ABSTRACT & COMMENTARY

Do Patients Need Routine Pelvic Exams?

By Jeffrey T. Jensen, MD, MPH, Editor

SYNOPSIS: A review of the published literature finds no value to the routine screening pelvic examination in asymptomatic non-pregnant women.


The American College of Physicians (ACP) published this guideline to present the evidence and provide clinical recommendations on the utility of screening pelvic examination for the detection of pathology in asymptomatic, nonpregnant, adult women. Investigators from the Minneapolis Veterans Affairs Health Care System’s Evidence-based Synthesis Program Center conducted a systematic review of the literature to address the utility of the screening pelvic examination in symptomatic women by evaluating the following key questions: 1) How accurate is the exam for detection of cancer (other than cervical), pelvic inflammatory disease, or other benign gynecologic conditions? 2) What are the benefits (reduced mortality and morbidity rates) and harms (overdiagnosis, overtreatment, or diagnostic procedure-related harms)? and 3) What are the examination-related harms and indirect benefits of performing screening pelvic examinations in asymptomatic women? The investigators conducted a systematic review of the published literature in the English language from 1946 through January 2014 identified using MEDLINE and hand-searching. They evaluated a variety of outcomes including morbidity, mortality, and harms (i.e., overdiagnosis, overtreatment, and diagnostic procedure-related harms). They also considered patient fear, anxiety, embarrassment, pain, and discomfort. Based on the review of the literature, the ACP recommends against performing screening pelvic examination in asymptomatic, non-pregnant, adult women.

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This simple study attempts to evaluate the utility of the screening pelvic examination based on the available literature. Although gynecologists raised on a steady diet of routine exams vary in their opinions, most are comfortable with the notion of the annual exam. Many women see this as high-quality health care. Most of us were trained with the belief that the routine exam was needed to adequately screen for cervical cancer and that the pelvic bimanual added additional value in the screening for other pelvic abnormalities. We also
understand that the annual exam provides an opportunity for screening and health care counseling for important preventive health issues from hypertension to hyperlipidemia and for contraception counseling.

However, a number of cracks have appeared in the ice over the last 30 years. First and foremost has been the understanding that cervical cancer is a sexually transmitted infection and that highly specific molecular probes can reduce the need for annual pap testing.¹ We have also learned that the pelvic exam is not needed prior to a prescription for hormonal contraception.² Chlamydia is much more prevalent than gonorrhea, and we have urine-based PCR tests that do not require collection of cervical samples.³ Women may prefer this.⁴ Therefore, the justifications for most pelvic exams in otherwise healthy asymptomatic young women go out the window. Add to this the lack of benefit from detection of an adnexal mass by pelvic exam and you pretty much lose all of the potential benefit from a pelvic on an asymptomatic woman.

But what does the evidence say? To be clear, the authors identified no studies that addressed the diagnostic accuracy of the pelvic examination for a number of benign conditions so could not access the possibility of benefit. To be fair, the absence of evidence does not imply the possibility of benefit, but it does indicate that we should look carefully at what we do. Consider a serious condition like ovarian cancer. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening randomized controlled trial found no benefit for routine pelvic exams in the diagnosis and prognosis for ovarian cancer.⁵ The authors of the systematic review found no studies that specifically evaluated the utility of the routine pelvic exam to screen for pelvic inflammatory disease, bacterial vaginosis, or other benign gynecologic conditions. For example, it is possible but unknown whether detection of a benign ovarian mass like a dermoid cyst reduces the risk of subsequent torsion. However, if you think that the screening pelvic might have benefit for detection of other conditions, I invite you to propose and conduct a study.

The ACP recommendations rely heavily on literature that evaluates the displeasure that many women associate with the routine pelvic. While this does represent a barrier to care for many women, I can’t help but feel that investigators may bring their own biases to these studies. My humble opinion is that no one dislikes the routine pelvic examination more than general internists and other primary care providers (PCPs) facing time pressures and inadequate facilities to carry out the exam. Recall the cheers of the PCPs after the WHI findings that hormone replacement therapy was more harmful than good. Internists always disliked the evaluation of HRT-related postmenopausal bleeding.

So should you provide routine pelvic exams? I think we can leave this up to our patients. Many women find value in the routine annual health care exam that includes a pelvic. Others may not need this care. Some clinicians worry about documentation and billing for other health care screening when a pelvic is not done. ACOG released a statement on June 30, 2014, that reiterated the 2104 Committee Opinion which acknowledged that no current scientific evidence supports or refutes an annual pelvic exam for an asymptomatic, low-risk patient. ACOG suggests that “the decision about whether to perform a pelvic examination be a shared decision between health care provider and patient, based on her own individual needs, requests, and preferences.” I agree with these recommendations, but it will be interesting to see how insurers view the decision to pay for this exam in the future. For now, at least be aware of the controversy when you recommend and perform this exam.

References
ABSTRACT & COMMENTARY

More Promise from Olaparib in Recurrent Ovarian Cancer: The BRCA Cohort

By Robert L. Coleman, MD

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Dr. Coleman reports he receives research funding from Clovis Pharmaceuticals, who is developing rucaparib, a PARP inhibitor in women with ovarian cancer, and serves as co-principle investigator for several AztraZeneca sponsored trials of olaparib and other agents.

SYNOPSIS: Olaparib, a poly (ADP)-ribose polymerase (PARP) inhibitor, demonstrated substantial delay until progression when administered to women as a maintenance therapy with BRCA-mutant recurrent ovarian cancer.


In a previous report, maintenance monotherapy with olaparib significantly prolonged progression-free survival (PFS) vs placebo in patients with platinum-sensitive recurrent serous ovarian cancer. The current analysis explores the hypothesis that olaparib is most likely to benefit patients with a BRCA mutation. A retrospective, preplanned analysis of data by BRCA mutation status from the original randomized, double-blind, Phase 2 study was conducted. Olaparib was administered at 400 mg twice daily and was compared to placebo in patients with platinum-sensitive recurrent serous ovarian cancer who had received two or more platinum-based regimens and who had attained at least a partial response to their most recent platinum-based regimen. Randomization was stratified by time to progression on penultimate platinum-based regimen, response to the most recent platinum-based regimen before randomization, and ethnic descent. The primary endpoint was PFS, analyzed for the overall population and by BRCA status. Two hundred sixty-five patients were randomized: 131 of 136 patients (96%) randomized to olaparib had their BRCA status known, of which 74 (56%) carried deleterious mutations. Similarly, 123 of 129 (95%) placebo patients had BRCA status known, of whom 62 (50%) were deleterious. Of patients with a BRCA mutation, median PFS was significantly longer in the olaparib group than in the placebo group (11.2 months vs 4.3 months; hazard ratio [HR], 0.18; 95% confidence interval [CI], 0.10-0.31; \( P < 0.0001 \)); similar findings were noted for patients with wild-type BRCA, although the difference between groups was lower (7.4 months vs 5.5 months; HR, 0.54; 95% CI, 0.34-0.85; \( P = 0.0075 \)). At the second interim analysis of overall survival (58% maturity), overall survival did not significantly differ between the randomized cohorts (HR, 0.88; 95% CI, 0.64-1.21; \( P = 0.44 \)), the patients with mutated BRCA (HR, 0.73; 95% CI, 0.45-1.17; \( P = 0.19 \)), and the patients with wild-type BRCA (HR, 0.99; 95% CI, 0.63-1.55; \( P = 0.96 \)). Serious adverse events were reported in 25 (18%) patients who received olaparib and 11 (9%) who received placebo. The most common grade 3 or worse adverse events in the olaparib group were fatigue (7% vs 3%) and anemia (5% vs < 1%). Tolerability was similar in patients with mutated BRCA and the overall population. These results support the hypothesis that patients with platinum-sensitive recurrent serous ovarian cancer with a BRCA mutation have the greatest likelihood of benefiting from olaparib treatment.

COMMENTARY

Recurrent ovarian cancer, for the most part, is incurable with currently available treatment strategies. And while several promising new therapies are under active investigation, it is generally agreed that they are unlikely to be associated with a robust and lasting treatment effect due to the heterogeneity of ovarian cancer biology and the therapeutic target of interest. This concern drives the impetus to clearly define the roles of selected tumor targets and the effort to develop companion diagnostics that could accurately identify patients most likely to benefit from a specific therapy. Ovarian cancer is a disease characterized by global genomic instability and few driving mutations. However, our understanding of DNA repair mechanisms has identified a limited number of genes, such as BRCA, that could be leveraged for therapy.

The current study was a large, placebo-controlled, double-blind, randomized, Phase 2 study of the PARP inhibitor olaparib in women with recurrent platinum-sensitive ovarian cancer. In the initial analysis, olaparib was associated with a significant, near doubling of PFS compared to placebo. At the time of the initial report, limited data on BRCA mutation status were known. The current report provides this information on 95% of the study subjects. The study was clearly enriched for these patients with more than 50% being...
BRCA-positive. This is neither an uncommon finding among platinum-sensitive patients nor in trials of PARP inhibitors because the potential benefit of this class of agent is well known. Unique in this trial, though, was expansion of the BRCA analysis to somatic (tumor) BRCA mutation, which contributed another 15% to the BRCA germline population. Taken together, the impact of using a drug that has synthetic lethality under mutant BRCA conditions was substantial — and clinically meaningful — accounting for a near 7-month delay in progression. The authors tried to provide some context to this endpoint by measuring the times to both the next line of therapy and the subsequent line of therapy following this. In both instances, the effect was maintained. Overall survival, now nearly 60% mature, was still no different between the arms; however, crossover treatment to a subsequent PARP inhibitor in the placebo arm was 23% (vs 0%), which could confound this endpoint.

The sponsor of this trial (AstraZeneca) recently presented these data to the U.S. FDA's Oncologic Drug Advisory Committee (ODAC) for accelerated approval (June 25, 2014, www.fda.gov/ODAC). Several concerns were raised by the committee about the retrospective subgroup analyses, particularly in the assessment of toxicity, lack of patient reported outcomes, and a seemingly under performance of the control group. While extremely rare, myelodysplastic syndrome was diagnosed in three patients (vs one patient) in the olaparib arm, and while severe gastrointestinal toxicity and treatment discontinuations were uncommon findings (4.4% vs 1.6%, \(P = \text{NS}\)), the impact of low level (Grade 1-2) gastrointestinal toxicity to an otherwise asymptomatic population is not trivial and was not captured well in the study. Finally, the expected PFS in the statistical plan was 9 months in the placebo arm, but was just 4.8 months in the trial, raising questions about a spurious positive result. Nevertheless, despite the committee’s unfavorable vote (2 for, 11 against), the data strongly support the hypothesis that administering a drug in this class to patients whose tumors are vulnerable due to BRCA loss would have clinically meaningful treatment effects. Fortunately, there are multiple confirmatory Phase 3 trials underway with several PARP inhibitors. Hopefully, these will confirm these observations and encumber the first truly individualized cancer therapeutic for women with ovarian cancer.

References

ABSTRACT & COMMENTARY

Reduced Fetal Movement, Uterine Arteries, and Stillbirth

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationships relevant to this field of study.

SYNOPSIS: A recent study has shown a link between abnormal uterine artery waveforms in the second trimester and reduced fetal movements later in pregnancy, as well as with stillbirth and small for gestational age.


Guidelines abound for screening and management of almost all of the common complications of pregnancy. These guidelines are published by various medical organizations and are based on expert opinion as well as evidence-based information. Often the same topics are taken on by separate official groups and sometimes the recommendations within these guidelines do not match.

One of the more controversial concepts involves the use of uterine artery Doppler wave form analysis to screen for preeclampsia. This month I will focus on a recent study correlating the results of uterine artery Dopplers and decreased fetal movement with late stillbirth (SB) and the presence of small for gestational age (SGA) babies.1 This paper then will be used to segue into a broader discussion of the role of maternal fetal movement...
perception in the assessment of fetal condition.

A team from the United Kingdom reviewed patients’ perinatal records between 2008 and 2012, during which time it was common to screen patients between 19 and 23 weeks for later development of preeclampsia with uterine artery Doppler waveform analysis. These patients also had been counseled to report any perceived reduced fetal movements (RFM) to their providers. Since almost all patients were delivered at the same hospital (St. Georges in London), the authors were able to capture essential birth data on 17,649 patients of the original 19,030 who had care during the study period. Seven hundred forty-two (4.2%) women reported RFM, 1494 (8.5%) delivered SGA babies (birth weight less than the 10th percentile), and 53 (0.3%) had a SB after 36 weeks.

Patients with abnormal uterine artery waveforms (pulsatility indices > the 95th percentile) were far more likely to have RFM (odds ratio [OR], 5.3; 95% confidence interval [CI], 4.21-6.01), SGA (OR, 2.41; 95% CI, 2.09-2.79), and were significantly more likely to have a SB (OR, 1.50; 95% CI, 1.21-1.98). The combination of abnormal uterine artery waveform and RFM gave a four times greater chance of SGA and a five times greater chance of SB than if neither was found.

**COMMENTARY**

The results of the study were difficult to sort out regarding SB because of the relatively small number of late SBs in the study (53 of 17,649), but the data linking uterine artery waveforms with SGA and RFM suggest a placental cause for both — the former being a well-accepted fact, but not the latter.

The greatest thrust for using uterine artery waveforms in the second trimester has been to screen for preeclampsia. Although it is not standard practice in the United States, it is commonly employed in Europe, as documented by its incorporation into practice guidelines. The major criticism of this screening tool, which has been shown in other studies to have value in predicting SB and SGA, involves the dilemma of what to do with this information. Some studies do show benefit in using low-dose aspirin, especially if given early, to prevent severe preeclampsia in women with abnormal uterine artery waveforms — which is the reason for the positive spin employed in the European guidelines.

The featured study now provides a possible reason for starting third trimester fetal movement counts in those patients with abnormal second trimester uterine artery waveforms, and even, perhaps, in some patients who have not had this type of testing. Hot off the press is ACOG’s opinion on the subject of fetal movement assessment, a subject that is covered briefly in the newest guidelines for antenatal fetal surveillance in the July 2014 issue of *Obstetrics and Gynecology*. In the 10-page document, one paragraph (20 lines worth) was devoted to fetal movement assessment and its association with SB only. The authors stated that there is no evidence that a formal assessment of RFM has reduced the fetal death rate. They also pointed out that it does increase slightly the number of antepartum visits and fetal evaluations (but without an increase in interventions). The authors said that “although not all women need to perform a daily fetal movement assessment, if a woman notices a decrease in fetal activity, she should be encouraged to contact her health care provider and further assessment should be performed.”

I agree that it would be unproductive to use formal kick counts in everyone, but it would make sense for all patients at their first visit to be encouraged to pay attention to their fetuses’ general activity level. In high-risk patients (hypertension, history of previous SB or SGA, inadequate fetal growth in the current pregnancy, oligohydramnios, and with various fetal anomalies), we recommend that patients do daily fetal movement counts in the third trimester. We use this method in SGA pregnancies, in particular, as an adjunctive method of surveillance between visits for non-stress tests, Dopplers, and ultrasound assessments of fetal growth. Our protocol is for the patient to choose the same time each day, usually after a meal, to get in a comfortable position — but not on her back. Then she determines how long it takes to discern 10 separate fetal movements. If that time exceeds 2 hours, she is instructed to give us a call. In the vast majority of cases, this goal is attained well before the first hour has elapsed.

This method gives the patient a chance to participate in her own care and, while it has not yet been proven to prevent SB (a difficult study to take on), unlike just about anything in health care today, it does not cost a dime. In the featured study, 48 patients with SB did not report a “subjective” decrease in fetal movement. It is unclear how many of these patients might have been in a higher risk category to warrant a more formal approach to tracking fetal movement — one that might have detected a bona fide drop in fetal movement before demise.

**References**

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ameter than age, serum follicle-stimulating hormone (FSH), or serum inhibin B. This indirect knowledge of the remaining ovarian primordial follicle reserve helps physicians select an ovarian stimulation protocol that would be most helpful to obtain oocytes for freezing or fertilization. However, more recent studies have utilized AMH to help in the diagnosis of polycystic ovary syndrome (PCOS), predict which patients are at higher risk of ovarian hyperstimulation syndrome (OHSS) when undergoing IVF, and determine potential ovarian function after the use of chemotherapy agents in cancer patients.

PREDICTOR OF PCOS

The majority of clinicians use the Rotterdam criteria to aid in making the diagnosis of PCOS. This diagnostic classification states that a patient can be diagnosed with PCOS if she has two of the following three signs: hyperandrogenism (HA), oligomenorrhea/anovulation, and/or polycystic-appearing ovaries on ultrasound (> 12 antral follicles). However, this “easy-to-use” method in defining PCOS has not been readily accepted by some researchers, even a few who were part of the Rotterdam “consensus.” These anti-Rotterdam folks strongly feel that hyperandrogenism MUST be part of a diagnosis of PCOS or else it is something else. No clear agreement has been established as to whether HA is required at this point, but two studies have argued that serum AMH > 5 ng/mL should replace ultrasound to define ovarian morphology.

In the first paper, a French group retrospectively documented 240 women who were referred to their center to evaluate hyperandrogenic symptoms. They were divided into three separate groups: non-PCOS without HA and ovulatory cycles (Group 1), PCOS diagnosis with either HA or oligo-anovulation (Group 2), and PCOS with both HA and oligo-anovulation (Group 3). Analysis of ultrasound in each group demonstrated that patients with PCOS were more likely to have an AMH > 5 ng/mL than > 12 antral follicles. From these
patients, the investigators concluded that serum AMH was more sensitive than follicle count to diagnose PCOS and that AMH should replace ultrasound morphology as part of the diagnostic classification.

The second paper observed 56 women who met Rotterdam criteria and 44 who met criteria set forth by the Androgen Excess-PCOS Society (which includes HA in all subjects). They concluded that AMH (> 3 ng/mL) was a better determinant of PCOS ovarian morphology than follicle number. However, they felt that AMH could not be used alone to make this diagnosis, but in conjunction with HA and oligo-anovulation.

Overall, these studies both highlight that the use of ultrasound to count follicles and determine morphology may be very subjective. Serum AMH >5 ng/mL, a biochemical measure, appears to be a better and more consistent substitute.

PREDICTOR OF OHSS
OHSS is one of the most serious complications of controlled ovarian hyperstimulation with exogenous gonadotropins. This condition can develop during ovulation induction for timed intercourse, intrauterine insemination, or IVF. It is subcategorized as mild, moderate, or severe with symptoms that range from mild post-hCG bloating to pulmonary compromise from ascites or pleural effusions that may require hospitalization or, at worse, result in death. Risk factors for OHSS include younger age (< 35 years), lean habitus, signs of PCOS, the presence of multiple (total > 35) small or intermediate follicles, and excessively high levels of estradiol on the day of hCG administration (> 4000 pg/mL).11 Despite these known risk factors, 100% prediction of OHSS is difficult. Because patients have developed OHSS with an older age, high body mass index (BMI), and low estradiol levels, other ways to predict OHSS are needed.

Chinese investigators measured serum AMH levels prospectively in 262 IVF cycles.12 The incidence of OHSS in this group of subjects was 7.7%, which correlates with previously published rate of 8%. They used a receiver operating characteristic (ROC) curve analysis to estimate the cutoff values of the measured variables that increased the risk of OHSS (AMH, estradiol, BMI, age, number of follicles measured, and number of follicles retrieved). Pre-cycle AMH levels > 3.36 ng/mL best correlated with risk of OHSS. The second variable that weakly correlated with AMH to increase OHSS risk was when the estradiol concentration was > 1613 pg/mL.

Fertility specialists who observe patients undergoing an IVF cycle who have AMH levels > 3.3 ng/mL, despite estradiol levels that are < 4000 pg/ml, still need to consider OHSS as a consequence and, therefore, give appropriate precautions to the patient.

PREDICTOR OF POST-CHEMOTHERAPY OVARIAN RESERVE
Cancer therapies, particularly use of chemotherapy agents, have an adverse effect on short- and long-term reproductive function by increasing the risk of early menopause and infertility. However, continuous improvement of survival rates and potential resurgence of ovarian function after treatment presents the clinician and patient with important quality-of-life issues. Chemotherapy regimens, particularly those that include alkylating agents, are toxic to ovarian germ cells by damaging follicles whether they are primordial, preantral, or antral. Factors that cause this damage include apoptotic processes, cortical fibrosis, and blood vessel compromise.13,14

Two prospective studies have determined that AMH should be obtained before chemotherapy treatment and then after these ovarian-toxic agents are completed to determine future reproductive potential.15,16

Anderson and colleagues found that all 33 patients undergoing chemotherapy for early stage breast cancer were noted to have a decrease in AMH (1.29 ng/mL vs 0.09 ng/mL), inhibin B (58.2 pg/mL vs 22.9 pg/mL), and estradiol (297 pg/mL vs 101 pg/mL) with an increase in FSH (10.4 mIU/mL vs 25.5 mIU/mL) 5 years after initial treatment.15 Over this time frame, these same patients were compared to 14 patients who did not take chemotherapy and were found to have a significant difference when observing all measures of ovarian reserve. When dividing the chemotherapy-using patients who had return of menses to those who developed amenorrhea after 5 years, those with normal menses had a higher AMH concentration (0.16 ng/mL vs 0.06 ng/mL) compared to those who were amenorrheic.

In the second study, 46 adolescent and young adult women were given alkylating chemotherapy for several cancers.16 When comparing AMH levels 12 months after treatment, patients who had pretreatment AMH levels > 2 ng/mL were noted to have progressively increasing levels with a recovery rate of 11.9% per month. However, if pretreatment AMH levels were < 2 ng/mL, the recovery rate for AMH was only 2.6% per month.

Both of these papers demonstrate pretreatment AMH levels, particularly if > 2 ng/mL, help predict the potential for return of ovarian function after the use of chemotherapeutic alkylating agents.

CONCLUSION
Although AMH is used most often in the clinical setting to judge the fertility reserve of an older reproductive woman, it may have value outside this arena. AMH...
allows both patients and clinicians to help predict the extent of primordial follicles remaining in the ovaries for many reasons. If there are too many follicles, patients may have a diagnosis of PCOS or may be at risk for OHSS. If there are too few, patients may have issues with their future fertility because of age or because of exogenous agents that directly destroy germ cells. Future applications for AMH may include a role in predicting when to safely stop oral contraceptives in the perimenopausal woman or whether ovarian shielding during radiation for cancer treatment truly has a protective effect.

REFERENCES


CME QUESTIONS

1. The U.S. Preventive Services Task Force recommends that a screening pelvic exam be performed in healthy asymptomatic women: a. annually beginning at menarche. b. annually starting at coital debut. c. annually starting at age 30. d. annually at menopause. e. only if they become symptomatic.

2. Which of the following best describes the findings in the trial of olaparib for recurrent ovarian cancer? a. The analysis was a prospective evaluation of BRCA mutation status. b. Progression-free and overall survival were significantly longer in the olaparib arm. c. Only women with germline BRCA were included in the subpopulation. d. Treatment discontinuation was significantly higher in the olaparib arm. e. The sensitivity analyses included both time to first line of subsequent therapy and time to second subsequent therapy.

3. Studies have shown that uterine artery waveform analysis has predictive value and all but one of the following conditions: a. Severe preeclampsia b. Stillbirth c. SGA d. Placental abruption