Letters to the Editors

Response to commentaries on retention of the ovaries and long-term survival after hysterectomy

We would like to respond to the three invited commentaries in this journal on the topic 'Does retention of the ovaries improve long-term survival after hysterectomy?'[1–3]. All three referred to our recent article on ovarian conservation published in *Obstetrics and Gynecology*[4].

Professor Studd expresses his opinion that we should not have included the oophorectomy and no estrogen therapy (ET) arm in our study, since this choice is unacceptable to him. However, this is clearly the most common situation found clinically. Studies show that actual continuation rates of ET are very low and, despite Dr Davy's comments, continuation rates for bisphosphonates or statins are no higher.

In 1999, prior to publication of the Women's Health Initiative (WHI), and 'at a time when medical support for ET and publicity for ET were high', only 31% of women continued to use ET for 5 years or longer following hysterectomy and oophorectomy[5]. In the 6 months following publication of the WHI, continuation rates of ET decreased from 12.6% to 9.1% and new starts also decreased significantly[6].

Even women initiating therapy with ET, estrogen and progestin, bisphosphonates or raloxifene for treatment of documented osteoporosis ($n =$ 58 109) had medication continuation rates less than 25% at 12 months[7]. Statin continuation rates are 18% at the end of 1 year[8]. It should be noted that these studies do not account for women who never see a doctor, who never get a prescription, or who get a prescription but choose not to fill it and, therefore, underestimate the risk of disease for large numbers of women.

Despite Professor Studd's feeling that physicians should appropriately counsel women about long-term hormone therapy after oophorectomy, women have side-effects, fears and belief systems about medications which may preclude use despite a physician's recommendation. The mortality data presented in our paper for oophorectomy with ET is calculated for 100% continuation rates to age 80. Lesser continuation rates, as noted in real life, would proportionally increase mortality and, therefore, oophorectomy is a disservice for the vast majority of these women.

There is no evidence to support oophorectomy as prophylaxis for the future possibility of pelvic pain, residual ovary syndrome, mild endometriosis or ovarian cyst formation. Among 2561 women having a hysterectomy without oophorectomy for any indication and followed for 20 years, subsequent oophorectomy was performed in just 2.8%[9]. Furthermore, while oophorectomy may be indicated in the rare situation of severe premenstrual syndrome with a woman's full understanding and consent, recommending this for women with a few bad days per month, as implied by Professor Studd, would not be acceptable to most women.

It is now clear that benign ovarian cysts are common among postmenopausal women and do not require surgical intervention. The study inappropriately quoted by Drs Davy and Oehler reported that 19% of 234 women over age 45 had cysts, all 5 cm or smaller, found at autopsy[10]. None were malignant. Earlier studies of postmenopausal women subjected to surgery for adnexal masses with benign sonographic appearance and normal CA-125 levels found no malignant tumors[11]. Sonographic screening of 7705 asymptomatic postmenopausal women found unilocular cysts in 3.3%. No woman was found to have cancer[12]. Many gynecologic oncologists would recommend expectant management for postmenopausal women with no increase in cyst size or increase of CA-125[13,14].

Professor Studd takes issue with data 'that hysterectomy reduces risk of ovarian cancer by 40%'. However, as cited in our study, virtually all epidemiologic data support this view. In addition, our sensitivity analysis using no decrease in the risk of ovarian cancer following hysterectomy did not alter outcomes. Regarding Dr Shapiro's comment, we did note that, as used by convention in many other studies, average risk of ovarian cancer included women without germline mutations. Dr Davy comments that oophorectomy reduces the risk of subsequent breast cancer, but such protection occurs only when oophorectomy is performed before age 50 and only persists for the first 10 years following surgery. This is not a very convincing reason to perform oophorectomy.

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Professor Studd states that the WHI found ET before age 60 decreases the risk of myocardial infarction and breast cancer. He interestingly uses relative risks here (rather than absolute risk) and fails to mention that the confidence intervals are wide and the results are not statistically significant. Apparently, it is Professor Studd's analysis, rather than our own, that approximates meta-physics.

We agree with Dr Shapiro's statement that there are many risk factors (menopausal status, age, lipoprotein patterns, etc.) for mortality that our study did not take into account. We purposely constructed the model without too much complexity by choosing the five conditions most commonly associated with oophorectomy. This does not invalidate the model or results. Dr Shapiro criticizes exclusion of venous thromboembolism and colon cancer from our analysis, but we are not aware of evidence that these outcomes are influenced by oophorectomy.

The authors collectively fail to understand the difference between meta-analysis and decision analysis. Meta-analyses require a systematic review of the literature with specific inclusion and exclusion criteria to answer a specific clinical question and entail statistical pooling of the numeric data from more than one study. We did not perform a meta-analysis. Decision analysis, as performed in our study, while based on a comprehensive literature review, uses probabilities derived from epidemiological data and creates a Markov model where all possible outcomes are considered. In our study, the outcomes were mortality following hysterectomy with and without oophorectomy, and with and without hormone replacement therapy.

The evidence grading system used in our study is one of the most commonly used and has been validated in health services research and epidemiology[15]. We used the best sources of mortality data available: SEER and National Vital Statistics. Relative risk estimates were derived from each of the selected best-quality studies. Histories of hysterectomy with or without oophorectomy were adequately precise and had been validated by study authors. Variations among individual studies were captured by our sensitivity analyses. Confidence intervals were also captured by our extensive sensitivity analyses, including worst-case scenarios. While Professor Studd sees our findings as politically correct, the results of the analysis were not known until the computer generated the survival data. No scenario for oophorectomy was found to confer any survival advantage.

Professor Studd recommends a randomized trial to answer this important question. As discussed in our paper, there are major obstacles to this type of study. Women are not very likely to accept randomization to oophorectomy or ovarian conservation, large groups of women would need to be studied, and a 30-year wait for true outcome data (rather than surrogate) is not practical. Even if such a study were begun, it is likely that other research (such as a reliable proteiomics blood test for early ovarian cancer) might make the eventual findings irrelevant.

We agree that the public health consequences regarding incidental oophorectomy are major, in that approximately 300 000 US women are subjected to this procedure annually. Up until now, this decision was based on one factor alone – the risk and fear of ovarian cancer. Professor Studd states that 'It is hard to believe that estrogens are more dangerous than conserved ovaries' and then pleads for castration. What ever happened to 'evidence' and the principle 'first, do no harm'?

Our study was not meant to replace a woman's decision as to whether or not she should have an oophorectomy. We chose to model a typical woman's survival with regards to the impact of oophorectomy and allow individual women to determine their own particular risks and concerns regarding the related conditions. Further stratifying the data will be the goal of future research, pending availability of additional studies. We are presently seeking funding for a study in collaboration with the Nurses' Health Study group in order to apply data from those 122 000 women to our model. Hopefully, our present study will raise awareness among women and their gynecologists regarding the public health consequences of routinely performed oophorectomy.

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Authors' reply

We would like to respond to the letter from Dr Parker and colleagues[1]. The thrust of our comments was whether to retain ovaries at the time of hysterectomy[2]. Our commentary emphasized that we felt that it was important to make women aware of the risks of ovarian cancer and the opportunity to decrease this if they were already undergoing laparotomy for a gynecological reason. Our emphasis, as stated several times in our comments, was purely related to the peri- or postmenopausal woman already undergoing a planned procedure.

We agree that benign ovarian cysts in postmenopausal women do not require surgical intervention. However, this is not the issue. The very appropriately quoted study from Dorum and colleagues shows that ovarian cysts are common among postmenopausal women[3]. That no ovarian cancer was found is no surprise as they performed autopsies on only 234 women. The ovarian cancer incidence is about 50/100 000 postmenopausal women and it would have been a pure chance to detect one[4]. But, although ovarian cysts in postmenopausal women are benign in the majority of cases, it has to be appreciated that no currently available test is perfect, offering 100% specificity and sensitivity. Ultrasound often fails to differentiate between benign and malignant lesions, and serum CA-125 levels, although raised in over 80% of ovarian cancers, are raised in only 50% of stage I cases. Although expectant management of postmenopausal women with low-risk ovarian cysts (less than 3% risk of cancer) is usually suggested, guidelines also recommend a follow-up with ultrasound scans and CA-125 measurements every 4 months for 1 year[5]. This creates significant stress and anxiety for the woman until the ovarian malignancy is excluded – in many cases by a surgical intervention.

As long as we do not have a reliable early diagnostic test for ovarian cancer, an oophorectomy

remains the only means to decrease the incidence of this deadly disease. Therefore, from the gynecological oncological perspective, a bilateral salpingo-oophorectomy should be part of a hysterectomy for benign disease in a peri- or postmenopausal woman.

Ultimately, only a prospective randomized trial comparing oophorectomy versus ovarian preservation at the time of surgery for benign disease is going to give a definitive answer to this controversy. Meanwhile, we wish to ensure that women are given sufficient information prior to planned surgery to best protect themselves against cancer, unnecessary worry about subsequent ovarian masses, and the possible need for further surgery at an older age where they might be less resilient.

None of the comments by Parker and colleagues change any of these arguments.

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Author's reply

I would like to reply to the letter of Parker and colleagues[1] concerning my commentary discussing the validity of the epidemiological evidence for whether retention of the ovaries improves long-term survival after hysterectomy[2]. Among the principal determinants of mortality in elderly women are coronary heart disease, stroke, and cancers of the breast and large bowel. Other outcomes such as pulmonary embolism are common, and caused by supplemental hormones. The claim that a valid prediction of the risk of such outcomes in oophorectimized women can be made, while ignoring menopausal and other relevant factors, is absurd.

I have described the defects of meta-analysis elewhere[3,4]. If anything, the decision analysis of Parker and colleagues was even more defective: whereas meta-analysis at least purports to synthesize the total evidence across an array of studies, Parker and his colleagues simply selected those studies that they deemed to be the best evidence[5]. The rest of us are under no obligation to agree with them, or with the implied claim that a commonly used and validated (i.e. ostensibly 'objective') quality grading system[6] renders our judgments redundant. Common use is not a criterion of validity. Nor is a system valid simply because a task force decrees that it is[6].

Finally, histories of hysterectomy with or without oophorectomy have only been incompletely checked ('validated') in a limited number of studies, and hardly checked at all if they occurred in the distant past; the estimation of mortality using relative risk estimates derived from incidence data is questionable; and what is meant by the phrase 'confidence intervals were also captured by sensitivity analyses, including worst-case scenarios' is unclear: unless the lowest reported confidence limits were evaluated, the sensitivity analyses were incomplete.

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