination criteria:

- Onset of a pregnancy
- Onset of menopause
- Taking of hormone preparations
- Acute abdominal or gynecological operations
- Onset of other criteria mentioned in 4.2.2
- Change of residence

The onset of one of these described conditions in the course of the study is defined as a termination criterion in accordance with the above-described termination criteria.

4.3. Assessments

Main target parameters

Two different options were available for selection here, one is the objective criterion pertaining to myoma size and the other is the intensity of the symptoms and their influence on quality of life. There are several references from the literature that a reduction in size of myoma does not bring about a reduction of symptoms that can be regularly observed. Some clinical studies show a clear decline in symptoms even when the reduction in volume is relatively small, while other authors ascertain that despite a considerable reduction in volume, symptoms do not improve much (Eisinger, Fiscella, Bonfiglio, Meldrum, & Fiscella, 2009; Hindley et al., 2004b; Stewart et al., 2006). As the relation between the size of the myoma and symptomatic appears to be inconsistent, the focus was set on symptoms actually experienced by the patient, as simply the size of the myoma is only of theoretic interest to the patient, if it is not in any proportional relationship to the symptoms.

Assessment instruments

The UFS-QOL was selected as an assessment instrument to record the primary target parameter. In contrast to VAS or other available questionnaires, it represents the most extensive method of documenting the intensity of symptoms and their influence on the quality of life.

Sonography was selected over other methods such as hysteroscopy or MRI in order to determine the secondary target parameter, “myoma size”, because of its cost-benefit ratio. Even though these other methods are superior as far as measurement accuracy is concerned, they are considerably more expensive and not available in all gynecological practices. TVS has a sensitivity of 0.83 (Dueholm, Lundorf, Hansen, Ledertoug, & Olesen, 2001b) according to the respective comparative studies and is used in many published studies as the assessment instrument (Dueholm, Forman, Jensen, Laursen, & Kracht, 2001b; Dueholm, Lundorf, Hansen, Ledertoug, & Olesen, 2002b). Ellipse was selected to examine the sonographed interface of the myoma in the form of a

geometric approach. Once the corresponding leiomyomata are identified, two-dimensional diameters of all leiomyomata are recorded. This enables the myoma size to be calculated two-dimensionally. The choice of this interface as a target parameter means that the third dimension of the myoma is not included in the results. As the volume of an entity changes more intensively than its surface, doing without the third dimension tends to represent an under-exaggeration of the percentile changes in myoma size. However, as the third dimension cannot be clearly evaluated via TVS, in order to calculate volume we had to use a rotation ellipsoid, for example, and interpolate the length of the third axis from the two measured diameters. This means, however, that a speculative component could flow into this target parameter. To assess the overall leiomyoma burden, the calculated leiomyoma volumes were added together to yield a total leiomyoma volume for each subject. In this way, the assessment is justified even for those patients with a uterus myomatosis.

4.4. Intervention

In the following, a number of aspects of osteopathic treatment are explained, in particular with respect to the design of a pragmatic trial.

4.4.1. Osteopathic Diagnosis and Treatment

One phenomena that has at least been observed in Europe is that in training to become an osteopath, many different techniques are taught to be used in diagnosis and treatment. The osteopathic cornerstones set by A.T. Still on the function of the human organism, such as the existence of self-healing energy, rule of the artery, etc. are taught everywhere, but are sometimes interpreted differently. In order to justify the heterogeneity of the range of osteopathic treatments available to the patient, the choice of diagnostic and treatment by the participating osteopath has not been regulated strictly. The only clear stipulation is the local, differentiated examination of the pelvic area, which should include the musculo-skeletal structure and the visceral structure. The osteopath is free to conduct the examination as he/she wishes. He/she should act in manner suitable to qualification, training and experience. Dysfunctions and the treatment

thereof are kept track of by entries in the examination and treatment protocol. This means that the type of intervention remains within the framework of the requirements peculiar to pragmatic trials.

4.4.2. Osteopathic research staff

Here, more precise prerequirements have been defined to shape study participation. As described in the chapter above, training at the different schools varies widely. The large majority of qualifications are offered as part-time courses and only to graduates of medical professions. In Germany this includes doctors, physiotherapists, alternative practitioners and sometimes people from paramedical professions. This means that osteopathic graduates do not necessarily practice osteopathy first and foremost, but either concentrate on their former profession, or develop a combination of osteopathy and other types of therapy. This is what makes it necessary to define the above-mentioned prerequirements in order to guarantee that only those osteopaths participate who are experienced in osteopathic manual medicine. It is therefore our opinion that this limitation does not represent any contradiction to the requirements set by pragmatic trials in the use of practitioners with normal expertise and only ordinary attention to their training, experience and performance.

4.4.3. Adverse Events

As frequently described in the literature, studies on the effectiveness of complementary medical measures often leave out documentation of any adverse events. This has also been observed in osteopathic studies. Generally speaking, osteopathic treatment is considered to be a gentle, side-effect-free therapy. This reputation can be beneficial when in competition with some conventional medical methods, but this has not been proven with respect to any possible side effects. Which is why it is even more necessary to document any undesirable side effects in osteopathic studies. We fulfill this concern by providing a special questionnaire for the documentation of side effects and the final questionnaire (see Appendix).

4.5. Statistics

We have planned this study in accordance with the general requirements of pragmatic trials, in which an analysis of the intention to treat is conducted.

4.5.1. Sample Size Calculation

The α and β - errors were placed in the usual context of 0.05 and 0.80 respectively. The estimated impact of osteopathic treatment is 20% and 5% for expectant management. Findings in literature served as a starting point, where, for example, 3% of untreated women exhibited a decrease in myoma size. In the only osteopathic study, a volume reduction of myomas of 18% was attained. Medicinal therapies attained a volume reduction of 35% to about 60%. In light of these figures, an estimated effectiveness of 20% from expectant management plus osteopathic treatment and 5% for expectant management appears to be realistic. Taking into account people who drop out of the study on uterine myoma, 18 additional participants are considered necessary to ensure that a sufficient number of test persons can be used in the calculations at the end of the study. This is even more important as the overall duration of the study, including follow-up is a complete year. Therefore 100 study participants are required per group.

4.5.2. Clinical Relevance

The statistical evaluation of the study should take the presentation of the clinical relevance of the results into account as an important criterion. For this reason, not only the significant values are established in the form of p-values, but the percentile changes of the target parameters are also ascertained in the respective groups. This makes the clinical relevance of the results considerably more evident, with respect to a similar progression of both groups, or when clear differences are documented between the intervention and the control group.

4.6. Review of the study design with the help of PRECIS (Pragmatic-Explanatory Continuum Indicator Summary) tool

For effectiveness trials, we have used a different term, namely, pragmatic trials. They are primarily designed to determine the effects of an intervention under usual conditions. The efficacy or explanatory trials are primarily designed to determine the effects of an intervention under ideal circumstances. Trialists should ensure that their design decisions are consistent with the trial's stated purpose. Therefore I used PRECIS, the Pragmatic-Explanatory Continuum Indicator Summary to recheck my study protocol's ability to achieve its indicated intention. This tool was developed by an international group of scientists and published 2009 in the Journal of Clinical Epidemiology and the Canadian Medical Association Journal (CMAJ) (Thorpe et al., 2009a; Thorpe et al., 2009b). It consists of the domains, Participants, Interventions and Expertise, Follow-up and Outcomes, Compliance/Adherence and Analysis. The PRECIS tool represents the results graphically.

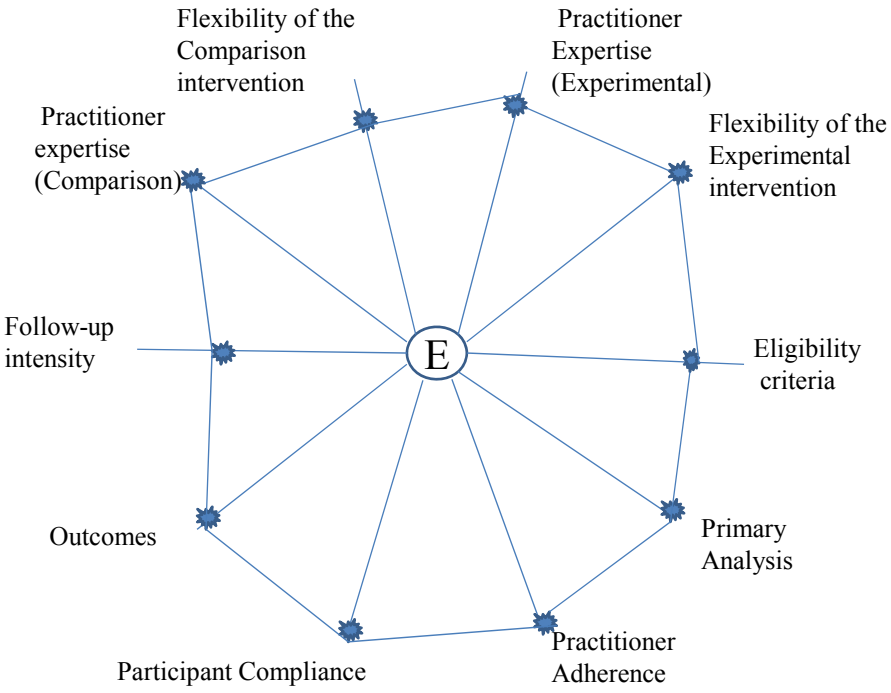


Figure 4: PRECIS cartwheel

The PRECIS cartwheel is shown in the illustration. The spokes depict the pragmatic-explanatory continuum, the hub of the wheel indicates the explanatory maximum and the centrifugal end of the spokes the pragmatic maximum. This graphic shows the result of my examination. It is clear that a few small concessions were made to the maximal pragmatic alignment. For example, in the eligibility criteria PRECIS requires all interested participants, who have the condition, to be enrolled, regardless of their anticipated risk, responsiveness, co-morbidities, or past compliance. This contradicts the criteria requiring the myoma to be at least 2 cm, exemption of acute infectious or malignant diseases. Or in the follow-up criteria: No formal follow-up visits are required at all. Instead, administrative databases (such as mortality registries) are searched for detection of outcomes. All in all, we can, however, determine that the study protocol is very close to the pragmatic trial maximum and therefore fulfills its stated purpose.

4.7. Conclusion

For those women with asymptomatic or mild symptom fibroids, the use of complementary and alternative therapies is intended to manage mild symptoms or prevent further fibroid growth. For this wide subgroup of patients the main outcome is the avoidance of surgical treatment to be measured through long-term follow up. By conducting this study we hope to make a contribution to the women concerned being able to simply reach their menopause without needing surgery or another form of therapy that could have a negative influence on reproduction. If women who already suffer from stronger symptoms would also profit from osteopathic treatment, expansion of osteopathic medicine to include these patients would be inevitable.

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Appendix A

Search strategies

Basic strategy for literature on uterine fibroids

Table A Search terms linked with "or"

1 exp Fibroma/ (0)
2 fibroma$.tw. (15)
3 leiomyom$.tw. (2)
4 exp Myoma/ (0)
5 myoma$.tw. (12)
6 hysteromyom$.tw. (1)
7 fibroma$.tw. (15)
8 fibroid$.tw. (15)
9 exp Leiomyoma/(

Table B Subheadings

Classification
Definition
Diagnosis
Drug therapy
Epidemiology
Ethnology
Etiology
Genetics
History
Mortality
Physiopathology
Prevention and control
Surgery
Therapy
Ultrasonography

Table C Examples of limits and quantity of hits

Subheading Diagnosis	
Without limits	Limits: Humans, Female, Publication Date from 1990 to 2010/05
19779 articles	8685 articles
2175 reviews	1139 reviews
Subheading Etiology	
Without limits	Limits: Female, Publication Date from 1980 to 2010/05
9727 articles	5755 articles
1044 reviews	667 reviews

Strategy for interventional trials on uterine fibroids

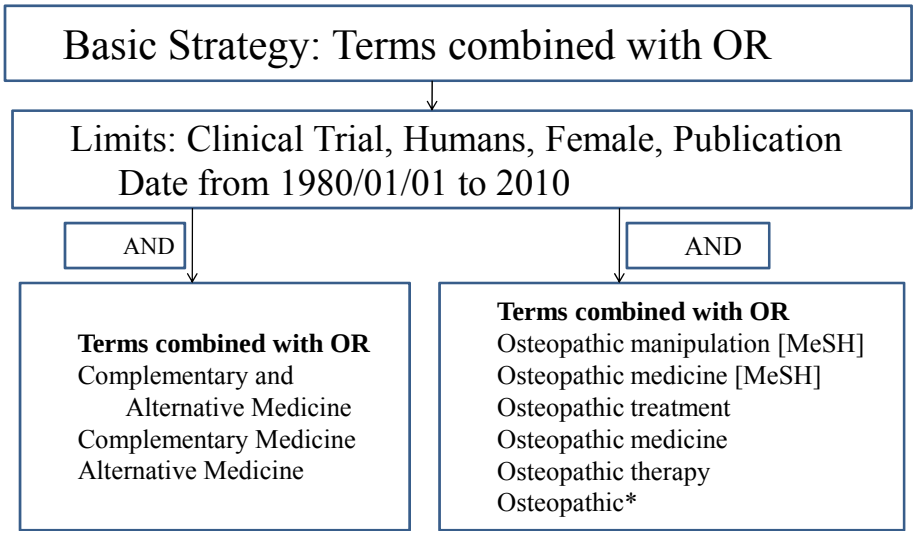


Figure A: Search strategy

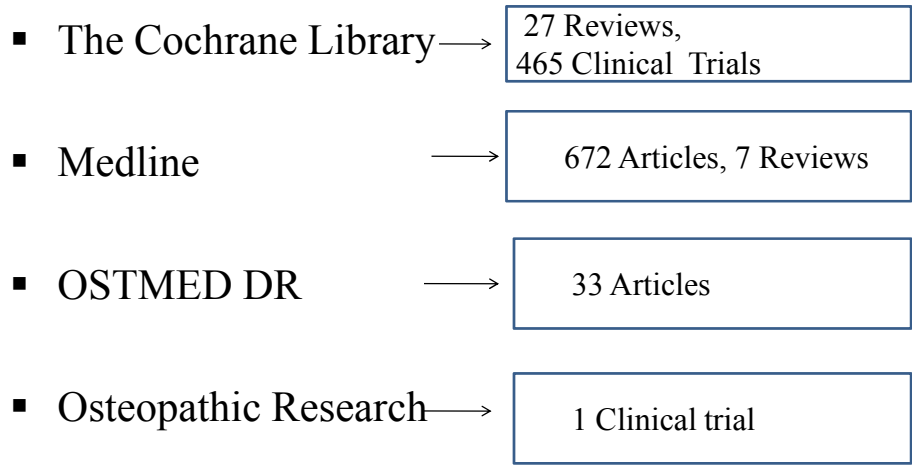


Figure B: Citations of literature of clinical trials on uterine fibroids

Appendix B

Study material

Information sheet

about the study

"The effectiveness of osteopathic treatment on uterine fibroids"

Dear patient,

First of all we would like to thank you for your interest in our study which has been set up to examine the effect of osteopathic treatments on the symptoms and growth of myomas in the uterus. This study is supported by the { Verband der Osteopathen Deutschlands (VOD), der Universität XXX und XXX }.
Below you will find important information about the objectives and course of events in this research work:
The aim of the study is to find out if it is possible to influence the symptoms and also size or growth of uterine myoma positively with osteopathic treatment. This would provide a treatment method that could be applied at an early stage. According to what we know today, it would be a method without any undesirable side effects worthy of mention. Additionally, further treatment methods could be avoided, for which it has not been finally clarified whether or not fertility of the treated women might be damaged.
The study is conducted by osteopaths with at least three years of professional experience in cooperation with gynecological specialist doctors.

What does osteopathic treatment mean?

In both osteopathic examinations and treatments, the osteopath works exclusively with his/her hands on the body. The aim here is to improve tension and mobility of different tissues. This study focuses on changes in the pelvic organs and lower abdominal organs. As the osteopath works according to a holistic approach to illness, the whole body is examined and dysfunctions with regard to mobility and tension are treated to enable the body to self regulate and self heal. No medication is used within the context of this kind of therapy.

Patient information sheet 2

Further information on osteopathy can easily be found on the internet. The Verband der Osteopathen Deutschland VOD provide an informative website with many links: http://www.osteopathie.de/

Study program

Before you can be enrolled for the study, a check has to be carried out to see if you are suitable for participation. This includes an ultrasonographic examination by a gynecologist to determine the exact size of the myoma. After you have confirmed your agreement to participating in the study in writing and have filled out the required questionnaire, you are officially enrolled for the study. You receive a total of five osteopathic treatments, one or two ultrasonographic examinations at intervals of three months and should also fill out a short questionnaire after each menstrual period plus one more questionnaire after intervals of three and six months. In addition, you are asked to keep a so-called medication diary, in which you only enter medication that you might take related to myoma complaints. The waiting period until the first treatment can be up to three months for reasons to do with the study schedule. The examinations and treatments in connection with this study are free of charge.

Data security

In order to carry out a scientific evaluation of the study, your personal data has to be documented and stored. To protect the personal and health-related data that is gathered in the context of this clinical study, we have developed the following procedure:

Patient information sheet 3

Your name, first name and date of birth are registered during the first examination by the osteopath and added to the declaration of agreement. A code word or code number is created from this information.
The declaration of agreement with the unencrypted data is stored with the osteopath.
All health-related data gathered and gained in the context of this study and the results of the clinical study are only registered under the previously composed code word and therefore pseudonymized. The key that is used to allocate this data to your personal data is stored on a computer that is separated from the other data stored with the respective osteopath and is only accessible to this osteopath. The study results are published anonymously. The data are stored according to the statutory period and afterwards destroyed or deleted. You may contradict further processing of your data at any time.
You can withdraw from this study even having signed an agreement at any time without disadvantage.
No special insurance for the test persons is taken out for this study. However, the insurance protection from the osteopath's corporate liability insurance exists.
Participation in this study is voluntary. If you reject participation this is at no disadvantage.
If you have any questions about the study or your participation, please contact:

Address
Osteopath

Declaration of agreement

For the study concerning "The effectiveness of osteopathic treatment on uterine fibroids"

Name:

First name:

Date of birth:

I hereby agree to take part in the study on uterine myoma.

I have been extensively informed about the background and purpose of the study as well as any possible risks related to the therapy. I have received and read an information sheet about the study.

I know that I can terminate participation in this study at any time. Participation can also be terminated by the respective therapist.

For the purposes of the scientific evaluation, it is required that clinical data are used to conduct the study.

My personal data will be treated with the utmost confidentiality in accordance with the applicable data security stipulations. Anonymity of my person is therefore guaranteed.

…….. ……..

City/Date Signature

Initial questionnaire

For the study on "The effectiveness of osteopathic treatment on uterine fibroids"

Code number:

Personal data:

Age (in years): …….

Number of births: ……..

Profession: …….

Do you smoke? ❍ No ❍ Yes

To which ethnic group do you belong? (Please select)

❍ Caucasian

❍ Asian

❍ African-Caribbean

❍ Middle-eastern

❍ Others

When did your first period start? …….

Have you tried unsuccessfully to have children? ❍ No ❍ Yes

If yes, are you, or were you being treated by a doctor? ❍ No ❍ Yes

Symptoms:

Please select:

Do you suffer from recurring bladder infections? ❍ No ❍ Yes

Do you feel pain when having sex? ❍ No ❍ Yes

Is your menstrual cycle regular? ❍ No ❍ Yes

If yes, how long does a cycle last (in days): ……

Initial questionnaire

Sheet 2

Code number:

Do you suffer from:

- ❍ Dizziness
- ❍ Varicose veins
- ❍ Restless legs
- ❍ Swollen legs
- ❍ Cold feet
- ❍ Hot flushes

At the present time do you have:

- ❍ Stomach ache
- ❍ Back ache
- ❍ Head ache
- ❍ Other types of pain, if yes, what?

……..

……

Do you suffer from the following shortly before (premenstrual) or during your period?

- ❍ Head ache
- ❍ Stomach ache or pain in the lower abdomen
- ❍ Back ache (lumbar or pelvic region)
- ❍ Irritability
- ❍ Feeling of heaviness in the legs

Visual Analog Scale VAS 1

For the study on "The effectiveness of osteopathic treatment on uterine fibroids"

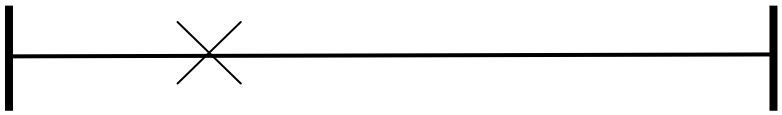
Code number: ……..

Treatment day: ……..

Date: ……..

Please indicate how you would rate your pain. The left and right borders of the line symbolize the most extreme form that you can imagine. The following example should indicate what is meant:

Today's weather is:



Nice **Awful**

My – please select: ❍ head ache, ❍ lower abdominal pain, ❍ back ache or ❍ other pain - shortly before and during my last period were:

Not painful **Maximum amount of pain imaginable**

Record of undesirable side effects

For the study on "The effectiveness of osteopathic treatment on uterine fibroids"

Code number:
Treatment day:
Date:

During or since the last osteopathic treatment, have you had any previously unknown complaints or have other already existing complaints got worse?
If yes, what:
1.)……
2.)……
3.)……
Please rate how often they occur: (by selecting)

For 1.)	For 2.)	For 3.)
1 = seldom	1 = seldom	1 = seldom
2 = frequently	2 = frequently	2 = frequently
3 = always	3 = always	3 = always

How would you rate these complaints now with reference to strength or intensity?
(Please select)

For 1.)	For 2.)	For 3.)
1 = light symptoms	1 = light symptoms	1 = light symptoms
2 = worsening symptoms	2 = worsening symptoms	2 = worsening symptoms
3 = strong symptoms	3 = strong symptoms	3 = strong symptoms

Declaration on osteopath's professional experience

For the study on "The effectiveness of osteopathic treatment on uterine fibroids"

I hereby declare that I am in possession of at least three years of professional experience as an osteopath and that during this time at least 80% of my professional activities involve treating my patients with manual osteopathic medicine. In addition, the osteopathic evaluation of the skeletal and visceral pelvis is part of my daily work and I am familiar with the gynecological symptoms and the respective patients.

…….. ……

City/Date Signature

Gynecological report sheet for initial examination

For the study on "The effectiveness of osteopathic treatment on uterine fibroids"

Gynecologist carrying out examination:

Code number:……

Date of initial examination: …….

Date of begin of last menstrual period: ……

The inclusion criteria are fulfilled and the exclusion criteria have been checked (see attached sheet):

❍ Yes ❍ No

Size of myoma is cm sagittal: …….

Size of myoma in cm transversal: ……..

Ms_____, date of birth _____,

resident at _____

appears to be suitable, in my opinion, to take part in the osteopathic study on uterine myoma. At the time of the examination there are no reasons why the test person cannot take part in the osteopathic treatment.

…… …….

City Date Signature and stamp of doctor

Gynecological report sheet for final examination

For the study on "The effectiveness of osteopathic treatment on uterine fibroids"

Gynecologist carrying out examination:

Code number:……

Date of final examination: …….

Date of begin of last menstrual period: ……

The termination criteria have been checked and have not been fulfilled by the test person:
❍ Yes ❍ No

Size of myoma is cm sagittal: …….

Size of myoma in cm transversal: ……..

…….....…… …….

City Date Signature and stamp of doctor

Gynecological report sheet for follow-up

For the study on "The effectiveness of osteopathic treatment on uterine fibroids"

Gynecologist carrying out examination:

Code number:……

Date of follow-up examination: …….

Date of begin of the last menstrual period: ……

The termination criteria have been checked and have not been fulfilled by the test person:
❍ Yes ❍ No

Size of myoma is cm sagittal: …….

Size of myoma in cm transversal: ……..

……..... …….

City Date Signature and stamp of doctor

Supplementary gynecological report sheet

For the study on "The effectiveness of osteopathic treatment on uterine fibroids"

In the context of the study to review the effectiveness of the osteopathic treatment on uterine myoma, specialist initial and final examinations plus a follow-up examination are planned. In addition, the medical inclusion and exclusion as well as termination criteria must be safeguarded by a medical specialist. The attached report sheet forms the basis for documenting insight.

Inclusion criteria:

- Uterine myoma diagnosed by specialist medic
- Minimum diameter of the myoma or dominant myoma of 2 cm
- Test persons may not be in menopause
- Negative pregnancy test
- Test persons should be aged 18 at least or be of age in accordance with the stipulations of the country in which the study is being conducted.
- Should understand English or the language of the country in which the study is being carried out
- Minimum score in the severity symptom score of the UFS-QOL of 34

Exclusion criteria:

- The taking of or application of all types of contraceptives
- If contraceptives were no longer taken less than two months before the initial gynecological examination
- Any complementary medicine or conventional medical treatment of the uterine myoma (medication as needed against acute pain is permitted and is documented)
- Acute infection
- Malignant diseases
- Surgical intervention of urogenital organs (with the exception of conizations and curettage)
- Endometrial polyps
- Adenomyosis

Supplementary gynecological report sheet
Sheet 2

Termination criteria:

- Onset of a pregnancy
- Onset of menopause
- Taking of hormone preparations
- Acute abdominal or gynecological operations
- Onset of other criteria mentioned in 4.2.2
- Change of residence

The appointments for the final and follow-up examinations are at intervals of three months. Please note that the examinations should take place at the same time in the monthly cycle as the initial examination.

If you have any questions, please contact us at this telephone number: …….
or this email address: …...

Final questionnaire

For the study on "The effectiveness of osteopathic treatment on uterine fibroids"

Code number:

Have you had any other treatment for myoma in the meantime?
❍ No ❍ Yes
If yes, what
…….
The following questions refer to symptoms from the last 4 weeks:
Please select:

Do you suffer from recurring bladder infections? ❍ No ❍ Yes

Do you feel pain when having sex? ❍ No ❍ Yes

Is your menstrual cycle regular? ❍ No ❍ Yes

If yes, how long does a cycle last (in days): ……..

Do you suffer from:

❍ Dizziness

❍ Varicose veins

❍ Restless legs

❍ Swollen legs

❍ Cold feet

❍ Hot flushes

At the present time do you have:

❍ Stomach ache

❍ Back ache

❍ Headache

Final questionnaire

Sheet 2

Code number:

❍ Other types of pain, if yes, what?

……..

……

Do you suffer from the following shortly before (premenstrual) or during your period?

❍ Headache

❍ Stomach ache or pain in the lower abdomen

❍ Back ache (lumbar or pelvic region)

❍ Irritability

❍ Feeling of heaviness in the legs

❍ Other symptoms

The Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire

Hospital No: _____ **Patient's Date of birth: _____**

Date: _____

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE
(UK English version of the UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the last 3 months.

There are no right or wrong answers. Please be sure to answer every question by ticking (✓) the most appropriate box for you. If a question does not apply to you, please mark "not at all" as a response.

During the last 3 months, how distressed were you by…	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Variations in the length of your menstrual periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Variations in the number of days between each menstrual period?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Feeling tightness or pressure in your pelvic area (lower part of the belly)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Frequent urination during the daytime?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Frequent night-time urination?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Feeling tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the last 3 months.

There are no right or wrong answers. Please be sure to answer every question by ticking (✓) the most appropriate box for you. If the question does not apply to you, please tick "none of the time" as your option.

During the last 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you worry because you did not know when your period would start or how long it would last?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Made you anxious about travelling?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Interfered with your physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. Caused you to feel tired or worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. Made you spend less time on exercise or other physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Made you feel as if you are not in control of your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. Made you concerned about soiling your underwear?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. Made you feel less productive?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Made you feel self-conscious of weight gain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Made you feel that it was difficult to carry out your usual activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Interfered with your social activities (e.g., going out to the cinema, restaurants, parties, etc)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Made you feel conscious about the size and appearance of your stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Made you concerned about soiling bed linen?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

During the last 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23. Made you feel sad, discouraged, or hopeless?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Made you feel down-hearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Made you feel exhausted ?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Caused you to be concerned or worried about your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28. Made you feel inconvenienced by always having to carry extra pads, tampons, and clothing in case of accidents?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Made you feel uncertain about your future?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Made you feel irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Made you concerned about soiling your outer clothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Affected the size of clothing you wear during your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Made you feel that you are not in control of your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Made you feel weak as if energy was drained from your body?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Decreased your sex drive?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
37. Caused you to avoid sexual relations?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Discriminant Validity of the UFS-QOL

Table 3. Discriminant Validity of the UFS-QOL

UFS-QOL subscale*	Normal ($N = 29$)	Uterine leiomyomata ($N = 110$)	P
Symptom severity	22.5 (21.1)	44.0 (25.5)	<.001
Concern	84.0 (23.5)	55.2 (34.6)	<.001
Activities	90.8 (14.7)	67.1 (30.0)	<.001
Energy/mood	83.9 (20.6)	64.1 (26.1)	<.001
Control	93.3 (17.2)	62.3 (31.6)	<.001
Self-consciousness	79.0 (29.0)	57.2 (30.5)	<.001
Sexual function†	80.2 (32.0)	65.0 (34.9)	.04
HRQL total†	86.4 (17.7)	62.6 (25.5)	<.001

Abbreviations as in Table 2.

* High HRQL scores indicate better HRQL, whereas high symptom severity scores indicate increasing symptom severity.

† $N = 104$ because of missing data.

(Spies et al., 2002a)

Introduction to scores in UFS-QOL

To calculate a symptom score for symptom severity, create a summed score from the items listed below and then use the formula below the table to transform the value. This will provide symptom scores where higher score values are indicative of greater symptom severity or bother and lower scores will indicate minimal symptom severity (high scores = bad).

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Symptom Severity	Sum 1 – 8	8, 40	32

Transformation for Symptom Severity raw scores ONLY:

$$\text{Transformed Score} = \frac{(\textit{Actual}\text{ raw score} - \textit{lowest}\text{ possible raw score})}{\textit{Possible raw score range}} \times 100$$

For the HRQL subscales (concern, activities, energy/mood, control, self-conscious, and sexual function), create summed scores of the items listed below for each individual subscale. To calculate the HRQL total score, sum the value of each individual subscale (do not sum individual items). Use the formula below the table to transform all values. Higher scores will be indicative of better HRQL (high = good).

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Concern	9+15+22+28+32	5, 25	20
Activities	10+11+13+19+20+27+29	7, 35	28
Energy/mood	12+17+23+24+25+31+35	7, 35	28
Control	14+16+26+30+34	5, 25	20
Self-conscious	18+21+33	3, 15	12
Sexual function	36+37	2, 10	8
HRQL TOTAL	Sum of 6 Subscale Scores	29, 145	116

Formula for transformation of HRQL raw scores ONLY:

$$\text{Transformed Score} = \frac{(\textit{Highest}\text{ possible score} - \textit{Actual raw}\text{ score})}{\textit{Possible raw score range}} \times 100$$

Missing Items

For the subscale analyses, if < 50% of the scale items are missing, the scale should be retained with the mean scale score of the items present used to impute a score for the missing items. If ≥ 50% of the items are missing, no scale score should be calculated, the subscale score should be considered missing. If a subscale score is missing, the HRQL total cannot be calculated.

Circular to recruit test persons

Addresses of osteopaths

Address of midwife, general practitioner, physiotherapist, etc.

Dear Mr/Ms,

Within the framework of a clinical study, we are still looking for test persons with uterine myoma. The objective of the study is to examine the effectiveness of osteopathic treatment on uterine fibroids. Individual case observations and a randomized study that has already been carried out has given cause to assume that affected women can be helped via osteopathic treatment. To review this assumption scientifically, we are conducting this study.
The study is being carried out under the management of (Institute for XXXXX) and is supported by XXXX.
We have attached our patient information sheet.
Your support in helping us to find suitable test persons would be very valuable to us and we hope very much that you will contact us. Telephone calls under XXXXXXXX or emails at this address are very welcome: xxxxxxxxxx@xxxx.xxx
Thank you very much in advance for your help.

Yours sincerely,

Annex: Information for patients

Circular on recruitment for test persons to gynecologists

Address of osteopath

Address of gynecologist

Dear Ms/Mr,

Within the framework of a clinical study, we are still looking for test persons with uterine myoma. The objective of the study is to examine the effectiveness of osteopathic treatment on uterine myoma. Individual case observations and a randomized study that has already been carried out has given cause to assume that affected women can be helped via osteopathic treatment. To review this assumption scientifically, we are conducting this study. The study is being conducted under the management of (Institute for XXXXX) and is supported by XXXX. On the one hand, we need suitable test persons and on the other, we are dependent on specialist medical support, as certain medical inclusion criteria, such as myoma size, exclusion of other illnesses, etc. can only be checked by gynecologists. We have attached information for patients and also a supplementary gynecological report sheet to give you more detailed information. Your support in helping us find suitable test persons would be extremely valuable. We would be happy to provide more information about our study personally and will contact your office/secretary in the course of the next few days to make a telephone appointment - providing you are interested. If you would like to contact us sooner, you are welcome to ring this number XXXXXXXXX or send us an email: xxxxxxxxxx@xxxx.xxx.
Thank you very much in advance for your help.

Yours sincerely,

Annex: Information for patients, supplementary gynecological report sheet

Example of filled-out report and treatment protocol

Osteopathic report and treatment protocol
T1

Diagnosed dysfunctions	Treated dysfunction	Intens. of dysf.	Applied treatment principle	Intens. of dysf. after treatment
Compression symphysis	**X**	**2**	myotensive, hvla	**0**
Lig. cardinale left	**X**	**3**	MF	**1**
M. psoas left		**2**		**2**
left USG		**2**		**2**
Sut. OM right SSB	**X**	**3** **2**	A A	**1** **1**

MF=myofascial, MT=myotensive, hvla=high velocity low amplitude, AR= autonomous rhythm, A=Other
Coding of intensity of dysfunction: 0 = no dysfunction, 1 = low dysfunction, 2 = medium dysfunction, 3 = severe dysfunction

Example of filled-out report and treatment protocol

Osteopathic report and treatment protocol
T2

Diagnosed dysfunctions	Treated dysfunction	Intens. of dysf.	Applied treatment principle	Intens.. of dysf. after treatment
Compression symphysis	**X**	1	MF	0
Lig. cardinale left	**X**	1	MF	0
Sut. OM right SSB Maxilla right	**X**	1 1 2	MF MF MF, AR	0 0 1
Ilium right intraosseous	**X**	2	MF, AR	1
Left USG		**2**		**2**
Fascia recto-utero.vesico-pubica left	**X**	2	MF	0

MF=myofascial, MT=myotensive, hvla=high velocity low amplitude, AR= autonomous rhythm, A=Other
Coding of intensity of dysfunction: 0 = no dysfunction, 1 = low dysfunction, 2 = medium dysfunction, 3 = severe dysfunction

Osteopathic report and treatment protocol

T1

Diagnosed dysfunctions	Treated dysfunction	Intens. of dysf.	Applied treatment principle	Intens. of dysf. after treatment

MF=myofascial, MT=myotensive, hvla=high velocity low amplitude, AR= autonomous rhythm (PRM, MRT, CSI or similar), A=Other

Coding of intensity of dysfunction: 0 = no dysfunction, 1 = low dysfunction, 2 = medium dysfunction, 3 = severe dysfunction