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Oophorectomy, Hysterectomy, Vaginal estrogens: What the research tells us about cancer risk reduction

Chlebowski, R. T. (2002). "**Breast cancer risk reduction**: strategies for women at increased risk." Annu Rev Med **53**: 519-40.

Breast cancer risk reduction now represents an achievable medical objective. Current interventions include selective estrogen receptor modulators (SERMs), **prophylactic surgery**, and lifestyle change. For SERMs, current evidence supports tamoxifen use for breast cancer risk reduction whereas raloxifene requires further study. Prophylactic mastectomy and **prophylactic oophorectomy**, effective in retrospective clinical experiences, should be considered only for women at **substantial risk** willing to accept the irreversible consequences of these procedures. Although dietary fat intake is under clinical trial evaluation, lifestyle change, including weight loss, dietary change, and increased physical activity, can be recommended based on other health considerations. Use of any intervention requires careful breast cancer risk assessment, risk-benefit calculations, and informed decision making with full patient participation. **Future breast cancer risk assessment may incorporate additional biologic measures of estrogen exposure and/or analyses of collected breast cells.** Under active evaluation are novel SERMs, aromatase inhibitors/inactivators, gonadotrophin-releasing hormone agonists, retinoids, statins, and tyrosine kinase and cyclooxygenase-2 inhibitors.

Rhodes, D. J. (2002). "Identifying and counseling **women at increased risk for breast cancer.**" Mayo Clin Proc **77**(4): 355-60; quiz 360-1.

Women at increased risk for breast cancer should be identified and counseled about options for risk reduction. Identifying such women is simplified with use of the National Cancer Institute Risk Assessment tool, a computer-based tool that incorporates information on 6 risk factors for estimating an individual's risk of developing breast cancer. However, the tool does not incorporate all known or possible risk factors and may underestimate risk, particularly among women with a complex family history of breast cancer for whom alternative models of risk assessment are more appropriate. **Women found to have an increased risk of breast cancer should be counseled about options for management, including close surveillance, lifestyle modifications, chemoprevention with tamoxifen, enrollment in a breast cancer prevention clinical trial, and prophylactic mastectomy and/or oophorectomy.** In the absence of consensus about which risk level is best suited to which option, decisions about risk reduction depend as much on an individual's priorities and risk aversion as on numerical risk estimates.

Einbeigi, Z., J. M. Meis-Kindblom, et al. (2002). "Clustering of **individuals with both breast and ovarian cancer**--a possible indicator of BRCA founder mutations." Acta Oncol **41**(2): 153-7.

In a cohort of 60436 women with a diagnosis of invasive breast carcinoma and known to reside in Sweden in 1960, 321 had a subsequent diagnosis of ovarian carcinoma. Assuming no correlation between the

two cancers, one would expect that 191 women would develop ovarian cancer (standardized incidence ratio (SIR) 1.7; 95% confidence interval 1.5-1.9). Women with breast cancer before 40 years of age were at highest risk for developing ovarian cancer (SIR 4.5). Between 40 and 49 years of age, the SIR was 1.9, and at 50 years of age or older, the SIR was 1.3. Most of the excess in ovarian cancer occurred in southern Sweden. The geographic distribution of these cases coincided with the distribution of families with known BRCA1 and BRCA2 gene mutations. **These results suggest that genetic factors account for the excess in ovarian cancer that occurs in breast cancer patients and that geographic clustering of patients who have both breast and ovarian cancer may indicate the presence of a BRCA founder mutation.**

Parazzini, F., C. Braga, et al. (1997). "Hysterectomy, oophorectomy in premenopause, and risk of breast cancer." *Obstet Gynecol* **90**(3): 453-6.

OBJECTIVE: To analyze the risk of breast cancer in women who underwent pelvic surgery in premenopause using data from two case-control studies conducted between 1983 and 1994 in six Italian centers. **METHODS:** Subjects were 5984 women with histologically confirmed breast cancer diagnosed within the year before interview who were admitted to the major teaching and general hospitals in the areas included in the studies. Controls were 5504 women who resided in the same geographic areas and were admitted for acute conditions to the same network of hospitals in which cases had been identified. Women were not included if they had been admitted for gynecologic, hormonal, or neoplastic disease. **RESULTS:** A total of 719 cases (12%) and 801 controls (15%) underwent pelvic surgery before menopause. **The risk of breast cancer was reduced in women who underwent bilateral oophorectomy with hysterectomy (odds ratio [OR] adjusted for age, calendar year at interview, study, and center, 0.8, 95% confidence interval [CI] 0.7, 0.9) and hysterectomy alone (OR 0.7, 95% CI 0.6, 0.8). The protection tended to increase with time since surgery,** but no relationship emerged when age at menopause was included in the analysis. No clear relationship emerged between time since unilateral oophorectomy with or without hysterectomy or since hysterectomy alone and breast cancer risk. **CONCLUSION:** The risk of breast cancer is lower in women who undergo bilateral oophorectomy before menopause, and the protection increases with time from surgery.

Schairer, C., I. Persson, et al. (1997). "Breast cancer risk associated with gynecologic surgery and indications for such surgery." *Int J Cancer* **70**(2): 150-4.

Risk of breast cancer was assessed in relationship to gynecologic operations using data from a record-linkage study involving 15,844 women in the Uppsala Health Care Region of Sweden, who underwent surgery between 1965 and 1983. Data abstracted from medical records for the breast cancer cases and a random sample of the cohort allowed examination of risk associated with these operations in regard to menopausal status and indications for the operations. **Among women who were pre-menopausal at the time of operation, a bilateral oophorectomy before the age of 50 years was associated with a 50% reduction in the risk of breast cancer compared with the background population, a reduction in risk evident within 10 years of the operation.** A bilateral oophorectomy after the age of 50 years in pre-menopausal women or after a natural menopause was not associated with any reduction in risk. There were no reductions in risk associated with a unilateral oophorectomy or hysterectomy among women who were pre-menopausal at the time of operation. In fact, hysterectomy alone was associated with a slight increase in breast cancer risk when the operation was due to myomas, abnormal bleeding, and, possibly, severe forms of endometriosis but not to other reasons. Risk did not vary substantially by indications for oophorectomy, including benign ovarian neoplasms and functional ovarian cysts, though endometriosis was associated with a non-significant increase in breast cancer risk.

Annegers, J. F., H. Strom, et al. (1979). "**Ovarian cancer**: incidence and case-control study." *Cancer* **43**(2): 723-9.

The incidence of ovarian cancer in Rochester, Minnesota over the 40-year period 1935 through 1974 was determined; and risk factors for epithelial ovarian cancer occurring in Rochester from 1945 to 1974 were examined in 116 patients and 464 controls. Among the characteristics studied, only nulliparity was found to be a significant risk factor--relative risk 1.8. Other suspected risk factors--including hypertension, obesity, age at menopause, prior therapeutic pelvic radiation, and prior exposure to exogenous estrogen--were found not to differ significantly between patients and controls. **The ovarian cancer patients were found to have a significantly lower frequency of prior hysterectomy and of unilateral oophorectomy than the control group. Thus our data show that hysterectomy, even when one or both ovaries are preserved, is associated with a lower risk of subsequent ovarian cancer.**

Axelrod, J. H., R. Fruchter, et al. (1984). "Multiple primaries among gynecologic malignancies." *Gynecol Oncol* **18**(3): 359-72.

Seventy-eight synchronous or metachronous tumors among 2362 patients followed by the Downstate Gynecologic Tumor Registry are reviewed. Significant synchronous tumor pairs include **cervix (invasive and in situ)-ovary**, cervix (in situ)-uterus, cervix (in situ)-kidney, **endometrium-ovary**, endometrium-rectosigmoid, and **ovary-breast**. Significant metachronous pairs include cervix (invasive and in situ combined)-lung, cervix (invasive and in situ combined)-upper alimentary tract, and cervix (invasive)-rectosigmoid. In the case of in situ and invasive cervical cancer-lower genital tract, significance was determined for both synchronous and metachronous pairs. Long survival is an important factor in the appearance of a second tumor as demonstrated in patients with cervical carcinoma. Synchronous data prove to be valuable in assessing in risk of second primaries in patients surviving for short periods. The roles of cigarette smoking, hormones, immunosuppression, radiotherapy, and screening are discussed.

Parazzini, F., E. Negri, et al. (1992). "**Family history of reproductive cancers and ovarian cancer risk**: an Italian case-control study." *Am J Epidemiol* **135**(1): 35-40.

The relation between family history of ovarian, breast, and endometrial cancer and risk of epithelial ovarian carcinoma was analyzed within the framework of a case-control study conducted from 1983 to 1989. The study included 755 cases of ovarian cancer and 2,023 controls in hospital for a spectrum of acute nongynecologic, hormonal, or neoplastic conditions in the Greater Milan area, Italy. Eighteen cases (2%) and 24 controls (1%) reported a history of ovarian cancer in a first-degree relative: The corresponding multivariate adjusted odds ratio (OR) was 1.9 (95% confidence interval (CI) 1.1-3.6). The risk of ovarian cancer was elevated in women reporting a family history of breast cancer (OR = 1.6, 95% CI 1.1-2.3), but no significant association emerged with a family history of endometrial cancer (OR = 1.3, 95% CI 0.8-1.7). When the data were stratified by family history of breast cancer, a family history of ovarian cancer was over 10 times more frequent in both cases and controls who reported a family history of breast cancer than in cases and controls reporting no family history of breast cancer. **The estimated odds ratio for ovarian cancer associated with a family history of the disease was 2.3 (95% CI 1.1-4.5) in women not reporting a family history of breast cancer**, but no association emerged in the subgroup of women reporting a family history of breast cancer. These results confirm that a family history of ovarian cancer increases the risk of the disease, but the percentage of ovarian cancer cases explained by a family history of the disease is small: **Less than 1% of observed cases in this study could be attributed to this "family risk factor."**

Bergfeldt, K., B. Rydh, et al. (2002). "**Risk of ovarian cancer in breast-cancer patients with a family history of breast or ovarian cancer**: a population-based cohort study." *Lancet* **360**(9337): 891-4.

BACKGROUND: Patients with breast cancer who have mutations in the high penetrance genes BRCA1 and BRCA2, have an increased risk of ovarian cancer. Because these mutations are rare, easily obtained information such as age and family history of breast or ovarian cancer might be preferable for assessment of ovarian cancer risk in clinical practice. **METHODS:** We linked data from the Swedish Cancer Register to the Swedish Generation Register and generated a cohort of 30552 breast-cancer patients born after 1931, with information on breast and ovarian cancer diagnosis from 146117 first-degree relatives. Standardised incidence ratios (SIRs) with 95% CIs were calculated with nationwide rates of ovarian cancer, adjusted for age and calendar year. **FINDINGS:** During a mean follow-up of 6 years, 122 incident ovarian cancers were identified in the cohort, yielding an overall SIR of 2.0 (95% CI 1.6-2.4). The risk was higher in breast-cancer patients diagnosed before the age of 40 years, with a family history of breast cancer (5.6; 1.8-13.1) or ovarian cancer (17.0; 3.5-50.0). A consistently increased risk was noted in patients with a relative who was diagnosed before the age of 50 years, with either breast or ovarian cancer. Women with a family history of ovarian cancer have an almost 10% risk of developing ovarian cancer before the age of 70. **INTERPRETATION: In young women with breast cancer, the risk of ovarian cancer is greatly raised when a family history of breast or ovarian cancer is present. Close medical surveillance, and perhaps even prophylactic oophorectomy, might be justified in high-risk groups.**

Nahhas, W. A. (1997). "Ovarian cancer. Current outlook on this deadly disease." *Postgrad Med* **102**(3): 112-20.

The lifetime risk of ovarian cancer in the US population is about 1.4%. The risk is increased in women who have a strong family history of the disease. Unfortunately, no accurate screening tests are available. Transvaginal sonography and CA-125 determinations can be valuable in very high risk patients. **Attempts at prevention with oral contraceptive use and indicated or prophylactic oophorectomy/hysterectomy should be seriously considered.** Conservative treatment is appropriate in selected patients with early-stage ovarian cancer. However, because the majority of patients present with advanced disease, maximum cytoreductive surgery followed by chemotherapy is usually required. Such an approach results in a high incidence of initial clinical remission and can prolong survival to 2 or 3 years. Eventually, however, relapse and death often occur in spite of additional therapy. Another operation may be needed for secondary cytoreduction or palliation. Bowel obstruction, recurrent ascites, and pleural effusion are often terminal events.

Coukos, G. and S. C. Rubin (2002). "**Prophylactic oophorectomy.**" *Best Pract Res Clin Obstet Gynaecol* **16**(4): 597-609.

Because of the lack of effective alternatives and the simplicity of the procedure, prophylactic oophorectomy is viewed as the best available tool for reducing the individual risk of ovarian cancer. The genetics of hereditary ovarian cancer are described in this chapter and a careful risk-versus-benefit assessment is provided with respect to two populations of patients that appear suitable candidates for this procedure. These include patients with increased risk of developing ovarian cancer due to hereditary genetic predisposition, in which the lifetime risk of ovarian cancer may be as high as 16-65%, depending on the penetrance of the germ-line mutation. **Additionally, routine salpingo-oophorectomy in patients over 40 years undergoing scheduled gynaecological surgery or colorectal surgery might reduce the overall incidence of ovarian cancer by as much as 5% in the general population.**

Meijer, W. J. and A. C. van Lindert (1992). "**Prophylactic oophorectomy.**" *Eur J Obstet Gynecol Reprod Biol* **47**(1): 59-65.

The risks and benefits of prophylactic bilateral salpingo-oophorectomy (BSO) accompanying hysterectomy are reviewed. The potential reduction in the risk of subsequent ovarian cancer is quantified using literature data and a mathematical model. The risks of subsequent breast cancer from low-dose ERT are estimated using a comprehensive mathematical model. **It is shown that BSO may have a substantial protective effect on breast cancer risk despite subsequent low-dose or non-low-dose ERT, when BSO is performed at an early age.** In women with a family history of ovarian cancer or breast cancer, the individual risks must be assessed on the basis of a pedigree analysis. In conclusion, a decision on BSO must be based on weighing the potential benefits of reduced ovarian and breast cancer risks against the psychological importance of retaining the ovaries and the risk of osteoporosis and cardiovascular disease when compliance with ERT is less than perfect. The provided quantitative data may help in making the right decision.

Fong, Y. F., F. K. Lim, et al. (1998). "**Prophylactic oophorectomy: a continuing controversy.**" *Obstet Gynecol Surv* **53**(8): 493-9.

Prophylactic oophorectomy remains a controversial issue among gynecological surgeons. A woman's history of hereditary ovarian cancer syndrome is currently considered the most important indication for prophylactic oophorectomy. This is because of the high risk of ovarian cancer developing in these women and the poor prognosis that is generally associated with ovarian cancer. The purpose of prophylactic oophorectomy in women with no family history of hereditary ovarian cancer syndrome who present for hysterectomy because of other gynecological indications is, however, less clear. The attitude of the patients toward removal of normal ovaries deserves special consideration when counseling for prophylactic oophorectomy in this group of women. **Knowledge about the risk of ovarian cancer in the conserved ovaries, cancer phobia, possible psychological effects of prophylactic oophorectomy, and the need for long-term hormone replacement therapy if prophylactic oophorectomy is carried out, are all important considerations in the counseling process.**

Kontoravdis, A., D. Kalogirou, et al. (1996). "**Prophylactic oophorectomy in ovarian cancer prevention.**" *Int J Gynaecol Obstet* **54**(3): 257-62.

OBJECTIVE: To evaluate prophylactic oophorectomy in the prevention of ovarian cancer.
METHOD: Between 1970 and 1990, 5262 hysterectomies were performed at Areteion Hospital, Athens.
RESULTS: Ovarian cancer was subsequently diagnosed in 520 women (9.9%). The mean interval from hysterectomy to diagnosis of ovarian cancer was 7.2 years. **If prophylactic bilateral oophorectomy had been practiced routinely in women undergoing hysterectomy at age 40 or above, 9.4% of cases would have been prevented.** **CONCLUSION:** We recommend bilateral oophorectomy for all women with a positive family history of ovarian carcinoma and for all women undergoing hysterectomy after the age of 40. The decision for prophylactic oophorectomy as a complementary procedure to other indicated gynecologic surgeries should depend on the individual patient and her ability to comply with lifelong estrogen replacement therapy.

Cape, D. B. and N. Kreiger (1999). "Gynaecological surgical procedures and risk of colorectal cancer in women." *Eur J Cancer Prev* **8**(6): 495-500.

This study explored the relationship between certain gynaecological procedures and the risk of colorectal cancer in Ontario women. The cohort comprised all women undergoing gynaecological surgery for tubal ligation, unilateral and bilateral oophorectomy, and hysterectomy between 1979 and 1993 in Ontario. Person-years were calculated until death, a cancer diagnosis, or the end of the study period, after linkage to the Ontario Cancer Registry and the Ontario mortality file. Relative risk estimates were based on comparing

observed and expected cancers in the cohort, the expected based on population incidence rates. In a cohort of more than 730,000 women, mean follow-up time was approximately 7.5 years. **The risk of colorectal cancer was reduced following certain of the surgical procedures.** Relative risk (RR) estimates for bilateral tubal sterilization [RR = 0.81; 95% confidence intervals (CI) = 0.70-0.93], hysterectomy (RR = 0.89; 95% CI = 0.81-0.97) and **hysterectomy with bilateral salpingo-oophorectomy (RR = 0.84, 95% CI = 0.75-0.94) all were substantially lower than 1.0**, while neither unilateral oophorectomy nor tubal sterilization yielded risks different from 1.0. No pattern of altered risk was evident across age groups or over time since the surgical procedure. While there is potential for uncontrolled confounding by such exposures as hormone replacement therapy, the observed risks are consistent with a hypothesis of lowered endogenous oestrogen levels being associated with reduced risk of colorectal cancer. **(i.e. removal of ovaries reduces colon cancer 16%)**

Swisher, E. M., S. Babb, et al. (2001). "**Prophylactic oophorectomy** and ovarian cancer surveillance. Patient perceptions and satisfaction." *J Reprod Med* **46**(2): 87-94.

OBJECTIVE: To evaluate decision making, information gathering, satisfaction and regret in women at increased risk of ovarian cancer who had undergone prophylactic oophorectomy or ovarian cancer surveillance. **STUDY DESIGN:** Thirty women undergoing prophylactic oophorectomy (median age, 47 years) and 30 women who had undergone ovarian cancer surveillance (median age, 43) completed an in-depth telephone interview consisting of open-ended questions. **RESULTS:** Most commonly cited concerns before prophylactic oophorectomy included the physical discomfort of surgery and recovery (40%) and issues of immediate menopause and hormone replacement (37%). Fourteen women (47%) would have liked more information prior to surgery. Two women (7%) expressed regret about their decision. The remaining 28 women (93%) undergoing prophylactic oophorectomy expressed no regret about the decision. Nine women (37%) would have liked more information prior to considering ovarian cancer surveillance. Nearly half the women undergoing surveillance did not recall receiving any information about prophylactic oophorectomy as an option. Fifteen women (50%) expressed some regret about ovarian cancer surveillance, and three were frankly dissatisfied. **CONCLUSION: Few women undergoing prophylactic oophorectomy had regret about their decision, though half these women would have liked more information prior to surgery. Many women undergoing ovarian cancer surveillance had some regret about or dissatisfaction with their decision.**

Negri, E., C. Pelucchi, et al. (2003). "**Family history of cancer and risk of ovarian cancer.**" *Eur J Cancer* **39**(4): 505-10.

The aim of this study was to examine the relationship between history of cancer in first-degree relatives and ovarian cancer risk. Between 1992 and 1999, we conducted a case-control study in Italy on 1031 women with epithelial ovarian cancer and 2411 women admitted to hospital for acute non-neoplastic conditions. Odds ratios (OR) were estimated using unconditional logistic regression, adjusted for age and several potential confounders. Overall, 27 cases and nine controls reported a family history of ovarian cancer (OR = 7.0; 95% confidence interval (CI) 3.1-16). The OR was 23 (95% CI 2.6-212) below age 50 years, based on 10 cases and one control only. **The risk of ovarian cancer was also increased in women with a family history of cancer of the stomach (OR = 1.5; 95% CI 1.0-2.1), intestine (OR = 1.7; 95% CI 1.2-2.4), lung (OR = 1.3; 95% CI 1.0-1.8), breast (OR = 2.3; 95% CI 1.7-3.1), lymphomas (OR = 2.3; 95% CI 1.0-5.1) and all sites (OR = 1.6; 95% CI 1.4-1.9). Our results confirm the higher ovarian cancer risk in women with a family history of ovarian and breast cancer, and suggest a few associations with other sites.**

Tiller, K., B. Meiser, et al. (2002). "Psychological impact of **prophylactic oophorectomy** in women at increased risk of developing ovarian cancer: a prospective study." *Gynecol Oncol* **86**(2): 212-9.

OBJECTIVES: The objectives of this study were twofold: to prospectively assess whether expressed intention to undergo prophylactic oophorectomy translated into uptake and to evaluate the psychological impact of the procedure in a sample of unaffected women with a strong family history of breast/ovarian cancer. **METHODS:** Ninety-five women, initially assessed at the time of their first attendance at a familial cancer clinic, were followed-up 3 years later. A total of 22 women (23.2%) in this study had undergone a prophylactic oophorectomy. Ten women (10.5%) who had undergone a prophylactic oophorectomy during the 3-year follow-up period were compared to 73 women (76.9%) who did not have a prophylactic oophorectomy. Twelve women (12.6%) who had the procedure prior to study entry were also assessed for psychological adjustment and associated information needs. **RESULTS:** Age emerged as a significant predictor of uptake of prophylactic oophorectomy ($\chi^2 = 7.13$, $P = 0.009$). Among those who had the procedure after study entry, a significant reduction in ovarian cancer anxiety was observed ($Z = -2.19$, $P = 0.029$). Of the 22 women who had undergone a prophylactic oophorectomy in total (both before and after study entry), 86.4% reported a high degree of satisfaction with their decision to have the procedure. A low level of screening uptake was also reported by women who did not have a prophylactic oophorectomy but for whom screening was recommended. **CONCLUSION: Findings demonstrate that prophylactic oophorectomy is successful in reducing anxiety about ovarian cancer. The results also suggest that women perceive that the benefit of anxiety reduction may outweigh the potentially adverse effects of the procedure, given that women expressed a high level of satisfaction with their decision.**

Gehrig, P.A., V.L. Bae-Jump, J.F. Boggess, P.A. Groben, W.C. Fowler, Jr., and L. Van Le. 2004. **Association between uterine serous carcinoma and breast cancer.** *Gynecol Oncol.* 94: 208-211.

OBJECTIVE: Endometrial cancer and breast cancer are two common malignancies found in women. As a result of estrogen dependency, an association is thought to exist between these entities. This study was undertaken to determine if the endometrial carcinomas, which develop in women with a history of breast cancer, were more likely to be of the endometrioid or the serous histology, which is generally considered non-estrogen-dependent. **METHODS:** A retrospective chart review was conducted for the years 1984-2001. All women who were diagnosed at our institution with endometrial carcinoma were identified. The women who also had a prior history of breast cancer were identified and comprise the cohort for this study. Information regarding age at diagnosis, tumor stage, histologic subtype, and tamoxifen exposure were recorded and analyzed. **RESULTS:** About 1166 women were diagnosed with endometrial cancer during the study period, of whom 54 (4.6%) had a pre-existing diagnosis of breast cancer. Of the 54 women in this study, 41 had tumors of the endometrioid histology and 13 had a tumor of the serous subtype. There was no difference with regards to median age at the time of diagnosis or years of tamoxifen exposure. Women with breast cancer were more likely to develop uterine serous carcinoma (USC) as compared to one of endometrioid histology (OR 2.6; 95% CI 1.29-5.23). **CONCLUSIONS: Women with breast cancer who subsequently developed endometrial cancer exhibited a 2.6-fold increased risk of developing a USC as compared to an endometrioid carcinoma. These findings suggest that there may be an underlying genetic predisposition linking breast cancer and USC.**

Hysterectomy

Grover, C. M., M. Kuppermann, et al. (1996). "Concurrent hysterectomy at bilateral salpingo-oophorectomy: benefits, risks, and costs." *Obstet Gynecol* **88**(6): 907-13.

OBJECTIVE: To evaluate the medical and economic consequences of concurrent hysterectomy at the time of bilateral salpingo-oophorectomy (BSO) for benign ovarian disease in peri- and postmenopausal women. **METHODS:** Decision analysis was used to compare the health outcomes and economic costs of performing BSO with concurrent hysterectomy versus BSO alone in theoretic cohorts of 10,000 women undergoing surgery for benign adnexal disease. A model was constructed incorporating probabilities of possible outcomes from the National Hospital Discharge Database, the National Cancer Institute SEER Program, and the literature. Data on associated costs were obtained from the California State Discharge Database, Medicare, and the literature. **RESULTS:** Performing concurrent hysterectomy in a cohort of 10,000 45-year-old women would prevent approximately 71 future deaths from gynecologic disease at a cost of five immediate deaths from the surgery. However, short-term complications are much more frequent in women undergoing hysterectomy. On average, hysterectomy at age 45 adds approximately 0.071 years of life expectancy; at age 55, it adds 0.026 years. The procedure results in cost savings of approximately \$1913 per patient at age 45 and \$1112 at age 55. **CONCLUSION: Concurrent hysterectomy causes short-term morbidity, but appears to increase average life expectancy slightly among perimenopausal women and is cost-saving. Medical outcomes and economic consequences favor the procedure.**

Olsson, J. H., M. Ellstrom, et al. (1996). "A randomised prospective trial comparing laparoscopic and abdominal hysterectomy." *Br J Obstet Gynaecol* **103**(4): 345-50.

OBJECTIVE: To compare short term clinical results in a prospective randomised trial of laparoscopic hysterectomy compared with abdominal hysterectomy. **METHODS:** One hundred and forty-three women scheduled for total abdominal hysterectomy, with or without salpingo-oophorectomy and with a maximum uterine width of less than 11 cm, were prospectively randomised to undergo the procedure by laparoscopic hysterectomy (n = 71) or abdominal hysterectomy (n = 72). During laparoscopic hysterectomy, the uterine arteries as well as the upper portion of the cardinal ligaments were transected laparoscopically. The perioperative and post-operative courses of the groups were compared. **RESULTS:** The number of women with a complication did not differ significantly between laparoscopic hysterectomy (27%) and abdominal hysterectomy (33%) groups. The post-operative fall in erythrocyte volume fraction was significantly greater following abdominal hysterectomy (5.6% compared with 4.1% median value, P < 0.001). Post operative pain, assessed by the patients two days after surgery on a visual analogue scale, was significantly higher following abdominal hysterectomy (4.2 compared with 3.6 units median value, P < 0.05). Although laparoscopic hysterectomy took longer (148 min compared with 85 min median value, P < 0.001), the women undergoing this procedure had a shorter post-operative time in hospital (two compared with four days median value, P < 0.001) and a shorter convalescence (16 compared with 35 days median value, P < 0.001). **CONCLUSIONS: Laparoscopic hysterectomy is a safe procedure for selected patients scheduled for abdominal hysterectomy, and offers benefits to the patients in the form of less operative bleeding, less post-operative pain, shorter time in hospital and shorter convalescence time.**

Kritz-Silverstein, D., D. Goldani Von Muhlen, et al. (2000). "Prevalence and clustering of menopausal symptoms in older women by hysterectomy and oophorectomy status." *J Womens Health Gend Based Med* **9**(7): 747-55.

This study examines the association of hysterectomy and oophorectomy with the prevalence and clustering of menopausal symptoms in a large population-based sample of older women. Subjects were 1121 women aged 50-89 from the Rancho Bernardo Study. Information on menopause, hysterectomy, oophorectomy, estrogen use, and other covariates was obtained in 1984-1987. A 1989 mailed survey obtained information on menopausal symptoms. In this sample, 22.1% reported hysterectomy with bilateral oophorectomy, and 25.3% reported hysterectomy with ovarian conservation. Mean time since hysterectomy

was 26 (+/-12) years. Overall, 37% reported current estrogen use, and 40% reported past use. The duration of estrogen use was longer for women who had a hysterectomy ($p < 0.001$). Age-adjusted comparisons indicated that more women who had a hysterectomy, with or without bilateral oophorectomy, reported greater energy after menopause ($p = 0.003$ and $p = 0.001$, respectively), and more women with bilateral oophorectomy reported greater interest in sex ($p = 0.007$) and that life was getting better ($p = 0.012$) than women with natural menopause. Principal components factor analysis of the symptom data for all women yielded four factors: psychological, vasomotor, positive feelings, and self-image. Analyses performed within each group of women yielded similar factors and loadings. Adjusted comparisons of factor scores indicated that positive feelings were significantly higher in women who had a hysterectomy, with or without bilateral oophorectomy ($p < 0.01$) than in women with natural menopause. This difference was limited to current estrogen users. Vasomotor symptoms, psychological symptoms, and negative self-image did not differ by hysterectomy or oophorectomy status before or after stratification for estrogen use ($p > 0.10$). **This study found after a hysterectomy, women are more likely to recall positive feelings about their menopause than women with natural menopause. Relief from symptoms leading to hysterectomy and use of replacement estrogen may be partly responsible. Results do not support the thesis that surgical menopause is associated with a sustained increased prevalence of vasomotor, psychological, or other symptoms.**

Khastgir, G. and J. Studd (2000). "Patients' outlook, experience, and **satisfaction with hysterectomy**, bilateral oophorectomy, and subsequent continuation of hormone replacement therapy." *Am J Obstet Gynecol* **183**(6): 1427-33.

OBJECTIVE: Our purposes were to investigate patients' opinions of hysterectomy, bilateral oophorectomy, and hormone replacement therapy and to evaluate whether their outlook and experience influenced the overall satisfaction and continuation of hormone replacement therapy. **Study Design:** We conducted a questionnaire survey of 200 patients before and 2 years after hysterectomy with or without bilateral oophorectomy. Postoperatively all patients received long-term estradiol and testosterone replacement. The inquiries of patients' views included (1) preoperative awareness of indication and outlook, (2) postoperative recovery, symptom relief, and experiences with hormone replacement therapy, (3) perceived benefits and problems, (4) changes in physical well-being, psychologic state, and sexual activity, (5) continuation of hormone replacement therapy, and (6) overall satisfaction. **RESULTS:** The outlook toward hysterectomy, bilateral oophorectomy, and hormone replacement therapy was positive in 77.4%, 87.1%, and 76.3%, respectively. **The experience was positive in the majority, with a satisfactory postoperative recovery (70.6%), complete symptom relief (77.9%), and minimal side effects with hormone replacement therapy (5.2%). The benefits included improved physical well-being (79.9%), lower depressive symptoms (32.0%), and better sexuality (31.4%). The continuation rate of hormone replacement therapy was 97.4%, and overall satisfaction was positive in 88.7% of patients. The independent predictors of satisfaction were outlook toward hysterectomy and incomplete symptom relief.** **CONCLUSION:** The outcome of hysterectomy, bilateral oophorectomy, and hormone replacement therapy was satisfactory to most patients.

Kjerulff, K. H., P. W. Langenberg, et al. (2000). "Effectiveness of hysterectomy." *Obstet Gynecol* **95**(3): 319-26.

OBJECTIVE: To measure the effectiveness of hysterectomy in relieving adverse symptoms and to identify factors associated with lack of symptom relief. **METHODS:** In a 2-year prospective study, data were collected before and at 3, 6, 12, 18, and 24 months after hysterectomy in 1,299 women who had hysterectomies for benign conditions at 28 hospitals across Maryland. Effectiveness was measured in terms

of relief of symptoms such as problematic vaginal bleeding, pelvic pain, and urinary incontinence. Psychologic function and quality of life before and after surgery also were assessed. **RESULTS:** Symptom severity, depression, and anxiety levels decreased significantly after hysterectomy and quality of life improved, particularly in the area of social function. However, 8% of women had at least as many symptoms at problematic-severe levels 1 and 2 years after hysterectomy as before. In multiple logistic regression, several presurgical patient characteristics predicted lack of symptom relief, including therapy for emotional or psychologic problems, depression, and household income of \$35,000 or less. **CONCLUSION: Significant improvements were seen after hysterectomy for all three aspects of health status (symptoms, psychologic function, and quality of life), which persisted or continued to improve throughout the 2 years of follow-up. However, hysterectomy did not relieve symptoms for some women, particularly those who had low incomes or were in therapy at the time of hysterectomy.**

Rhodes, J. C., K. H. Kjerulff, et al. (1999). "Hysterectomy and sexual functioning." *Jama* **282**(20): 1934-41. **CONTEXT:** Women considering hysterectomy often are concerned about its potential effects on their sexual functioning but the effects of hysterectomy on sexual functioning remain unclear. **OBJECTIVE:** To examine changes in sexual functioning after hysterectomy. **DESIGN AND SETTING:** A 2-year prospective study (Maryland Women's Health Study) of hysterectomy, which included measures of sexual functioning prior to hysterectomy and at 6, 12, 18, and 24 months after hysterectomy, performed during 1992 and 1993. **PATIENTS:** Of 1299 women interviewed prior to hysterectomy, 1101 (84.8%) completed the study and provided information about their sexual functioning. Most were between the ages of 35 and 49 years, white, married or living with a partner, and high school graduates. **MAIN OUTCOME MEASURES:** Frequency of sexual relations, dyspareunia, orgasm, vaginal dryness, and sexual desire. **RESULTS: The percentage of women who engaged in sexual relations increased significantly from 70.5% before hysterectomy to 77.6% and 76.7% at 12 and 24 months after hysterectomy. The rate of frequent dyspareunia dropped significantly from 18.6% before hysterectomy to 4.3% and 3.6% at 12 and 24 months after hysterectomy. The rates of not experiencing orgasms dropped significantly from 7.6% before hysterectomy to 5.2% and 4.9% at 12 and 24 months after hysterectomy. Low libido rates also decreased significantly from 10.4% before hysterectomy to 6.3% and 6.2% at 12 and 24 months after hysterectomy. The distribution of women not reporting vaginal dryness in the past month improved significantly from 37.3% before hysterectomy to 46.8% and 46.7% at 12 and 24 months after hysterectomy. Prehysterectomy depression was associated with experiencing dyspareunia, vaginal dryness, low libido, and not experiencing orgasms after hysterectomy. CONCLUSIONS: Sexual functioning improved overall after hysterectomy. The frequency of sexual activity increased and problems with sexual functioning decreased.**

O'Hanlan, K. A., G. S. Huang, et al. (2004). "Selective incorporation of total laparoscopic hysterectomy for adnexal pathology and body mass index." *Gynecol Oncol* **93**(1): 137-43.

OBJECTIVES: We studied patients undergoing adnexectomy with total laparoscopic hysterectomy (TLH) for ovarian pathology, over a 6-year period. **METHODS:** Chart abstraction, analyzed by ANOVA, Fisher's Exact Test with significance at $P < 0.05$, stratifying by body mass index (BMI, kg/m²): ideal < 25; overweight 25-29.9; obese 30+). **RESULTS:** Of 354 patients undergoing TLH, 90 cases had adnexal pathology: 69 complex masses, 16 BRCA1/2 mutations, 5 unstaged ovarian carcinomas; 48 having ideal BMI, 26 overweight, and 16 obese. Mean age (51 years) and parity (1.2 children) were similar between BMI groups. Thirty-four percent were nulliparous. All 90 underwent TLH, adnexectomy, washings; with 14 appendectomies, 5 lymphadenectomies, 3 node samplings, 6 omentectomies, 8 ureterolyses, and 1 Burch. Mean surgery duration (156 min), blood loss (152cc), and hospital stay (1.9 days) were similar across BMI

groups. Mean nodal yield from each lymphadenectomy was 14, and 2.6 from sampling. Mean size of pelvic masses was 8 cm (range 3-19 cm). There were seven cases of ovarian carcinoma: 2 Stage IA, 1 IB, 2 IC, 1 IIC, 1 IIIB; 1 recurrent breast cancer, 16 adenofibromas, 15 endometriomas, 10 dermoids, and 41 serous/mucinous cystadenomas. Mean complication rate was 6.6% (ns): 1 seroma, 1 hematoma, 1 obstructive adhesions, and 3 urological injuries. All urological injuries were within the first third of patients.

CONCLUSIONS: TLH appears feasible for women with adnexal pathology regardless of BMI, in an oncological practice. This pilot data can facilitate guidelines for a randomized controlled trial of TLH with TAH and LAVH, and help surgeons avoid our early complications.

O'Hanlan, K.A., G.S. Huang, L. Lopez, and A.C. Garnier. 2004. Total laparoscopic hysterectomy for oncological indications with outcomes stratified by age. *Gynecol Oncol.* 95: 196-203.

Objective: We hypothesize that there is no difference in surgical outcomes of patients undergoing total laparoscopic hysterectomy (TLH) for various oncological indications, when stratified by age categories. **Methods:** Data was analyzed by ANOVA and Chi Square Test with significance of $p < 0.05$, stratified by age (Young: < 50 years, Middle 50-64, Senior age 65+).

Results: There were 208 patients, age 26-86 years: 85 young, 82 middle and 41 senior women. Pre-operative diagnoses included 13 cases of cervical dysplasia, 10 cervical/upper vaginal carcinoma, 60 endometrial neoplasias, 22 prophylaxes of familial ovarian carcinoma, 95 with complex pelvic mass, and 8 with early ovarian carcinoma. Mean BMI was 27.2kg/m² for all groups. Parity increased with age (1.0, 1.3, 2.0; $p = .001$). Surgical duration was longer for Young, than Middle or Senior (168, 147, 140 minutes, $p = .0095$). All groups had a similar mean blood loss (133 cc, ns), and similar mean length of hospital stay (1.8 days, ns). Overall complication rate was 7.7% with no variance by age: 1 seroma, 1 hematoma, 1 diverticulitis, 1 incisional hernia, 1 vaginal non-healing, 1 adhesive bowel obstruction, and 5 urologic complications (2 bladder, 3 ureteral; 4 treated with catheter or stent, 1 re-implant. Re-operation was required in 2.8%.

Conclusions: Null hypothesis accepted: **TLH appears feasible and safe for oncological practice indications throughout the life span.** This pilot data can facilitate guidelines for a randomized controlled trial of TLH with TAH and LAVH.

O'Hanlan, K. A., L. Lopez, et al. (2003). "Total laparoscopic hysterectomy: body mass index and outcomes." *Obstet Gynecol* **102**(6): 1384-92.

OBJECTIVE: This retrospective review of patients undergoing total laparoscopic hysterectomy examines whether differences in outcomes exist on the basis of body mass index (BMI). **METHODS:** All cases of total laparoscopic hysterectomy performed from September 1996 to July 2002 for benign diagnoses, and microinvasive cervical, early endometrial, and occult ovarian carcinoma were reviewed. There were 330 patients analyzed by BMI category (range, 18.5-54.1): ideal (n = 150) less than 24.9 kg/m², overweight (n = 95) 25 to 29.9 kg/m², and obese (n = 78) 30 kg/m² or more. Seven patients were converted to laparotomy (four ideal BMI, two overweight, one obese) leaving 323 (98%) for analysis. Mean age (50 years), height (65 in.), and parity (1.2) were similar, with 39% nulligravidas in each group. **RESULTS:** Mean operating time (156 minutes), blood loss (160 mL), and length of hospital stay (1.9 days) did not vary by BMI group. Total complication rates (8.9%), and major (5.5%) and minor (3.4%) complication rates were similar in each BMI group. Urologic injury was observed in 3.1%, with two-thirds occurring in the first one-third of the patient series. **CONCLUSION: Total laparoscopic hysterectomy is feasible and safe, resulting in short hospital stay, minimal blood loss, and minimal operating time for patients in all BMI groups.** The laparoscopic approach may extend the benefits of minimally invasive hysterectomy to the very obese, for whom abdominal surgery poses serious risk.

Khastgir, G. and J. Studd (2000). "Patients' outlook, experience, and satisfaction with hysterectomy, bilateral oophorectomy, and subsequent continuation of hormone replacement therapy." *Am J Obstet Gynecol* **183**(6): 1427-33.

OBJECTIVE: Our purposes were to investigate patients' opinions of hysterectomy, bilateral oophorectomy, and hormone replacement therapy and to evaluate whether their outlook and experience influenced the overall satisfaction and continuation of hormone replacement therapy. **Study Design:** We conducted a questionnaire survey of 200 patients before and 2 years after hysterectomy with or without bilateral oophorectomy. Postoperatively all patients received long-term estradiol and testosterone replacement. The inquiries of patients' views included (1) preoperative awareness of indication and outlook, (2) postoperative recovery, symptom relief, and experiences with hormone replacement therapy, (3) perceived benefits and problems, (4) changes in physical well-being, psychologic state, and sexual activity, (5) continuation of hormone replacement therapy, and (6) overall satisfaction. **RESULTS:** The outlook toward hysterectomy, bilateral oophorectomy, and hormone replacement therapy was positive in 77.4%, 87.1%, and 76.3%, respectively. **The experience was positive in the majority, with a satisfactory postoperative recovery (70.6%), complete symptom relief (77.9%), and minimal side effects with hormone replacement therapy (5.2%). The benefits included improved physical well-being (79.9%), lower depressive symptoms (32.0%), and better sexuality (31.4%). The continuation rate of hormone replacement therapy was 97.4%, and overall satisfaction was positive in 88.7% of patients. The independent predictors of satisfaction were outlook toward hysterectomy and incomplete symptom relief.** **CONCLUSION:** The outcome of hysterectomy, bilateral oophorectomy, and hormone replacement therapy was satisfactory to most patients.

Kuppermann, M., R.E. Varner, R.L. Summitt, Jr., L.A. Learman, C. Ireland, E. Vittinghoff, A.L. Stewart, F. Lin, H.E. Richter, J. Showstack, S.B. Hulley, and A.E. Washington. 2004. Effect of **hysterectomy vs medical treatment on health-related quality of life and sexual functioning: the medicine or surgery (Ms) randomized trial**. *Jama*. 291: 1447-1455.

CONTEXT: Although a quarter of US women undergo elective hysterectomy before menopause, controlled trials that evaluate the benefits and harms are lacking. **OBJECTIVE:** To compare the effect of hysterectomy vs expanded medical treatment on health-related quality of life. **DESIGN, SETTING, AND PARTICIPANTS:** A multicenter, randomized controlled trial (August 1997-December 2000) of 63 premenopausal women, aged 30 to 50 years, with abnormal uterine bleeding for a median of 4 years who were dissatisfied with medical treatments, including medroxyprogesterone acetate. The participants, who were patients at gynecology clinics and affiliated practices of 4 US academic medical centers, were followed up for 2 years. **INTERVENTIONS:** Participants were randomly assigned to undergo hysterectomy or expanded medical treatment with estrogen and/or progesterone and/or a prostaglandin synthetase inhibitor. The hysterectomy route and medical regimen were determined by the participating gynecologist. **MAIN OUTCOME MEASURES:** The primary outcome was mental health measured by the Mental Component Summary (MCS) of the 36-Item Short-Form Health Survey (SF-36). Secondary outcomes included physical health measured by the Physical Component Summary (PCS), symptom resolution and satisfaction, body image, and sexual functioning, as well as other aspects of mental health and general health perceptions. **RESULTS:** At 6 months, women in the hysterectomy group had greater improvement in MCS scores than women in the medicine group (8 vs 2, $P = .04$). They also had greater improvement in symptom resolution (75 vs 29, $P < .001$), symptom satisfaction (44 vs 7, $P < .001$), interference with sex (41 vs 22, $P = .003$), sexual desire (21 vs 3, $P = .01$), health distress (33 vs 13, $P = .009$), sleep problems (13 vs 1, $P = .03$), overall health (12 vs 2, $P = .006$), and satisfaction with health (31 vs 14, $P = .01$). By the end of the study, 17 (53%) of the women in the medicine group had requested and received hysterectomy, and these women reported

improvements in quality-of-life outcomes during the 2 years that were similar to those reported by women randomized to the hysterectomy group. Women who continued medical treatment also reported some improvements ($P < .001$ for within-group change in many outcomes), with the result that most differences between randomized groups at the end of the study were no longer statistically significant in the intention-to-treat analysis. **CONCLUSIONS: Among women with abnormal uterine bleeding and dissatisfaction with medroxyprogesterone, hysterectomy was superior to expanded medical treatment for improving health-related quality-of-life after 6 months. With longer follow-up, half the women randomized to medicine elected to undergo hysterectomy, with similar and lasting quality-of-life improvements; those who continued medical treatment also reported some improvements.**

Learman, L.A., R.L. Summitt, Jr., R.E. Varner, H.E. Richter, F. Lin, C.C. Ireland, M. Kuppermann, E. Vittinghoff, J. Showstack, A.E. Washington, and S.B. Hulley. 2004. Hysterectomy versus expanded medical treatment for abnormal uterine bleeding: clinical outcomes in the medicine or surgery trial. *Obstet Gynecol.* 103: 824-833.

OBJECTIVE: To compare clinical outcomes after randomization to hysterectomy versus medical treatment in patients with chronic abnormal uterine bleeding refractory to medroxyprogesterone acetate. **METHODS:** We randomly assigned 63 premenopausal women with abnormal uterine bleeding refractory to cyclic medroxyprogesterone acetate treatment to receive either a hysterectomy or expanded medical treatment. Within each randomized group, the specific treatment approach was determined by patient and provider preference. The primary analysis compared changes in clinical outcomes at 6 and 24 months by using an intention-to-treat approach. Secondary as-treated analyses after adjustment for baseline covariates compared participants randomly assigned to medical treatment who continued the medical approach with those who crossed over to hysterectomy. **RESULTS:** The intention-to-treat analyses at 6 months revealed greater symptom improvement in the hysterectomy group than in the medicine group for pelvic pain ($P < .01$), urinary urgency ($P = .03$), incomplete bladder emptying ($P = .03$), breast pain ($P = .02$), and cessation of vaginal bleeding (87% versus 11%, $P < .001$). Seventeen of 32 women assigned to medicine (53%) eventually crossed over and received a hysterectomy, and by 24 months the statistically significant differences by intention-to-treat were limited to greater improvement in hot flushes ($P < .01$) and cessation of vaginal bleeding ($P < .01$). Within-group analyses at year 2 showed statistically significant improvements from baseline on most symptoms for women who had a hysterectomy, whether through randomization or crossover. Women remaining on medical treatments had statistically significant improvements in pelvic pain, pelvic/bladder pressure, and stress incontinence. In a nonrandomized comparison with women who remained on medical treatments through year 2, those crossing over to hysterectomy experienced greater improvements in bleeding ($P < .01$), pelvic pain ($P < .01$), low back pain ($P = .02$), breast pain ($P = .01$), urinary frequency ($P = .01$), and urgency ($P = .02$). However, they also experienced more days off from work or usual activities ($P < .01$) and more days spent in bed ($P < .01$) than those who remained on medicine. **CONCLUSION: For patients with abnormal uterine bleeding refractory to medroxyprogesterone acetate, hysterectomy is superior to expanded efforts with oral medications for alleviating clinical symptoms but may lead to more days of restricted activity.**

Roussis, N.P., L. Waltrous, A. Kerr, R. Robertazzi, and M.F. Cabbad. 2004. Sexual response in the patient after hysterectomy: total abdominal versus supracervical versus vaginal procedure. *Am J Obstet Gynecol.* 190: 1427-1428.

OBJECTIVE: The present study examines the patient's own appraisal of her sexual responsiveness after hysterectomy. **STUDY DESIGN:** Four hundred women who had undergone hysterectomy within a 3-year

period were selected randomly and asked to respond to a questionnaire that was devised to ascertain the patient's own objective evaluation of self-image, sexuality, and sexual response before and after hysterectomy. The confidential responses were analyzed, noting the presence of any significant divergence between demographic and procedural cohorts. **RESULTS:** Of 126 respondents, 48.4% underwent total abdominal hysterectomy; 34.1% underwent vaginal hysterectomy, and 17.4% underwent supracervical hysterectomy. The mean patient age was 49.7+/-8.7 years. No direct correlation was found between hysterectomy type and age. Most women did not report any significant deterioration in mental attitude after the procedure ($P = .788$). Self and body image also remained consistent, with only 25.3% indicating a change for the worse. Only 10.3% of respondents felt less feminine after hysterectomy; nearly 70% of the respondents did not feel less feminine. **Responses that pertained to libido, sexual activity, or feelings of femininity did not reveal significant changes ($P > .05$). Satisfaction with procedural choice was positive (54.8%), with only 7.1% responding unfavorably.** **CONCLUSION:** The responses suggest that neither self-image nor sexuality need diminish after hysterectomy. The type of hysterectomy that was performed did not appear to affect the attitudes of the respondents.

Wydra, D., K. Ciach, S. Sawicki, J. Wilhelm, and J. Emerich. 2004. [Comparison of sexual behavior after total or subtotal hysterectomy]. *Ginekol Pol.* 75: 274-280.

OBJECTIVES: Sexual life after supracervical or total hysterectomy is still controversial. **DESIGN:** The aim of study was to compare the impact of hysterectomy on frequency and quality of a woman's sexual life in women after supracervical vs total hysterectomy with nonmalignant conditions. **MATERIAL AND METHODS:** A total of 539 women after total hysterectomy performed in Department of Gynecology in Gdansk and 65 women after supracervical hysterectomy operated in the hospital in Kartuzy in 1990-2000 were interviewed about symptoms as well as advantages and disadvantages after hysterectomy. **RESULTS:** **There was no statistical difference between those groups comparing: sexual desire, dyspareunia, frequency of sexual relation, orgasm, vaginal dryness after operation.** **CONCLUSION:** Total hysterectomy is recommended in benign conditions of uterine because of risk of cancer in the cervical stump after supracervical hysterectomy.

Zobbe, V., H. Gimbel, B.M. Andersen, T. Filtenborg, K. Jakobsen, H.C. Sorensen, K. Toftager-Larsen, K. Sidenius, N. Moller, E.M. Madsen, M. Vejtorp, H. Clausen, A. Rosgaard, C. Gluud, B.S. Ottesen, and A. Tabor. 2004. Sexuality after total vs. subtotal hysterectomy. *Acta Obstet Gynecol Scand.* 83: 191-196.

BACKGROUND: The effect of hysterectomy on sexuality is not fully elucidated and until recently total and subtotal hysterectomies have only been compared in observational studies. **AIMS:** To compare total abdominal hysterectomy (TAH) to subtotal abdominal hysterectomy (SAH) regarding effects on sexuality. **METHODS:** In a Danish multicenter trial 319 women were randomized to TAH ($n = 158$) or SAH ($n = 161$); 185 women had self-selected TAH ($n = 80$) or SAH ($n = 105$) in a simultaneously conducted observational study. Women were followed for 1 year by strict data collection procedures, including postal questionnaires. Results were analyzed by intention to treat (ITT) analyses. **RESULTS:** No significant differences were observed between TAH and SAH at 1-year follow-up in both the randomized trial and the observational study regarding women's desire for sex, frequency of intercourse, frequency of orgasm, quality of orgasm, localization of orgasm, satisfaction with sexual life, and dyspareunia. None of these sexual variables changed significantly from entry to the 1-year follow-up, apart from dyspareunia, which was significantly ($p = 0.009$) reduced in both intervention groups. Significant ($p < 0.05$) predictors for satisfaction with sexual life after hysterectomy were the preoperative satisfaction with sexual life [odds ratio (OR) 32, 95% confidence interval (CI) 10-125], good relationship with partner (OR 50, 95% CI 9-354), physical well-being (OR 0.30, 95% CI 0.09-0.88) and hormone replacement therapy (OR 0.23, 95% CI 0.06-0.78). **CONCLUSIONS:** **Both TAH and SAH significantly reduce**

dyspareunia without having a negative effect on sexual function. The shift toward SAH seems unwarranted.

Vaginal Estrogens

The research shows us that sometimes vaginal estrogen is not only safe, even with a history of breast cancer, but it is necessary for optimal vaginal health, especially for sexually active women whose vaginal function will deteriorate significantly without estrogen. When the ovaries fail to function either due to age or after breast cancer chemotherapy, vaginal estrogen can provide a lifeline of benefit to the vaginal and urethral walls without increasing the serum levels of estrogen over that of the menopausal women. This meets the needs of the Medical Oncologist to reduce estrogen delivery to the breast tissue, and helps the patient continue her normal relations with her spouse and avoid frequent urinary tract infections, urinary urgency, urinary frequency, urinary leakage and bleeding.¹⁻⁴

In summary, it is essential that we oncologists use the evidence-based research to provide women the opportunity to have their vaginal lining supported by local estrogen as needed, by safely using doses that have been proven to not increase serum levels over menopausal levels.

Handa, V. L., K. E. Bachus, et al. (1994). "Vaginal administration of low-dose conjugated estrogens: systemic absorption and effects on the endometrium." *Obstet Gynecol* **84**(2): 215-8.

OBJECTIVE: To test the hypothesis that a very-low-dose regimen of vaginal estrogen would provide effective relief from atrophic vaginitis without endometrial proliferation. **METHODS:** Twenty postmenopausal women with symptoms, signs, and cytologic evidence of atrophic vaginitis were enrolled. Each subject was treated with 0.3 mg of conjugated estrogens, administered vaginally 3 nights per week for 6 months. We examined the following outcomes: symptoms, vaginal cellular (cytologic) maturity, endometrial histology, sonographic evaluation of endometrial thickness, Doppler measures of uterine artery blood flow, and serum levels of estrone and estradiol. Pre- and post-treatment data were compared for each subject. **RESULTS:** Satisfactory relief of symptoms occurred in 19 of 20 cases. Vaginal cellular maturation improved significantly with therapy ($P < .01$). **There were no significant changes in endometrial thickness, uterine artery blood flow, or serum estrogen levels.** Endometrial proliferation was observed in one case. **CONCLUSIONS:** Relief from atrophic vaginitis can be achieved with 0.3 mg of conjugated estrogens administered vaginally two times per week. Endometrial proliferation may occur at this low dose, albeit rarely.

Notelovitz, M., S. Funk, et al. (2002). "Estradiol absorption from vaginal tablets in postmenopausal women." *Obstet Gynecol* **99**(4): 556-62.

OBJECTIVE: To evaluate absorption of estradiol (E2) and compare two low doses of 17 beta-E2 (25 microgram and 10 microgram) in postmenopausal women with atrophic vaginitis. **METHODS:** In a double-masked, randomized, parallel-group study, 58 postmenopausal women were treated with 25 microgram or 10 microgram of 17 beta-E2 for 12 weeks. We report data for 42 eligible subjects who had serum E2 concentrations below 20 pg/mL at baseline and complete data available at the baseline visit (30 minutes before tablet insertion) and weeks 2 and 12. Serum E2 and FSH concentrations were measured at specified intervals. The area under the curve, maximal concentration, and time to maximal concentration were measured for serum E2 concentrations. Maturation values of vaginal epithelial cells were assessed as

indicators of change in vaginal epithelium condition in response to treatment. **RESULTS:** After 12 weeks of treatment, the area under the curve, maximal and average over 24-hour E2 concentration were higher in the 25-microgram (563 pg. hour/mL, 49 and 23 pg/mL) than in the 10-microgram (264 pg. hour/mL, 22 and 11 pg/mL) group. Seventy-four percent in the 25-microgram and 96% in the 10-microgram groups had low systemic absorption of E2, that is, area under the curve (0-24 hour) less than 500 pg/mL. **All but three women who received 25 microgram had mean FSH levels below 35 mIU/mL.** **CONCLUSION:** Treatment with 25 or 10 microgram of 17 beta-E2 vaginal tablets resulted in low absorption of estrogen without systemic effects often associated with hormone replacement therapy. **After 12 weeks of therapy for atrophic vaginitis, absorption patterns remained consistent, and women did not have accumulations of circulating E2.**

Rioux, J. E., C. Devlin, et al. (2000). "17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis." *Menopause* 7(3): 156-61.

OBJECTIVES: The efficacy and safety of 25-microg 17beta-estradiol vaginal tablets (Vagifem) were assessed and compared with 1.25-mg conjugated equine estrogen vaginal cream (Premarin Vaginal Cream) for the relief of menopausal-derived atrophic vaginitis, resulting from estrogen deficiency. **DESIGN:** In a multicenter, open-label, randomized, parallel-group study, 159 menopausal women were treated for 24 weeks with either vaginal tablets or vaginal cream. Efficacy was evaluated by relief of vaginal symptoms and concentrations of serum estradiol and follicle-stimulating hormone. Safety was monitored by the incidence of adverse events, evaluation of endometrial biopsies, and clinical laboratory results. Patients also assessed the acceptability of the study medications. **RESULTS:** Composite scores of vaginal symptoms (dryness, soreness, and irritation) demonstrated that both treatments provided equivalent relief of the symptoms of atrophic vaginitis. At weeks 2, 12, and 24, increases in serum estradiol concentrations and suppression of follicle-stimulating hormone were observed in significantly more patients who were using the vaginal cream than in those who were using the vaginal tablets ($p < 0.001$). Fewer patients who were using the vaginal tablets experienced endometrial proliferation or hyperplasia compared with patients who were using the vaginal cream. Significantly more patients who were using the vaginal tablets rated their medication favorably than did patients who were using the vaginal cream ($p < \text{or} = 0.001$). Patients who were receiving the vaginal tablets also had a lower incidence of patient withdrawal (10% versus 32%). **CONCLUSIONS:** Treatment regimens with 25-microg 17beta-estradiol vaginal tablets and with 1.25-mg conjugated equine estrogen vaginal cream were equivalent in relieving symptoms of atrophic vaginitis. **The vaginal tablets demonstrated a localized effect without appreciable systemic estradiol increases or estrogenic side effects.** Vaginal tablet therapy resulted in greater patient acceptance and lower withdrawal rates compared with vaginal cream therapy.

Simunic, V., I. Banovic, et al. (2003). "Local estrogen treatment in patients with urogenital symptoms." *Int J Gynaecol Obstet* 82(2): 187-97.

OBJECTIVES: Determination of the efficacy and safety of vaginally administered low dose (25 microg) micronized 17beta-estradiol in the management of patients with urogenital symptoms. **METHODS:** A total of 1612 patients with urogenital complaints were randomized to receive 25 microg of micronized 17beta-estradiol ($n=828$) or placebo ($n=784$) in a multicenter double-blind placebo-controlled study running for 12 months. Female patients were treated once a day over a period of 2 weeks, and then twice a week for the remaining of the 12 months with an active or placebo tablet. The assessment included full history-questionnaire, micturition diary, gynecologic and cystometric examination, transvaginal ultrasound, and serum 17beta-estradiol level determination. It was carried out at the beginning, and after 4 and 12 months of treatment. **RESULTS:** The overall success rate of micronized 17beta-estradiol and placebo on subjective and

objective symptoms of postmenopausal women with vaginal atrophy was 85.5%, and 41.4%, respectively. A significant improvement of urinary atrophy symptoms was determined in vaginal ERT group as compared with the beginning of the study (51.9% vs. 15.5%, $P=0.001$). **The maximal cystometric capacity (290 ml vs. 200 ml, $P=0.023$), the volume of the urinary bladder at which patients first felt urgency (180 vs. 140, $P=0.048$), and strong desire to void (170 ml vs. 130 ml, $P=0.045$) were significantly increased subsequent to the micronized 17beta-estradiol treatment. The number of patients with uninhibited bladder contractions significantly decreased following micronized 17beta-estradiol as compared with pretreatment values (17/30, $P=0.013$).** Side effects were observed in 61 (7.8%) patients treated with low dose micronized 17beta-estradiol. **Therapy with 25 microg of micronized 17beta-estradiol did not raise serum estrogen level nor stimulated endometrial growth.** CONCLUSIONS: Local administration of 25 microg of micronized 17beta-estradiol is an effective and a safe treatment option in the management of women with urogenital complaints.

Ballagh SA. Vaginal rings for menopausal symptom relief. *Drugs Aging*. 2004;21(12):757-766.

The vagina is an alternative delivery site of sex steroids for menopausal women. New ring technology provides continuous and consistent delivery of steroids for up to 3 months. Rings rest on the pelvic floor muscles in a nearly horizontal position and are usually imperceptible. Steroid is delivered directly into the systemic circulation which may result in less alteration of coagulation/fibrinolysis pathways as seen with transdermal hormone therapy. Fewer adverse effects are noted when progesterone is applied vaginally, possibly due to lower serum levels of metabolites such as alloprenanolone. Women often switch to a ring for the longer dosing interval but also appreciate the reduced messiness. Over 5700 healthy US women who evaluated an unmedicated ring as a drug delivery platform found it very acceptable independent of age or prior use of barrier contraceptives. Marketed rings in the US include: (i) a ring for systemic and vaginal menopausal therapy that provides average serum estradiol levels of 40.6 pg/mL for the 0.05 mg and 76 pg/mL for the 0.1 mg dose; (ii) **a ring for urogenital menopausal symptoms only that minimally elevates serum estradiol, usually within the menopausal range, treating atrophic vaginitis and urethritis;** and (iii) a ring labelled for contraception that provides ethinyl estradiol 15 microg and etonogestrel 120 microg appropriate for nonsmoking perimenopausal women. A ring for combination hormone therapy and another releasing progesterone for contraception in lactating women have been reported in the literature, but are not yet available commercially. These may offer future options for hormone therapy. Women with a uterus receiving estrogen, even in low doses, should be given progestogen to prevent endometrial hyperplasia or carcinoma. Even women who have had an endometrial ablation are likely to have some endometrial tissue remaining since long-term amenorrhoea is uncommon. Since no marketed combination ring product is available, other forms of progestogen are necessary. Vaginal rings offer a novel approach to menopausal hormone therapy producing consistent serum levels sustained for up to 3 months per unit dose with lower adverse effects than other vaginal products and high acceptability among users.

Park K, Ahn K, Lee S, Ryu S, Park Y, Azadzo KM. Decreased circulating levels of estrogen alter vaginal and clitoral blood flow and structure in the rabbit. *Int J Impot Res*. May 2001;13(2):116-124.

Aging and menopause related decline in circulating levels of estrogen has been shown to adversely affect female sexual arousal function. Our aim was to study the effects of circulating levels of estrogen on the hemodynamic mechanism of vaginal and clitoral engorgement and on the structure of the vaginal and clitoral cavernosal tissue in the rabbit. New Zealand White female rabbits (3.5-4 kg) were randomly divided into three groups with five rabbits in each group: control; bilateral oophorectomy; bilateral oophorectomy undergoing subcutaneous injection of estrogen (40 microg/kg/day). After 6 weeks, the serum levels of 17 beta-estradiol were measured and systemic blood pressure was monitored. Vaginal and clitoral cavernosal

blood flows were measured with laser Doppler flowmeter before and after pelvic nerve stimulation. Cross sections of the clitoris and vagina were processed for histologic examination and histomorphometric image analysis. Serum level of 17 beta-estradiol (pg/ml; mean \pm s.d.) revealed a significant decrease in the oophorectomy group (25.4 \pm 5.1) compared with the control (38.5 \pm 7.6) and estrogen replacement (115.9 \pm 57.3) groups ($P<0.05$). **Nerve stimulation-induced peak vaginal and clitoral intracavernosal blood flows in the oophorectomy group (28.9 \pm 16.3 and 6.1 \pm 1.4, respectively) were significantly less than those recorded in the control (48.9 \pm 6.5 and 11.0 \pm 2.4, respectively) or estrogen replacement (48.7 \pm 12.2 and 10.1 \pm 2.8, respectively) group ($P<0.05$). In histology, marked thinning of the vaginal epithelial layers, decreased vaginal submucosal microvasculature, and diffuse clitoral cavernosal fibrosis were evident in the oophorectomy group but not in the estrogen supplement and control groups.** In histomorphometry, the percentage of clitoral cavernosal smooth muscle in the oophorectomy group (49.6 \pm 6.2) was significantly decreased compared with the control (56.8 \pm 2.6) and estrogen replacement (58 \pm 3.0) groups ($P<0.05$). Our studies show that decline in circulating levels of estrogen impairs the hemodynamic mechanism of vaginal and clitoral engorgement and leads to histopathologic changes in the vagina and clitoral cavernosal tissue. These observations suggest that decreased circulating levels of estrogen, a physiologic change in the menopausal state, may play a role in the development of female sexual arousal dysfunction.

Taechakraichana N, Intraragsakul A, Panyakhamlerd K, Numchaisrika P, Limpaphayom K. Estradiol and follicle-stimulating hormone levels in oophorectomized women using vaginal estrogen. *J Med Assoc Thai*. Nov 1997;80(10):626-630.

To assess the changing estradiol (E2) and follicle-stimulating hormone (FSH) level in oophorectomized women using vaginal estrogen. Serum estradiol and FSH were evaluated in 32 oophorectomized women using a daily dose of 2 g base of 1.25 mg vaginal conjugated equine estrogen (CEE) cream. The blood sample for hormone assay was collected 8-10 hours from the time of vaginal application. E2 and FSH levels were measured in the serum sample before and after commencing the study at 4, 8 and 12 weeks using the time-resolved fluoroimmunoassay method. Serum estradiol significantly increased from baseline value at 4, 8 and 12 weeks. (Mean \pm SD of E2 value at 0, 4, 8, 12 weeks: 9.97 \pm 12.13, 249.83 \pm 170.46, 299.38 \pm 190.65, 322.82 \pm 218.31 pmol/L, respectively, $P < 0.05$) On the other hand, serum FSH significantly decreased from baseline value at 4, 8 and 12 weeks. (Mean \pm SD of FSH value at 0, 4, 8, 12 weeks: 77.64 \pm 27.24, 40.33 \pm 21.64, 38.84 \pm 22.33, 30.90 \pm 24.32 IU/L, respectively, $P < 0.05$) In conclusion, a daily dose of 2 g vaginal CEE cream raised the serum estradiol level close to the normal level in the follicular phase of the normal menstrual cycle. However, even though FSH significantly decreased it did not reach the premenopausal level.

Handa VL, Bachus KE, Johnston WW, Robboy SJ, Hammond CB. Vaginal administration of low-dose conjugated estrogens: systemic absorption and effects on the endometrium. *Obstet Gynecol*. Aug 1994;84(2):215-218.

OBJECTIVE: To test the hypothesis that a very-low-dose regimen of vaginal estrogen would provide effective relief from atrophic vaginitis without endometrial proliferation. **METHODS:** Twenty postmenopausal women with symptoms, signs, and cytologic evidence of atrophic vaginitis were enrolled. Each subject was treated with 0.3 mg of conjugated estrogens, administered vaginally 3 nights per week for 6 months. We examined the following outcomes: symptoms, vaginal cellular (cytologic) maturity, endometrial histology, sonographic evaluation of endometrial thickness, Doppler measures of uterine artery blood flow, and serum levels of estrone and estradiol. Pre- and post-treatment data were compared for each subject. **RESULTS:** Satisfactory relief of symptoms occurred in 19 of 20 cases. Vaginal cellular maturation improved

significantly with therapy ($P < .01$). **There were no significant changes in endometrial thickness, uterine artery blood flow, or serum estrogen levels.** Endometrial proliferation was observed in one case.

CONCLUSIONS: Relief from atrophic vaginitis can be achieved with 0.3 mg of conjugated estrogens administered vaginally three times per week. Endometrial proliferation may occur at this low dose, albeit rarely.

Bakos O, Lundkvist O, Wide L, Bergh T. Ultrasonographical and hormonal description of the normal ovulatory menstrual cycle. *Acta Obstet Gynecol Scand.* Dec 1994;73(10):790-796.

OBJECTIVE. To describe the changes in uterine volume, endometrial thickness and follicular size during the normal menstrual cycle by use of transvaginal ultrasonography and to correlate these changes with the endocrine events in the same cycle. **METHODS.** A group of 23 healthy women with normal body mass index and with a history of regular menstruations were monitored with repeated hormonal and vaginal ultrasonographical investigations during the menstrual cycle. **RESULTS.** Sixteen of the women fulfilled the hormonal criteria for ovulation. The mean length of the cycles was 28 days (range 25-30 days) with a mean length of the follicular and the luteal phases of 14.4 days (range 12-17 days) and 13.5 days (range 12-16 days), respectively. **The estradiol level in serum the day before the peak of the luteinizing hormone varied between 490 and 1710 pmol/l (mean 1087 pmol/l).** Ultrasonographically, the most clinically relevant changes were the increase in diameter of the dominant follicle and the growth of the endometrium. At ovulation the dominant follicle had a mean diameter of 21.4 mm (range 17.4-27.0), whereas the endometrium had a mean thickness of 12.8 mm (range 10.0-15.9). When analysed over the entire follicular phase, the serum estradiol concentration correlated both with the diameter of the dominant follicle ($r = 0.93$, $p = 0.0001$) and with the thickness of the endometrium ($r = 0.79$, $p = 0.0001$). However, no such correlations were found when only the last part of the follicular phase was analysed. In the luteal phase there was no correlation between the size of the corpus luteum and the serum concentration of progesterone.

CONCLUSIONS. Vaginal ultrasonography is a practical and reliable method to monitor structural changes in the ovaries and the uterus during the menstrual cycle. The results are of clinical importance for a better understanding of the physiological changes and helpful when monitoring induction of ovulation in assisted reproduction.

Chan, W.S., J. Ray, E.K. Wai, S. Ginsburg, M.E. Hannah, P.N. Corey, and J.S. Ginsberg, 2004. Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. *Arch Intern Med.* 164: 741-747.

BACKGROUND: Use of the oral contraceptive pill (OCP) has been reported to be associated with stroke. With current OCPs containing less than 50 micro g of ethinyl estradiol, and many earlier studies reporting the association between OCPs and stroke, subjected to biases, we determined whether such an association exists and, if so, the magnitude of the risk. **METHODS:** Two independent searches were conducted to obtain relevant articles from MEDLINE, EMBASE, and Science Citation (1970 to June 2000). Eligible articles published in English describing OCP use and stroke outcomes were retrieved, and relevant data were abstracted. Pooling of results from these studies was performed using odds ratios (ORs) provided, and heterogeneity was calculated using chi(2) analysis. **RESULTS:** From 779 potential articles, 36 eligible studies describing 20 distinct populations were retrieved (4 cohort and 16 case-control studies). The pooled OR from the cohort studies demonstrated no increased stroke risk with OCP use (0.95; 95% confidence interval [CI], 0.51-1.78; $P = .01$); the pooled OR from the case-control studies showed a significant association (2.13; 95% CI, 1.59-2.86; $P < .001$). The risk of stroke with OCP use, however, was significant only with thrombotic stroke (2.74; 95% CI, 2.24-3.35; $P = .009$) and not with hemorrhagic stroke or stroke death. There was statistically significant heterogeneity among these studies, and potential biases and

confounders were not adequately addressed. **CONCLUSIONS: These results cast doubt on a true association between low-dose OCPs and stroke because of the low absolute magnitude of the ORs, the severe methodological limitations, and the ORs of less than 1.0 in the cohort studies. The association is tenuous at best and perhaps nonexistent.**

Kyrle, P.A., E. Minar, C. Bialonczyk, M. Hirschl, A. Weltermann, and S. Eichinger. 2004. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med.* 350: 2558-2563.

BACKGROUND: Whether a patient's sex is associated with the risk of recurrent venous thromboembolism is unknown. **METHODS:** We studied 826 patients for an average of 36 months after a first episode of spontaneous venous thromboembolism and the withdrawal of oral anticoagulants. We excluded pregnant patients and patients with a deficiency of antithrombin, protein C, or protein S; the lupus anticoagulant; cancer; or a requirement for potentially long-term antithrombotic treatment. The end point was objective evidence of a recurrence of symptomatic venous thromboembolism. **RESULTS:** Venous thromboembolism recurred in 74 of the 373 men, as compared with 28 of the 453 women (20 percent vs. 6 percent; relative risk of recurrence, 3.6; 95 percent confidence interval, 2.3 to 5.5; $P < 0.001$). The risk remained unchanged after adjustment for age, the duration of anticoagulation, and the presence or absence of a first symptomatic pulmonary embolism, factor V Leiden, factor II G20210A, or an elevated level of factor VIII or IX. At five years, the likelihood of recurrence was 30.7 percent among men, as compared with 8.5 percent among women ($P < 0.001$). **The relative risk of recurrence was similar among women who had had their first thrombosis during oral-contraceptive use or hormone-replacement therapy and women in the same age group in whom the first event was idiopathic.** **CONCLUSIONS:** The risk of recurrent venous thromboembolism is higher among men than women.