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Hormone Replacement Therapy Formulations and Risk of Epithelial Ovarian Cancer

ABSTRACT & COMMENTARY

SIT AND ASSOCIATES FROM THE UNIVERSITY OF PITTSBURGH assessed the association between the use of hormone replacement therapy (HRT) and the risk of invasive epithelial ovarian cancer in women participating in a population-based, case-control study conducted in the Delaware Valley from 1994 to 1998. Cases aged 45 or older at diagnosis ($n = 484$) were compared to community controls ($n = 926$) frequency matched by age and area of residence. Information on HRT formulation, timing, and duration were obtained by in-person interviews conducted by trained interviewers. HRT formulations were classified as opposed (estrogen + progestin) or unopposed (estrogen alone). They were further categorized according to the estrogen component as either conjugated equine estrogen (CEE), the most common formulation, or non-CEE. Overall, no association was found between any use of HRT and epithelial ovarian cancer. Although use of unopposed non-CEE was associated with a significant decrease in risk among hysterectomized women ($OR = 0.17$), this was not true for women with intact uterus ($OR = 1.14$). No significant differences in ovarian cancer risk were observed for other HRT formulations. Sit et al concluded that their results did not suggest any consistent pattern of altered risk for ovarian cancer and the overall use of HRT by specific formulations of HRT (Sit A, et al. *Gynecol Oncol.* 2002;86:118-123).

■ COMMENT BY DAVID M. GERSHENSON, MD

The recent findings of several epidemiologic studies of the benefits and risks of HRT have understandably concerned the public and have challenged the dogma like never before. As obstetrician-gynecologists, we are as perplexed as the public by the conflicting results arising from these very complex epidemiologic investigations. While much of the recent media attention has focused on the influence of HRT on breast tissue, bones, and the cardiovascular system, a number of studies, like this one by Sit et al, have addressed the risk of ovarian cancer. The findings regarding the association between HRT and risk of ovarian cancer have been very conflicting. In a thor-

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ough review of the subject in an editorial accompanying this article authored by Dr. Harvey Risch, possible explanations for this disparity in the findings are discussed.¹ As Dr. Risch points out, variables within these studies include the type of HRT formulation, the duration of use, the latency period, and age during usage. He suggests that, if there is an increased risk of ovarian cancer associated with HRT, the magnitude of risk increase is most probably small. In yet another recent study published in the *Journal of the American Medical Association*, Lacey and colleagues found that women who used estrogen-only HRT were at significantly increased risk of ovarian cancer.² (See following abstract.) This was true particularly for those women who used the medication for 10 or more years. Interestingly, those women in this study who used short-term estrogen-progestin-only replacement therapy were not at increased risk. Until more definitive information is forthcoming, it will be left to each physician and woman to arrive at their best personal decision regarding HRT. But, in my view, the influence of HRT on ovarian cancer risk should take a

backseat to other considerations—osteoporosis, breast cancer risk, cardiovascular disease, vasomotor symptoms, vaginal symptoms, the uterine cancer risk—in this decision-making process. ■

References

1. Risch HA. *Gynecol Oncol*. 2002;86:115-117.
2. Lacey JV, et al. *JAMA*. 2002;288:334-341.

Menopausal Hormone Replacement Therapy and Risk of Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *There appears to be an increase in ovarian cancer with long-term estrogen-only hormone replacement therapy.*

Source: Lacey J, et al. *JAMA*. 2002;288:334-341.

BETWEEN 1973 AND 1980, THE AMERICAN CANCER Society and the National Cancer Institute conducted the Breast Cancer Detection Demonstration Project (BCDDP). More than one quarter of a million women were involved in this study. Follow-up of these participants began in 1979, and 4 phases have been completed. Questions concerning hormone therapy were asked. Initially no distinction was made between estrogen-only replacement therapy (ERT) and estrogen-progestin replacement therapy (EPRT). A distinction was made beginning in 1987.

Using appropriate exclusions, 44,247 women were available for inclusion in this study. Diagnoses of ovarian cancer were verified through medical record review, cancer registry information and the National Death Index. Three hundred twenty-nine cases of ovarian cancer were diagnosed, virtually all of the epithelial type. The mean length of follow-up of the women in the study was 13½ years. The mean age at the start of follow-up was slightly less than 57 years. Parity, use of oral contraceptives, and hysterectomy were inversely associated with ovarian cancer. Estrogen-only hormone replacement therapy was significantly associated with ovarian cancer. Longer use of estrogen resulted in higher risk ratios. For those women who used ERT for 20 years or more, there was a greater than 3-fold increase in ovarian cancer. The increase was approximately 7% per year of ERT usage. There was no significant increase in risk for those women who took only EPRT.

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In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Speroff is involved as a consultant, and does research for Wyeth Ayerst, Pfizer, Ortho, and Novo Nordisk. Dr. Berga is a consultant for Women First, Inc., and is involved in research for Pfizer and the NIH. Dr. Gershenson is involved in research for Pharmacia-Upjohn, Oncotech, Genetech, SmithKline Beecham, Atairigen, and the National Cancer Institute. Dr. Noller and Dr. Hobbins report no relationships related to this field of study.

■ COMMENT BY KENNETH L. NOLLER, MD

This important study was greatly overlooked because of the tremendous publicity surrounded by the decision of the Women's Health Initiative not to continue the estrogen plus progestin arm of their study due to various increased risks. That is unfortunate as this well-done study suggests that there also are risks associated with estrogen-only therapy.

Over the past several years, I have frequently commented on study design, *P*-values, and confidence intervals. Certainly the most powerful type of study uses a prospective, randomized study (experimental) design. Cohort studies, such as this report, are less powerful. Nonetheless, if performed properly and if the risk ratio is significantly elevated, they are quite believable. While an increase of risk of 20% or 30% is usually believable in a prospective randomized trial, a similar increase in a cohort study is questionable.

In this study by Lacey et al, there was a 3-fold (300%) increase in ovarian cancer among estrogen-only hormone replacement users. There was a smaller increase in women who took the medication for only 10 years, but there was a definite dose response association. That is, the risk of ovarian cancer increased with increasing length of usage.

This is quite a good study and it could stand alone. However, other articles have found a similar association, and thus I think it is reasonable for us to believe that the use of estrogen replacement therapy may actually increase a woman's risk of developing epithelial ovarian cancer. What is harder to understand is why this association would be true. So far I am not aware that anyone has developed a believable pathophysiological explanation. ■

Recurrent Micropapillary Serous Ovarian Carcinoma: The Role of Secondary Cytoreductive Surgery

ABSTRACT & COMMENTARY

Synopsis: *Optimal secondary cytoreductive surgery is feasible in the majority of patients with recurrent micropapillary serous carcinoma of the ovary and is an independent predictor of subsequent survival.*

Source: Bristow RE, et al. *Cancer*. 2002;95:791-800.

BRISTOW AND COLLEAGUES PRESENT A RETROSPECTIVE report of 26 patients with recurrent micropapil-

lary serous ovarian carcinoma (MPSC) from the Johns Hopkins Hospital. The major purpose of this study was to characterize the clinical outcome of patients with recurrent MPSC and to evaluate the effect of secondary cytoreductive surgery on survival. The median age of the patients at recurrence was 46 years. The mean progression-free interval was 32 months, and 92% of patients had advanced stage disease at the time of the initial diagnosis. Twenty-one patients underwent secondary cytoreductive surgery; tumor debulking was performed in 91% of cases and 52% of patients required intestinal resection. Optimal resection (residual disease < 1 cm) was achieved in 15 patients (71%). Patients undergoing optimal secondary cytoreduction had a median survival time of 61 months from date of disease relapse compared with 26 months for those patients in whom suboptimal residual disease remained ($P < .02$) and 30 months for nonsurgical patients ($P < .01$). On multivariate analysis, optimal secondary cytoreduction was found to be the only independent predictor of survival. Salvage chemotherapy produced an objective response in 25% of patients with measurable disease. Bristow et al concluded that optimal secondary cytoreductive surgery is feasible in the majority of patients with recurrent MPSC and is an independent predictor of subsequent survival.

■ COMMENT BY DAVID M. GERSHENSON, MD

Within the past few years, Kurman and associates¹ from Johns Hopkins have published extensively on so-called micropapillary serous ovarian carcinoma (MPSC). The MPSC pattern is proliferative microscopically and is considered by most gynecologic pathologists to be a subset of serous borderline tumor. However, the pattern is distinct from the typical serous borderline pattern and, in general, is associated with more aggressive behavior—principally, a higher frequency of associated invasive peritoneal implants and a greater risk of relapse. Kurman's group has suggested that the typical serous borderline pattern is essentially almost always associated with a benign course and should be reclassified as "atypical proliferating tumors." They believe that the micropapillary pattern should actually be an entirely separate category—one almost always associated with a more aggressive course in the advanced stages. The ultimate goal of this group appears to be abandonment of the serous borderline category altogether. However, the vast majority of both gynecologic pathologists and gynecologic oncologists have not embraced this concept; they believe that the biologic behavior of MPSC, while more aggressive than the typical serous borderline tumor pattern, is much closer to it than to invasive ovarian cancer. In fact, extensive data from our group and that of others suggest that

the typical pattern in the advanced stages is not infrequently associated with an aggressive clinical course and that not infrequently the 2 patterns are admixed in the same primary tumor. While Bristow et al have split out their series of patients with recurrent MPSC, we would consider these relapsed patients to have invasive low-grade serous carcinoma, as described in a series from our institution that is not dissimilar from Bristow's series.² Thus, the controversy continues regarding the optimal classification of serous borderline tumor. By focusing just on the so-called MPSC, Bristow et al promote their philosophy, which, in my opinion, is not supported by fact. However, I do agree entirely with the clinical observations detailed in this nice study; the controversy is focused on nomenclature and classification. ■

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2. Crispens MA, et al. *Obstet Gynecol*. 2002;99:3-10.

Walking Compared with Vigorous Exercise for the Prevention of Cardiovascular Events in Women

ABSTRACT & COMMENTARY

Synopsis: *Prospective, but nonrandomized, data indicated that both walking and vigorous exercise are associated with substantial reductions in the incidence of cardiovascular events among postmenopausal women, regardless of race, ethnic group, age, or body mass index. Prolonged sitting increased the risk of cardiovascular disease.*

Source: Manson JE, et al. *N Engl J Med*. 2002;347:716-725.

IN THIS STUDY, MANSON AND ASSOCIATES SOUGHT TO determine the relationship between exercise and cardiovascular health by using the data collected in the Women's Health Initiative Observational Study (WHIOS). They calculated a total physical activity score and correlated it with the incidence of coronary events and total cardiovascular events among 73,743 postmenopausal women ages 50-79 years. Vigorous exercise was defined as that in which "you work up a sweat and your heart beats fast" and included aerobics, jogging, tennis, and swimming laps. Participants were also asked

to report moderate and mild forms of exercise as well as the hours per day spent engaged in sedentary behavior, including sitting, lying down, and sleeping. The primary end points were newly diagnosed coronary heart disease and total cardiovascular events. Potential confounding variables that were controlled for included age, smoking history, body mass index (BMI), waist/hip circumference, alcohol consumption, age at menopause, use of hormone replacement therapy, parental history of premature cardiovascular disease, race or ethnic group, education, family income, and dietary variables.

During a mean follow-up time of 3.2 years, there were 345 newly diagnosed cases of coronary disease, 309 strokes, and 1551 cardiovascular events. A strong inverse and graded relationship was found between total physical activity score and the risk of coronary heart disease. Risk reduction was similar for walking and vigorous exercise and maximal for those who engaged in both walking and vigorous exercise. These associations were seen regardless of age, race, and BMI. Walking pace was an important determinant of risk reduction. After accounting for age and energy expenditure, the relative risk of cardiovascular disease was increased among women who were sedentary for 16 hours vs. 4 hours daily, with a relative risk of 1.68 (1.07-2.64).

■ COMMENT BY SARAH L. BERGA, MD

Am I killing myself as I sit here writing this commentary? Are you killing yourself while you sit there reading it? Most of us have jobs that involve a lot of reading and writing. Is it possible to counteract all that sitting with bouts of exercise? What should we advise our patients? I lead a relatively active life, but most of the activities that comprise an academic life involve sitting. It is very difficult to read journals and grants while running. I have seen some people try while on the treadmill or stationary exercise bike, but I wonder how much information they absorb while multi-tasking in that manner. I cannot imagine how one could run on the treadmill and type on a computer, although I must acknowledge that I have never tried it and, until I read this article, I had no reason to think that I should try. I suspect that your predicament is not so dissimilar.

Like most good studies, this one raises as many questions as it answers. It seems to imply that you cannot make up for hours of sitting by an hour of running or walking. This is disturbing, because I think that this is the strategy that most busy professionals use in their daily life. If you have a ton of desk work to do, you try to do it efficiently and then look for those opportunities to give the body a break. What if it doesn't work that way? Then we would have to seriously think about how

to redesign our approach to work. Modern society depends on paperwork, even if we do it electronically. Lots of forms are needed to sell and buy and distribute the goods. And if we eat high-fat, high-carbohydrate foods while doing that paperwork, it is even worse for our waistlines and cardiovascular health.

Despite the embedded perversity about sitting, this study does offer lots of answers. The main point is that no matter who you are, walking will improve your cardiovascular health. This is the information patients need to hear. Any amount of exercise will help, so it is important to do some. This study did not find an upper limit to the benefit of ever-increasing amounts of exercise, although we know that too much exercise can compromise reproductive competence, especially when coupled with undernutrition. This is hardly a worry of relevance for the majority of postmenopausal women, however, because most are battling the bulge and years of relative inactivity.

This article was not the lead one for this week of the *New England Journal of Medicine*. Instead, the editors chose one on the deplorable degree of physical inactivity in adolescent girls.¹ The editorial by cardiologist Paul Thompson focused on both articles.² Essentially, the issue of physical inactivity is relevant for all of us, men and women alike, at all ages. Dr. Thompson notes, however, that in the Harvard Alumni Study,³ no further reduction in cardiovascular events was found in men with an energy expenditure of more than 2000 Kcal per week, a value that corresponds to the highest quintile in the WHI-OS study of postmenopausal women. Thus, he suggests that there is a threshold effect or at least a progressive decline with progressive activity. In short, despite my initial fears, neither you nor I are likely to be killing ourselves by writing or reading this synopsis. ■

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1. Kimm SY, et al. *N Engl J Med*. 2002;347:709-715.
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Special Feature

Is It Time To Rethink The Way We Perform Cesarean Sections?

By John C. Hobbins, MD

WHEN MOVING FROM NEW HAVEN TO DENVER, I noticed that the technique of performing a Cesarean

an section was almost identical. An informal poll of colleagues at other institutions revealed that, with minor variations, there seems to be a common way of performing Cesarean section in the United States that has changed little over the last 20 years. Perhaps it is time to re-evaluate this technique, step-by-step.

The Skin Incision

Most physicians use a Pfannenstiel incision whose outline approximates the upper margin of a bikini. The Joel Cohen incision, which is used on occasion when doing a fast entry for fetal distress, is less curved than a Pfannenstiel and crosses the mid-line an inch above the Pfannenstiel. Although many have obsessed over the benefits of one vs. the other, the real difference between the 2 seems to be cosmetic (eg, the chances of seeing the incision when one is wearing a bathing suit). Frankly, I am certainly the last one to comment about women's fashions, but almost anything can hide the slightly higher incision. The incision, which should be passé, is the vertical one, which is billed as the way to get into the uterus the fastest. However, it is really not any faster than the Joel Cohen incision and is a cosmetic disaster.

Traversing the Subcutaneous Tissue

This is usually accomplished by a sharp knife dissection down to the fascia, which is exposed in its entirety throughout the length of the incision. The 2 little vessels that are incised laterally with impunity are forgotten quickly, but they will often bleed throughout the rest of the procedure unless coagulated or tied off.

Traversing Fascia to Peritoneum

The most common way to accomplish this is to make a nick in the fascia in the mid-line and to extend the incision out laterally with scissors under direct visualization. In primary Cesarean sections, the recti are manually reflected laterally, but with repeat Cesarean section one has to chip away at the scar tissue in the mid-line to get a plane that can be opened sometimes manually with encouragement.

Entering the Peritoneum

This is accomplished either by poking a finger through the tented up peritoneum or by pulling this thin layer upward with tissue forceps and entering carefully with a scalpel or scissors. Reflecting the peritoneal portion of the "bladder flap" downward appears to be a standard technique. Some will stop this endeavor just below where the incision is planned in the uterus, but most others will take this down bluntly and sharply to the symphysis pubis.

The Uterine Incision

Transverse incisions are usually made initially below the bladder flap reflection in the mid-line and carried out laterally in a “smile” by scissors or by “east/west” manual manipulation accomplished by a single finger of both hands. Vertical uterine incisions extend from just below the bladder flap in the mid-line upward to a point where the lower uterine segment ends (in term uteri) and this virtually always necessitates the use of strong scissors.

Removal of the Infant

Here there are many variations on the common theme. After membranes are ruptured, the operator’s hand is inserted through the incision with palm up and insinuated downward under the presenting part, which is then lifted upward through the incision. Some operators will use a vacuum extractor with large babies once the vertex is exposed, to diminish the chances of incision extension. An uncommon variation (but one I really like) is to dislodge the head vaginally just before the operation begins to diminish the changes of extension of the incision laterally by the forceful maneuvering necessary to deliver a well-entrenched head in the pelvis.

Closure of the Uterus

One layer vs. 2 layers. Many surgeons feel that the uterine incision is stronger if 2 layers are applied. Frankly, in a transverse incision, if big bites of tissue are incorporated into a single layer there is little evidence to support the concept that if “some is good, more is better.” Although, a recent nonrandomized trial suggests a single layer closure is associated with a higher risk of later uterine rupture, there is no evidence from a randomized trial that a single closure is more risky. In vertical incisions, sometimes a third layer is required in the upper, thicker segment of the uterus.

Locking vs. nonlocking. Most operators today use a continuous locking suture to close the uterus. The misconception is that the locking suture provides the best hemostasis. This is not necessarily true in the uterus, and all that locking does is to compromise the microcirculation of tissue in the margin, whose job is to heal into a strong postoperative scar.

Peritoneal Closures

The real major evolution in Cesarean section technique over the last decade has been to abandon closure of the bladder reflection and the abdominal peritoneum because it is clear that reperitonealization will occur in spite of attempts to put things back the way they were.

Fascia and Subcutaneous Closure

Although there are some minor variations, the most common technique is to close the fascia in one layer with 1 or 2 running sutures. Some will close the subcutaneous tissue with interrupted or a running suture. Some will not. It probably does not matter.

Skin Closure

Here is where everyone has his or her own pet techniques so I will not touch upon this, as it has no great clinical effect.

Conclusion

It is becoming clear that with Cesarean section the less one does, the better the outcome. Two recent examples come to mind. A study emanating from Vienna compared outcome when the bladder flap was vs. when it was not taken down.¹ This maneuver takes extra time and creates a space in a vascular area that is ideal for hematoma formation. Investigators randomized patients according to whether a bladder flap was reflected. The procedure added an average of 5 minutes to the operation and resulted in a statistically significantly greater hemoglobin drop, a 50% increase in microhematuria, and a greater need for postoperative analgesics.

On another note, our colleagues in Milan, Italy, adopted a well-conceived hybrid technique of Cesarean section and compared it, in a randomized trial, to their usual technique, which was essentially the same as that performed in the United States.² This hybrid method involved a Joel Cohen entry and components described by an obstetrician named Stark. It features an almost complete avoidance of retractors, not cutting the superficial subcutaneous arteries, “blind” scissor opening of the fascia, minimal (1”) mobilization of the bladder flap with a sponge, gentle removal of the fetal head, single layer closure of the uterus and fascia, no reperitonealization, and stay sutures thru the skin and subcutaneous tissue.

Halfway through they stopped the study and abandoned the old technique because the hybrid was 20 minutes shorter, significantly less blood loss was encountered, and postoperative recovery time was almost halved.

It may be difficult to modify a surgical technique that has been drummed into every American obstetrician, but it is at least worth discussing. ■

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2. Bujold E, et al. *Am J Obstet Gynecol.* 2002;186(6):1326-1330.

CME Questions

8. What is the histologic subtype of serous borderline tumor associated more frequently than the typical serous borderline tumor pattern with risk of relapse and a higher frequency of invasive peritoneal implants?

- Papillary serous
- Micropapillary
- Clear cell
- Mucopapillary
- Psammomacarcinoma

9. According to the article by Lacey et al, all of the following were found to decrease the risk of developing epithelial ovarian cancer *except*:

- pregnancy.
- oral contraceptive use.
- hysterectomy.
- estrogen replacement therapy.

10. Based on the foregoing article and editorial, which of the following statements is most true?

- Sitting more than 4 hours per day increases the risk of cardiovascular disease.

- For cardiovascular health, the more hours spent in vigorous intense exercise, the better.
- Walking will not improve cardiovascular health.
- Any amount of exercise reduces the risk of cardiovascular disease, but the reduction in risk is greater with greater levels of activity.
- Exercise will not improve cardiovascular health if BMI is > 28.

Attention CME Subscribers

Due to an American Health Consultants error, the correct answer to CME questions #6 and #7 were left off. The correct answer to #6 should have been choice "e: In the present study, oral contraceptive use did not appear to increase the risk of breast cancer in women, regardless of the duration, dose, or age at use." The correct answer to question #7 should have been choice "d: All of the above." These questions will be omitted from the CME test. Please leave the space blank on your answer sheet. They will not count against your score. We regret any confusion this might have caused. ■

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