ABSTRACT & COMMENTARY

Finding New Clinical Activity in Endometrial Cancer from Optimizing Molecular Pathways

By Robert L. Coleman, MD

Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman reports he was the senior author on this paper and the grant holder.

SYNOPSIS: Everolimus, an mTOR inhibitor, combined with letrozole produced unexpected clinical activity in a cohort of previously treated recurrent endometrial cancer patients. Objective response rate was notable for a high number of complete responders, particularly those given metformin in treatment for everolimus-related glucose intolerance.


Comprehensive molecular profiling of endometrial cancer has demonstrated that the phosphoinositol-3 kinase (PI3K) pathway is the single most frequently dysregulated pathway in endometrial cancer (EC). Targeted agents have been developed to block signaling at several nodes in the pathway; however, preliminary efficacy reports have not been robust. Similarly, hormonal manipulation has led to objective response in some patients, but resistance derived from PI3K pathway activation has been documented. These observations prompted the exploration of a Phase 2 trial combining the mTOR inhibitor, everolimus, in combination with the aromatase inhibitor, letrozole. Eligible patients were women with incurable EC, which was measurable, and had received two or fewer prior cytotoxic regimens. Everolimus was administered orally at 10 mg daily and letrozole was administered orally at 2.5 mg daily. Each cycle consisted of 4 weeks of therapy. Patients were treated until progression, toxicity, or complete response (CR). The primary endpoint was the clinical benefit rate (CBR), which was defined as CR, partial response (PR), or stable disease (≥ 16 weeks in duration). Translational studies were performed to correlate biomarkers with response. Thirty-five patients were evaluable for response. The CBR was 40%; the median number of cycles among responders was 15 (range, 7 to 29 cycles). The confirmed objective response rate (RR) was 32% (95% confidence interval, 17-49%) including nine CRs and two PRs. Twenty percent of patients were removed from therapy after a prolonged CR. None of the patients discontinued treatment as a result of toxicity.
Farewell and Welcome
Dr. Robert Coleman, a member of the editorial board of OB/GYN Clinical Alert since 2004, has been elected as the next President of the Society of Gynecologic Oncologists. Congratulations to Rob as he takes over this important leadership role. Unfortunately for us, the additional duties have made it difficult to keep up with his editorial work, so Dr. Coleman has decided to step down with this month’s commentary. His insights into the complex epidemiology and treatment of gynecologic cancer will be missed. Please join me in wishing him well with his SGO Presidency and his research and clinical activities. We will miss you Rob.

Welcome Molly Brewer, DVM, MD, as our newest Associate Editor. Dr. Brewer is Professor of Gynecologic Oncology and Chair of the Department of OB/GYN at the University of Connecticut. She completed her residency training in OB/GYN at OHSU and her oncology fellowship at MD Anderson. In addition to her interest in women’s cancer, Molly has considerable expertise and interest in medical education. Please join me in welcoming her to the editorial board of OB/GYN Clinical Alert.

Serous histology was the best predictor of lack of response, and patients with endometrioid histology and CTNNB1 mutations responded well to the combination. The authors concluded everolimus plus letrozole results in a high CBR and RR in patients with recurrent EC, and recommended further development of this combination in recurrent endometrioid EC.

## COMMENTARY

Every once in a while (unfortunately not often enough), we get it right … that is, biological rationale supported by real-life observations in the clinic. In this case, two modestly active agents produced greater than expected results when combined. In many cases, the efficacy gained is simply an additive effect of cytotoxic/biological agents. However, it is usually at the expense of greater toxicity. There are many examples of this in endometrial cancer investigation. Generally, it leads to tempered clinical adoption due to efficacy-toxicities trade-off considerations in individual patients. Since recurrent endometrial cancer patients are frequently elderly with multiple comorbidities, the clinical exercise in management recommendations based on toxicity are particularly relevant. The current study is notable in that the observed efficacy appears to be greater than expected for additive effects. Although hormonal therapy has been used in endometrial cancer patients for years (indeed, megestrol acetate is the only approved anticancer agent in endometrial cancer), the global efficacy is between 8% and 20%, and generally of short duration. In addition, the single-agent activity of PI3K inhibitors has been modest at best, with infrequent objective responses. Indeed, the current paper’s investigative lead had previously reported on the clinical activity of everolimus in a similar cohort of patients and demonstrated no objective response and a 20% clinical benefit rate, all attributed to stable disease. Others have reported higher rates of response, but only in patients not previously treated with chemotherapy. The mechanism underlying this trial’s success is likely due to drug-drug interaction targeting a resistance or escape route for cancer cell survival. Similar observations were observed in a Phase 3 trial of patients with endocrine-resistant breast cancer, leading to regulatory approval of the combination of exemestane and everolimus.

Although the exact mechanism is still being explored, it was interesting that patients with uterine serous cancer recorded no responses to the combination. This is likely due to the high prevalence of pathologial P53 aberrations driving that pathobiology. In addition, efficacy to the combination did not solely depend on hormone receptor expression, as objective responses were observed in estrogen- and progesterone-receptor negative tumors. Further, hyperglycemia, a frequent finding in endometrial cancer patients due to chronic obesity and an adverse event caused from everolimus-induced enhanced gluconeogenesis, was associated with a remarkable response rate. Metformin, primarily used to treat this insulin-resistance, has been shown to impair cancer cell growth signaling by amplifying AMPK, another regulator of the PI3K pathway. The interaction provided another avenue of PI3K pathway signaling control. These observations have already provided the impetus for several new studies to explore and validate these findings. Currently, the triplet (everolimus, letrozole, and metformin) is being studied in a similar population, limited to patients with endometrioid adenocarcinoma (NCT01797523); the combination is being compared to endocrine therapy alone in a randomized Phase 2 trial within the Gynecologic Oncology Group Foundation (NCT02228681); and a Phase 2/3 trial of paclitaxel/carboplatin with or without metformin is being conducted in the NRG
A Farewell Message

It is with mixed emotions that I announce my departure from OB/GYN Clinical Alert. In serving as section contributor of gynecologic oncology for more than 10 years, I have truly enjoyed the outlet for reporting important scientific works that this periodical affords. It is unique, timely, and nimble in its format, which provides an opportunity to rapidly discuss important topics from the literature through data synthesis and context by clinical commentary. I equally enjoyed reading the contributions of my co-contributors in each issue, learning what goes on in the world of obstetrics and gynecology outside of oncology. Unfortunately, time commitments from my expanding administrative and leadership responsibilities to our professional organization, the Society of Gynecologic Oncology, has caused me to reduce my regular efforts to the Alert. While I am excited to embark on this next iteration of professional development, I will miss the collegiality of the editorial team and my co-contributors. However, I know I leave the publication in the very capable hands of my good friend and colleague, Dr. Molly Brewer. Molly is one of the smartest and most insightful people I know, and I look forward to her stewardship of the oncology section. I would also like to commend the professionalism and kindness of the editorial team and my many co-contributors over the years – it’s been an honor to serve with you and I wish you the best of success. RLC

REFERENCES

ABSTRACT & COMMENTARY

Hormonal Contraception and Glioma: Is There Reason for Concern?

By Jeffrey T. Jensen, MD, MPH

SYNOPSIS: A large case-control study using the Danish National database found a slight increase in the risk of glioma in ever-users of hormonal contraception, which increased with duration of use. Users of progestin-only methods were at higher risk. However, these findings should not influence clinical practice or perception of contraceptive safety.


The authors used the extensive Danish population-based administrative and health registries to perform a case-control study evaluating the association of current and past use of hormonal contraception and glioma. Cases included all women in the Danish Cancer registry database between the ages of 15 to 49 years with a first-time diagnosis of a histologically verified glioma between 2000 and 2009. Each case was age-matched to eight population controls identified in the Danish National Patient Register. Hormonal contraceptive use, categorized according to type and duration, was inferred using prescription data from a pharmacy database. The categories of contraceptive use were combined estrogen–progestogen, progestogen-only, or mixed use. Only use of oral products and the levonorgestrel intrauterine system (LNG-IUS) were evaluated, as few women reported use of the vaginal ring, implant, injection, or patch. Duration was categorized as < 1 year, 1 to < 5 years, or ≥ 5 years. The authors used conditional logistic regression to compute odds ratios (ORs) with 95% confidence intervals (CIs) for glioma associated with hormonal contraceptive use, adjusting for potential confounders (age, years of schooling, and history of allergy or asthma). A total of 317 cases were identified and matched to 2126 controls. Ever-use of a hormonal contraceptive was associated with an elevated risk of glioma (OR, 1.5; 95% CI, 1.2-2.0), and the OR increased slightly with longer duration of use (≥ 5 years; OR, 1.9; 95% CI, 1.2-2.9) and then disappeared with past use (OR, 1.2; 95% CI, 0.8-2.0). Of great interest, the increase in risk appeared confined to users of progestogen-only methods. For progestogen-only tablets, the odds were significantly increased (OR, 3.3; 95% CI, 1.6-6.9); the point estimate was only increased for the LNG-IUS (OR, 2.4; 95% CI, 0.8-6.8). The overall increase in risk associated with combined methods (OR, 1.4; 95% CI, 1.0-1.8) was not statistically significant, but the odds ratio became significant with use of ≥ 5 years (OR, 1.7; 95% CI, 1.1-2.8). In contrast, the odds of glioma associated with ≥ 5 years use of a progestogen-only method was 4.1 (95% CI, 0.8-20.8), but, again, the confidence interval included 1.0. The authors conclude that long-term use of hormonal contraceptives was associated with an increased risk of glioma, and that further studies are needed to evaluate this potential risk.

COMMENTARY

This paper received a burst of attention from the media that quickly fizzled. But I suspect trial lawyers are already preparing Internet websites to serve the “interest” of...
families of young women diagnosed with one of these rare tumors. At first review, several features of this manuscript should draw suspicion. It is highly unlikely that the British Journal of Pharmacology is on your monthly reading list or that it was the preferred journal for publication of this paper. This strongly suggests failed peer review in more appropriate journals. This is not necessarily a black mark, as many papers make the rounds. But most authors prefer publication in a relevant journal. In this case, that would include the numerous publications devoted to contraception, gynecology, reproductive endocrinology, neurology, neurosurgery, or epidemiology. This is important, as these journals maintain lists of reviewers with sufficient expertise to evaluate manuscripts and place results in context with what is known about a topic.

The published results of this paper warrant critical appraisal. First, although glioma is a devastating diagnosis, these tumors are extremely rare. Data from the Central Brain Tumor Registry of the United States (1998-2002) puts the average annual age-adjusted incidence rate of primary malignant brain and central nervous system tumors among adults aged 20 years as 9.0 per 100,000 person-years. For glioblastoma, the female rate was 2.4/100,000 and the median age of diagnosis was 64 years. Although the incidence has been slowly increasing, this is thought to be related to more common use of diagnostic imaging (MRI, CT). Suffice to say, the disease is rare, particularly in young women. On the other hand, if a young woman develops a brain tumor, it is likely to be a glioma.

Although brain tumors are rare in young women, hormonal contraceptive use is common. This makes evaluation of risk difficult. A case-control design is appropriate for a rare disease, but we must be careful to not over-interpret the data. The Bradford Hill criteria for epidemiologic studies provide guidance: 1) Strength of association: Risk estimates should be moderate to large. Most of the odds ratios in the present study are < 2, suggesting a weak association. Of note, the association with progestogen pills was OR 3.3 (95% CI, 1.6-6.9); 2) Dose response: The biologic effect should increase with greater exposure. In this study, increasing duration of use did increase the OR, but the associations remained weak except for progestogen-only pills. 3) Biologic plausibility: There should be a biologic mechanism to mediate the effect. There is evidence to suggest that estrogens may influence the development of gliomas; the incidence is lower in premenopausal females compared to males, some gliomas and glioblastomas express estrogen receptors (ER) and aromatase, and experiments in rodents have shown that estradiol and certain SERMs inhibit proliferation of gliomas. Progesterone receptor (PR) is expressed in some gliomas, and progesterone is believed to be endogenously produced in the central nervous system and responsible for normal development. Could the increased PR exposure of the progestogen-only pill, in association with ovarian suppression and low estrogen levels, be a mechanism for an increase in glioma risk? Possibly, but the evidence is weak. Progesterone is known to be neuroprotective following stroke or head trauma, and is associated with schwannomas and meningiomas. But, in contrast to these tumors, treatment with mifepristone does not influence the growth of gliomas. In other words, progesterone signaling seems to be related to growth of myelin and meninges, and not to neurons and other brain connective tissue.

REFERENCES

ABSTRACT & COMMENTARY

NIPT and Invasive Procedures

By John C. Hobbins, MD

Professor, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora

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

SYNOPSIS: A single prenatal testing center with a large volume of patients has experienced a dramatic drop in the rate of chorionic villus sampling and amniocentesis after the introduction of noninvasive prenatal testing.

Noninvasive prenatal testing (NIPT) has affected the logistics of screening for various forms of fetal aneuploidy, as well as the economics surrounding the delivery of NIPT to a large segment of the public.

Larion et al assessed how NIPT has affected the downstream need for invasive testing. They analyzed data regarding invasive procedures before and after the advent of NIPT. The study covered two time periods: the first being the 35 months prior to February 2012, when NIPT was first introduced in Virginia, and the second representing the next 16 months (March 2012-June 2013). During the first 4-month block of the “after” study group, NIPT was only offered to high-risk patients, but following a shift in policy, it was offered to all pregnant patients. During the last 16 months of the study (the after group), first trimester nuchal translucency and biochemistry testing (the standard “combined screen”) decreased by 48%, while NIPT rose by 55%. Prior to March 2012, the average rate of chorionic villus sampling (CVS) was 5.7 per month. This dropped dramatically during the next 4-month intervals to 1.8 per month, representing a 72% decrease from baseline rates prior to NIPT. Similarly, the amniocentesis rates decreased from pre-NIPT rates of 26 per month to 12 per month, representing a 52.5% drop in these invasive procedures.

**COMMENTARY**

There is no doubt that the introduction of NIPT has changed the way we and patients think about the screening for, and the ultimate diagnosis of, fetal aneuploidy. In fact, our own statistics show even a more dramatic plunge in the number of invasive procedures done at our centers. This represents a huge spinoff bonus in patient care because the amniocentesis and CVS procedures are now being done for better reasons (and with a higher yield per procedure).

Today, there is a buffet of options for screening/diagnostic approaches to fetal aneuploidy, which include nuchal translucency (NT) alone, combined screening (NT and first-trimester biochemistry), NIPT, or the approach of yesteryear (usually in patients of advanced maternal age) CVS or amniocentesis. From a fetal risk standpoint, the last approach now seems inadvisable for most patients.

Since cost is also of concern today, screening first with a standard combined screen makes sense in low-risk patients, with NIPT being used as a second “contingency” option if the results are not reassuring. High-risk patients, however, could benefit from NIPT as a first-line approach to aneuploidy testing, with invasive testing being used for confirmation. Sonek and Cuckle have shown these approaches to be more cost effective, while maintaining a high detection rate. Nevertheless, it is very likely that companies offering NIPT will soon be charging less for their services in order to be competitive in a potential market of 4 million pregnancies per year. Then it may be economically feasible to offer NIPT to all patients, which will set off a new set of logistical, ethical, and educational factors to manage.

It has been recommended that all patients with a positive NIPT result (as of now for trisomy 21, 18, 13, or XO) have confirmation of aneuploidy through invasive testing. However, we have had a few patients who have had positive NIPTs, as well as strong ultrasound evidence of aneuploidy, who have balked at the need for either CVS or amniocentesis prior to termination of pregnancy. Since this does involve cost and some discomfort, it is difficult to muster a strong argument against this stance under these specific circumstances. Nevertheless, without other supporting evidence, the false-positive rates, especially for trisomy 18 and trisomy 13, are high enough to warrant confirmation in the vast majority of cases. Also, an emerging concern is that patients whose fetuses have these two conditions, in particular, tend to have lower levels of fetal DNA in their circulations, causing a higher rate of “indeterminate” results. Since patients in this category have a risk as high as 1 in 5 for fetal aneuploidy, they also can benefit from invasive testing.

As the need for amniocentesis and CVS decreases, there will be fewer procedures available with which to train our clinicians. This will have the greatest impact on CVS-related complications, since loss rates, complications, and need for repeat insertions can vary according to the adequacy of training and the number of cases done per year by the individuals performing the procedures. In my opinion, you cannot adequately train an individual to do these procedures on a simulator. I can just see the wheels turning toward credentialing for yet another clinical activity.

**REFERENCES**


**SPECIAL FEATURE**

**Postoperative Delirium in Older Adults**

*By Chiara Ghetti, MD*

Associate Professor of Obstetrics and Gynecology, Division of Female Pelvic Medicine and Reconstructive Surgery, Washington University School of Medicine, St. Louis, MO

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


April 2015 93
As an urogynecologist, I have become increasingly interested in the unique needs of the elderly woman. The elderly operative patient has very different and specific needs compared to a younger woman. In addition to a higher risk of medical comorbidities, elderly women are affected by cognitive impairment, depression, gait, and balance disturbances. As discussed in a prior OB/GYN Clinical Alert, the prevalence of incontinence increases with age. Prolapse is the most common indication for gynecological surgery for women older than 50 years in the United States. Previous studies have shown that approximately 40% of women undergoing prolapse surgery are 60 years of age or older. The U.S. Department of Health and Human Services reports that the number of Americans aged 65 or older increased by 3.4 million, or 10%, from 1996 to 2006, with current estimates placing 1 in 8 Americans in this age category. This older cohort of women is expected to continue to increase in number, with estimates suggesting that by 2030 in the United States 1 in 5 adults will be 65 years of age or older. As the U.S. population ages, the proportion of elderly female patients undergoing gynecologic surgery will increase. This shifting demographic lends increasing importance of the effects of surgery on the elderly patient.

Delirium is a common complication of the older patient undergoing surgery and is the most common surgical complication affecting older adults. Delirium diagnosis and treatment is an essential component of optimal surgical care of the older adult, but teaching regarding delirium may be underemphasized in surgical training. The American Geriatrics Society, in collaboration with an interdisciplinary, multi-society panel from the American Geriatrics Society’s Geriatrics-for-Specialists Initiative, recently published a best practice statement regarding postoperative delirium in older adults to provide evidence-based recommendations to aid practitioners in the care of older women.

BACKGROUND
Delirium is a sudden change in cognitive function and is a form of brain dysfunction, in essence it represents acute brain failure. Delirium can precipitate a series of major postoperative complications, prolonged hospitalization, loss of functional independence, reduced cognitive function, and death. The annual cost of delirium in the United States is estimated to be $150 billion. However, delirium is preventable in up to 40% of patients, and its prevention can significantly improve the perioperative outcomes of older adults. These guidelines were developed to aid clinical decision-making for provider caring for elderly patients in the operative setting; however, the authors emphasize they are not intended to replace clinical judgment or individual patient choices or values. The original wording of recommendations of the Best Practice Statement Regarding Postoperative Delirium in Older Adults are presented below in italics.

I. POSTOPERATIVE DELIRIUM RISK FACTORS
• Health care professionals caring for surgical patients should perform a preoperative assessment of delirium risk factors, including age > 65 years, chronic cognitive decline or dementia, poor vision or hearing, severe illness, and presence of infection.

II. DELIRIUM DIAGNOSIS
• Health care professionals caring for postsurgical patients should be trained in the recognition and documentation of signs and symptoms associated with delirium, including hypotensive presentations.
• Health care professionals should assess and clearly document preoperative cognitive function in older adults at risk of postoperative delirium.
• Health care professionals competent in diagnosing delirium should perform a full clinical assessment in any patient suspected of having symptoms of delirium, found positive on a delirium screening test, or having an acute cognitive change on repeated cognitive testing.

The diagnosis of delirium is made primarily from history and physical examination and informed by witness reports, medical records, laboratory, and radiologic findings. While screening tools are recommended (see III below), the hallmark symptoms of delirium are changes in level of arousal, consciousness, and cognition that occur over a short time, over hours or days. In more detail, symptoms can comprise: 1) a change in level of arousal (this can include drowsiness or decreased arousal or increased arousal with hyper vigilance); 2) an abrupt change in cognitive function, including problems with attention, difficulty concentrating, new memory problems, new disorientation, or difficulty tracking conversations and following instructions; 3) thinking and speech that is more disorganized, difficult to follow, slow, or rapid; 4) quick-changing emotions, easy irritability, tearfulness; and 5) fluctuating symptoms and/or level of arousal. Additionally, delirium can be characterized by: 1) delayed awakening from anesthesia; 2) uncharacteristic refusals to engage with postoperative care; 3) expression of new paranoid thoughts or delusions (i.e., fixed false beliefs); 4) new perceptual disturbances (e.g., illusions, hallucinations); 5) motor changes such as slowed or decreased movements; 6) purposeless fidgeting or restlessness; 7) new difficulties in maintaining posture such as sitting or standing; 8) changes in sleep/wake cycle; 9) decreased appetite; and/or 10) new incontinence of urine or stool.

III. DELIRIUM SCREENING
• When screening a patient for delirium, a health care professional trained in the assessment of delirium should use a validated delirium screening instrument for optimal delirium detection.
• The health care team may consider instituting daily postoperative screening of older patients for the development of delirium in order to initiate delirium treatment as early as possible.

Studies have demonstrated that providers do not accurately diagnose delirium based on a bedside evaluation alone. A variety of screening measures exist that are specific to different patient populations. The use of screening measures may allow for earlier delirium diagnosis and activation of applicable treatment. One such screening tool, Confusion Assessment Method (CAM), is used by many as a screening tool.
administration of cholinesterase inhibitors has not been shown to be effective in reducing postoperative delirium and may cause increased harm (including death).

VII. NONPHARMACOLOGIC PREVENTION AND TREATMENT OF POSTOPERATIVE DELIRIUM

- Health care systems and hospitals should implement formal educational programs with ongoing (at least quarterly) formal and/or informal refresher sessions for health care professionals on delirium in at-risk older surgical adults to improve understanding of the epidemiology, assessment, prevention, and treatment of delirium.
- Health care systems and hospitals should implement multicomponent nonpharmacologic intervention programs delivered by an interdisciplinary team for the entire hospitalization in at-risk older adults undergoing surgery to prevent delirium.
- Health care professionals should consider multicomponent interventions implemented by an interdisciplinary team in older adults diagnosed with postoperative delirium to improve clinical outcomes.
- There is insufficient evidence to recommend for or against hospitals creating, and health care professionals using, specialized hospital units for the inpatient care of older adults with postoperative delirium to improve clinical outcomes.

At least 10 moderate- to high-quality studies have documented the effectiveness of non-pharmacologic prevention in reducing the incidence of delirium.

VIII. MEDICAL EVALUATION OF POSTOPERATIVE DELIRIUM

- The health care professional should perform a medical evaluation, make medication and/or environmental adjustments, and order appropriate diagnostic tests and clinical consultations after an older adult has been diagnosed with postoperative delirium to identify and manage underlying contributors to delirium.

It is critically important for the surgeon to identify and treat the underlying causes of a patient’s delirium. Additionally, including a geriatric or medical consultant in the perioperative care of an elderly patient may be helpful.

IX. PHARMACOLOGIC TREATMENT OF POSTOPERATIVE DELIRIUM

- The prescribing practitioner may use antipsychotics at the lowest effective dose for the shortest possible duration to treat patients who are severely agitated or distressed, and are threatening substantial harm to self and/or others. In all cases, treatment with antipsychotics should be employed only if behavioral interventions have failed or are not possible, and ongoing use should be evaluated daily with in-person examination of patients.
- The prescribing practitioner should not prescribe antipsychotic or benzodiazepine medications for the treatment of older adults with postoperative delirium who are not agitated and threatening substantial harm to self or others.
- The prescribing practitioner should not use benzodiazepines as a first-line treatment of the agitated postoperative delirious patient who is threatening...
substantial harm to self and/or others to treat postoperative delirium, except when benzodiazepines are specifically indicated (including but not limited to treatment of alcohol or benzodiazepine withdrawal). Treatment with benzodiazepines should be at the lowest effective dose for the shortest possible duration, and should be employed only if behavioral measures have failed or are not possible and ongoing use should be evaluated daily with in-person examination of the patient.

Evidence supporting the benefits of pharmacologic therapy in the treatment of postoperative delirium is inconsistent. There is no evidence of benefit from treatment of antipsychotics in patients without agitation; hence, the use of antipsychotics should be reserved for short-term management of acute agitation in cases in which the patient’s safety or the safety of others is at risk.

Delirium confers significant morbidity to postoperative elderly patients. These recommendations are intended to provide a framework to address delirium in perioperative patients. While a comprehensive approach to the prevention and treatment of delirium will require direct involvement of both individual providers and entire hospital and health care systems, an increased understanding of delirium, its risk factors, symptoms, appropriate screening and diagnosis, as well as the non-pharmacologic and pharmacologic interventions to prevent and treat delirium, will allow us to more accurately and successfully diagnose and manage postoperative delirium.

REFERENCES

CME QUESTIONS

1. Which of the following was a characteristic of the population in the endometrial cancer trial?
   a. Allowance for unlimited prior regimens
   b. Measurable or evaluable disease
   c. Potentially curable disease
   d. Allowance for unlimited prior regimens
2. The odds ratio of glioma associated with contraception use was:
   a. three-fold higher among users of progestogen-only pills
   b. three-fold lower among users of combined oral contraceptives
   c. significantly reduced when women used the vaginal ring
   d. highest among women using a copper IUD.
3. Which of the following is appropriate to the findings in the featured study on noninvasive prenatal testing?
   a. During the second part of the study, NIPT was only offered to high-risk patients
   b. The rate of amniocentesis dropped by one-third.
   c. The rate of NIPT rose at about the same rate as standard testing dropped.
   d. The rate of NIPT rose faster than the drop in the rate of CVS.
4. An 82-year-old woman is post-op day #1
   a. The patient is unable to stay focused on questions
   b. Her symptoms seem to fluctuate
   c. She appears drowsy at times
   d. The family member who is with her says she has had increased confusion over the last 2 months.

IN FUTURE ISSUES

Low-lying Intrauterine Devices: To Remove or Not to Remove?
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