Hysterectomy and risk of stress-urinary-incontinence surgery: nationwide cohort study

Daniel Altman, Fredrik Granath, Sven Cnattingius, Christian Falconer

Summary

Background Hysterectomy for benign indications has been associated with an increased risk for lower-urinary-tract sequela, but results have been inconclusive. We aimed to establish the risk for stress-urinary-incontinence surgery after hysterectomy for benign indications.

INTERPRETATION: Hysterectomy for benign indications, irrespective of surgical technique, increases the risk for subsequent stress-urinary-incontinence surgery. Women should be counselled on associated risks related to hysterectomy, and other treatment options should be considered before surgery.

World J Urol
DOI 10.1007/s00345-010-0585-8

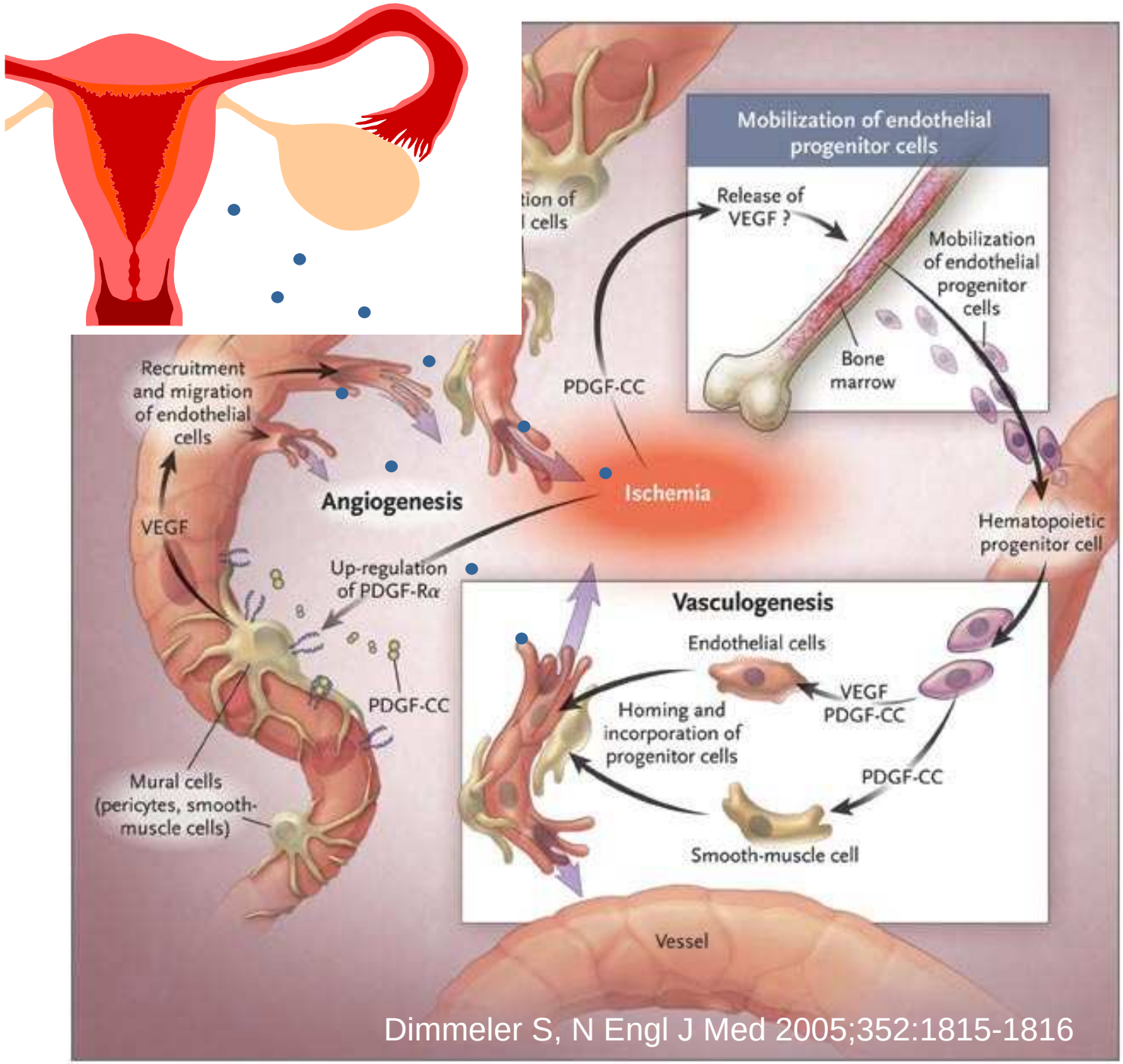
ORIGINAL ARTICLE

Genetic susceptibility to urinary incontinence: implication of polymorphisms of androgen and oestrogen pathways

J. N. Cornu · B. Merlet · O. Cussenot · G. Cancel-Tassin · C. Ciofu · G. Amarenco · F. Haab

Received: 3 January 2010 / Accepted: 5 July 2010

… AR polymorphism (combination of 2 alleles containing more than 21 CAG repeats) is significantly associated with UUI (P = 0.02). Polymorphisms of ESR-1, CYP17 and CYP19 were not associated with any subtype of urinary incontinence. …



Dimmeler S, N Engl J Med 2005;352:1815-1816

Increased risk of thyroid cancer among women with hysterectomies

Riitta Luoto, MD,[a] Seija Grenman, MD,[b] Salla Salonen, StudMed,[b] and Eero Pukkala, PhD[c]

Tampere, Turku, and Helsinki, Finland

OBJECTIVE: Hysterectomy with bilateral oophorectomy has been suggested to increase the risk of thyroid cancer. We studied the relationship between hysterectomy and thyroid cancer in a population-based setting in Finland.

STUDY DESIGN: Women undergoing hysterectomy between 1986 and 1995 (n = 17,900) were identified from the National Hospital Discharge Registry. The cohort was followed up through the Finnish Cancer Registry until 1997.

RESULTS: There were 118 cases of thyroid cancer diagnosed, 103 papillary and 15 follicular or medullar type. The incidence for thyroid cancer was significantly elevated (standardized incidence ratio [SIR] 1.38, 95% CI 1.15-1.64). The increase in the incidence of thyroid cancer was not dependent on the extent of operation but on the length of follow-up. Thyroid cancer incidence was increased 0.5 to 1.4 years after hysterectomy (SIR 2.00, 95% CI 1.31-2.93), but decreased thereafter (SIR 1.30, 95% CI 0.99-1.67). Hysterectomy with and without oophorectomy was associated with a similar increase in the incidence of thyroid cancer.

CONCLUSION: Women who have undergone hysterectomy have an increased risk of thyroid cancer during the first 2 years after the operation. Thyroid cancer and bleeding disorders may share a common background. (Am J Obstet Gynecol 2003;188:45-8.)

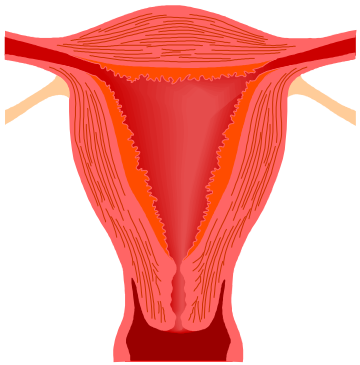
0013-7227/03/$15.00/0
Printed in U.S.A.

Endocrinology 144(10):4250–4252

doi: 10.1210/en.2003-0848

Modulation of Uterine Iodothyronine Deiodinases—A Critical Event for Fetal Development?

The outer ring deiodination of T_4 leads to the production of T_3, which is considered the active thyroid hormone that interacts with nuclear receptors and regulates gene transcription (1–3). T_3 outer ring deiodination (ORD) also generates another biologically active metabolite, the 3,5-diiodothyronine that exerts important metabolic effects, as described recently (4). Therefore, the ORD is considered an activating thyroid hormone metabolic pathway. Iodothyronine deiodinases are classified into three isoenzymes, based on several biochemical criteria and on different protein serum and intracellular T_3 levels during fetal development have to be regulated to be maintained in a narrow range, depending on tissue demands. During embryogenesis, thyroid hormone receptors are expressed and occupied before the onset of fetal thyroid function, showing that an important maternal-fetus thyroid hormone transfer occurs early in gestation (17). Nevertheless, there is a marked gradient of T_4 from the mother to the fetus and circulating T_4 and T_3 are lower in the fetus, probably due to the fact that during development D3 is the predominant enzyme expressed in most



Carvalho DP, Endocrinology, 2003;144(10):4250-4252.

0013-7227/03/$15.00/0
Printed in U.S.A.

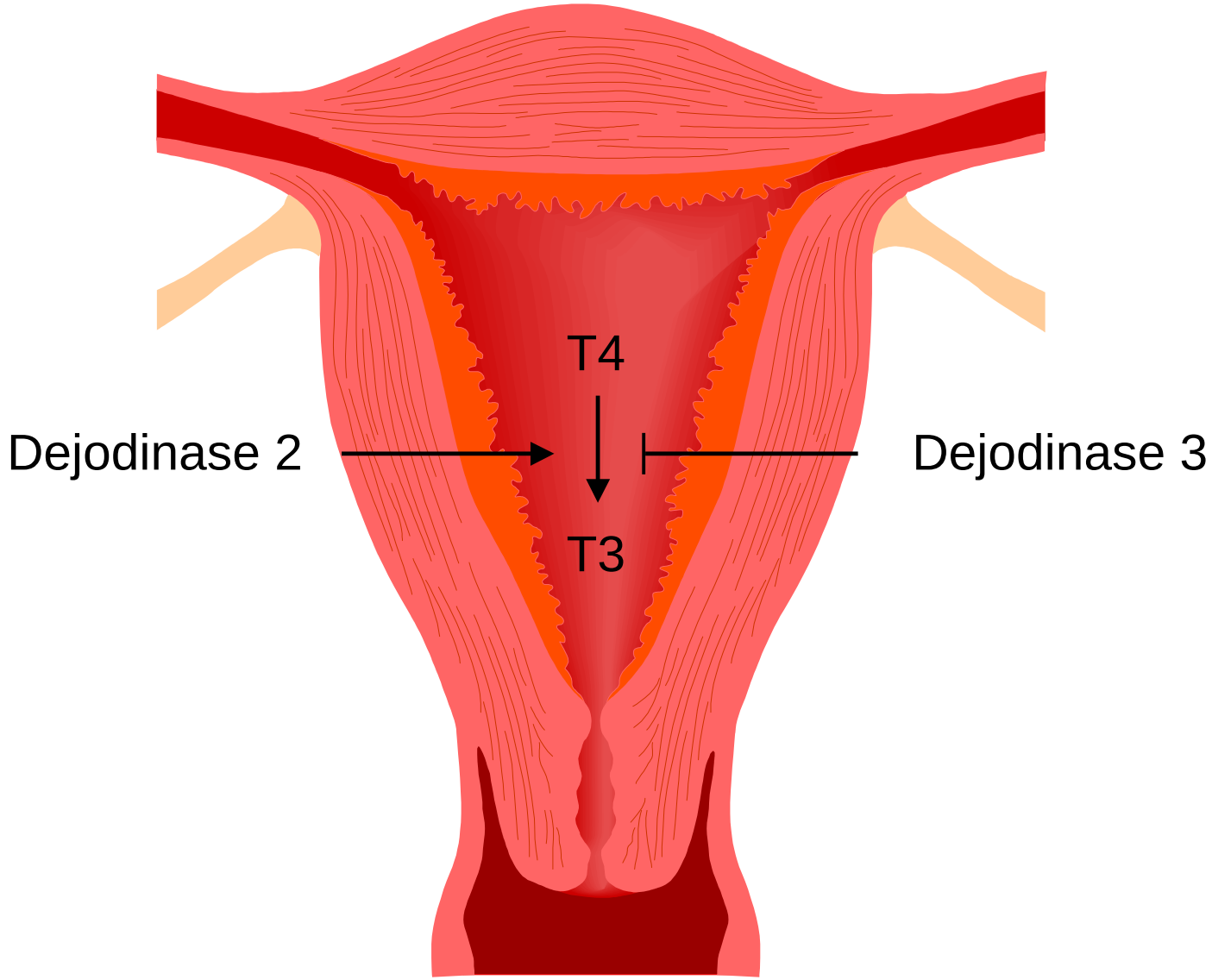
The Journal of Clinical Endocrinology & Metabolism 88(3):1384–1388

doi: 10.1210/jc.2002-021291

Type 3 Iodothyronine Deiodinase Is Highly Expressed in the Human Uteroplacental Unit and in Fetal Epithelium

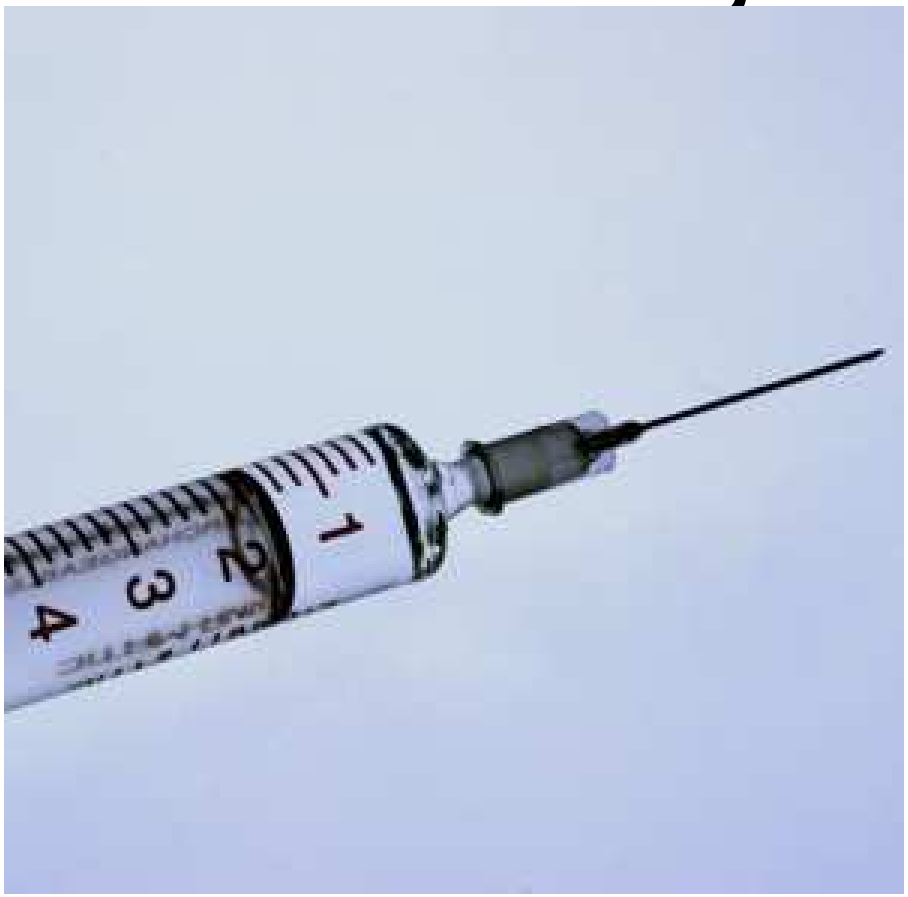
STEPHEN A. HUANG, DAVID M. DORFMAN, DAVID R. GENEST, DOMENICO SALVATORE, AND P. REED LARSEN

Division of Endocrinology, Diabetes, and Hypertension (S.A.H., P.R.L.) and Department of Pathology (D.M.D., D.R.G.), Brigham and Women's Hospital, Boston, Massachusetts 02115; Division of Endocrinology (S.A.H.), Children's Hospital Boston, Boston, Massachusetts 02115; and Dipartimento di Endocrinologia ed Oncologia Molecolare e Clinica, Universita'degli Studi di Napoli "Federico II" (D.S.), 80138 Naples, Italy



Carvalho DP, Endocrinology, 2003;144(10):4250-4252.

GnRH-Analoga



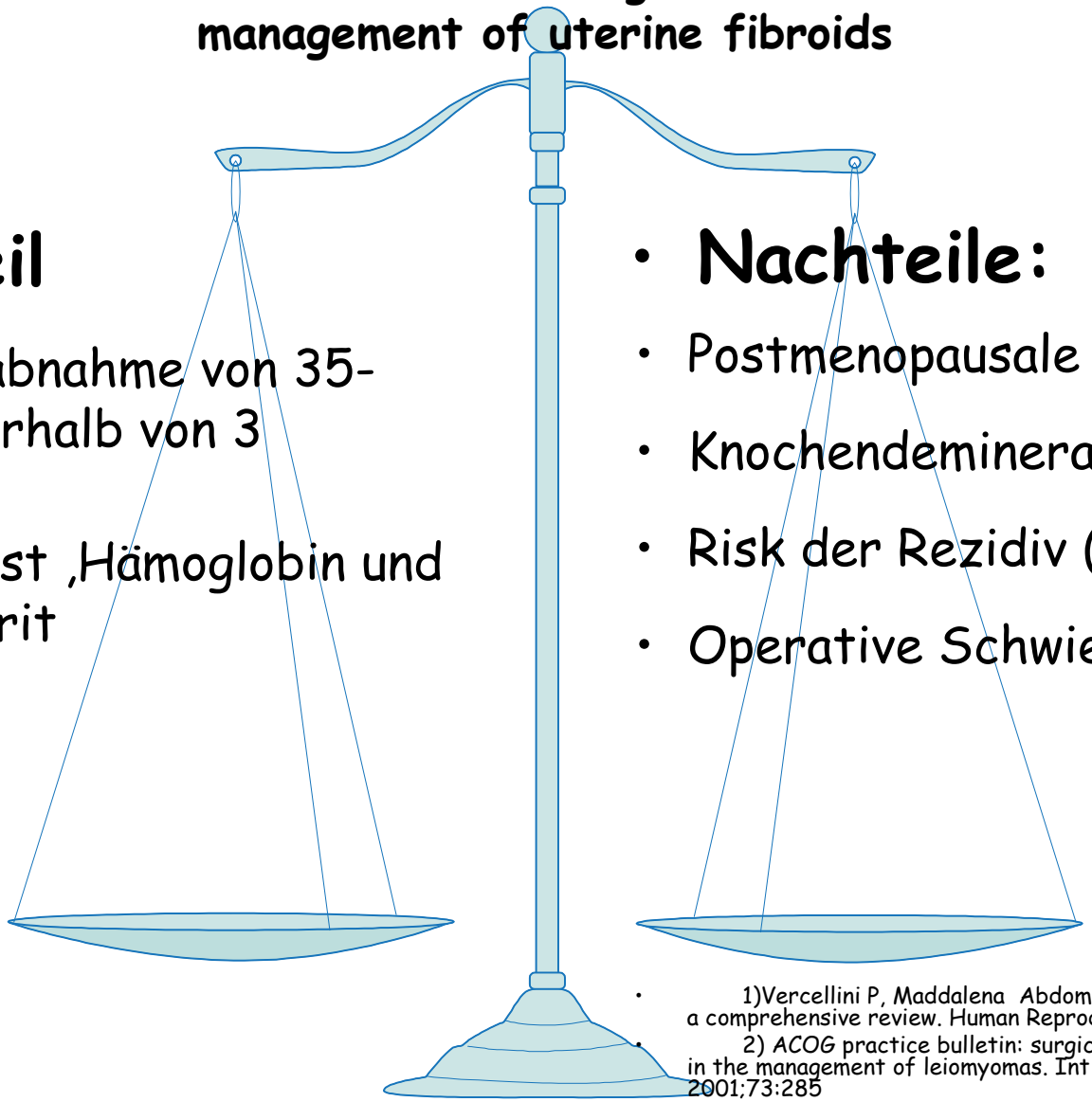
ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas.

American College of Obstetricians and Gynecologists.

PMID: 18669742 [PubMed - indexed for MEDLINE]

Gn-RH Analoga

Controversies and challenges in the modern management of uterine fibroids



- **Vorteile:**
- Volumenabnahme von 35-65% innerhalb von 3 Monaten
- Blutverlust ,Hämoglobin und Hämatokrit

- **Nachteile:**
- Postmenopausale Symptome
- Knochendemineralisation (2.7%)
- Risk der Rezidiv (1)
- Operative Schwierigkeiten (2)

- 1)Vercellini P, Maddalena Abdominal myomectomy for infertility: a comprehensive review. Human Reprod 1998;13:873- 879
- 2) ACOG practice bulletin: surgical alternatives to hysterectomy in the management of leiomyomas. Int J Gynaecol Obstet 2001;73:285

ACOG PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

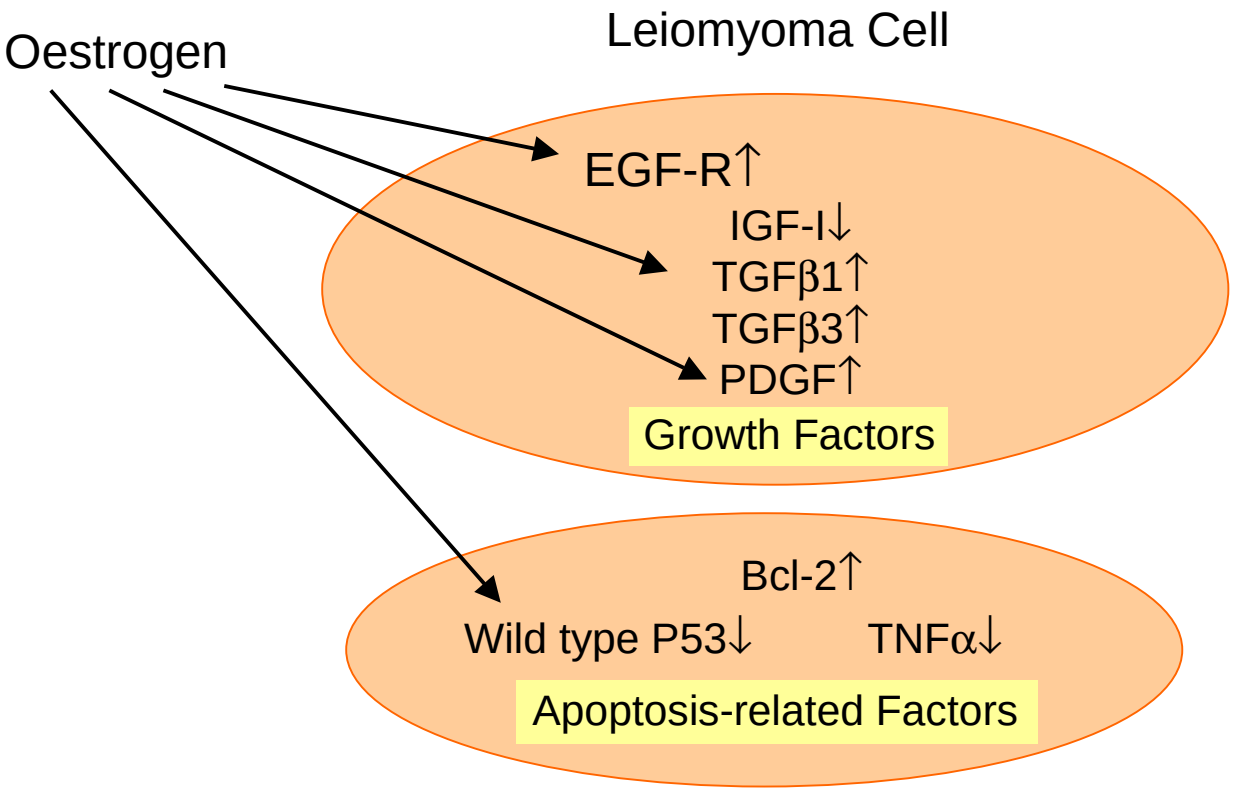
NUMBER 96, AUGUST 2008

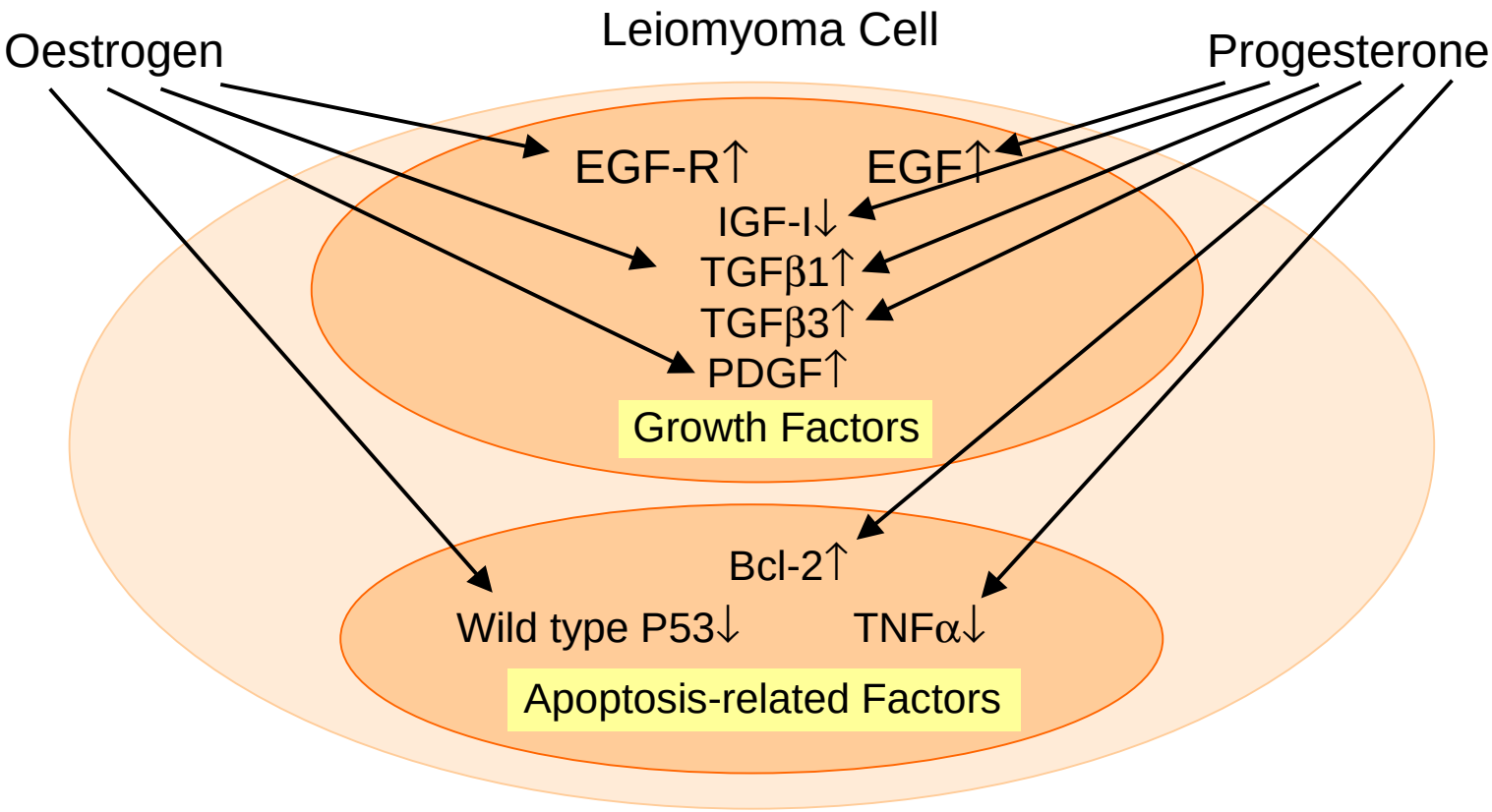
Replaces Practice Bulletin Number 16, May 2000 and Committee Opinion Number 293, February 2004

Alternatives to Hysterectomy in the Management of Leiomyomas

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone agonists lead to amenorrhea in most women and provide a 35–65% reduction in leiomyoma volume within 3 months of treatment (14). The GnRH agonist leuprolide acetate is approved by the U.S. Food and Drug Administration (FDA) for preoperative therapy in women with anemia in conjunction with supplemental iron, and it is most useful in women with large leiomyomas. The effects of GnRH agonists are temporary, with gradual recurrent growth of leiomyomas to previous size within several months after cessation of treatment. In addition, the significant symptoms of pseudomenopause and adverse impact of the induced hypoestrogenism on bone density limit their suggested use to no more than 6 months without hormonal add-back therapy.


Oestrogen
Leiomyoma Cell
EGF-R↑
IGF-I↓
TGFβ1↑
TGFβ3↑
PDGF↑
Growth Factors
Bcl-2↑
Wild type P53↓
TNFα↓
Apoptosis-related Factors

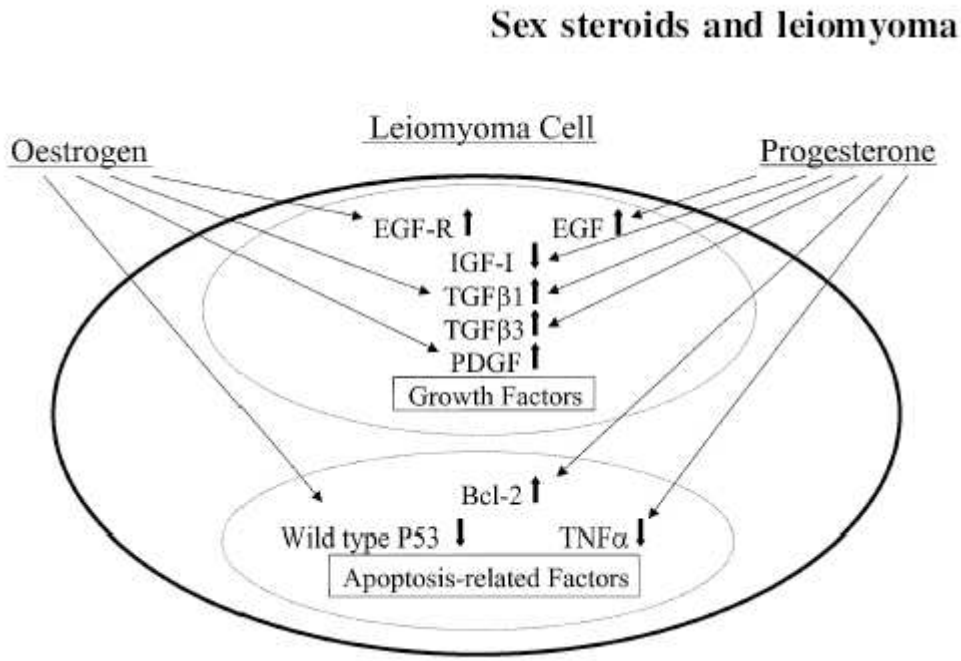

Oestrogen
Leiomyoma Cell
Progesterone
EGF-R↑
EGF↑
IGF-I↓
TGFβ1↑
TGFβ3↑
PDGF↑
Growth Factors
Bcl-2↑
Wild type P53↓
TNFα↓
Apoptosis-related Factors

Human Reproduction Update, Vol.10, No.3 pp. 207–220, 2004 DOI: 10.1093/humupd/dmh019

Sex steroidal regulation of uterine leiomyoma growth and apoptosis

T.Maruo[1], N.Ohara, J.Wang and H.Matsuo

Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, 650-0017, Japan



ACOG
PRACTICE
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CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

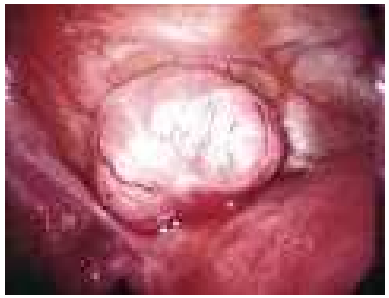
NUMBER 96, AUGUST 2008

Replaces Practice Bulletin Number 16, May 2000 and Committee Opinion Number 293, February 2004

Alternatives to Hysterectomy in the Management of Leiomyomas

Epidemiologic studies also suggest that both combined oral contraceptives andprogestin-only contraceptives also may decrease the risk of developing clinically significant leiomyomas.

Nonsteroidal antiinflammatory drugs are effective inreducing dysmenorrhea, but there are no studies that document improvement in women with dysmenorrhea caused by leiomyomas.



uterine fibroids

The Oxford Family Planning Association found a reduced risk of uterine fibroids in OC users

Ross RK, Pike MC, Vessey MP, et al.Risk factors for uterine fi broids: reduced risk associated with oral contraceptives. BMJ (Clin Res Ed) 1986; 293(6543): 359-62 .

Increasing duration of pill use was associated with increased protection; 10 years of use resulted in a 30% risk reduction. These findings were confirmed by a large, case-control study demonstrating a 50% reduction in risk in women with more than 7 years of OC use compared with nonusers (OR 0.5, 95%CI 0.3 – 0.9)

Chiaffarino F, Parazzini F, La Vecchia C, et al. Use of oral contraceptives and uterine fi broids: results from a case-control study.Br J Obstet Gynaecol 1999 ; 106 (8): 857 -60[50]

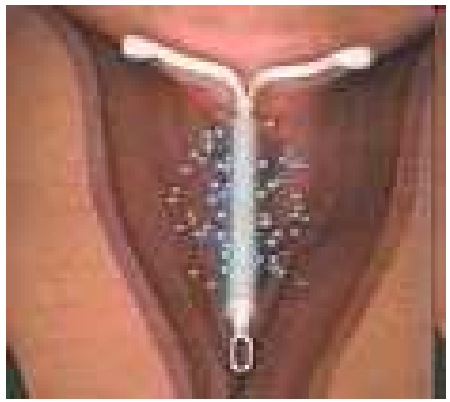
Fertil Steril. 2009 Nov 5. [Epub ahead of print]

Levonorgestrel-releasing intrauterine device insertion ameliorates leiomyoma-dependent menorrhagia among women of reproductive age without a significant regression in the uterine and leiomyoma volumes.

Murat Naki M, Tekcan C, Ozcan N, Cebi M.

Obstetrics and Gynecology Department, Dr. Lutfi Kirdar Kartal Research and Training Hospital, Kartal, Istanbul, Turkey.

Levonorgestrel- (LNG) releasing intrauterine device (IUD) insertion revealed significant reduction in visual bleeding scores and spotting with an increase in amenorrhea and uterine pulsatility index scores. LNG-IUD can be considered as a simple and effective alternative to surgical treatment in the management of leiomyoma-dependent menorrhagia of reproductive-age women.



Based on the limited data available it appears overall that combined OCs and the levonorgestrel intrauterine system have little effect on the development of uterine leiomyomas.

Kaunitz AM. Progestin-releasing intrauterine systems and leiomyoma. Contraception 2007;75:S130-3. (Level III)

Human Reproduction Vol.16, No.10 pp. 2103–2108, 2001

Effects of the levonorgestrel-releasing intrauterine system on proliferation and apoptosis in the endometrium

T.Maruo[1,5], J.B.Laoag-Fernandez[1], P.Pakarinen[2], H.Murakoshi[1], I.M.Spitz[3] and E.Johansson[4]

[1]Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, Kobe, Japan, [2]Department of Obstetrics and Gynecology, University of Helsinki, Finland, [3]Institute of Hormone Research, Jerusalem, Israel and [4]Population Council, New York, USA

[5]To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. E-mail: maruo@kobe-u.ac.jp

BACKGROUND: The levonorgestrel-releasing intrauterine system (LNg-IUS) has been shown to be effective in the management of menorrhagia. In order to evaluate the effects of LNg-IUS on endometrial proliferation and apoptosis, proliferating cell nuclear antigen (PCNA) expression, apoptosis, Fas and Bcl-2 protein expression in the endometrium were determined at the early proliferative phase of the menstrual cycle before and 3 months after LNg-IUS insertion. METHODS: PCNA, Fas and Bcl-2 protein expression were analysed using an avidin–biotin immunoperoxidase method. Apoptosis was assessed by the terminal deoxynucleotidyl transferase-mediated deoxy-UTP nick-end labelling (TUNEL) method. RESULTS: PCNA, immunolocalized both in the nuclei of endometrial glands and stroma was less abundant 3 months after insertion ($P < 0.05$). Bcl-2 protein, immunolocalized in the cytoplasm of endometrial glands but not in the stroma, became scanty 3 months after insertion. Fas antigen, immunolocalized only in endometrial glands before insertion, became prominent in both endometrial glands and stroma 3 months after insertion. The apoptosis-positive rate of the nuclei in both endometrial glands and stroma was significantly higher 3 months after insertion relative to that before insertion ($P < 0.05$). CONCLUSIONS: LNg-IUS resulted in a decrease in endometrial proliferation and an increase in apoptosis in endometrial glands and stroma. The increase in apoptosis associated with increased Fas antigen expression and decreased Bcl-2 protein expression in the endometrium may be one of the underlying molecular mechanisms by which LNg-IUS insertion causes the atrophic change of the endometrium.

Cochrane Database Syst Rev. 2005 Oct 19;(4):CD002126.

Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding.

Lethaby AE, Cooke I, Rees M.

University of Auckland, Department of Obstetrics and Gynaecology, Private Bag 92019, Auckland, New Zealand. a.lethaby@auckland.ac.nz

Update of:

Cochrane Database Syst Rev. 2000;(2):CD002126.

CONCLUSIONS: The levonorgestrel-releasing intrauterine device (LNG IUS) is more effective than cyclical norethisterone (for 21 days) as a treatment for heavy menstrual bleeding. Women with an LNG IUS are more satisfied and willing to continue with treatment but experience more side effects, such as intermenstrual bleeding and breast tenderness. The LNG IUS results in a smaller mean reduction in menstrual blood loss (as assessed by the PBAC chart) than endometrial ablation but there is no evidence of a difference in the rate of satisfaction with treatment. The LNG IUS treatment costs less than hysterectomy but there is no evidence of a difference in quality of life measures between these groups. There are no data available from randomised controlled trials comparing progesterone-releasing intrauterine systems to either placebo or other commonly used medical therapies for heavy menstrual bleeding.

Estrogen receptor α and β in uterine fibroids: a basis for altered estrogen responsiveness

Panagiotis Bakas, M.D.,[a] *Angelos Liapis, M.D.,*[a] *Spiros Vlahopoulos, Ph.D.,*[b] *Maria Giner, M.D.,*[a] *Stella Logotheti, B.Sc.,*[b] *Georgios Creatsas, M.D.,*[a] *Aggeliki K. Meligova, B.Sc.,*[c] *Michael N. Alexis, Ph.D.,*[b,c] *and Vassilis Zoumpourlis, Ph.D.*[b]

[a] 2nd Department of Obstetrics and Gynaecology, Aretaieio Hospital, University of Athens; [b] Biomedical Application Unit; and [c] Molecular Endocrinology Programme, Institute of Biological Research and Biotechnology, National Hellenic Research Foundation, Athens, Greece

Objective: To investigate the relative expression and the DNA-binding status of estrogen receptors α and β in fibroids and normal myometrial tissue to explore the molecular basis of altered estrogen responsiveness of leiomyomas.
Design: Biopsy samples from uterine fibroids and adjacent normal myometrial tissue at the follicular phase of the menstrual cycle.
Setting: Aretaieio University Hospital and the National Hellenic Research Foundation, Athens, Greece.
Patient(s): Thirty-five patients who underwent hysterectomy or myomectomy because of myoma symptoms.
Intervention(s): None.
Main Outcome Measure(s): Deoxyribonucleic acid–binding status of estrogen receptors α and β.
Result(s): The level of messenger RNA expression of estrogen receptor α and β and the level of estrogen receptor as a whole are increased on average to a similar extent in leiomyomas compared with normal myometrium. Occasionally, however, estrogen receptor α is disproportionately increased in leiomyomas, and this appears to increase the amount of estrogen receptor α that binds to the estrogen-responsive element of estrogen target genes as homodimer rather than as heterodimer with estrogen receptor β.
Conclusion(s): The estrogen receptor α–to–estrogen receptor β expression ratio rather than the individual expression levels determines the fraction of DNA-binding homodimers of estrogen receptor α and possibly the growth potential of myomas. (Fertil Steril® 2008;90:1878–85. ©2008 by American Society for Reproductive Medicine.)

Key Words: Uterine myomas, estrogen receptor alpha, estrogen receptor beta, myometrium, fibroids

Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005287.

Selective estrogen receptor modulators (SERMs) for uterine leiomyomas.

Wu T, Chen X, Xie L.

West China Hospital, Sichuan University, Chinese Cochrane Centre, Chinese EBM Centre, No. 37, Guo Xue Xiang, Chengdu, Sichuan, China, 610041. txwutx@hotmail.com

Update of:

Cochrane Database Syst Rev. 2007;(2):CD005287.

BACKGROUND: Uterine fibroids are benign tumors that arise from individual smooth muscle cells of the uterus. Selective estrogen receptor modulators (SERMs) are ER ligands that act as estrogens in some tissues, while blocking estrogen action in others. There have been many clinical studies of various SERMs for uterine fibroid. However, their effectiveness is controversial. OBJECTIVES: To evaluate the evidence for the effectiveness and safety of selective estrogen receptor modulators in women with uterine fibroids. SEARCH STRATEGY: We searched The Cochrane Library, MEDLINE, the Register of Chinese trials developed by the Chinese Cochrane Centre, and the Chinese Med Database, Chinese Biomedical Disc (CBMDisc 1978 to July 2004); VIP (1989 to

CONCLUSIONS: There is no evidence from the limited number of studies that SERMs reduce the size of fibroids or improve clinical outcomes. Further studies are required to establish evidence of benefit of SERMs in treating women with uterine fibroids.

CYP A_1

T3801C
IL 462 Val ↑

158 VAL/MET ↓

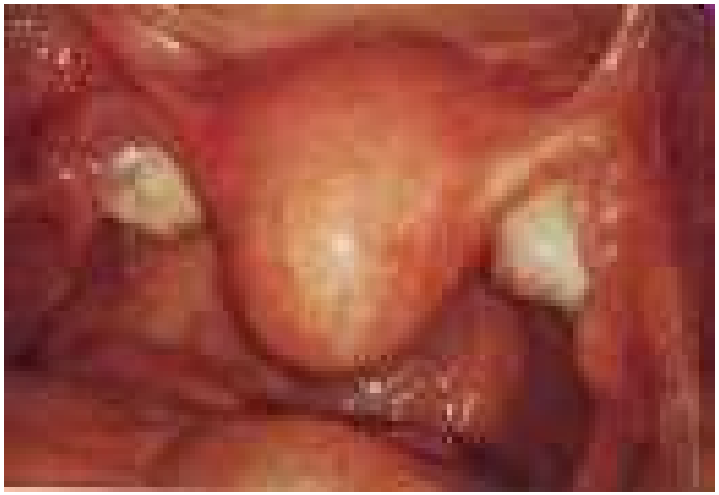
COMT

CYP B_1

Leu 432 VaL
AL 119 Ser ↑

158 VAL/MET ↓

COMT



Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006568.

Chinese herbal medicine for endometriosis.

Flower A, Liu JP, Chen S, Lewith G, Little P.

Complementary Medicine Research Unit , Dept Primary Medical Care, Southampton University, Norlington Gate Farmhouse, Norlington Lane, Ringmer, Sussex, UK, BN8 5SG.

AUTHORS' CONCLUSIONS: Post-surgical administration of CHM may have comparable benefits to gestrinone but with fewer side effects. Oral CHM may have a better overall treatment effect than danazol; it may be more effective in relieving dysmenorrhea and shrinking adnexal masses when used in conjunction with a CHM enema. However, more rigorous research is required to accurately assess the potential role of CHM in treating endometriosis.

Nona Roguy

Huoxue Sanjie

A pilot study on the off-label use of valproic acid to treat adenomyosis

Following on the heels of the discovery that endometriosis is an epigenetic disease, we conducted a pilot study on the off-label use of valproic acid to treat adenomyosis. We found that by the end of the 3-month treatment, all three recruited patients reported complete disappearance of dysmenorrhea, with an average of one-third reduction in uterus size. (Fertil Steril® 2008;89:246–50. ©2008 by American Society for Reproductive Medicine.)

Adenomyosis, defined as the presence of heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia, is a common gynecologic disease with a poorly understood pathogenesis and is responsible for menorrhagia, dysmenorrhea, and subfertility (1). Until recently, the diagnosis of adeno-

trichostatin A treatment (Wu and Guo, unpublished observation). In addition, trichostatin A suppresses IL-1β–induced COX-2 expression (13), and both trichostatin A and valproic acid (VPA) induce cell-cycle arrest in endometrial cells (Wu Y, Guo S-W, unpublished observations).

Liu X and Guo SW, Fertil Steril. 2008 Jan;89(1):246-50. Epub 2007 Jan 18.

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Department of Gynecology, Shanghai Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China.

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Mifepristone

3 Monate

Leiomyome verkleinert
Blutungsreduktion 70% -100%

Steinauer J et al. Obstet Gynecol 2004;103:1331-6.

0163-769X/05/$20.00/0
Printed in U.S.A.

Endocrine Reviews 26(3):423–438

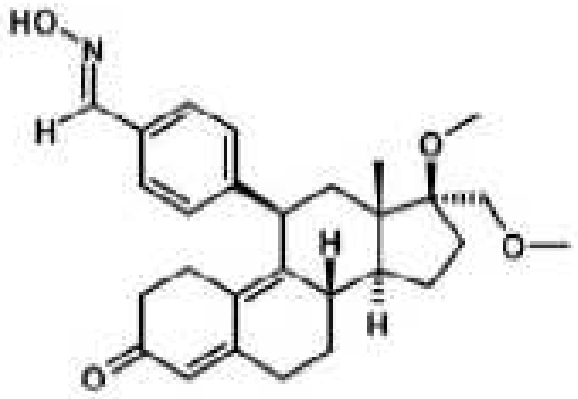
doi: 10.1210/er.2005-0001

Selective Progesterone Receptor Modulator Development and Use in the Treatment of Leiomyomata and Endometriosis

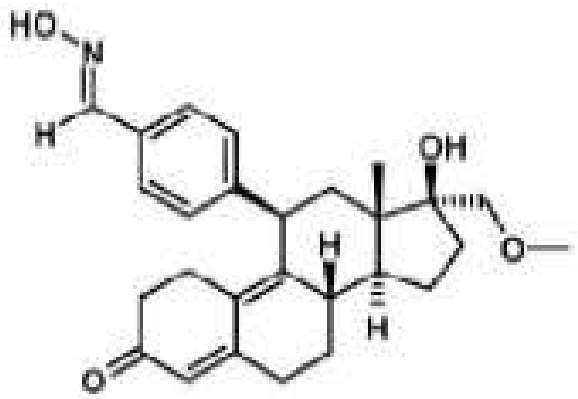
Kristof Chwalisz, Maria Claudia Perez, Deborah DeManno, Craig Winkel, Gerd Schubert, and Walter Elger

TAP Pharmaceutical Products, Inc. (K.C., M.C.P., D.D.), Lake Forest, Illinois 60045; School of Nursing (C.W.), Georgetown University, Washington, D.C. 20007; Jenapharm GmbH & Co. (G.S.), 07745 Jena, Germany; and EnTec GmbH (W.E.), 07745 Jena, Germany

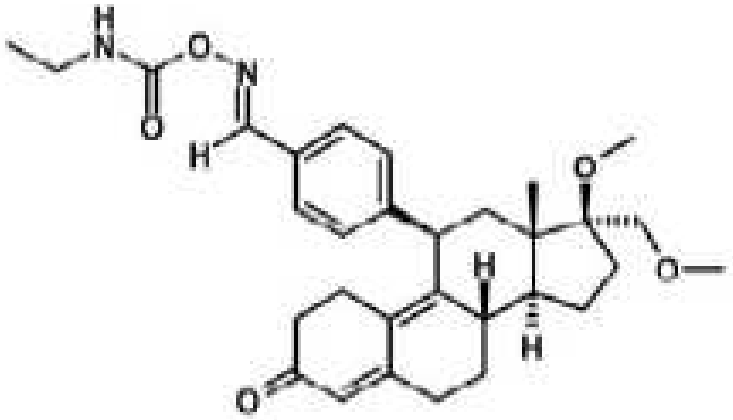
Selective progesterone receptor modulators (SPRMs) represent a new class of progesterone receptor ligands. SPRMs exert clinically relevant tissue-selective progesterone agonist, antagonist, or mixed agonist/antagonist effects on various progesterone target tissues *in vivo*. Asoprisnil (J867) is the first SPRM to reach an advanced stage of clinical development for the treatment of symptomatic uterine fibroids and endometriosis. Asoprisnil belongs to the class of 11β-benzaldoxime-substituted estratrienes that exhibit partial progesterone agonist/antagonist effects with high progesterone receptor specificity in animals and humans. Asoprisnil has no antiglucocorticoid activity in humans at therapeutic doses. It exhibits endometrial antiproliferative effects on the endometrium and breast in primates. Unlike progesterone antagonists, asoprisnil does not induce labor in relevant models of pregnancy and parturition. It induces amenorrhea primarily by targeting the endometrium. In human subjects with uterine fibroids, asoprisnil suppressed both the duration and intensity of uterine bleeding in a dose-dependent manner and reduced tumor volume in the absence of estrogen deprivation. In subjects with endometriosis, asoprisnil was effective in reducing nonmenstrual pain and dysmenorrhea. Asoprisnil may, therefore, provide a novel, tissue-selective approach to control endometriosis-related pain. SPRMs have the potential to become a novel treatment of uterine fibroids and endometriosis. (*Endocrine Reviews* 26: 423–438, 2005)



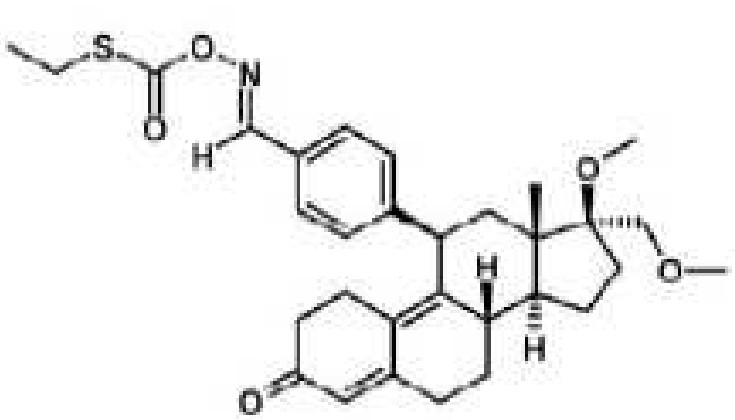
J 867 (Asoprisnil)



J 912



J 956 (Asoprisnil ecamate)



J 1042

A randomized, controlled trial of asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata

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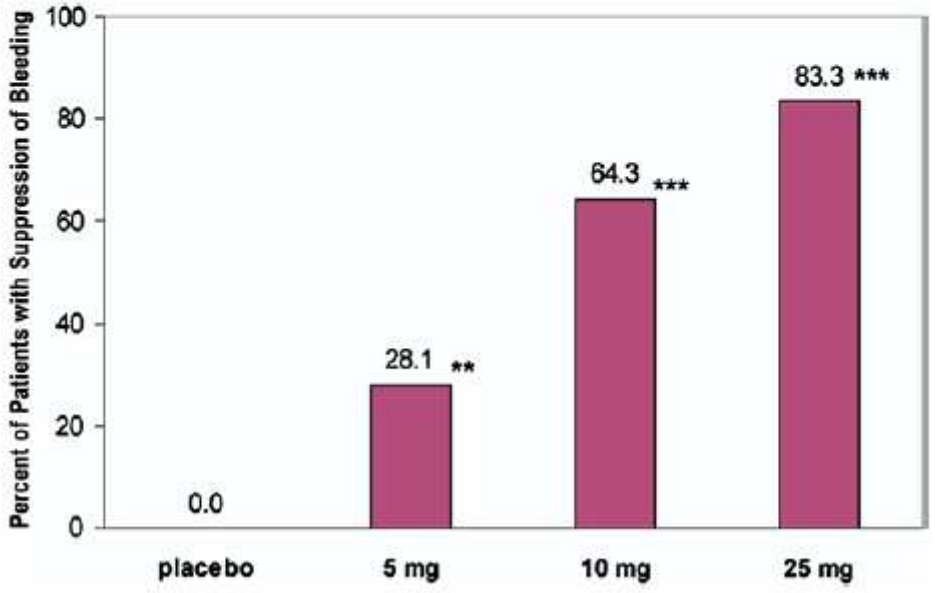
[a] TAP Pharmaceutical Products Inc., Lake Forest, Illinois; and [b] EnTec GmbH, Jena, Germany

Objective: To determine efficacy and safety of asoprisnil in patients with leiomyomata.
Design: Phase 2, multicenter, prospective, randomized, double-blind, placebo-controlled, parallel-group study.
Setting: Twenty-eight sites in the United States and 1 in Canada.
Patient(s): One hundred twenty-nine women with leiomyomata.
Intervention(s): Asoprisnil (5, 10, or 25 mg) or placebo orally daily for 12 weeks.
Main Outcome Measure(s): Uterine bleeding changes by using daily bleeding diaries, hemoglobin concentrations, dominant leiomyoma and uterus volume measured sonographically, patient-reported symptoms related to bloating and pelvic pressure, endometrial thickness and morphology, hormonal parameters, and standard safety measures.
Result(s): Asoprisnil suppressed uterine bleeding in 28%, 64%, and 83% of subjects at 5, 10, and 25 mg, respectively, and reduced leiomyoma and uterine volumes. Median percentage decrease from baseline in leiomyoma volume was statistically significant at 25 mg compared with placebo after 4 and 8 weeks of treatment; by week 12, leiomyoma volume was reduced by 36%. There was a significant reduction in bloating with the two highest doses and in pelvic pressure with 25 mg by week 12. Asoprisnil was associated with follicular-phase estrogen concentration and minimal hypoestrogenic symptoms.
Conclusion(s): After 12-week treatment, asoprisnil controlled uterine bleeding while reducing leiomyoma volume and the associated pressure symptoms. Asoprisnil was well tolerated. (Fertil Steril® 2007;87:1399–412. ©2007 by American Society for Reproductive Medicine.)

Key Words: Amenorrhea, asoprisnil (J867), leiomyoma, pelvic pressure, selective progesterone receptor modulators (SPRMs), menorrhagia, progesterone receptor, endometrium

FIGURE 2

Suppression of uterine bleeding during treatment with asoprisnil. Suppression of uterine bleeding was defined as having no light, medium, and heavy bleeding from the end of baseline menses through the end of dosing. $^{**}P \leq .01$ and $^{***}P \leq .001$ compared with placebo, by using Fisher's exact test.



Chwalisz. Treatment of leiomyomata with asoprisnil. Fertil Steril 2007.

8 Ländern / 42 Zentren

- 1-Österreich
- 2-Belgien
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- 5-Israel
- 6-Italien
- 7-Holland
- 8-Spanien

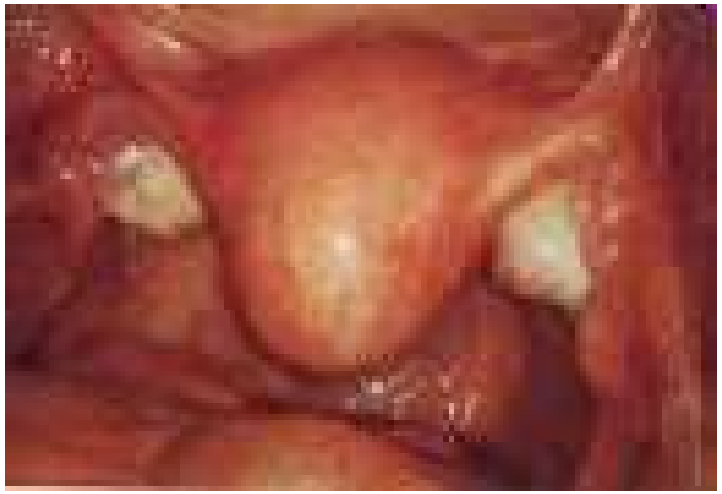
The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL THERAPEUTICS

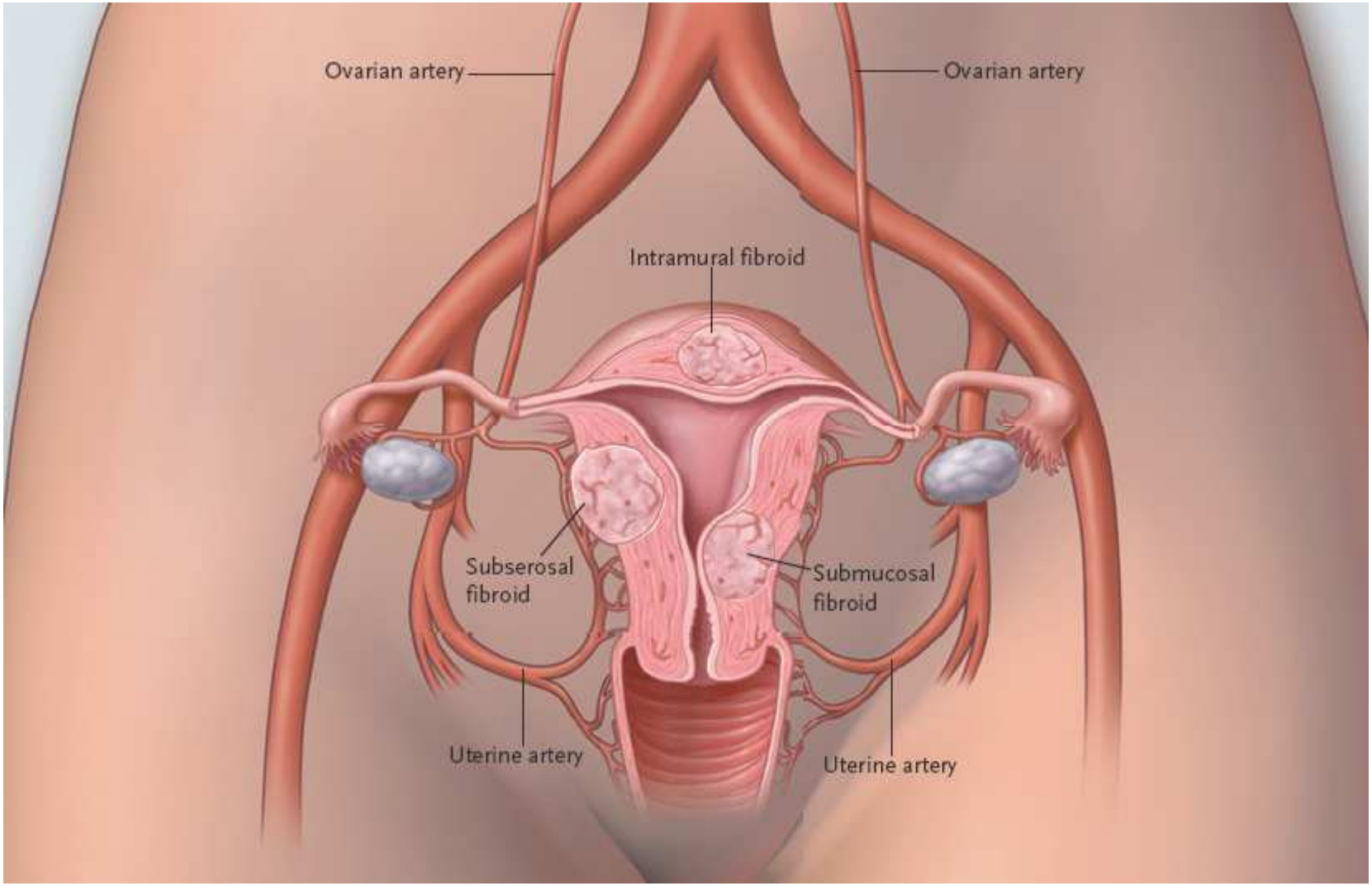
Uterine Fibroid Embolization

Scott C. Goodwin, M.D., and James B. Spies, M.D., M.P.H.

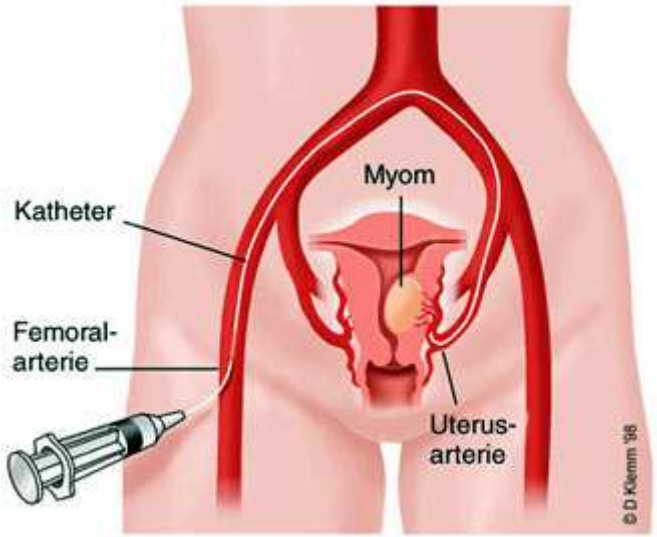
This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.*

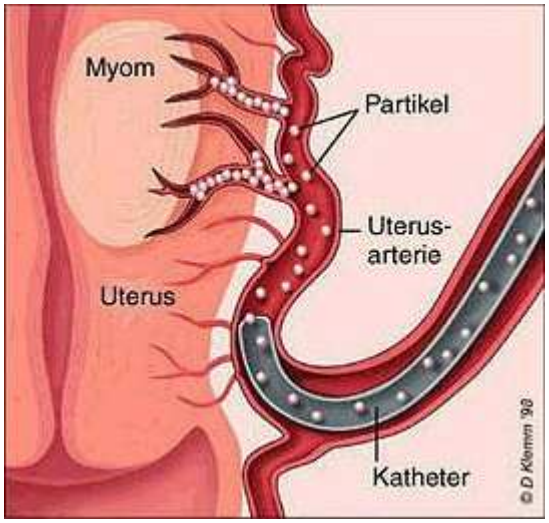


Fibroids are the most common indication for hysterectomy in the United States; a total of 300,000 hysterectomies to remove fibroids are performed each year. The overall cost of treating fibroids was estimated at $2.1 billion in 2000.[7] More than 70% of those costs were directly related to hysterectomy.


Ovarian artery
Ovarian artery
Intramural fibroid
Subserosal fibroid
Submucosal fibroid
Uterine artery
Uterine artery

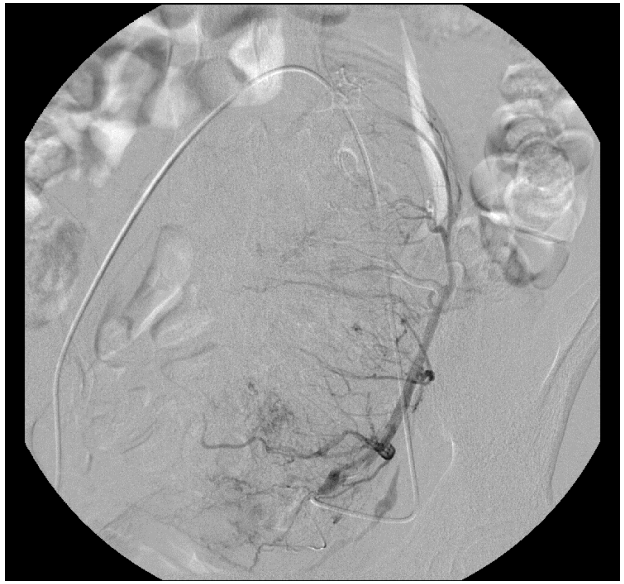
Uterine Artery Embolisation (UAE)

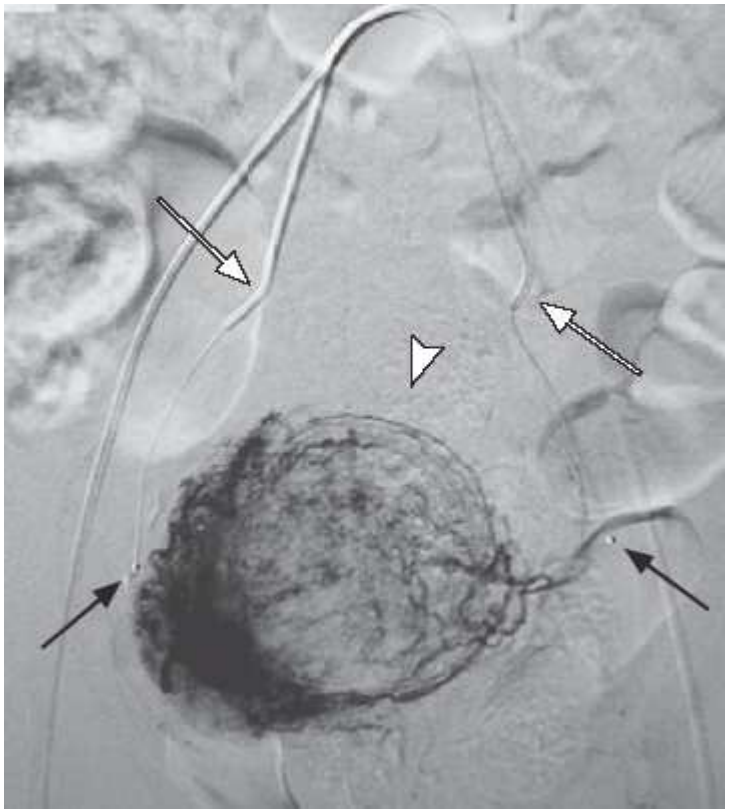


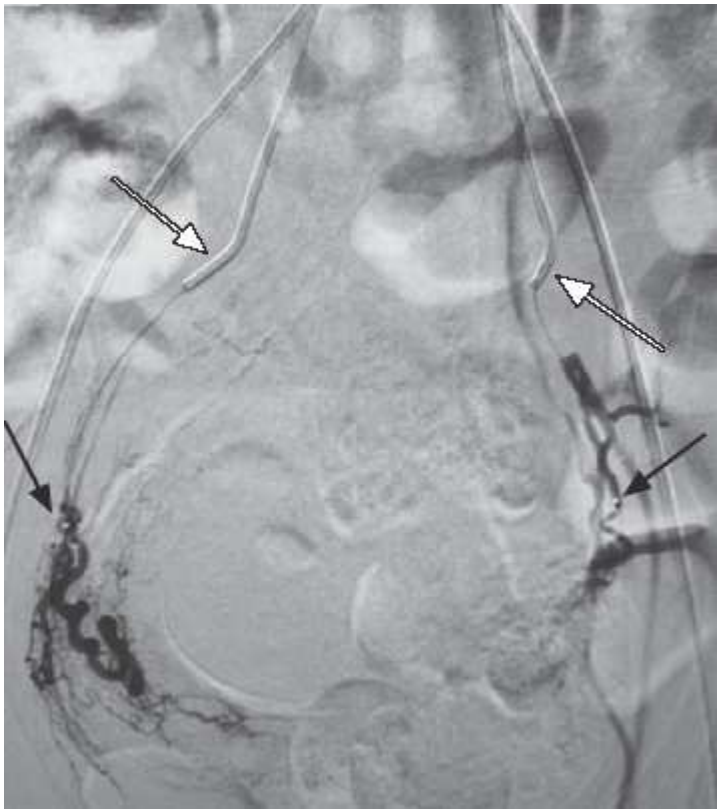


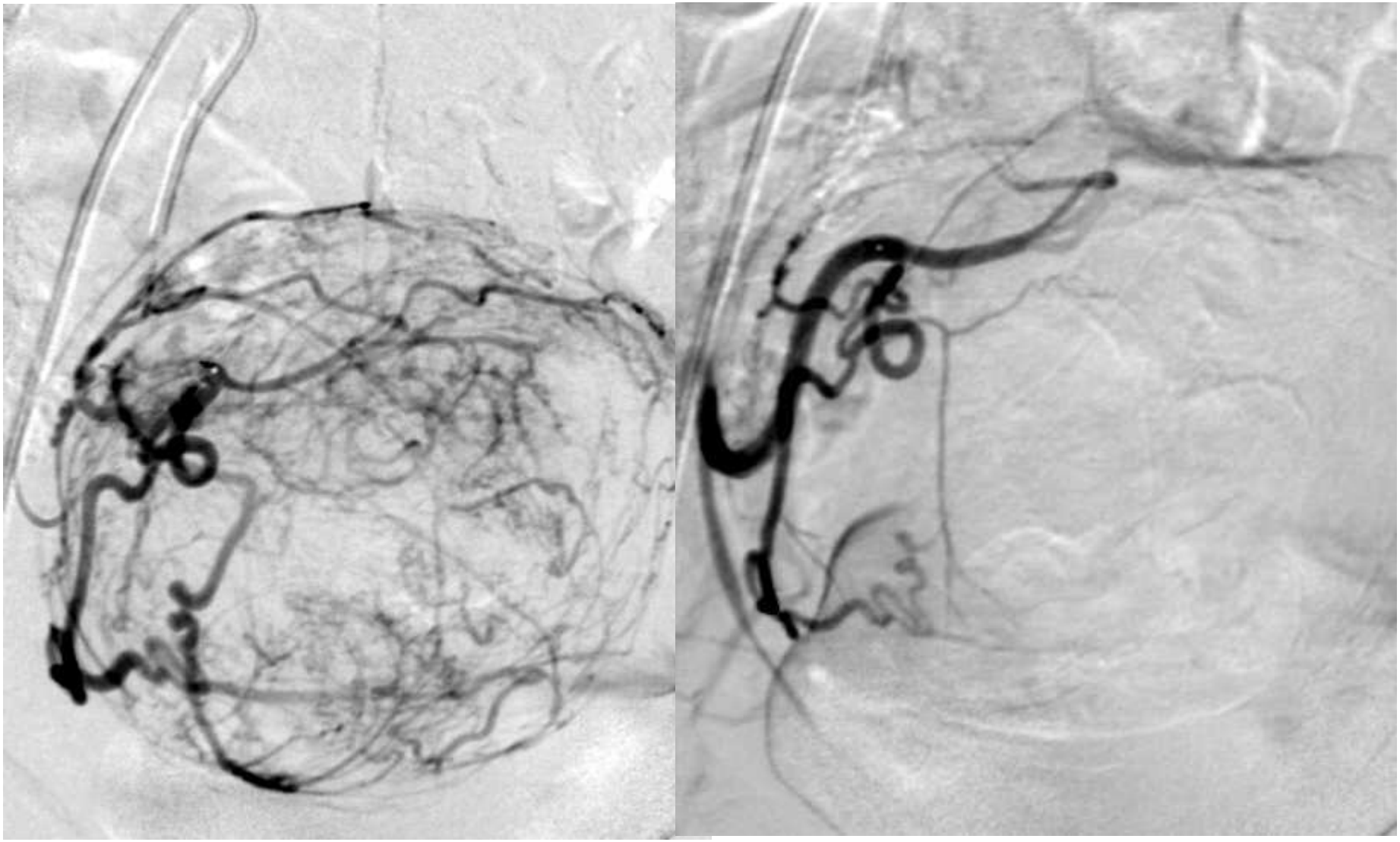
Polyvinylalkohol (PVA)

150-300 µm



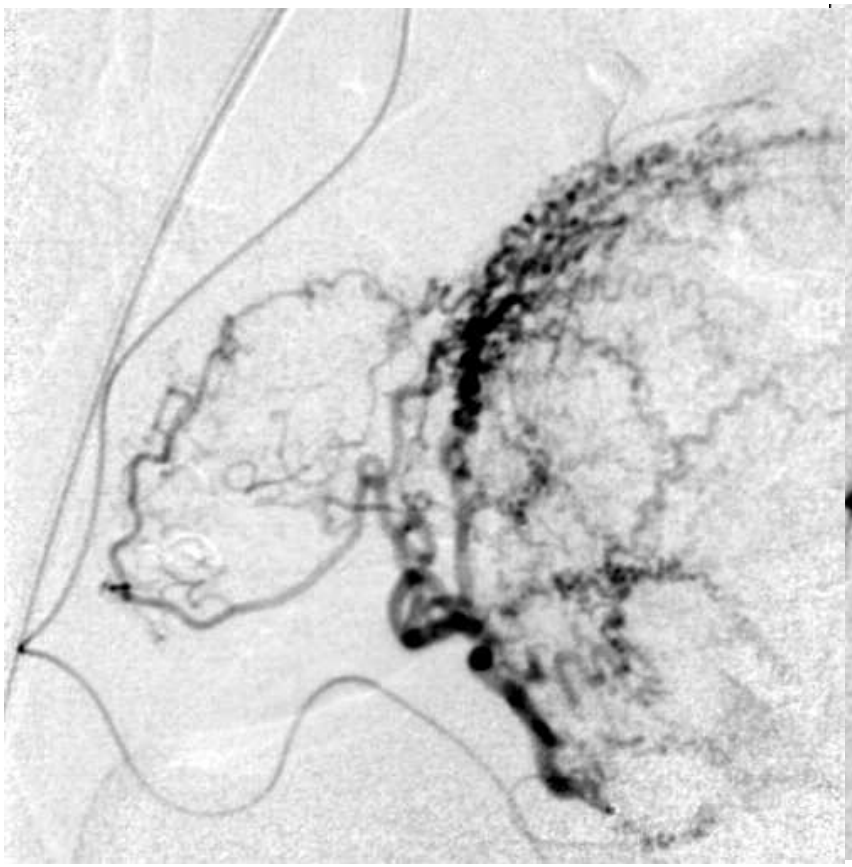


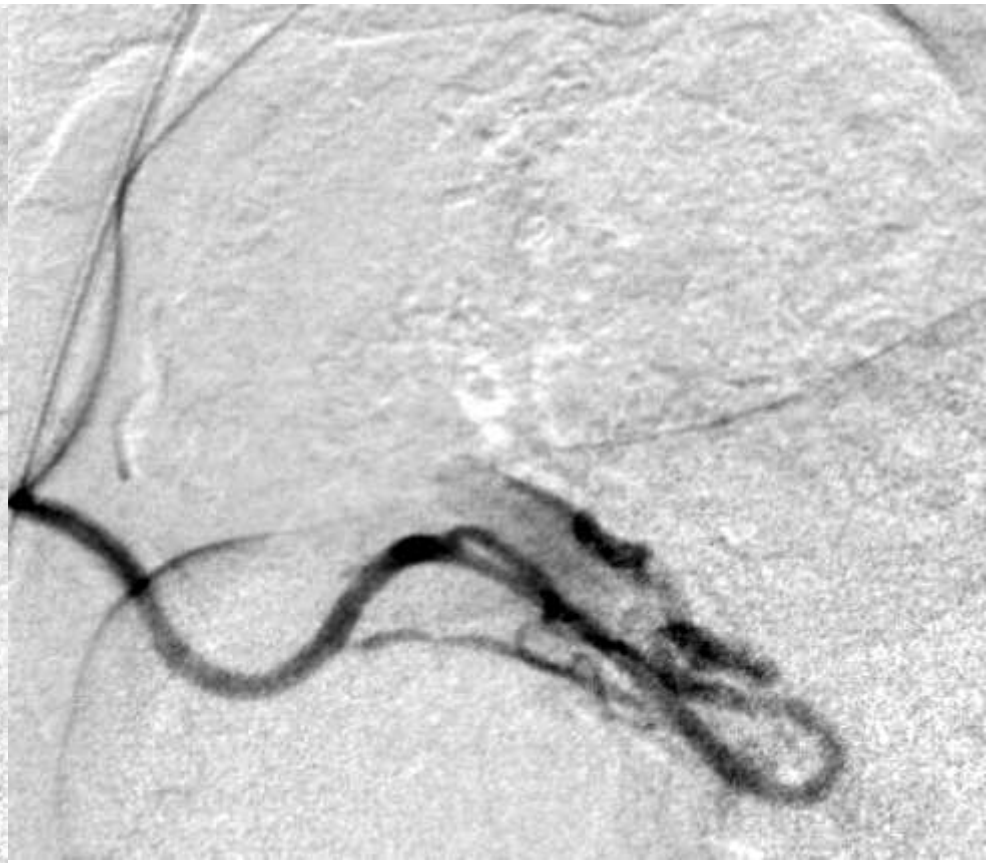




selektiv A. uterina vor

post embo





selektiv A. uterina vor

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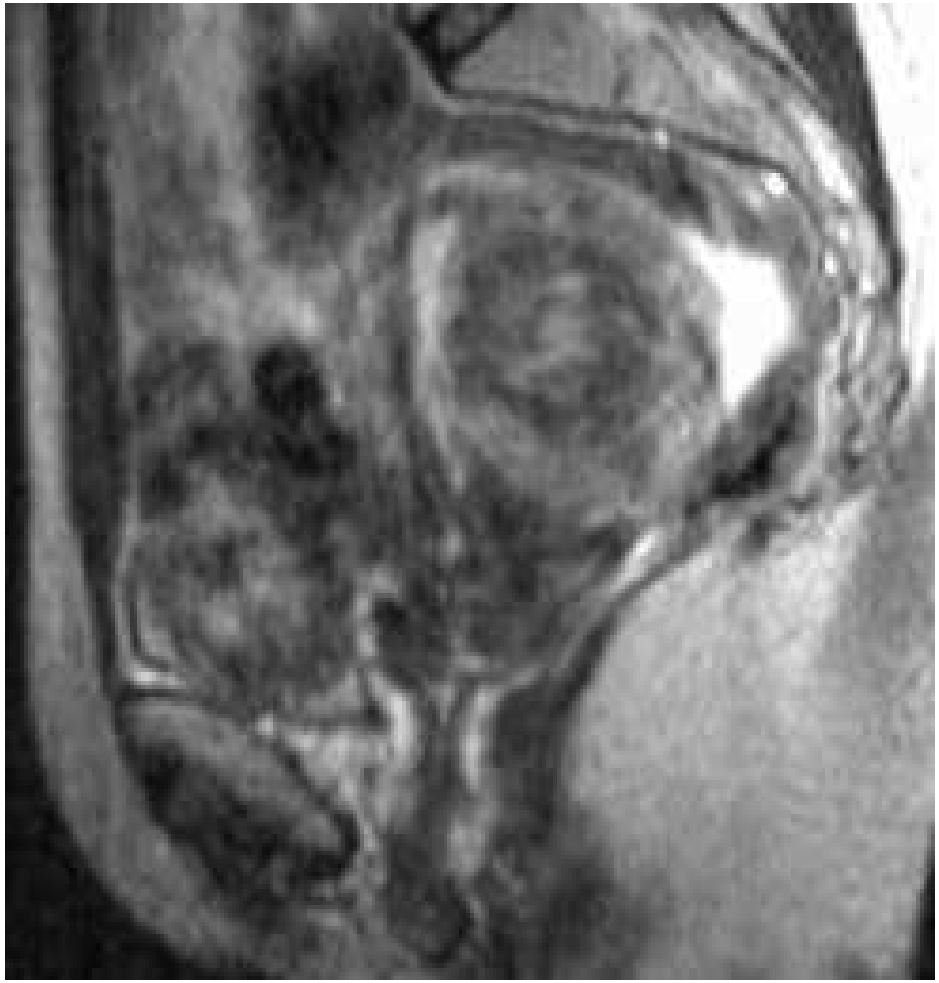
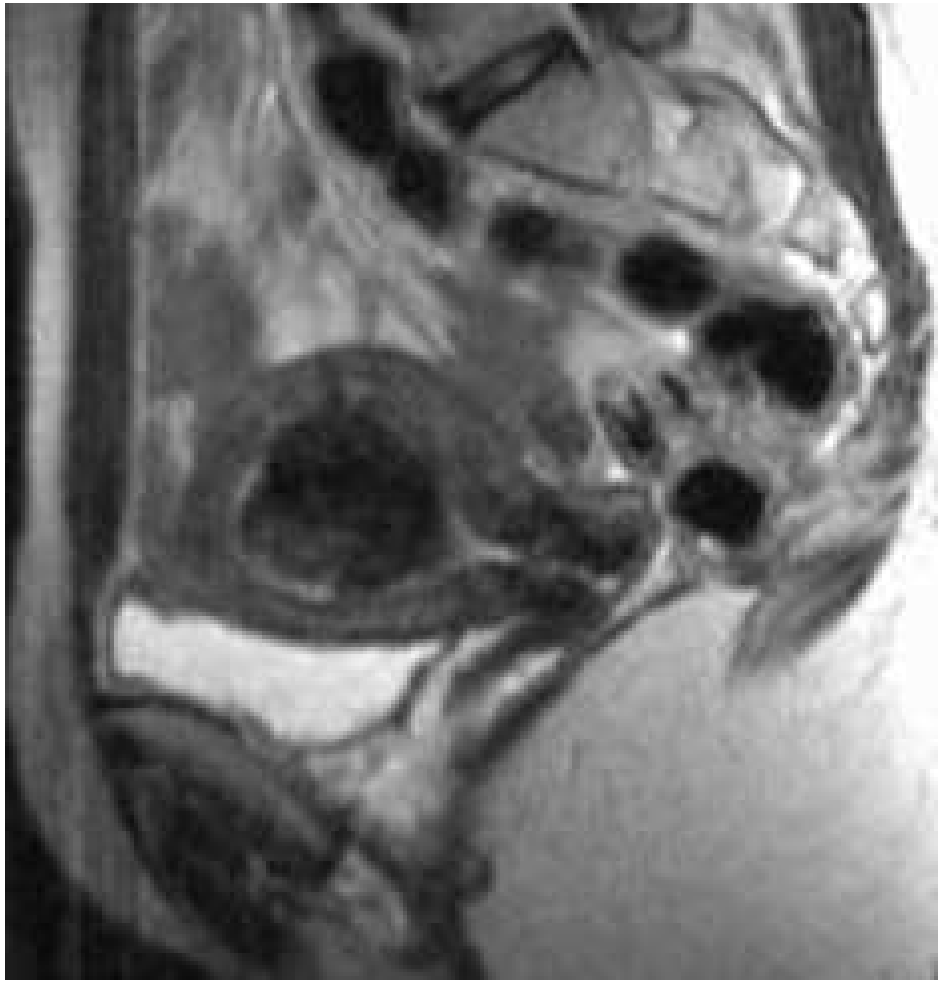


Prae Embo



Post Embo

Patientin kontrollierte Anästhsie

- Morphin - 2,5 mg Bolus i.v.
- Maximal 4 mal ein Bolus in einer Stunde
- Sperrintervall 5 – 10 minuten
- Antiemetikum

KONSENSUSPAPIER

Uterusarterien-Embolisation zur Myombehandlung

Ergebnisse eines radiologisch-gynäkologischen Expertentreffens

T.J. Kröncke, M. David, J. Ricke et al.

4. Kontraindikationen für eine UAE

4.1. Absolute Kontraindikationen sind:

- bestehende Schwangerschaft;
- floride Infektion;
- malignitätsverdächtige Prozesse.

4.2. Relative Kontraindikationen sind:

- Kinderwunsch;
- Niereninsuffizienz;
- Kontrastmittelunverträglichkeit;
- manifeste Hyperthyreose;
- GnRH-Vorbehandlung in den vorausgegangenen drei Monaten (Risiko von Gefäßspasmen).

5. UAE bei Patientinnen mit Kinderwunsch

Die UAE ist keine Methode im Rahmen der Kinderwunschbehandlung. Bevor bei einer Patientin mit nicht abgeschlossener Familienplanung eine Hysterektomie in Erwägung gezogen wird, sollte die Möglichkeit einer UAE geprüft werden.

GUIDELINES

The American College of Obstetricians and Gynecologists (ACOG) concludes "based on good and consistent evidence (level A)" that "uterine artery embolization is a safe and effective option for appropriately selected women who wish to retain their uteri."[50] The ACOG also recommends caution when considering embolization in women who desire to retain their ability to conceive, because age-related amenorrhea can occur in a small minority of patients and because there is a possibility of abnormal placentation. The Society of Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe state that uterine artery embolization "is indicated for the presence of uterine leiomyomata that are causing significant lifestyle-altering symptoms, specifically mass effect on the bladder or intestines, and/or dysfunctional uterine bleeding that is prolonged, associated with severe dysmenorrhea, or is causing severe anemia."[51]

Since 1997, when uterine fibroid embolization was introduced into practice in the United States,[16] a number of large observational studies have been performed.[17-21] These studies have shown that menorrhagia is improved in 85 to 95% of patients, and similar rates of improvement have been noted with respect to pelvic pain, pressure, and urinary symptoms.

Goodwin SC, Spies JB, Worthington-Kirsch R, et al. Uterine artery embolization for treatment of leiomyomata: long-term outcomes from the FIBROID Registry. Obstet Gynecol 2008;111:22-33.

Pelage JP, Jacob D, Fazel A, et al. Midterm results of uterine artery embolization for symptomatic adenomyosis: initial experience. Radiology 2005;234:948-953.

Pron G, Bennett J, Common A, Wall J, Asch M, Sniderman K. The Ontario Uterine Fibroid Embolization Trial. 2. Uterine fibroid reduction and symptom relief after uterine artery embolization for fibroids. Fertil Steril 2003;79:120-127.

Spies J, Myers ER, Worthington-Kirsch R, Mulgund J, Goodwin S, Mauro M. The FIBROID Registry: symptom and quality-of-life status 1 year after therapy. Obstet Gynecol 2005;106:1309-1318.

Worthington-Kirsch R, Spies J, Myers E, et al. The Fibroid Registry for Outcomes Data (FIBROID) for uterine artery embolization: short-term outcomes. Obstet Gynecol 2005;106:52-59. [Erratum, Obstet Gynecol 2005;106:869.]

ADVERSE EFFECTS

In a registry of 3160 women undergoing uterine fibroid embolization, major complications (as defined by the Society of Interventional Radiology Clinical Practice Guidelines) occurred in 0.66% of registrants during the initial hospitalization and in 4.8% during the first month after the procedure.[21] More than half of these complications consisted of persistent or recurrent pain or nausea. In a single-center study of 400 consecutive patients, the event rate for major complications was 4.3% during the first year.[35]

DOI: 10.1111/j.1471-0528.2007.01525.x
www.blackwellpublishing.com/bjog

Uterine artery embolisation or hysterectomy for the treatment of symptomatic uterine fibroids: a cost-utility analysis of the HOPEFUL study

O Wu,[a] A Briggs,[a] S Dutton,[b,c] A Hirst,[c] M Maresh,[d] A Nicholson,[e] K McPherson[c]

[a] Public Health and Health Policy, Division of Community Based Sciences, University of Glasgow, Glasgow, UK [b] Centre for Statistics in Medicine and [c] Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford, UK [d] Department of Obstetrics and Gynaecology, St Mary's Hospital for Women and Children, Manchester, UK [e] Department of Radiology, Leeds General Infirmary, Leeds, UK
Correspondence: Dr O Wu, Public Health and Health Policy, Division of Community Based Sciences, University of Glasgow, 1 Lilybank Gardens, Glasgow G12 8RZ, UK. Email o.wu@clinmed.gla.ac.uk

Objectives To evaluate the relative cost-effectiveness of uterine artery embolisation (UAE) and hysterectomy in women with symptomatic uterine fibroids from the perspective of the UK NHS.

Design Cost-utility analysis.

Setting Eighteen UK NHS hospital trusts.

Population or sample Women who underwent UAE ($n = 649$; average follow up of 8.6 years) or hysterectomy ($n = 459$; average follow up of 4.6 years) for the treatments of symptomatic fibroids.

Methods A probabilistic decision model was carried out based on data from a large comparative cohort and the literature. The two interventions were evaluated over the time horizon from the initial procedure to menopause. Extensive sensitivity analysis was carried out to test model assumptions and parameter uncertainties.

Main outcome measures Costs of procedures and complications and quality of life expressed as quality-adjusted life years (QALYs).

Results Overall, UAE was associated with lower mean cost (£2536 versus £3282) and a small reduction in quality of life (8.203 versus 8.241 QALYs) when compared with hysterectomy. However, when the quality of life associated with the conservation of the uterus was incorporated in the model, UAE was shown to be the dominant strategy—lower costs and greater QALYs.

Conclusions UAE is a less expensive option to the health service compared with hysterectomy, even when the costs of repeat procedures and associated complications are factored in. The quality of life implications in the short term are also predicted to favour UAE; however, this advantage may be eroded over time as women undergo additional procedures to deal with recurrent fibroids. Given the hysterectomy is the current standard treatment for symptomatic fibroids, offering women UAE as an alternative treatment for fibroids is likely to be highly cost-effective for those women who prefer uterus-conserving treatment.

Keywords Cost-utility analysis, hysterectomy, uterine artery embolisation.

The Uterine Artery Embolization (UAE) versus Hysterectomy for Uterine Fibroids trial (EMMY; ClinicalTrials.gov number, NCT00100191) was a multicenter, randomized trial in which uterine fibroid embolization was compared with hysterectomy among 177 patients in the Netherlands.[22,23] Patients in the embolization group had a more rapid recovery and a shorter hospital stay than those in the hysterectomy group (2.7 vs. 5.1 days in the hospital), but were more often readmitted to the hospital (11.1% vs. 0%). Both groups had substantial and similar improvements in health-related quality of life, and similar proportions of patients considered themselves to be at least "moderately satisfied" with the outcome at 24 months (92% in the embolization group and 90% in the hysterectomy group). Patients who had

Health Technology Assessment 2008; Vol. 12: No. 5

A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study

A Hirst, S Dutton, O Wu, A Briggs,
C Edwards, L Waldenmaier, M Maresh,
A Nicholson and K McPherson

The mean cost of uterine fibroid embolization was $8,293

The mean total cost over the first year was $13,270

Dembek CJ, Pelletier EM, Isaacson KB, Spies JB.
Payer costs in patients undergoing uterine artery embolization, hysterectomy, or myomectomy for treatment of uterine fibroids.
J Vasc Interv Radiol 2007;18:1207-1213

Radiology

Symptomatic Uterine Fibroids:

Treatment with Uterine Artery Embolization or Hysterectomy—Results from the Randomized Clinical Embolisation versus Hysterectomy (EMMY) Trial[1]

Results: The SF-36 MCS and PCS, Health Utilities Index Mark 3, EuroQol 5D, and UDI scores were improved significantly in both groups at 6 months and afterward ($P < .05$). The DDI score was improved significantly in only the UAE group at 6 months and afterward ($P < .05$). No differences between groups were observed, with the exception of PCS scores at 6-week follow-up: Patients in the UAE group had significantly better scores than did patients in the hysterectomy group ($P < .001$). Improvement in PCS score at 24-month follow-up was significantly higher for patients who were employed at baseline ($P = .035$). At 24-month follow-up, patients in the hysterectomy group were significantly more satisfied than those in the UAE group ($P = .02$).

Conclusion: Both UAE and hysterectomy improved HRQOL. No differences were observed between groups regarding HRQOL at 24-month follow-up. On the basis of HRQOL results, the authors determined that UAE is a good alternative to hysterectomy.

Herrn
Prim.Prof.Dr. Gerhard Mostbeck, Zentralröntgeninstitut

Herrn
Prim.Univ.Prof.Dr. Othmar Zechner, Urologie

Herrn
Prim.Univ.Prof.Dr. Heinrich Salzer, Gynäkologie

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KAV – Teilunternehmung
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Fax: (+43 1) 49150-2209
E-Mail: wil.2me@wienkav.at
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http://www.wienkav.at/wil

23. Jänner 2009 / NK

Gesprächsprotokoll vom Freitag, 23.01.2009

Teilnehmer: Prim.Prof.Dr. Gerhard Mostbeck, Zentralröntgeninstitut
Prim.Univ.Prof.Dr. Othmar Zechner, Urologie
Prim.Univ.Prof.Dr. Heinrich Salzer, Gynäkologie
Prim.Univ.Prof.Dr. Meinhard Kneussl, 2. Medizinische Abteilung – Lungenabteilung
Univ.Doz. OA Dr. Felix Wantke, 2. Medizinische Abteilung – Lungenabteilung

Bei Frau besteht bekannterweise eine Lymphangiomyomatose (LAM) mit retroperitonealem Befall. Die Erstdiagnose wurde 2005 gestellt. Die Verifizierung der Diagnose 2008 im Rahmen einer Bronchoskopie ho.

Zum weiteren Procedere ist Folgendes geplant:
Bei Univ.Prof.Dr. Huber im AKH ist eine Hormon-Kombinationstherapie von Nolvadex 10 mg und Enantone-Gyn besprochen.

AB 28.01.2009

10 MG NOLVADEX

ENANTONE GYN

Erhobene Befunde:
Magnetresonanz vom 19.05.2009

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Krankenanstalten der Stadt Wien

Wilhelminenspital der Stadt Wien
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http://www.wilhelminenspital.info
http://www.wienkav.at/wil

MR – Tomographie des Abdomens vom 19.05.2009:

Es liegt eine auswärts durchgeführte und eingescannt eine Computertomographie vom 26.11.2008 zum Vergleich vor.

Im Vergleich zu dieser Computertomographie zeigen die sehr ausgedehnten retroperitonealen Tumormassen, die entlang der gesamten Aorta abdominalis vom retrocruralen Bereiche bis ins kleine Becken zu verfolgen sind, eine leichte Größen-abnahme. Insbesondere die großen Tumormassen die caudal der Aortenbifurkation zu beobachten waren sind etwa um die Hälfte ihrer Größe reduziert. Demgegenüber zeigt eine größere Tumormasse die an der linken Beckenwand dorsal der Iliaca Externagefäße gelegen sind keine eindeutige Größenänderung. Auch die multiplen polyzyklisch begrenzte Läsionen in der Leber zeigen keine eindeutige Änderung ihrer Form und Größe. MR-tomographisch kommen T2-gewichtet weiterepunktförmige hyperintense Läsionen in der Leber zur Darstellung die computertomographisch nicht erfasst wurden, dies ist jedoch methodisch bedingt. Bekanntes größeres Uterusmyom. Keine nachweisbaren Herde an den Nieren. Keine freie Flüssigkeit im Abdomen.

ZUSAMMENFASSUNG:

Größenreduktion der sehr ausgedehnten retroperitonealen Tumormassen, soweit die Methoden vergleichbar sind, insbesondere im Unterbauchbereich. Keine eindeutige Änderung der Veränderungen an der linken Beckenwand und der Leber.

- - - *Ergebnisteil* - - -

Untersuchungsdatum: 09-11-2009
Untersuchungszeit: 09:16

Befundender Arzt: Barnerth Elisabeth, Dr.
Vidierender Arzt: Barnerth Elisabeth, Dr.
Vidierungsdatum: 10-11-2009 03:07

Befund:

Sonographie der Nieren und des Retroperitoneums vom 09.11.2009: Sonographie des Oberbauches vom 09.11.2009: Soweit mit importierten auswärtigen Bildern (CT vom 26.11.2008) und einer hierorts durchgeführten Voruntersuchung (MR vom 19.05.2009) vergleichbar, besteht der Eindruck einer weiteren Größenabnahme der hypoechogenen Weichteilvermehrung im Retroperitoneum, welche entlang der Iliacalgefäße rechts bis maximal 1,7 cm, links maximal 1 cm teilweise semizirkulär um die Gefäße angeordnet ist.

- - - *Ergebnisteil* - - -

Untersuchungsdatum: 01-03-2010
Untersuchungszeit: 09:39

Befundender Arzt: Barnerth Elisabeth, Dr.
Vidierender Arzt: Barnerth Elisabeth, Dr.
Vidierungsdatum: 01-03-2010 09:55

Befund:

Sonographie der Nieren und des Retroperitoneums vom 01.03.2010:
Sonographie des Oberbauches vom 01.03.2010: Verglichen mit einer Voruntersuchung vom 09.11.2009 zeigt sich eine weitere Größenabnahme der hypoechogenen Weichteilvermehrung im Retroperitoneum, welche entlang um die Aorta und den Iliacalgefäßen bis maximal 1 cm teilweise semizirkulär um die Gefäße angeordnet ist. Allerdings ist die Abgrenzbarkeit gegenüber dem retroperitonealen Fettgewebe schlecht, sodass genaue Ausmessung schwierig sind. Auch der etwas größere Anteil zwischen rechtem Nierenhilus und Vena cava inferior zeigt eine Größenreduktion auf etwa 4 x 1 cm. Im Übrigen ergibt sich keine Befundänderung:

Progesteron			
Taveira-DaSilva et al. 2004 Chest	Retrospektiv 348 Pat.	139 Progesteron 136 keine Therapie	-
Eliasson et al. 1989 Chest	Meta-Analyse 30 Fälle	Progesteron und/oder Ovarektomie	+
McCarthy et al. 1980 N Engl J Med	Fallbericht (kein Abstrakt)	Progesteron	+
Tamox/Prog			
Urban et al. 1999 Medicine (Baltimore)	Retrospektive Auswertung 69 Fälle	57 Hormontherapie (Tamoxifen und/oder Progesteron)	-
Denoo et al. 1999 Chest	Fallbericht	Tamoxifen und Progesteron	+
Oh et al. 1999 Thorax	Retrospektiv 25 Fälle	Progesteron und/oder Tamoxifen	-
Sieker et al. 1988 Trans Am Clin Climatol Assoc	Review 13 Fallberichte	Progesteron (Tamoxifen)	+ (Tamoxifen -, nur ein Fall)
Svendsen et al. 1984	Fallbericht	Tamoxifen, Progesteron und Ovarektomie	Prog/Ovarekt. + Tamoxifen -

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bei der **J. C. Hinrichs**'schen Buchhandlung in Leipzig.

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der kaiserl. königl.

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Dr. Carl Blodig.

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Prof. Dr. C. D. Schroff.

II. Secretär:
Dr. A. Schauenstein.

Sechzehnter Jahrgang.

Neue Folge. III. Jahrgang.

1860. **№ 37.** **10. September.**

High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis

N.Sinaii[1], S.D.Cleary[2], M.L.Ballweg[3], L.K.Nieman[1] and P.Stratton[1]

Human Reproduction Vol.17, No.10 pp. 2715–2724, 2002

- US ENDOMETRIOSIS ASSOCIATION
- US – NIH

- ENDOMETRIOSIS AND RISK FOR FIBROMYALGIA
- CHRONIC FATIGUE SYNDROM
- SLE, RA
- SJÖRGEN SYNDROM
- HYPOTHYREOSE

US ENDOMETRIOSIS ASSOCIATION
US NIH

ENDOMETRIOSIS AND RISK FOR

- ALLERGIEN
- ASTHMA
- ECZEMA

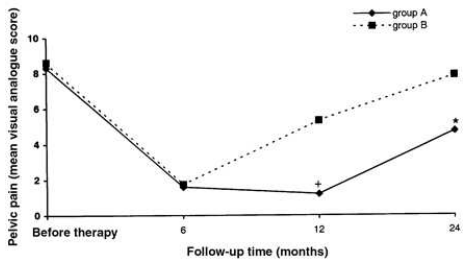
ENDOMETRIOSE
UND DYSPLASTISCHE NAEVI
MELANOM

Goserelin

- **Br J Obstet Gynaecol 1999;106(7):672-7**
  - no therapy vs. goserelin (Zoladex®) s.c. q28x6
  - n=269; AFS II/IV; 24 mos
- **Ergebnis**
  - **weniger Rezidive n. 1a: 13% vs. 21%**
  - **weniger Rezidive n. 2a: 23% vs. 36%**
  - rezidivfreies Intervall sign. länger

Low-Dose Danazol

- **Hum Reprod 1999;14(9):2371-4**
- alle: surgery + GnRH-Analogon (triptorelin 3.75mg) q28x6
  - rand.: danazol 100mg/d f. 6 mos vs. no further therapy
  - n=28; AFS III/IV; 24 mos follow-up
- **Ergebnis**
  - **Schmerzscore besser p<0.01**
  - **Rezidive 44 vs. 67% p<0.05**
  - side effects gleich



GnRH + Anastrozol

- **Hum Reprod 2004;19(1):160-7**
  - OP + Goserelin 3.6mg q28x6 +/- Anastrozol 1mg/d 6 mos
  - n=97; severe endometriosis (rASRM score >40); 24 mos follow-up
- **Ergebnis**
  - länger rez.-frei 2.4 vs. 1.7 mos (p=0.009)
  - weniger Schmerzrezidive 35% vs. 8%
  - BMD-Verlust höher; QOL gleich

Ebert AD, Bartley J, David M.

Aromatase inhibitors and cyclooxygenase-2 (COX-2) inhibitors in endometriosis: new questions--old answers?

Eur J Obstet Gynecol Reprod Biol. 2005 Oct 1;122(2):144-50. Epub 2005 Sep 12.

Treatment:

Endpoints

Assessments

Hefler & Nagele