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INSIDE

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Contraceptive Use and Unintended Pregnancy

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *In the most recent data from the National Survey of Family Growth, oral contraceptive pills remain the most widely used method of contraception, followed by female sterilization. Although more women are using highly effective methods like the IUD, the proportion at risk of unintended pregnancy and not using any method remains high at 7.3%.*

Source: Mosher WD, Jones J. *Use of Contraception in the United States: 1982-2008. Vital and Health Statistics.* Hyattsville, MD: U.S. Department of Health and Human Services; May 2010: Publication No. PHS 2010-1350. Available at: www.cdc.gov/nchs/data/series/sr_23/sr23_029.pdf.

National estimates of contraceptive use and method choice from the most recent 2006-2008 cycle of the National Surveys of Family Growth (NSFG) were compared to earlier estimates based on the 1982, 1995, and 2002 surveys. These data are important, as contraceptive use is a major factor affecting birth and pregnancy rates, as well as the rate of unintended pregnancy. The NSFG is a nationally representative survey conducted by the National Center for Health Statistics. The 2006-2008 data were collected through in-person interviews with 13,495 men and women 15-44 years of age. The contraceptive report is based on the sample of 7356 women interviewed in 2006-2008. The response rate for women in the 2006-2008 survey was about 76%.

More than 99% of women 15-44 years of age who have ever had sexual intercourse with a male reported that they had used at least one contraceptive method. The typical pattern of contraceptive use in the United States is to use the condom at first intercourse, the pill to delay the first birth, and female sterilization at completion of childbearing.

The percentage of women whose male partner had ever used the condom increased from 52% to 93% from 1982 to 2006-2008. Ever use of emergency contraception has increased from less than 1% in 1995 to almost 10% in 2006-2008.

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About 62% of the 61.9 million women aged 15-44 years were currently using contraception (at the date of interview) in 2006-2008. The other 38% were not using contraception for a variety of reasons. These included women who were "not at risk of unintended pregnancy" because they were currently pregnant or postpartum, trying to become pregnant, sterile for medical (noncontraceptive) reasons, unable to conceive, or had not had intercourse recently or ever. However, 7.3% of women were "at risk of unintended pregnancy" because they had been having intercourse in the last 3 months and were not using contraception.

Among current users of contraception, the leading method was the oral contraceptive pill, used by 10.7 million women; the second leading method was female sterilization, used by 10.3 million women. Between 2002 and 2006-2008, the proportion of IUD use increased from 2% to 5.5%. Age, parity, marital status, education, and income are closely related to the choice of method and the risk of unintended pregnancy.

■ COMMENTARY

With a population of almost 310 million,[1] the United States has the fastest rate of population growth among more developed nations. Although much of this growth is fueled by immigration, even modest adjustments in the total fertility rate have profound consequences for population growth, environmental impact, and the world economy. A major factor affecting U.S. birth and pregnancy rates is the use and efficacy of contraception.

These initial results from the much-anticipated 2006-2008 NSFG provide important information on U.S. family planning trends. Established in 1973 by the National Center for Health Statistics (NCHS), the NSFG contributes a periodic survey of factors affecting the formation, growth, and dissolution of families, including contraception, sterilization, and sexual activity. Results of the NSFG are dependable and highly significant because they come from a rigorous nationally representative, multistage area, probability sample drawn from 120 areas across the country designed to produce national estimates. The NCHS has conducted the survey in 1973, 1976, 1982, 1988, 1995, 2002, and 2006-2008. Reports in 1973 and 1976 recorded information only for married or divorced women; in 1982 the survey was expanded to include women aged 15-44, regardless of marital status. Thus, trends regarding contraceptive use between the 1982, 1995, 2002, and current 2006-2008 reports are comparable.

In the 2006-2008 sample, current users of a contraceptive method represented about 62% of the sample, the same as in 2002, but a decline of 2.3% since 1995. This translates to an estimated 554,000 fewer contraceptive users. The good news is that there has been an increase in the use of more effective (hormonal and IUD) methods and an increased use of condoms at first intercourse since 1995. Although use of oral contraceptives dropped slightly, when numbers of vaginal ring users are considered, the overall use of combined hormonal methods remains around 19%. Use of male and female sterilization remained about the same (16.7% and 6.1%), but there were fewer users of depo-Provera (from 3.3% in 2002 to 2.0%) and more users of the IUD (1.3% to 3.4%).

The renaissance in IUD use is more impressive when use is evaluated as a proportion of contraceptive users (from 2.0% to 5.5%). Between 2002 and 2006-2008, IUD use dramatically increased among women with one (2% to 8%) or two (3% to 11%) children. One notable area where the 2006-2008 data appear to lag behind clinical practice is the low proportion of IUD use reported among nulliparous women (0.3%). The safety of the IUD in young and nulliparous women appears to be similar to that of older parous women.[2] Since young nulliparous women experience the highest rates of unintended pregnancy and abortion,[3] use of highly effective, long-acting, reversible methods like the IUD should be encouraged in this group.

Contraception use at first premarital intercourse is important because 94% of women aged 15-44 have had premarital intercourse.[4] Teenagers who do not use a method have a higher risk of unintended pregnancy and sexually transmitted infection. While a growing proportion of the cohort experiencing first intercourse reported use of some method of contraception (84% between 2005-2008 compared to 76% in 2001-2004), this increase was due to equal growth in the use of condoms (from 64% to 72%)

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and withdrawal (3% to 9%), a method not associated with STI protection. Could this reflect the growing emphasis on abstinence education and away from sexuality and methods-based content during the last decade?

Another disturbing trend is the high proportion of women at risk for pregnancy that report non-use of contraception. This increased from 5.2% to 7.4% between 1995 and 2002, and remains at 7.3% in the current sample. Due to the large size of the NSFG sample, all these changes represent statistically significant differences; this 2.2% increase from 1995 to 2002 represents an additional 1.4 million women at risk of unintended pregnancy. This small increase is highly important because non-users of contraception contribute almost half of the total number of unintended pregnancies; about half of these are terminated by abortion. Perhaps not surprisingly, more than 44% of non-users cited "did not think they could get pregnant" as the reason for non-use. Seems to me that these numbers provide direct evidence of the lack of benefit (and probable harm) of the abstinence-only curriculum. Thank goodness the new administration sees this reality. Write your members of congress. Ending abstinence-only funding is an easy way to reduce federal spending! ■

Reference

1. U.S. & World Population Clocks. U.S. Census Bureau; 2010. Available at: www.census.gov/main/www/popclock.html.
2. Hubacher D. Copper intrauterine device use by nulliparous women. *Contraception* 2007;75(6 Suppl):S8-11.
3. Pazol K, et al. Abortion surveillance — United States, 2006. *MMWR Surveill Summ* 2009;58:1-35.
4. Finer LB. Trends in premarital sex in the United States, 1954-2003. *Public Health Rep* 2007;122:73-78.

Rescue Course of Antenatal Corticosteroids

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *A recent study supports another investigation suggesting the benefit of a rescue dose of antenatal corticosteroids in patients who will deliver prior to 35 weeks and have had more than 2 weeks elapse after their initial course of therapy.*

Source: McEvoy C, et al. Respiratory compliance in preterm infants after a single rescue course of antenatal steroids. *Am J Obstet Gynecol* 2010;202:544.e1-9.

In 1972, Liggins and Howie demonstrated that antenatal corticosteroids (ACS) stimulated the production of surfactant in premature human fetuses.[1] Since then, it has been accepted that steroids — in particular, betamethasone and dexamethasone — can reduce the incidence of respiratory distress syndrome (RDS) in preterm infants if given prior to 35 weeks. However, it has not been completely clear how often it can be given to attain its greatest effectiveness, with minimal risk.

McEvoy et al just published a randomized trial that dealt with the efficacy of giving a "rescue" course of betamethasone 2 weeks or more past the initial dosage and prior to 35 weeks' gestation. Rather than gathering large enough numbers of patients to show differences in the rates of respiratory distress syndrome (RDS), they concentrated on two indices of respiratory compliance in the neonate. The study included patients who had an initial course of steroids after 24 weeks.

Forty-four mothers delivering 56 infants (twins were included), all of whom had gotten an initial dose of betamethasone between 24 weeks and 32 weeks, were randomly assigned to receive a two-injection rescue course of betamethasone. Another 41 mothers and 57 infants were given placebos. Both study groups received their study drugs more than 2 weeks after the initial dose. In the end, there were 49 infants in each group that could be tested at about 20 hours post-delivery for passive respiratory compliance (Crs) and functional residual capacity (FRC).

Fewer infants in the treated group had RDS, but, not surprisingly, based on the small numbers of patients involved, the difference was not statistically significant. However, significantly fewer infants in the treated group needed > 30% oxygen or 40% oxygen than controls (13% vs 29%, and 9% vs 23%). Although there were no significant differences in groups for FRC, there was an 18% improvement in Crs in the treated group, demonstrating improved compliance.

The results in those delivered prior to 34 weeks showed an even greater difference in RDS, oxygen requirements, and Crs (a 30% difference).

■ COMMENTARY

There is now adequate evidence that ACS diminishes the incidence of RDS and associated neonatal morbidity if given before 35 weeks. However, when some studies suggested a loss of its effect after 1 week, there was a movement to respond to the adage "if some is good, more is better," by giving weekly courses of ACS until 34 weeks. The concept was backed up by data from a Cochrane review by Crowther et al,[2] which showed a reduction of

the severity of the disease when ACS was administered weekly, compared with a single course. However, based on the concept that ACS could suppress DNA synthesis, and evidence that fetal lambs exposed to ACS had a dose-dependent decrease in birth weight, there was a renewed effort to evaluate possible side effects for repeated doses of ACS. In the Cochrane review of 2007, there was only one randomized trial showing a reduction in average birth weight with repeated dosage, but there were two studies that suggested a higher rate of infants born with birth weights below the 10th percentile. One randomized trial addressed long-term follow-up at 2-3 years of age in children exposed to repeated dosage, compared with a single dose.[3] There were no differences between the groups with regard to body size, blood pressure, respiratory morbidity, or behavior scores. However, there was a greater tendency for the repeated-dose children to have "attention problems." Another randomized trial conducted by the NIH Perinatal Network had a similar study design.[4] Five hundred fifty-six infants, whose mothers, after a standard dose of ACS, were randomized in the same way, underwent neurological testing at 2-3 years of age. There were no differences in Bayley scores between the above groups at age 2-3 years. However, although the numbers were small, there was a higher rate of cerebral palsy (CP) in the repeated-dose group (6 children), compared with the single-dose group (1 child).

Now there are at least two studies underscoring the rationale for a single rescue course of ACS being used as a substitute for repeated dosage. Garite et al demonstrated a 50% decrease in combined neonatal morbidity with a rescue dose after 2 weeks, compared with placebo.[5] Also, in the featured study above, McEvoy et al, in addition to showing a better response to respiratory function testing with a rescue dose after 2 weeks, found no differences in head circumferences or birth weight between groups.

As of now, here is what is known about the risks and benefits of ACS:

1. There is evidence to back up its efficacy before 35 weeks, but the evidence is shaky at best after that time.

2. It seems that more than one dose is needed for maximal benefit if delivery does not occur within 2 weeks of the initial dose.

3. Even if the patient delivers within 48 hours of the first injection, there may be some benefit from ACS.

4. There is no solid evidence to indicate any long-term ill effects of ACS, in general. However, based on the potential DNA effect, the animal data noted above, and some unresolved concerns about CP and attention deficits, a rescue dose of ACS seems to be a better option than weekly ACS in patients who show signs of delivering prior to 35 weeks.

5. Although along the way it has been subject to some tinkering, the standard dosage of betamethasone is 12 mg every 24 hours × 2. Dexamethasone seems to be a suitable substitute, and was used during a period of time when betamethasone was not available in many hospitals. ■

References

1. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1972;50:515-525.
2. Crowther CA, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory distress. *Cochrane Database Syst Rev* 2007;3:CD003935.
3. Crowther CA, et al. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007;357:1179-1189.
4. Wapner RJ, et al. Long-term outcomes after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007;357:1190-1198.
5. Garite TJ, et al; for the Obstetrix Collaborative Research Network. Impact of a 'rescue course' of corticosteroids. *Am J Obstet Gynecol* 2009;200:248.e1-9.

BRCAness Correlates with Chemotherapy Responsiveness and Clinical Outcome in Ovarian Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman reports no financial relationship to this field of study.

Synopsis: *A BRCAness gene expression profile derived from ovarian cancer patients was independently validated with respect to chemosensitivity and survival in two cohorts of sporadic ovarian cancer. This is an important step in the clinical utility of a tool, which may be leveraged to indicate which patients without a genetic mutation in the BRCA genes may benefit from use of a PARP inhibitor.*

Source: Konstantinopoulos PA, et al. Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. *J Clin Oncol* 2010 Jun 14; Epub ahead of print.

The primary purpose of this study was to develop a gene expression profile of BRCA dysfunction ("BRCAness"), which could be used to discriminate sporadic ovarian cancer patients with or without dysfunction to the homologous repair pathway and correlate whether this profile would describe sensitivity to platinum-based chemotherapy and pharmacological inhibition of poly-ADP ribose polymerase (PARP).

To do this, the investigator interrogated a publicly available microarray dataset, which included 34 ovarian cancer patients with confirmed germline BRCA1/2 mutations and 27 ovarian cancer patients without mutation (sporadic). The resulting gene profile included 60 genes, which had 94% accuracy in discriminating these two cohorts. To address the applicability of the test, they applied the profile pre-clinically and clinically against independent samples. Preclinically, they demonstrated high fidelity prediction of platinum sensitivity/resistance and inducement of RAD51 loci (a marker of homologous recombination and PARP sensitivity) following ionizing radiation in pancreatic cancer cell lines. Further, the profile accurately predicted sensitivity to PARP inhibition in all 4 samples. Clinically, they assessed the profile for BRCAness against a set of previously described paired human tissue samples from 4 patients with known germline BRCA mutation, where sensitive initial biopsies were matched with biopsies from resistant tumors following therapy. In each of these cases, resistance was heralded by BRCA reversion mutations restoring BRCA function. In 6 of these 8 specimens, the profile accurately predicted BRCA status and chemosensitivity profile.

Next, they studied the profile in 70 patients with sporadic ovarian cancer (35 test negative for BRCA mutation and 35 untested but without a significant family history or ethnicity for germline mutation). Despite being similar for all known prognostic factors, the patients with a BRCAness profile had a significantly better disease-free and overall survival, and positive trends to increasing response to platinum therapy.

The authors concluded that the genomic profile of BRCAness correlates with responsiveness to platinum and PARP inhibitors and identifies a subset of sporadic patients with improved outcome. Additional evaluation of this profile as a predictive tool in patients with sporadic EOC is warranted.

■ COMMENTARY

In recent issues of the *OB/GYN Clinical Alert*, I have focused on the impact defining this population could have for effective therapeutic interventions. Last year this month, Fong et al published the results of a phase I clinical trial of olaparib, a PARP inhibitor, in patients with known germline mutations in BRCA 1/2. The remarkable response rate, even in patients with known refractory disease, offered hope for very personalized medicine with an agent associated with few adverse events. In June's Special Feature, I profiled a study that demonstrated the improvements in capturing patients at high risk for carrying BRCA mutations that occurred as a result of a policy change at a major cancer center. In both situations, the target has centered on patients with a known mechanistic opportunity to respond to a novel class of agents and in whom appropriate counseling would be of great value to their care.

The burgeoning availability of PARP inhibitors and the data from the current report would suggest this audience may be greatly expanded as up to one-third of patients with ovarian cancer may fit a profile that could benefit from this targeted therapy. While the proof of principle has yet to be validated in the clinic, the availability of this profile is poised to enter a clinical trial where allocation of treatment may be directed by the tumor profile or at least correlated with response to therapy in post-hoc analyses. ■

Contraceptive Care Made Easy

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

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Dr. Edelman reports no financial relationship to this field of study.

Synopsis: *The U.S. Medical Eligibility Criteria for Contraceptive Use is a newly released resource by the CDC to aid clinicians in the contraceptive care of women with comorbidities.*

Source: CDC. U.S. Medical Eligibility Criteria for Contraceptive Use. *MMWR* 2010;59:RR-4. Available at: www.cdc.gov/mmwr/pdf/rr/rr5904.pdf.

The U.S. medical eligibility criteria for contraceptive Use is a newly available, free, evidence-based resource for clinicians. This resource provides guidance to aid contraceptive decision-making for women (and men) with comorbidities. These guidelines were adapted and updated specifically for the United States from those initially developed by the World Health Organization (WHOMEC).[1] Among the more than 60 medical conditions addressed, rheumatoid arthritis, bariatric surgery, peripartum cardiomyopathy, endometrial hyperplasia, inflammatory bowel

Table. Examples from USMEC.*

Condition	Combined methods	Progestin-only pill	Injection	Implant	Levonorgestrel IUD	Copper IUD
Migraine with aura, any age	4	2	2	2	2	1
Inflammatory bowel disease	2/3**	2	2	2	2	1
Carrier/chronic viral hepatitis	1	1	1	1	1	1

* Methods not listed here, but included in the USMED: family planning methods, sterilization, lactational amenorrhea, and barrier methods.

** For women with IBD with no other risk factors for VTE, the benefits of COC/P/R use generally outweight the risks (Category 2). However, for women with IBD with increased risk for VTE (e.g., those with active or extensive disease, surgery, immobilization, corticosteroid use, vitamin deficiencies, fluid depletion), the risks for COC/P/R use generally outweight the benefits (Category 3).

disease, and solid organ transplantation have been added.

■ **COMMENTARY**

Although family planning is essential for all women, it is critically important for those women with medical conditions. Unfortunately, the contraceptive care of these women is often neglected due to a variety of reasons; one of which may be the discomfort that many of us feel when dealing with an unfamiliar medical problem. Now there is no excuse, the U.S. Medical Eligibility Criteria for Contraceptive Use (USMEC) provides evidence-based guidelines generated by a review of the literature by experts in family planning, OB/GYN, and specialties dealing with each medical disorder. Categories for contraceptive use are divided into 4 categories: 1 = No restriction; 2 = Advantages for use outweigh the risk; 3 = Risk may outweigh the benefits; 4 = Unacceptable risk. In addition, differences in risk for initiation vs continuation of a contraceptive method are addressed. For examples, see Table *(above)*.

It is important to note that this resource is meant to "guide" care and that there may be certain instances where the guidance is helpful, but needs to be individualized. The USMEC only deals with the contraceptive method risk of each medical condition. It also addresses if a medical condition (or the drug used to treat it) interferes with contraceptive efficacy as opposed to the inherent risk pregnancy confers. In other words, you and your patient may decide that the risk of the contraceptive method outweighs the risk of pregnancy. Or as a team, you may chose a contraceptive method whose efficacy is decreased by her medical condition (or drug) because she is going to combine it with a barrier method. Remember, any contraceptive method prevents more pregnancies than no contraceptive method.

This resource is available in its entirety from the CDC at: www.cdc.gov/mmwr/pdf/rr/rr5904.pdf. Also available at www.cdc.gov/reproductivehealth/Unintendedpregnancy/USMEC.htm are several job aids or 2-page summary tables (I highly recommend laminating these for use in the clinic). Coming soon is a USMEC wheel similar to our coveted pregnancy dating wheels. This website has quick links to the WHOMEC as well.[1] ■

Reference

1. World Health Organization. Medical eligibility criteria for contraceptive use. 4th ed. Geneva; 2009. Available at www.who.int/reproductivehealth/publications/family_planning/9789241563888/en/index.html.

Special Feature

Don't Let the Abdominal Wall Stand Between You and the Diagnosis

By Frank W. Ling, MD

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Dr. Ling reports no financial relationship to this field of study.

YES, WE'VE ALL HEARD THIS TONGUE-IN-CHEEK SUMMARY of why surgery is used to determine what is wrong with a patient. Supposedly, an operation gets to the patient's underlying problem. The message is not subtle.

Actually, I am using it in this case to encourage the reader to think of the abdominal wall as the potential source of the problem rather than something that is in the way of getting to the problem. To start the discussion, I'm summarizing a short case report that highlights the abdominal wall as the source of the patient's problem.[1]

Case Report

Case. A painful mass in the right lower quadrant appeared 2 weeks after a woman's cesarean delivery. Over

the next 6 years, the mass gradually grew in size to 3 cm. Her symptoms were not cyclic. Eventually, it was excised from the lateral margin of the Pfannenstiel incision and pathology confirmed a diagnosis of endometrioma involving the dermis and subcutaneous tissue.

Commentary. It is likely that exposure of the subcutaneous tissue to endometrial tissue at the time of the cesarean delivery was the mechanistic pathway of development. Interestingly, it has been reported that having a cesarean delivery prior to the onset of labor actually increases the risk of developing an abdominal wall endometrioma.[2] The incidence following cesarean delivery is less than half a percent[3] and the interval from the last surgery until presentation can range from 1 month to 20 years.[4] Even though common things occur commonly, and endometriomas of the abdominal wall are not common, they should certainly be in the differential diagnosis when considering the likely causes of a mass of the abdominal wall.

My personal experience with endometriomas of the abdominal wall is not published, but, because I have seen at least half a dozen cases, it did surprise me, when reading this recent case report, that it was reportable. It's a lot less common than I thought or there are a lot of folks like me who haven't reported seeing it relatively often. I can't say why I have seen so many, but there is nothing in the literature that tells me that the patient population that I have served over the past 32 years is unique or unusual.

Cyclic symptoms. Even though you would think that the mass would mimic endometriosis and have cyclic symptoms, that is true only about half the time. Also, attempts to treat such masses with medical therapy are only partially successful. This should not surprise us since medical treatment of endometriomas in the pelvis are invariably not successful. Surgery is certainly needed in those cases. Needless to say, other causes for masses of the abdominal wall would also not respond to medical/hormonal therapy, e.g., stitch granuloma, abscess, hematoma, or hernia.

Mechanical irrigation. The use of mechanical irrigation at the end of both cesarean delivery as well as gynecologic surgery for endometriosis may well reduce the potential risk of subsequent endometrioma formation. Since irrigation has been shown to reduce infection of the subcutaneous tissue layer, it may well be that a second reason to perform this irrigation is to reduce the risk of a possible endometrioma.

Plans for surgery. Another tip involves the plans for surgery once the diagnosis has been made. Because wide local excision is the appropriate surgical approach, the surgeon should be prepared to remove an area of tissue approximately twice the size of the suspected mass. Again, for the experienced gynecologic surgeon, it comes as no surprise that there is significant scarring in the abdominal wall surrounding the endometrioma, similar to the dense scarring encountered in the pelvis with extensive endometriosis. Planning to remove an area significantly larger than the palpable mass or the imaged mass will minimize the "surprise" factor for the closure once the wide local excision is accomplished.

Pain: Abdominal Wall

Far too often, gynecologists look right past the problem, both literally and figuratively. Admittedly, the example of the endometrioma makes an obvious point, i.e., a mass in the abdominal wall does not necessarily have to have intra-abdominal pathology associated with it. Beyond the issue of masses, we see many patients whose problems are assumed to be deeper than they really are.

This is particularly true with pelvic and abdominal pain. We allow that old adage in the title to lure us to a surgical approach, looking for the intra-abdominal source of pain. In the past, laparotomy of an "exploratory" nature was widely accepted. Today's version of that is diagnostic laparoscopy, with well-meaning attempts to see endometriosis, adhesions, or other potential causes of pain. In fact, our laparoscopic camera may be taking us right past the source of the problem, namely the abdominal wall. Figuratively, the surgeon is thinking intra-abdominal sources of pain and, thereby, goes right past the abdominal wall. Our trocars and scopes literally do the same thing. What are we missing? Maybe a lot.

If the clinician would routinely consider the abdominal wall as the potential source of pain, several conditions come into play. Certainly, those patients with abdominal incisions, particularly Pfannenstiels, may have an entrapped nerve or even a hyperirritable muscle bundle (trigger point) at either end. Indeed, trigger points can occur anywhere in the abdominal wall muscles, but the most common abdominal wall trigger points are reported to occur at the lateral margins of the rectus muscles in both lower quadrants. Injections to tender sites on the abdominal wall can eliminate pain in up to half of patients.[5]

Not only can there be trigger points in the muscles of the abdominal wall, but the muscles themselves may be the source of pain. Physical therapy modalities provided by a therapist with manual therapy expertise can prove beneficial.[6]

Spigelian hernias lie lateral to the rectus abdominis muscles and medial to the semilunar line. They occur at or below the arcuate line, probably because of a lack of a posterior rectus sheath. They may not produce any noticeable mass or swelling but can be a cause of pain and even bowel entrapment. Ultrasound can establish the diagnosis, but CT scan is more sensitive and specific. Surgical correction is recommended because of the risk of bowel compromise.

There is also a poorly defined proportion of patients

who may have neuropathic pain manifest by abdominal wall tenderness. These patients may or may not ultimately be found to have some form of fibromyalgia. Both fibromyalgia and neuropathic syndromes may respond to various medical interventions that can include both antidepressants and anticonvulsants.

Physical Examination

How best to avoid missing the abdominal wall? It's probably better done on physical examination than by history. First, have the patient point to the exact place where she hurts. Ideally, she can be instructed to use just one finger, rather than allowing her to wave her entire hand over a large area. Once the area of pain is found, superficial palpation can sometimes recreate the pain. If so, then the abdominal wall is a likely suspect. If superficial palpation does not recreate her pain, have her raise her head (like an abdominal crunch) then raise both her legs without bending her knees (like a leg lift). Gentle pressure on the tensed muscles may recreate her pain suggesting the abdominal wall as the painful source. If the pelvic examination is nontender, then the focus should definitely turn to the abdominal wall. Caution should be used in performing the pelvic since a bimanual examination of the adnexa might make the examiner think that it is the intra-abdominal organs that are painful. A one-handed examination of the pelvis, not exerting abdominal wall pressure from above, is a key way to distinguish pelvic from abdominal wall tenderness. Also, the astute clinician knows that the normal ovary is normally tender, so if adnexal tenderness is found, the question should be asked of the patient, "Is that the pain that is bothering you?" Not infrequently, the patient can state emphatically that the pain on physical examination is or is not the chief complaint. This, again, helps focus attention on either the pelvis or the abdominal wall.

Conclusion

Whether the busy clinician ever makes the correct diagnosis of abdominal wall pain or not, it is similar to the example of the endometrioma of the abdominal wall that we used to start this discussion. The battle is won if the abdominal wall is given a fair shot within the differential diagnosis. As long as we don't routinely look past the abdominal wall, but, instead, look at it and consider it a potential source of the problem, our patients will be subjected to a minimal amount of surgery that could have been avoided. ■

References

1. Kesterson JP, et al. Abdominal wall endometrioma following cesarean delivery: A case report. *J Reprod Med* 2008;53:881-882.
2. Wicherek L, et al. The obstetrical history in patients with Pfannenstiel scar endometriomas—an analysis of 81 patients. *Gynecol Obstet Invest* 2007;63:107-113.
3. Chatterjee SK. Scar endometriosis: A clinicopathologic study of 17 cases. *Obstet Gynecol* 1980;56:81-84.
4. Zhao X, et al. Abdominal wall endometriomas. *Int J Gynaecol Obstet* 2005;90:218-222.
5. Slocumb JC. Neurological factors in chronic pelvic pain: Trigger points and the abdominal pelvic pain syndrome. *Am J Obstet Gynecol* 1984;149:536-543.
6. Myers CA, et al. Musculoskeletal screening in the chronic pelvic pain patient. In: Sanfillip JS, Smith RP, eds. *Primary Care in Obstetrics and Gynecology.* New York: Springer Verlag; 1998.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

CME Questions

12. Which is *not* correct regarding ACS?

a. The incidence of RDS is diminished with repeated dosage vs a single initial course.
b. A rescue dose seems to improve pulmonary function.
c. Animal studies indicate the possibility of a dose-related decrease in fetal weight with ACS.
d. All of the above are true.

13. Which of the following factors encouraged the investigators that their profile was describing BRCAness?

a. RAD51 inducement by ionizing radiation
b. Clinical sensitivity to platinum-based therapy
c. Preclinical sensitivity to PARP inhibitors
d. Correct discrimination of BRCA mutation status in known ovarian cancer patients
e. All of the above are true.

14. Which of the following is *not* a USMEC category 4 contraceptive method in women of any age with migraines with aura?

a. Combined oral contraceptive pills
b. The contraceptive vaginal ring
c. The contraceptive transdermal patch
d. The levonorgestrel-releasing IUD

Answers: 12. d, 13. e, 14. d.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Aggressive Modification of Cardiovascular Risk Factors

In this issue: Aggressive approach to CVD reduces MI, folic acid and vitamin B12 for CAD, corticosteroids for acute exacerbations of COPD, prescription drug abuse among young adults, and ARBs and cancer risk.

CVD decreases with aggressive treatment

Aggressive modification of cardiovascular risk factors seems to be paying dividends, at least for a large population of insured patients in Northern California. In an analysis of nearly 18.7 million patient-years between 1999 and 2008, the rate of myocardial infarction (MI) increased in 1999 and 2000 and then decreased significantly every year thereafter (287 cases/100,000 person-years in 2000, decreasing to 208 cases/100,000 person-years in 2008; 24% relative decrease over the study period). The rate of ST-segment elevation MI decreased over the study period (133 cases/100,000 person-years in 1999 to 50 cases/100,000 person-years in 2008; $P < 0.001$) and the 30-day mortality rate decreased from 1999 to 2008 as well (adjusted odds ratio, 0.76; 95% confidence interval, 0.65-0.89). This occurred despite more aggressive diagnosis of MI.

The authors conclude, "The lower incidence of myocardial infarction — particularly ST-segment elevation myocardial infarction — is probably explained, at least in part, by substantial improvements in primary-prevention efforts, …" including statins and aggressive blood pressure reduction, as well as use of cardioprotective medications such as aspirin (*N Engl J Med* 2010;362:2155-2165).

An accompanying editorial points out that while these trends are generally the case in the United States, there are significant geographic differences. "The risk among residents of Oklahoma, the lower Mississippi corridor, and Appalachia, for example, is double that among other Americans, … " suggesting socioeconomic factors play a role. Hypertension and diabetes rates have increased slightly over the last decade, while smoking rates have decreased. Perhaps even more importantly, statin use has increased significantly (among those between age 45 and 64 years, statin use in men increased from 2.5% to 16.8% and from 1.9% to 13.5% in women; among those 65 years of age or older, statin use increased from 1.9% to 38.9% in men and from 3.5% to 32.8% in women). Aspirin, beta-blockers, and ACEIs/ARBs have also contributed to the decline in cardiovascular mortality in the United States (*N Engl J Med* 2010;362:2150-2153). ■

Folic acid and vitamin B12 for CAD

Unfortunately, lowering homocysteine with folic acid and vitamin B12 does not seem to be a benefit to patients with coronary artery disease. In a study from the United Kingdom, more than 12,000 survivors of myocardial infarction were randomized to 2 mg folic acid plus 1 mg vitamin B12 daily vs matching placebo, with the main outcomes being first major vascular event such as coronary event, stroke, or noncoronary revascularization. Folate and vitamin B12 were effective at reducing homocysteine levels by 28%; however, there was no difference in the rate of major vascular events over the 6.7 years of follow-up (25.5% active treatment vs 24.8% placebo; $P = 0.28$). Individually, there was no effect on major coronary events, stroke, or noncoronary

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revascularizations, nor was there a survival benefit from active treatment. Interestingly, the authors also looked at incidence of cancer and found no difference in that outcome either. The authors conclude that long-term reductions in blood homocysteine levels with folic acid and vitamin B12 do not have a beneficial effect on vascular or cancer outcomes (*JAMA* 2010;303:2486-2494). ■

Corticosteroids for exacerbations of COPD

Giving corticosteroids orally in lower doses is as effective as giving the drugs intravenously at higher doses for the treatment of acute exacerbation of COPD (ae-COPD), according to a recent study in the *Journal of the American Medical Association*. The records of nearly 80,000 patients in more than 400 hospital admissions for ae-COPD who received steroids were reviewed. The primary outcomes were treatment failure, defined as the initiation of mechanical ventilation, inpatient mortality, or readmission within 30 days. The vast majority of patients (92%) received IV steroids. After multivariate adjustment, the death rate was similar in the two groups (1.4% IV therapy vs 1.0% oral) and the composite outcome was also similar (10.9% IV vs 10.3% oral). In a propensity-matched analysis, the risk of treatment failure was actually significantly lower among orally treated patients (odds ratio, 0.84; 95% confidence interval, 0.74-0.95), as was the length of stay and cost. Of the orally treated patients, 22% were switched to IV therapy later in the hospitalization.

The authors conclude that for patients admitted for ae-COPD, low-dose steroids administered orally are as effective, and may be safer, than higher-dose IV steroids (*JAMA* 2010;303:2359-2367). An accompanying editorial suggests that rather than doing large non-inferiority studies to confirm these findings, sufficient evidence exists to change practice now with continued comparative effectiveness research via linked registries (*JAMA* 2010;303:2409-2410). ■

Prescription drug abuse in young adults

Prescription drugs are the new drugs of abuse among young adults. While drug use in general seems to be dropping in high schools, prescription drug abuse is skyrocketing. The recently published National Youth Risk Behavior Survey from the Centers for Disease Control and Prevention (CDC) showed that 1 of 5 high school students in the United States reported abusing a prescription drug at some time in their lives. The most commonly mentioned drugs were OxyContin®, Percocet®, Vicodin®, Adderall®, Ritalin®, and Xanax®. Prescription drug abuse was most common among white students (23%), followed by Hispanic students (17%), and then black students (12%). Not surprisingly, high school students were most likely to abuse drugs in their senior year (*MMWR* 2010;59:1-142). While many teens get their prescription drugs from medicine cabinets of family and friends, others order them online, and recently many drug dealers have begun specializing in prescription drugs.

Many young adults, however, seek opioids and benzodiazepines from physicians, especially in emergency departments (ED). A new report from *MMWR* reports that ED visits for nonmedical use of opioid analgesics increased 111% from 2004 to 2008 and increased 29% from 2007 to 2008 alone. The highest number of ED visits was recorded for oxycodone, hydrocodone, and methadone. ED visits for benzodiazepines also increased 89% over the same period. In 2008, the rates of visits for both opioids and benzodiazepines increased sharply after age 17 and peaked in the 21-24 year age group. During the 2004-2008 study period, the largest increase in ED visits to obtain drugs occurred among persons age 21-29 years. Findings were from the CDC and the Substance Abuse and Mental Health Services Administration, reviewing data from the Drug Abuse Warning Network (*MMWR* 2010;59:705-709). ■

ARBs and cancer risk

Do angiotensin receptor blockers (ARBs) increase the risk of cancer? In a widely reported study, researchers from Case Western Reserve performed a meta-analysis of 5 trials for which cancer data were available from more than 61,000 patients. Telmisartan was the ARB used in nearly 86% of the studies. Patients randomly assigned to receive ARBs had a rate of new cancer occurrence of 7.2% vs 6.0% for placebo (relative risk [RR], 1.08; 95% confidence interval [CI], 1.01-1.15; $P = 0.016$). The risk ratio was higher when the analysis was limited to trials where cancer was the prespecified endpoint (RR, 1.11; 95% CI, 1.04-1.18; $P = 0.001$). There was no difference in the rate of cancer deaths between the two groups. The authors conclude that this trial suggests that ARBs are associated with a modestly increased risk of new cancer diagnosis, but it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug and further research is warranted (*Lancet Oncology* 14 June 2010; early online publication). ARBs are involved in the regulation of cell proliferation, angiogenesis, and tumor progression, which are possible mechanisms for these findings. ■