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Review Article

Myoma Therapy Needs a Forensic Paradigm Shift?

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Abstract

Hysterectomy (HE) indications have decreased significantly in Germany in recent decades. Nevertheless, almost 90% are still benign indications. Myoma findings and menstrual problems are the most common indications. Oncological HE indications around 10% do not require discussion.

In the case of benign indications for uterine surgery, especially fibroids, long-term hormonal risks must be taken into account.

Anatomical Basis for HE Long-Term Risks Hormonal Type

HE and other uterine interventions can reduce blood flow to retained ovaries. The result is hormone deficits with more or less serious somatic consequences. These often only occur years later. Then affected women could go to court. The surgeon then has the burden of proof that his interventions did not cause any hormonal damage. This must be considered individually and prospectively before each uterine intervention.

Already in medical school it is taught (the author was a university lecturer for medical students for 30 years) that the ovaries have two blood supplies: cranial and caudal,

The two ovarian arteries, located in the suspensory ligament, are known to come from the abdominal aorta below the renal arteries.

In addition, there is a caudal blood supply to the ovaries from the ovaricus branch of the uterine artery. This supply route is destroyed every time the uterus is removed. Operations that preserve the uterus can also result in impairment of the ovarian ramus.

Both arterial supply routes form the Rete arteriosum ovarii (medical state examination question).

This arterial network receives little attention in practical surgical gynecology, although it is of clinical relevance.

Depression, Cognition and Neurodegeneration Related to HE

CNS problems after HE have been reported in several larger studies through 2021. This was partly appreciated by surgical gynecologists.

In Germany, from 2010 to 2017, the number of annual uterine removals fell from 120,000 to 77,000, almost halving.

Late hormonal consequences as a result of HE can hardly be predicted on an individual basis. The number of women critical of HE without cancer indications is still relatively small. This may change as a result of initial court proceedings and reports in the media.

HE risks in absolute numbers

A neurologist and epidemiologist at the Mayo Clinic published a study in 2009 [1], that was named “Best of the Year” by the Menopause Society there. In the introduction, it was pointed out that in the USA, 8 out of 10 women aged 45 to 64 years with a history of HE without cancer indications would have their ovaries removed. That was 300,000 castrations there every year. That compares with 14,800 women who died from ovarian cancer. This ratio of 1 to 20 was not considered appropriate for general castration with HE at this age.

Cardiac death from menopause onwards was reported to be 24 times higher than ovarian cancer. Please note: Heart attacks in healthy women only occur in the years after menopause.

Figures on the risk of dementia after HE were listed, more on that later.

The conclusion of the study author: do not carry out “prophylactic” castrations for HE. Very strict indications for an oophorectomy are needed.

The same study group previously published [2], results on the neuroprotective effects of estrogens. Ovarian removals on one and both sides led to an increased risk of cognitive impairments and even dementia. Overall, the risk increased by 50%. These risks were more linear: the earlier the women had premenopausal surgery, the more often neurological risks were evident.

A few years earlier, a study by the same researchers at the Rocca/Mayo Clinic [3], showed that HE alone caused cognitive impairment through estrogen deficiency.

At that time, data on uterine-preserving operations and, as a result, cognitive risks were not recorded. This is to be expected if the blood flow to the ovaricus ramus is damaged or interrupted during surgery. Given the current state of knowledge, large prospective studies on this are hardly ethically justifiable, but retrospective data collection is advisable.

Danish study confirms US data

With HE without ovary removal before the age of 50 [4], the risk of dementia increases significantly (RR 1.38) and further with unilateral and bilateral ovary removal (RR 2.10 and RR 2.23)

The study authors say: the brain is very vulnerable to iatrogenically induced estrogen deficit. Removing just one ovary doubles the risk.

This raises the question again: are the hormonal risks sufficiently taken into account during operations that preserve the uterus? This is anatomically plausible if the ovarian ramus has been compromised. Before every operation of this type, it is in the interest of the women and for forensic reasons that information should be given and the findings should be documented using imaging procedures before the operation. The above risks were confirmed in animal experiments [5].

A US study with women around the age of 74 [6], i.e. almost 30 years after menopause, was unable to determine any loss of cognition after HE. It was not examined whether this also applies after the first and second decade after menopause.

A Finnish study [7], showed in the table of results that HRT for at least 10 years after HE reduced the risk of dementia after HE: from 3.78% without HRT to 1.31% with a history of HRT.

In addition, a study states that less than ten years of HRT use has hardly any CNS benefit [8]. Then hardly any neuroprotection can be expected. A meta-analysis of HE from 2019 [9], comes to the conclusion: HE with adnexal removal at the age of 45 and earlier causes cognitive impairment. This also applies to HE after the age of 50. This is biologically plausible because testosterone continues to be produced in the ovaries and is metabolized into estrogen using the aromatase enzyme.

Finally, the results of our own pilot study from 1976. The majority of women did not want prophylactic HE. This was particularly true for those with higher school qualifications and higher intelligence (assessed using a test).

Myoma Therapies Resulting in Necrosis Obsolete

All myoma therapies that are associated with necrosis in myomas are to be classified more critically from the perspective of tumor lysis, here myoma lysis. These risks are known from oncology and are also presented there as emergencies, in extreme cases with a fatal outcome. These are metabolic complications that should not exceed a minimum.

In the case of cancer therapies, this risk can sometimes be justifiable on an individual basis. Can this also apply to fibroid therapy that triggers necrosis in fibroids?

Oncologists want to identify the tumor lysis symptom (TLS) early in high-risk patients in order to initiate targeted prophylactic measures. Cell breakdown to a large extent causes the cell's own proteins and DNA, including purine bases, to be released. Their breakdown and removal can overload the body, especially the renal secretory capacity.

The consequences include hyperkalemia and hyperphosphatemia. This can lead to metabolic acidosis and hyperuricemia. The somatic consequence is damaged kidneys and even the need for dialysis.

Cardiological events such as arrhythmias and neurological complications such as seizures are also reported in oncology.

In TLS, kidney damage occurs in up to a third and is more common than in other organs [11-14].

This needs to be taken into account more when treating myomas with necrosis. Similar to internal oncology, many laboratory controls would be indicated. To date, there are no generally valid diagnostic criteria that gynecologists could quickly adopt.

In childhood leukemia, TLS problems are reported to occur in frequencies of 40-70% [15-17]. Paraclinical changes are more common than clinical TLS manifestations.

What has so far been described primarily in hematological cancers should become the subject of more research in myoma therapies with induced necrosis. This can also result in significantly damaged cells that the body has to break down quickly.

The many laboratory values including ECG that oncological internists require for TLS are not outlined here. Some of these parameters should be collected at 8-hour intervals [18].

This is by no means just an oncological problem. In addition, necrotizing pancreatis is an example. This can lead to kidney failure in a very short time via TLS mechanisms.

All of these risks are hardly justifiable with benign tumors

such as fibroids because there are less risky fibroid therapy alternatives.

Radiological Therapies with Necrosis Consequences

As a gynecologist, the author has experience with interventional radiology for the treatment of severe bleeding in advanced cervical carcinomas through his responsibility for brachytherapy (afterloading/iridium). If embolization of the uterine artery was carried out on both sides in palliative situations, this was accompanied by severe pain , sometimes only controllable with morphine derivatives. At that time, TLS was not known for tumor decay. Given these clinical experiences, it was surprising that embolization was later performed for myoma therapy. The possible reduced blood flow to the ovaries as a result has not been discussed enough. Because of more and more TLS experiences, a rethink is necessary.

Consider Spontaneous Myoma Necrosis

How clinically risky fibroid necrosis is can be seen when it occurs during the puerperium. When the placenta is expelled, there is a massive drop in hormones and this can lead to myoma disintegration. It is well known that the volume of myomas decreases rapidly in the first few years after menopause. This happens in such small steps that no clinical problems arise. On the other hand, acute abdomen can occur after birth due to myoma necrosis and rapid interventions are necessary. Why this digression?

Endocrine Myoma Therapy is the Future

Therapies that are based on physiology are to be favored in today's medicine. This includes the recognition of spontaneous regression of fibroids from menopause onwards. This happens pain-free and without risks.

In addition, ulipristal acetate (UPA) (Esmya), approved in the EU in 2012. The effect on progesterone receptors (PR) is both agonistic and antagonistic. LH surge is prevented and thus ovulation.

Under UPA therapy, liver problems occurred extremely rarely and could hardly be explained biologically. The approval was therefore suspended and is revoked for more stringent indications. Then came an alternative.

Relugolix (Ryeqo/Orgovyx), as a GnRH receptor antagonist, inhibits the release of LH and FSH in the anterior pituitary gland. This reduces estrogen production. The prevented LH surge inhibits the development of the corpus luteum and progesterone formation does not occur.

This creates a hormonal situation similar to that of menopause. .

With the obligatory pill combination, serum estrogen levels are achieved as in the early follicular phase. The approved pill with estradiol 1 mg and norethisterone acetate 0.5 mg is used without pill breaks.

When therapy is discontinued, ovulation occurs after approximately three weeks.

The aim of therapy is to quickly achieve menstrual blood loss (MBA) below 80 ml. This was achieved in three out of four women in two approval studies. In over half of the women, the Hb levels increased by over 2 g/dl.

This was accompanied by a reduced myoma volume of 15% in relation to the primary myoma volume. Overall uterine volume was reduced by 13%.

Both together reduced/eliminated symptoms and uterine blood loss was stopped.

Side Effects and Risks of Endocrine Myoma Therapy

This endocrine therapy is designed for healthy women of reproductive age who suffer from fibroid symptoms, including high menstrual blood loss, and do not want surgical intervention.

Before starting therapy, family risks of embolism should be ruled out and questions should be asked about VTE events during pregnancy/postpartum and while taking pills. A history of heart attack and stroke should also be ruled out. These are extremely rare events in fertile age. Health-conscious lifestyle (BMI within the normal range, 10,000 steps daily/recorded with smartphone and avoidance of nicotine/alcohol consumption) and no genetic predisposition to VTE. Migraines with visual disturbances and liver problems are contraindications.

The combination pill use without a break corresponds to the approved long pill cycle. According to data from 2023, confirmed VTE occurs in 3 out of 10,000 women per year under this hormonal substitution during premenopause or after the age of 40 [19].

With the combination pill, estrogen serum levels are achieved as in the early follicular phase. This is sufficient to avoid all known estrogen deficiency damage.

With endocrine myoma combination therapy, the time between 43 and 50 years can be bridged. This is the age phase with the most common fibroid problems. This also prevents early menopause, which can increase the risk of multimorbidity by a factor of up to 3 [20]. German professional society statements do not address this [21]. If the uterus is removed a few years before menopause due to bleeding disorders, then a Symptom resolved, but hormonal problems persist. This can cause forensic problems if women are informed about it.

Are Combination Pills Alone Enough?

As early as 1984, the Oxford Family Planning Association study showed a 30% reduction in myoma size [22]. There was a large case-control study stated as 50% risk reduction. The duration of pill use is relevant. In 2013, a meta-analysis [23], showed that pill use for at least 5 years reduced the risk of myoma by 17% and hypermenorrhea could be reduced by 50%.

Combination pills alone also protect against fibroid problems.

Additional Cancer Protection through Combination Pills

Endocrine myoma therapy in combination with the pill is also expected to provide additional benefits that more or less "compensate" for the VTE risk.

The basic VTE risk in healthy women of reproductive age is 1-5 per 100,000/year. This risk is increased by a factor of 10 to 40 during pregnancy and the postpartum period.

Now about cancer prevention, published as a review article in JAMA 2018 [24]. In 50 to 71-year-old women with a history of taking pills for at least 10 years: the risk of ovarian cancer was almost halved (RR 0.6). Protection was even more pronounced among smokers and obese women (RR 0.47 and RR 0.36.)

The risk of breast cancer from the pill was increased in a Danish prospective cohort study (RR 1.2 and RR 1.38.) [25]. In absolute terms, this meant 1 additional breast cancer diagnosis per 7,700 women. It should be noted that these were pills from 25 years ago or more. This no longer applies to today's lower pill dosages. This was confirmed by a meta-analysis [26], no pill risk for breast cancer. Another US study confirmed that (RR 1.00) [27], no increased risk of breast cancer from combination pills. If there is a genetic predisposition to cancer, combination pills can also reduce the risk [28,29]. The dogma "the pill causes cancer" is anachronistic [30]. Progestogen monopills do not provide the above cancer protection and mathematically increase the risk of breast cancer (RR 1.21) [25].

SUMMARY

Uterus removals without cancer indications are performed less frequently. Instead, uterine-preserving surgeries are increasing. Common indications are fibroid symptoms and bleeding disorders.

Every time the uterus is removed, there is reduced blood flow to the ovary due to loss of supply via the ovaricus branch of the uterine artery. This causes estrogen deficiency risks related to brain functions.

Such problems can also occur during uterine-preserving operations. This cannot be ruled out with certainty preoperatively.

Myoma therapies that lead to necrosis are risky. This creates the risk of tumor lysis syndrome, known from oncology.

This means that endocrine myoma therapy is given high priority. This is especially true when combined with combination pills approved by FDA/EMA. This also results in high hormonal cancer protection in healthy women and VTE risks can be classified as marginal.

REFERENCES

1. Parker WH, Jacoby V, Rocca W. Effect of bilateral oophorectomy on women's long-term health. Women's Health. 2009; 5: 565-576.
2. Rocca W, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neuroendocrinology. 2007; 11: 1075-1083.
3. Rocca W, Grossardt BR, Shuster LT, Stewart EA. Hysterectomy, Oophorectomy, Estrogen, and the Risk of Dementia Neurodegenerative Dis. 2012; 10: 175-178.
4. Thien Kieu Thi Phung, Berit Lindum Waltoft, Thomas Munk Laursen, Annette Settnes, Lars Vedel Kessing, Preben Bo Mortensen, et al. Hysterectomy, Oophorectomy and Risk of Dementia: A Nationwide Historical Cohort Study. Dement Geriatr Cogn Disord. 2010; 30: 43-50.
5. Koebele SV, Bimonte Nelson HA. Hysterectomy Uniquely Impacts Spatial Memory in a Rat Model: A Role for the Nonpregnant Uterus in Cognitive Processes. Endocrinology. 2019; 160: 1-19
6. Kritz-Silverstein D, Barrett-Connor E. Hysterectomy, Oophorectomy, and Cognitive Function in Older Women. J Am Geriatr Soc. 2002; 50: 55-61.
7. Bushra Imtiaza, Tuppurainen M, Tiihonen M, Kivipelto M, Soininen H, Hartikainen S, et al. Oophorectomy, Hysterectomy, and Risk of Alzheimer's Disease: A Nationwide Case-Control Study. J Alzheimer's Dis. 2014; 42: 575-581.
8. Hogervorst E. Oophorectomy and hysterectomy may increase dementia risk but only when performed prematurely. J Alzheimers Dis. 2014; 42: 583-586.
9. Georgakis MK, Beskou-Kontou T, Theodoridis I, Skalkidou A, Petridou E et al. Surgical menopause in association with cognitive function and risk of dementia: A systematic review and meta-analysis. Psychoneuroendocrinology. 2019; 106: 9-19
10. Wenderlein M. Psychohygiene in gynecology. Deutsches Ärzteblatt. 1976; 417-420.
11. Belay Y, Yirdaw K, Enawgaw B. Tumor lysis syndrome in patients with hematological malignancies. J Oncol. 2017: 9684909
12. Jones GL, Will A, Jackson GH, Webb NJA, Rule S. Guidelines for the management of tumor lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2015; 169: 661-671
13. McKenna S, Cheung A, Wolfe A, Coleman BL, Detsky ME, Munshi L, et al. Clinical interventions to prevent tumor lysis syndrome in hematologic malignancy: a multisite retrospective chart review. Can J Hosp Pharm. 2019; 72: 435-445
14. Darmon M, Vincent F, Camous L, Canet E, Bonmati C, Braun T, et al. Tumor lysis syndrome and acute kidney injury in high-risk hematology patients in the rasburicase era. A prospective multicentre study from the Groupe de Recherche en Réanimation Respiratoire et Onco-Hématologique. Br J Haematol. 2013; 162: 489-497.
15. Cairo MS, Bishop M. Tumor lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004; 127: 3-11.
16. Alakel N, Middeke JM, Schetelig J, Bornhauser M. Prevention and treatment of tumor lysis syndrome, and the efficacy and role of rasburicase. Onco Target Ther. 2017; 10: 597-605
17. Cosmai L, Porta C, Foramitti M, Perrone M, Mollica L, Gallieni M, et al. Preventive strategies for acute kidney injury in cancer patients. Clin Kidney J. 2021; 14: 70-83
18. Nitschke U. Oncological emergencies in everyday treatment. Best practice oncology. 2022; 17: 78-90
19. von Stockum S, Becker K, Baeurfeind A, Franke C, Fruzzetti F, Calaf

J, et al. NOMAC-E2 compares to LNG combined contraceptives in women over forty: real-world PRO-E2 study. Gynnecol Endocrinol. 2023; 23: 1-5.

20. Xu X, Jones M, Mishra GD. Age at natural menopause and development of chronic conditions and multimorbidity: results from an Australian prospective cohort. HUM Reprod. 2020; 35: 203-211.

21. Rabe T. Intermittent administration of ulipristal acetate for conservative myoma therapy and bleeding control in hypermenorrhea due to uterine myomatous joint statement of the DGGGEF eV and the BVF eV J. Kommunikationsmed. Endocrinol. 2015; 12: 65-73.

22. Vessey MP, Lawless M. The Oxford-Family Planning Association contraceptive study. Clin Obstet Gynaecol. 1984; 11: 743-757.

23. Quin J, Yang T, Kong F, Zhou Q. Oral contraceptive use and uterine leiomyoma risk: a metaanalysis based on cohort and case-control studies. Arch Gynecol Obstet. 2023; 288: 22-27.

24. Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the Associations between Duration of Oral Contraceptive Use and Ovarian, Endometrial, Breast, and Colorectal Cancers. JAMA Oncol. 2018; 4: 516-521.

25. Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary Hormonal Contraception and the Risk of Breast Cancer. N Engl J Med. 2017; 377: 2228-2239.

26. Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008; 371: 303-314.

27. Cibula D, Zikan M, Dusek L, Majek O. Oral contraceptives and risk of ovarian and breast cancers in BRCA mutation carriers: a meta-analysis. Human Reproduction Update, Expert Rev Anticancer Ther. 2011; 11: 1197-1207.

28. Collaborative Group on Epidemiological Studies on Endometrial Cancer: Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118,964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012; 13:1141-1151.

29. Collaborative Group on Epidemiological Studies on Endometrial Cancer: Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 2015; 16: 1061-1070

30. Marsden J. Hormonal contraception and breast cancer, what more do we need to know? Post Reproductive Health. 2017; 0: 1-12.