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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Use of Letrozole vs Clomiphene Citrate for Ovulation Induction in Women with PCOS

By Michael A. Thomas, MD

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

SYNOPSIS: Polycystic ovarian syndrome patients with normospermic partners undergoing ovulation induction with letrozole had a higher live birth rate and no increase in adverse outcomes than women who received clomiphene citrate.

SOURCE: Legro RS, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med* 2014;371:119-129.

Polycystic ovary syndrome (PCOS) affects 5-10% of reproductive-aged women and is the most common cause of anovulatory infertility. The current first-line treatment options for this patient population include the oral agents clomiphene citrate (CC), which is approved by the FDA for this purpose, and letrozole (LE), an aromatase inhibitor increasingly used for ovulation induction but only approved for use in breast cancer treatment. Because smaller studies have shown no clear difference between these two medications, the National Institutes of Health's Reproductive Medicine Network (RMN), which is comprised of a consortium of university-based infertility practices, decided to perform a prospective, double-blind, multicenter trial of 750 infertile women with PCOS diagnosed using the Rotterdam criteria.[1] These women were randomly assigned in a 1:1 ratio to use either LE or CC for up to five treatment cycles. Starting doses were LE 2.5 mg and CC 50 mg. These medications were increased in subsequent cycles if no evidence of ovulation was documented (progesterone concentration > 3 ng/mL). Maximum LE dose was 7.5 mg and maximum CC dose was 150 mg. Enrolled participants had to be younger than 40 years of age, have at least one patent fallopian tube and have a normal uterine cavity, a male partner with a sperm concentration of at least 14 million/mL, and have intravaginal intercourse on a regular basis. The primary

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outcome of this study was live birth. Secondary outcomes included ovulation, pregnancy loss, singleton birth, and congenital anomalies.

Compared to CC, women who received LE had higher cumulative live births rates (27.5% [103/374] vs 19.1% [72/376], $P = 0.007$)] and ovulation rates (61.7% [834/1352] vs 48.3% [688/1425], $P = < 0.001$) per total treatment cycles. There were no overall differences between the two treatment groups in terms of demographic data, congenital anomalies, multiple gestation, ovarian torsion, ruptured corpus luteal cyst, ectopic pregnancy, heterotopic pregnancy, pregnancy of unknown location, hospitalization, premature labor, postpartum anemia requiring transfusion, fetal death, or neonatal death. Of those patients who ovulated, PCOS patients using LE had a higher rate of singleton birth (34.1% vs 26%, $P = 0.03$). When actively using the medications, patients taking LE noted an increase in fatigue and dizziness while those using CC had a higher incidence of hot flashes.

■ COMMENTARY

General gynecologists and some primary care providers routinely use oral agents for ovulation induction in PCOS patients in outpatient settings. Clomiphene citrate is a selective estrogen receptor modulator that antagonizes the negative feedback of estrogen at the level of the hypothalamus, which results in an increase in endogenous gonadotropins to stimulate the ovaries. Therefore, it works centrally to affect ovulation. Letrozole is an aromatase inhibitor that induces follicle development by blocking the conversion of androgens to estrogens, which secondarily increases gonadotropin production to stimulate the ovaries, as the hypothalamus perceives a lower ovarian production of estradiol. Both medications are easy to use with few side effects.

Over the last 50 years, CC has served as the first-line option in the treatment of infertility in women with PCOS with or without knowledge of semen parameters or tubal status. Usually the dose is titrated from 50 mg up to 250 mg until an ovulatory response is achieved, as determined by either the use of a urine test for the luteinizing hormone (LH) surge or visualization of a mature preovulatory follicle on ultrasound. However, CC can have some drawbacks that may make it undesirable for patients. These concerns include poor efficacy (22% rate of live birth rate over six cycles), higher than normal incidence of multiple births (3-8%), as well as mood changes and hot flashes.[2]

Clomiphene resistance (inability to develop a follicle at any dose) has been noted in up to 25% of PCOS patients.[2] Glucocorticoids, particularly dexamethasone (Dex), and metformin, an insulin receptor sensitizing agent, have been used to overcome CC resistance. Two large trials evaluated CC alone vs CC with Dex 0.5 mg (given cycle days 3-12).[3,4] The addition of Dex increased the ovulation and conception rates from 15-20% and 5% (CC only) to 75-88% and 40%, respectively. Despite these positive results, Dex and other glucocorticoids are associated with bloating, weight gain, mood changes, osteoporosis, and other adverse conditions.

Although metformin has been used alone as a medication to induce ovulation in PCOS patients, it has not been shown to be consistently effective for this indication. Metformin is a biguanide that works by suppressing hepatic gluconeogenesis and increasing peripheral insulin sensitivity.[5] Its administration in this patient population results in a reduction in all of the following: LH pulse amplitude, androstenedione levels, testosterone levels, ovarian volume, and Ferriman-Gallwey scores (numbered system in which a "score" of 0-4 is assigned to determine the extent of hair growth over nine sites from the upper lip to the inner thigh).[6] When used in combination with CC, metformin (up to 500 mg three times per day) has been shown to decrease CC resistance.[7] Despite this potential beneficial effect, the RMN had previously demonstrated that the use of CC with (26.8%) or without (22.5%) metformin conferred similar pregnancy rates.[8] Therefore, the addition of metformin offered no enhanced benefit to CC users.

Generally, LE therapy is initiated at a dose of 2.5 mg for 5 days, and the dose is increased stepwise up to 10 mg until ovulation is noted. Although a meta-analysis of six peer-reviewed papers involving 841 infertile PCOS patients treated with either LE or CC demonstrated no difference in

pregnancy rate, abortion rate, and multiple gestations,[9] methodological limitations prompted the RMN to perform a randomized, controlled trial to settle the question.

The primary goal of this study was to determine which oral ovulation induction (OI) agent offers the best possibility of pregnancy in a group of patients who need to "reboot" their hypothalamic-pituitary-ovarian axis to ovulate. LE was shown to result in higher rates of ovulation and live birth and a lower risk of multiple gestation (if ovulation is confirmed). These highly favorable findings would indicate that the use of CC for OI in patients with PCOS is dead. But will this study change prescribing habits? It is not likely, given that the majority of CC prescribers are generalists who either have never heard of LE and/or have never been instructed to use this medication during residency or a postgraduate course. Finally, LE is not FDA-approved for OI use. Although this last point has not stopped most fertility providers from making LE their favorite "go-to" wonder drug, generalists may be more hesitant to jump on the bandwagon until more long-term data eliminate any safety issues. The biggest concern is the potential risk of accidentally prescribing LE while a patient is pregnant with a female fetus, which theoretically could result in masculinizing a female fetus due to interference with the aromatization of maternal androgens to estrogen. Our center and others have LE users sign a waiver that explains these potential risks if fetal exposure takes place. This study opens the door for LE to become an additional fertility treatment modality for PCOS anovulation. Demonstration of superiority over CC should make LE the prime ovulation induction option for this patient population. ■

REFERENCES

1. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. *Fertil Steril* 2004;81:19-25.
2. Legro RS, et al. *N Engl J Med* 2007;356:551-566.
3. Parsanezhad ME, et al. *Fertil Steril* 2002;78:1001-1004.
4. Elnashar A, et al. *Hum Reprod* 2006;21:1805-1808.
5. Inzucchi SE, et al. *N Engl J Med* 1998;338:867-872.
6. Genazzani A, et al. *Fertil Steril* 2004;81:114-119.
7. Vandermolen DT, et al. *Fertil Steril* 2001;75:310-315.
8. Legro RS, et al. *N Engl J Med* 2007;356:551-566.
9. He D, Jiang F. *Reprod Biomed Online* 2011;23:91-96.

ABSTRACT & COMMENTARY

What Is the Best Oral Contraceptive Regimen for Obese Women?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a retained consultant for Bayer.

SYNOPSIS: According to this pharmacokinetic study, the cyclic use of 20 mcg ethinyl estradiol oral contraceptives is problematic for obese women. Ovarian activity was better suppressed with continuous use (omitting the hormone-free interval) of the same dose oral contraceptive or increasing to a higher dose 30 mcg ethinyl estradiol oral contraceptive.

SOURCE: Edelman AB, et al. Correcting oral contraceptive pharmacokinetic alterations to obesity: A randomized controlled trial. *Contraception* 2014;90:550-556.

This randomized trial compared two combined oral contraceptive regimens among obese (body mass index [BMI] ≥ 30 kg/m^2) women aged 18 to 35 years. Exclusion criteria included anemia, contraindications to hormonal contraception, irregular menstrual cycles, use of tobacco or drugs known to interfere with sex steroids, and prior treatment for metabolic disorders. After using a pill containing 20 mcg ethinyl estradiol (EE)/100 mcg levonorgestrel (LNG) in a cyclic fashion (21 active pills, 7 placebo pills) for two cycles, subjects were randomized to one of two groups: 1) continuous use of the same oral contraceptive with no hormone-free interval or 2) cyclic use of a higher dose pill containing 30 mcg EE/150 mcg LNG. Compliance was recorded on subject diaries and confirmed with serum LNG levels. Pharmacokinetic parameters measured included time to reach steady state and area under the curve, as well as ovarian follicular activity on ultrasound.

A total of 31 women enrolled and completed the study; 16 were allocated to continuous cycling and 15 to a higher dose pill. Prior to randomization, the average time to reach steady state concentrations of LNG was 12 days. After randomization, the continuous group remained in steady state, while it still required 12 days to achieve steady state with the higher dose. Nevertheless, the area under the curve for estrogen and LNG in both groups was similar. Prior to randomization, almost half of the subjects (45%) had evidence of follicular development while on the low-dose cyclic pill. After randomization,

there was a decrease in follicular activity in both groups (9%).

■ COMMENTARY

More than one-third (78.6 million) of adults in the United States are obese.[1] While many of us may assume obese women are subfertile due to anovulation, studies show that obese women have similar levels of sexual activity and unintended pregnancy compared to normal weight women.[2,3] Obese women who do not desire pregnancy should be using contraception given the potential for maternal and fetal morbidity.[3] While long-acting reversible contraceptives are considered first line for obese women for both safety and efficacy reasons, the oral contraceptive pill remains the most popular method in the United States. Therefore, it is critical to examine the effect of obesity on oral contraceptive efficacy. Even though adherence to oral contraceptives plays a large role in efficacy (99% with perfect use vs 91% with typical use),[4] it is important to know whether certain doses or regimens would offer obese women superior protection against pregnancy.

Pharmacokinetic studies show that obese women take twice as long to reach steady state therapeutic levels of contraceptive steroids when starting the pill or after the hormone-free interval due to changes in clearance.[5] Therefore, these episodes might represent a vulnerable time period for this population. Nevertheless, population studies to date have not demonstrated a significantly increased failure rate of oral contraceptives in obese women.[6] The Cochrane review on this topic concluded, with limited available data, that "the evidence did not generally show an association of BMI with effectiveness of hormonal contraceptives."[7] Unfortunately, overweight and obese women are seldom included in trials to obtain FDA approval for oral contraceptives, so high-quality data are lacking.

The authors of this pharmacokinetic study show that low-dose oral contraceptives (20 mcg EE/100 mcg LNG) suppress ovarian activity better when used continuously without a hormone-free interval. Without the hormone-free interval, obese women can maintain steady state therapeutic levels throughout the cycle. Alternatively, an increase in the dose of both the estrogen and progestin component allows for similar improvements in ovarian suppression. Although this study did not examine actual clinical evidence of failure (pregnancies) with these regimens and had a small sample size, the results are intriguing and make clinical sense. We have much more to learn about contraceptive steroid metabolism and clinical endpoints in obese women. Nevertheless, I would hesitate to prescribe a low-dose combined oral contraceptive pill to obese women unless they were willing to take it in a continuous fashion. ■

REFERENCES

1. Centers for Disease Control and Prevention. Available at: www.cdc.gov/obesity/data/adult.html. Accessed Dec. 1, 2014.
2. Kaneshiro B, et al. *Obstet Gynecol* 2008;112:586-592.
3. Edelman AB. *Contraception* 2009;80:583-590.
4. Trussell J. *Contraception* 2011;83:397-404.
5. Merki-Feld GS, et al. *Eur J Contracept Reprod Health Care* 2014 Nov 7; [Epub ahead of print].
6. McNicholas C, et al. *Obstet Gynecol* 2013;121:585-592.
7. Lopez LM, et al. *Cochrane Database Syst Rev* 2013;4:CD008452.

ABSTRACT & COMMENTARY

Fibroids and Pregnancy

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 in patients with fibroids has correlated the size, location, and number of fibroids with the rate of preterm birth, postpartum hemorrhage, need for cesarean section, and fetal size — findings that can be useful in counselling patients with fibroids.

SYNOPSIS: Lam SJ, et al. The impact of fibroid characteristics on pregnancy outcome. *Am J Obstet Gynecol* 2014;211:395.e1-5.

It is not easy to counsel patients with fibroids about what to expect when they become pregnant or even, more commonly, when fibroids are found for the first time during their pregnancies. The difficulty stems from misleading and/or conflicting data in the literature regarding complications and perinatal outcomes in this setting.

Lam et al reviewed data over a 10-year period in patients with fibroids whose size was ≥ 4 cm.[1] During that time, data were available on 121 patients with 179 pregnancies, representing 136 live births. Forty percent had a single fibroid. Nineteen percent had fibroids in the lower segment or had fibroids encroaching on the cervix. Those women with multiple fibroids had a greater risk of preterm birth (PTB) than women with a single fibroid (18% vs 6%). When fibroids were found in the lower uterine segment, cesarean section was required more frequently (86% vs 40%), and total blood loss at the time of delivery was greater (830 mL vs 530 mL).

Also, postpartum hemorrhage was greater in those with fibroids in the lower uterus (22% vs 11%). There was a positive relationship between fibroid size and the rate of postpartum hemorrhage, but, interestingly, there was no effect on birth weight. Smaller fibroids (4-7 cm) had less hospital admissions for "fibroid pain" than larger fibroids (> 7 cm) (5% vs 23%). Last, the size and location of the fibroid had no effect on the rate of preterm birth.

■ COMMENTARY

In a book published in 2008, I wrote that "fibroids (in pregnancy) are over-rated."[2] However, the take-home messages from this study are that the location of the fibroid does have an effect on the rates of cesarean section, blood loss, and postpartum hemorrhage. The size of the fibroid has an effect on the rates of postpartum hemorrhage and estimated blood loss. Neither location nor size has an effect on the rate of preterm birth, but the presence of multiple fibroids does increase the risk somewhat of preterm birth, with a rate of PTB of 18%. The overall prevalence of fibroids in pregnancy is under-reported in the literature (1.4% to 2.7%)[3] and overestimated in clinical practice — under-reported because fibroids can often go unrecognized with ultrasound when attention is concentrated on the fetus and over-estimated because an ultrasound exam can be misleading in the first and second trimesters by a prolonged, localized, uterine contraction that can masquerade as a fibroid (a "fibroid" that disappears on a later exam). Older women seeking treatment have a prevalence of fibroids between 12% and 25%.[4]

There is a misconception that fibroids can grow appreciably during pregnancy, thereby warranting heightened surveillance. Actually, the literature suggests that 60-78% of fibroids do not have any significant change in size during pregnancy.[5] If there is growth, it happens predominantly in the first trimester. Interestingly, smaller fibroids have a greater tendency to grow than larger ones. Two studies show that most fibroids decrease in size in the third trimester.[5,6]

In the featured study, the number of patients requiring admission for "fibroid pain" (5% with smaller fibroids and 25% with larger fibroids) was surprisingly high and far exceeds my experience. "Red degeneration" is a term that has been used sometimes to describe the mottled appearance that the fibroid takes on when it outstrips its blood supply — an event that often coincides in time with the onset of pain. Since this type of tissue necrosis can be accompanied by a release of prostaglandins, prostaglandin synthetase inhibitors (e.g., ibuprofen) are often the best approach to combating fibroid pain.

The above Australian study represents one of the largest sample sizes, consisting of data accumulated over a 10-year period. While giving us a rough idea of perinatal outcome and maternal complications according to size, location, and number of fibroids, the lack of controls does not allow risk to be assessed over baseline.

One of the concerns has been that either the fibroid will compete with the blood supply to the fetus or that a placenta implanting over a fibroid would be less able to supply adequate nutrients to the fetus. This study does not completely answer this question, but it did show that the size and location of fibroids had no effect on the birth weight in the overall population of patients with fibroids. The literature is confusing with regard to intrauterine growth restriction and fibroids. One study suggests a slightly higher rate of low birth weight babies in a population of women with fibroids,[7] but this study did not account for confounding factors such as maternal age or, more importantly, gestational age at delivery.

Suggestions for management of patients with fibroids in pregnancy:

1. Note the position, size, and "texture" at the time of the first visit and repeat the exam toward term since these findings can change with lengthening of the lower uterine segment with advancing gestational age.
2. Counsel the patient regarding the risks (or lack thereof) of various possible complications, but indicate that fibroids, by themselves, are not a reason for intervention such as elective cesarean section or early delivery.
3. Since the risk of preterm birth is elevated in patients with multiple fibroids, cervical length exams may be useful in identifying those patients at greater risk for early delivery.
4. An ultrasound evaluation after 30 weeks will help to identify the occasional fetus with growth restriction.
5. Be prepared for intrapartum or postpartum hemorrhage, especially when fibroids are noted in the lower uterine segment.
6. Fibroid pain can be managed successfully with prostaglandin synthetase inhibitors such as ibuprofen. However, this medication should be used with caution after 30 weeks of gestation because of the potential for premature closure of the ductus arteriosus. ■

REFERENCES

1. Lam SJ, et al. *Am J Obstet Gynecol* 2014;211:395.e1-5.
2. Hobbins JC. *Obstetric Ultrasound: Artistry in Practice*. Malden, MA: Blackwell Publishing; 2008.
3. Cooper NP, Okolo S. *Obstet Gynecol Surv* 2005;60:132-138.
4. Klatsky PC, et al. *Am J Obstet Gynecol* 2008;198:357-366.
5. Rosati P, et al. *J Ultrasound Med* 1992;11:511-515.
6. Lev-Toaff AS, et al. *Radiology* 1987;164:375-380.

SPECIAL FEATURE

Talcum Powder…the 'Pluto' of Prognostic Factors for Ovarian Cancer

By Robert L. Coleman, MD

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

SYNOPSIS: A large prospective cohort study of perineal talc use demonstrated no increased risk of ovarian cancer overall or within any histological subtype. In addition, no association with talc application method was observed.

SOURCE: Houghton SC, et al. Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst* 2014;106:dju208 doi:10.1093/jnci/dju208.

Risk for ovarian cancer has been linked to talcum powder use for several years. Its structural properties and its historical link to asbestos have driven the biological plausibility. The preponderance of data to support this association has come from case-control studies; however, the only prospective cohort study from the Nurse's Health Study did not show this effect, with the exception of serous invasive ovarian cancers. The current analysis from the Women's Health Initiative Observational Study cohort prospectively assessed perineal powder use and risk of ovarian cancer. In this study, perineal powder use was assessed at baseline by self-report regarding application to genitals, sanitary napkins, or diaphragms and duration of use. The primary outcome was self-reported ovarian cancer centrally adjudicated by physicians. Cox proportional hazard regression was used to estimate risk, adjusting for covariates, including person-time until diagnosis of ovarian cancer (n = 429), death, loss to follow-up, or September 17, 2012. A total of 61,576 postmenopausal women without a history of cancer or bilateral oophorectomy were followed for a mean of 12.4 years. Fifty-three percent reported ever using perineal powder. Ever use of perineal powder (hazard ratio [HR] 1.06; 95% confidence interval [CI], 0.87-1.28) was not associated with risk of ovarian cancer compared with never use. Individually, ever use of powder on the genitals (HR = 1.12; 95% CI, 0.92-1.36), sanitary napkins (HR, 0.95; 95% CI, 0.76-1.20), or diaphragms (HR, 0.92; 95% CI, 0.68-1.23) was not associated with risk of ovarian cancer compared with never use, nor were there associations with increasing durations of use. There was no association between ever use and ovarian cancer histology, including invasive serous cancer. Estimates did not differ when stratified by age or tubal ligation status. Based on these findings, perineal powder use does not appear to influence ovarian cancer risk.

■ COMMENTARY

The discovery of prognostic factors in any disease serves not only to provide insight into disease pathogenesis, such as obesity and endometrial cancer with the implication of estrogen, but also to explore potential preventive interventions that can modulate risk, such as use of coagulation and cardiovascular disease with aspirin.[1] In ovarian cancer, the most lethal of all the gynecologic cancers, prognostic factors carry added value as they highlight potential modifiable habits that might also impact mortality. As most are aware, ovarian cancer usually presents when the disease is widespread, causing symptoms of bloating, pelvic pressure, early satiety, and bladder dysfunction.[2] Although these symptoms are frequently reported by patients in whom the diagnosis is ultimately made, the disconnection between a specific set of symptoms and stage of disease challenges any attempt to use this approach to modify mortality. Screening of otherwise normal women has also presented significant challenges for ovarian cancer. The disease is rare and has low prevalence even in menopausal women. This places substantial pressure on the performance of testing that would be utilized in a triage algorithm. The most frequently used screening modalities are the combination of examination, biomarkers such as CA125, and imaging such as transvaginal ultrasound. While these approaches have value in identifying women with the disease, the way in which they are implemented in an asymptomatic population, including recognition of abnormality (what's abnormal?), frequency of testing (yearly? every 6 months? every 3 months?), and intervention of aberration (repeat assessment? referral? surgery?), is critical to the goal of identifying disease that is different from a non-screened population. In a disease like ovarian cancer, in which a clearly defined preinvasive state is not universally recognized or identifiable, the ultimate endpoint of a screening program is "stage shifting," or the alteration in the proportion of women diagnosed with earlier stage disease relative to the general population. Since stage I ovarian cancer is highly curable, this is a reasonable strategy to reduce mortality.

Unfortunately, stage I ovarian cancer is usually diagnosed by serendipity. Indeed, a report from the Prostate, Lung, Colorectal and Ovarian cancer screening trial demonstrated once-a-year screening with CA125 and transvaginal ultrasound not only did not increase the number of early-stage cases, but it increased morbidity due to complications from unnecessary surgery.[3] The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) randomized screening trial of more than 200,000 menopausal women assessing two different diagnostic triage algorithms (vs standard of care) in asymptomatic menopausal women has completed accrual and is expected to report in 2015. This trial's primary endpoint is overall survival. An initial report of the prevalence data from the two screening algorithms demonstrated an efficiency and precision difference among women undergoing referral and surgical intervention.[4] A separate prospective cohort study utilizing a two-step risk of ovarian cancer algorithm (ROCA), which, incidentally, is similar to one of the two screening strategies being utilized in the UKCTOCS trial, showed promise of the stage migration effect.[5] In this trial, 4051 asymptomatic menopausal women underwent annual CA125 and utilized a ROCA mathematical algorithm to provide risk estimates of ovarian cancer. The resulting "low-," "intermediate-," and "high-risk" designation proscribed the next intervention, namely, repeat annual CA125, repeat CA125 in 3 months, and transvaginal ultrasound and gynecologic oncology referral, respectively. Ten women ultimately underwent surgical intervention, and four invasive ovarian cancers were found (40% positive predictive value; one stage IA, two stage IC and one stage IIC). While promising, proper evaluation of this approach will require the sample size, follow-up, and design (control group) of the UKCTOCS trial to assess the ultimate merit of screening in this disease.

Thus, in the absence of effective screening, attention has focused on prevention strategies. Many of these interventions, such as oral contraceptives, aspirin, salpingectomy, salpingo-oophorectomy, and tubal ligation, were identified as significant prognostic factors associated with reduced odds of diagnosis.[1] As intuitive as these factors may seem and as easy as they are to identify, the business of properly assigning risk and the directionality of effect (positive, negative, or neutral) is much more difficult. In addition, the leap from identification of a prognostic factor to the effect of modulating risk by doing some sort of intervention (medication, surgery, habit alteration) based on that factor is a substantial gamble. Prognostic factors that accurately reflect the risk of developing a disease in a population require careful assessment of exposures. Most of the trials that serve to identify risk and the associated factors are done in retrospect and are subject to a profound effect of recall bias.[6] It's not hard to imagine that a woman with advanced stage ovarian cancer following surgery and chemotherapy might attribute blame to a specific habit, such as talcum powder use, and the amount of exposure differently relative to a woman without disease. Studies of oral contraceptive use, a noted prognostic factor associated with reduced risk of ovarian cancer, where centralized records of prescriptive practice exist, highlight this recall bias effect. In addition, accuracy of intended exposure, such as prescriptions made and actual use, provide another element of bias that is difficult to control. So while retrospective case-control trials are the primary resource from which prognostic factors are developed, they are often fraught with substantial bias hurdles that can lead to inconclusive or even disparate findings.

Such is the case with talcum powder. Talc is a water-absorbing mineral composed of magnesium silicate that has structural similarities and co-occurs with asbestos. The link of asbestos and cancer is relatively strong, so the implication of talc and cancer has been long suspected. The mechanism through which asbestos causes cancer is not completely understood, but its induction of a chronic inflammatory response and alteration in local immunogenicity to antigens in the microenvironment have been documented. Both of these factors have also been implicated in the carcinogenesis of ovarian cancer. Talc is a frequent component of genital powders and is usually applied directly on the perineal skin in a variety of ways. Historically, talcum powders used in cosmetics were not purified talc and had contamination with asbestos factors. However, in 1976, the Cosmetic, Toiletry and Fragrance Association (now known as the Personal Care Products Council) issued stringent purity standards for talc used in cosmetics, including specifications that talc must contain no detectable fibrous asbestos mineral. Nevertheless, talc fibers have been identified in the vagina, cervix, uterus, and ovaries in women who have reported perineal talc use. The quantity of these fibers is substantially reduced in ovarian tissue relative to the vagina and, while granulomatous inclusions have also been identified, the direct association of these foreign body reactions and cancer has not been observed. A comprehensive analysis of the safety assessment of talc used in cosmetics was conducted in 2006 by the International Agency for Research on Cancer's Cosmetic Ingredient Review Expert Panel and released for public consumption 2010.[7] In this report, toxicokinetics, preclinical and clinical toxicology, reproductive and developmental toxicity, genotoxicity, and carcinogenicity were extensively reviewed. Their concluding statement is summarized:

> In 2010, the IARC Working Group determined that there is *limited* evidence in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibers…. For humans, the evaluation of

the IARC working group was that perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*, and that inhaled talc not containing asbestos or asbestiform fibers is *not classifiable as to its carcinogenicity (Group 3)*. In evaluating the carcinogenicity of talc in humans, the Working Group reviewed cohort studies of talc miners and millers, cohort and case-controlled studies examining the association of cosmetic talc use and the risk of ovarian cancer in humans, and the animal data and evidence regarding the potential mechanisms through which talc might cause cancer in humans. The Working Group found there is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibers and there is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

The strength of their Group 2B conclusion rested on the volumes of retrospective reports, including a meta-analysis of 20 case-control studies and a pooled analysis of eight other population-based, case-control studies implicating a risk of up to 35% between talc use in perineal powders and ovarian cancer. However, the only two prospective cohort studies, including the current trial from the Women's Health Initiative Observational Study, provided no association.[8] The current trial is the largest *prospective* trial to assess the implied risk and is strengthened by it low risk of recall bias. However, only data on duration of use (vs duration and frequency of use) were available. To date, a dose-response relationship has not been made.

In again…out again…what conclusions/recommendations can be made about talc and ovarian cancer? One clear assurance is that talcum powder used in cosmetics is regulated to be asbestos free. Second, evidence of migration of talc fibers from the perineum to the fallopian tubes and ovaries is present, but is devoid of the asbestos-inducing inflammatory response, disrupting the biological plausibility of talc exposure and cancer. Third, the strength of association, if present at all, is weak and the current study's design and conclusions should be reassuring to users. Finally, it is unlikely that modifying exposure to this "Pluto of a prognostic factor" will modulate any potential diagnostic risk or mortality from ovarian cancer. ■

REFERENCES

1. Coleman RL, et al. *Nat Rev Clin Oncol* 2013;10:211-224.
2. Goff BA, et al. *Cancer* 2007;109:221-227.
3. Buys SS, et al. *JAMA* 2011;305:2295-2303.
4. Menon U, et al. *Lancet Oncol* 2009;10:327-340.
5. Lu KH, et al. *Cancer* 2013;119:3454-3461.
6. Schulz KF, Grimes DA. *Lancet* 2002;359:431-434.
7. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Available at: http://monographs.iarc.fr/ENG/Monographs/vol93/mono93.pdf. Accessed Nov. 1, 2014.
8. Gertig DM, et al. *J Natl Cancer Inst* 2000;92:249-252.

CME QUESTIONS

1. **Which medication, when used with in conjunction with clomiphene citrate, has been shown to decrease clomiphene citrate resistance in polycystic ovary syndrome patients?**
   a. Conjugated equine estrogens
   b. Testosterone cream
   c. Growth hormone
   d. Dexamethasone
   e. Spironolactone
2. **Which of the following is correct regarding fibroids in pregnancy?**
   a. The greatest growth is in the first trimester.
   b. They rarely diminish in size.
   c. The bigger they are, the greater their effect on preterm birth.
   d. Size is more important than location regarding adverse effects.
3. **Superior ovarian suppression was achieved with which of the following in the trial by Edelman et al?**
   a. Using a pill containing progestin-only
   b. Decreasing the dose of ethinyl estradiol to 10 mcg
   c. Increasing the dose of ethinyl estradiol to 30 mcg
4. **Which of the following findings was *not* consistent between the two prospective cohort studies addressing the risk of ovarian cancer and talcum powder use?**
   a. The overall risk between ever and never use
   b. The risk associated with invasive serous cancer
   c. The risk associated with talcum powder type
   d. The risk associated with location of talcum powder use

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