Isotretinoin and Contraception: Should iPLEDGE Be Changed?

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SYNOPSIS: In this study of female dermatologic patients, knowledge of the typical effectiveness of contraceptive methods increased after viewing a simple information sheet. Given the teratogenicity of isotretinoin, expanding the use of highly effective contraceptive methods among women of child-bearing potential using this medication is essential.


This is an intervention study of 100 women visiting a single dermatology practice in April and May 2014 to test the effectiveness of a one-page information sheet on women's contraceptive knowledge. A convenience sample of English-speaking women aged 18-45 years completed anonymous surveys assessing their knowledge of the typical effectiveness of contraceptive methods before and after reviewing the sheet. Women were asked to rate the methods as being “most effective, > 99% effective,” “medium effective, 92-97% effective,” “least effective, < 89% effective,” or they had never heard of the method.

Participants were mostly white (66%) with a college education (64%) and had a mean age of 27.5 (SD 6.0) years. At baseline, only 3% of participants correctly identified the typical effectiveness categories of all available contraceptives. The majority of women (75%) overestimated the effectiveness of condoms and half (51%) overestimated the typical effectiveness of oral contraceptives. Women also underestimated the effectiveness of the implant (55%) and intrauterine devices (39%). One-third had “never heard of” the implant and 16% had “never heard of” the intrauterine device (IUD). Women spent a mean of 31 (SD 27) seconds reviewing the contraceptive information sheet. For all methods except the vaginal ring, there was significant improvement in contraceptive knowledge after viewing the information sheet. For women who initially inaccurately identified...
the typical effectiveness of a method, the proportion who improved was highest among withdrawal (69%), IUD (67%), implant (64%), and patch (62%).

■ COMMENTARY

Isotretinoin (Accutane® among others) is a very effective treatment for severe acne but is a known teratogen. Congenital anomalies associated with isotretinoin include skull, ear, and eye abnormalities, facial dysmophia, cleft palate, cerebral malformations, hydrocephalus, cardiovascular abnormalities, and disorders of the thymus and parathyroid gland. The FDA regulates the prescription of isotretinoin to women of childbearing potential through the iPLEDGE program. Pregnancy must be ruled out prior to initiating therapy and on a monthly basis thereafter to continue the prescription. In addition, the patient must use two forms of contraception continuously 1 month before, during, and 1 month after isotretinoin therapy, unless the patient commits to continuous abstinence. The two forms of contraception must include one primary form defined by the iPLEDGE program as IUDs, implants, sterilization, depot medroxyprogesterone acetate, and the combined hormonal pill, patch, or vaginal ring and one secondary form (male condoms, diaphragm, vaginal cap, or vaginal sponge).1 The progestin-only pill, female condoms, breastfeeding, withdrawal, and fertility awareness methods are not permitted.

Despite these precautions, studies show that there continue to be about 150 isotretinoin-exposed pregnancies each year.2 These pregnancies are usually due to noncompliance with the iPLEDGE stipulations and/or preferential use of oral contraceptives and condoms, which have higher typical failure rates than IUDs and implants. Research has shown that providers have limited knowledge of correct contraceptive prescribing practice for women using potentially teratogenic medications.3 In addition, studies show that while women understand the teratogenic risk of isotretinoin, they do not feel adequately counseled on how best to avoid pregnancy.4 The point of this study was to test the performance of an information sheet about contraceptive effectiveness in increasing knowledge. Despite a short perusal of the information, most women’s knowledge improved, although how long this information would be retained and whether it would translate into more women on isotretinoin choosing highly effective contraception (IUDs and implants) is unknown.

Although this study focused on patients, it is arguably more important to focus on providers, given that they should be counseling women prior to prescribing isotretinoin and providing them with contraception. I reviewed an iPLEDGE Program Prescriber Contraception Counseling Guide and an iPLEDGE Program Birth Control Workbook for patients.5 Interestingly, these state that the makers of isotretinoin will reimburse one visit for contraceptive counseling. The Guide makes a strong point that the woman should select a primary form of contraception with a low failure rate and references a table of typical-use failure rates. Some of these failure rates are not quite accurate and are likely based on older estimates. For example, the typical-use failure rate for the pill is quoted as 5%, the patch 1%, and the ring 1%. In reality, all these methods are estimated to have a typical-use failure rate of 9%. Despite these inaccuracies, the Guide does highlight that oral contraceptives have the highest typical-use failure rate and that they should not be prescribed to women who the clinician thinks will not comply with a daily method. In my opinion, the Guide does recommend too strongly that the patch and the ring are better alternatives than the pill. The Guide also does not emphasize IUDs and implants; however, the etonogestrel implant was not available at the time of the program creation in 2006. In addition, at that time, IUDs were not as popular among adolescents and younger women as they are now.4

Given that the iPLEDGE program has not been as successful as hoped, it may be time to revise it. Several experts argue that the focus of contraceptive counseling for patients considering isotretinoin should be IUDs and implants, the most effective reversible methods.7 In addition, if these methods are used, a secondary form of contraception, such as condoms, should not necessarily be required. Methods requiring high adherence, such as oral contraceptives, are not optimal for use with isotretinoin, and couples do not always use condoms reliably as a backup. With all the new evidence about the real-life efficacy of contraceptives and the resurfing popularity of IUDs in the United States, I agree that the iPLEDGE Program Prescriber Contraception Counseling Guide should be revised. Although OB/GYNs do not typically prescribe isotretinoin, we do have a role to play in providing contraception with accurate efficacy data and can partner with dermatologists to accomplish this goal.

REFERENCES
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AHC Media
Are We Ready to Give Up the Pap Smear?

By Molly A. Brewer, DVM, MD, MS

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SYNOPSIS: This is a review of the ATHENA trial, which evaluated the prevalence of hrHPV in a large cohort of women and evaluated the most sensitive screening strategy.


This recent study presents data from the ATHENA (Advancing the need for advanced HPV diagnostics) trial conducted in 23 states from 2008-2009. In this study, 40,901 women > 25 years of age were screened with liquid-based cytology and HPV using the cobas-HPV assay (Roche), a PCR-based assay that tests for 14 HPV genotypes that are considered to be high risk subtypes (hr). These hr genotypes include HPV 16 and HPV 18, as well as 12 pooled HPV genotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Depending on the result of both cytology and HPV, women were triaged to different algorithms. Women with abnormal cytology and hrHPV positivity went on to colposcopy and biopsy. Those women with < CIN2 were eligible for the 3-year follow-up study with yearly Pap smears and HPV testing.

Out of the 40,901 women in the study, 9353 women were selected for colposcopy. Those with > CIN2 exited the study and those with ≤ CIN2 were eligible for the 3-year screening cohort. These patients had Pap smear and hrHPV testing each year. The authors used a post-hoc analysis to compare the performance of three screening strategies: 1) cytology with hrHPV testing performed only for ASCUS without colposcopy; 2) a hybrid strategy: women aged 25-29 years old with hrHPV positive and negative cytology only had repeat cytology in 1 year, while women > 30 years old only had repeat hrHPV testing performed; 3) HPV strategy in which HPV negative women were rescreened in 3 years, HPV 16 or 18 positive women underwent colposcopy, and those women positive for the other 12 hr genotypes had reflex cytology and colposcopy if the cytology was ASCUS or greater. If the cytology was negative, women were rescreened with HPV and cytology in 1 year.

At baseline, 10.5% were hrHPV positive and 6.4% had ASCUS or greater cytology. Of the 40,901 women, there were 274 CIN3 or higher and 157 CIN2 or higher. HPV 16 was predictive of CIN3: 17% of those HPV16 positive had CIN3 at baseline, and after 3 years the cumulative incidence rate (CIR) was 25.2%. In contrast, the women with hrHPV positive but HPV 16/18 negative had a CIR of 5.4%. More than 50% of the women with CIN2/3 were HPV16/18 positive up to the age of 40 and then it dropped to 43% and 45% in 40-49 and > 50, respectively. Those women who were cytology negative had a CIR of 0.78% compared to those who were hrHPV negative who had a CIR of 0.34%. The HPV primary in women ≥ 25 years had the highest adjusted sensitivity over 3 years.

COMMENTARY

So is the Pap smear a thing of the past? In their clinical commentary, Huh et al discuss this issue of using HPV for screening for high-grade dysplasia and cancer. This commentary was in response to an FDA application for using HPV as a standalone screening test for cervical precancer and cancer. We now understand that for cervical cancer to occur, except for some rare subtypes, patients must have a hrHPV infection that is persistent. Infection with HPV is extremely common among young sexually active women, but many women have only transient infections, the majority of which will clear the HPV infection without any intervention. Thus, using HPV testing to screen women, particularly those ages 25-29, will have a high rate of positive tests, but a few women will have a persistent infection and even fewer will develop high-grade dysplasia or cancer. The current guidelines state that HPV should not be used alone and, in fact, women ages 25-29 should have cytology without HPV testing because of the transient nature of the infection in this age group. Unfortunately for cytology to be predictive, we need multiple negative Pap smears to reach a reasonable specificity.
Mammograms: The Cost of Overdiagnosis

By Jeffrey T. Jensen, MD, MPH

SYNOPSIS: In the United States, the costs associated with the management of false-positive mammograms and breast cancer overdiagnosis is estimated to be $4 billion each year.

A national U.S. health care insurance plan (not further identified) to identify costs of false-positive mammograms and breast cancer overdiagnoses in the 12 months following mammography screening. The study cohort included all female beneficiaries of the plan between the ages of 40-59 years who underwent a routine screening mammography during 2012 and who remained covered by the plan during the next 12 months. Women considered to be at high risk for breast cancer or those with a previous personal diagnosis of any breast disorder or cancer were excluded. Mammography screening outcomes were assessed separately for the age groups 40-49 and 50-59. Two primary outcomes were identified: false-positive mammograms and screen-detected breast cancer (invasive breast cancer and ductal carcinoma in situ [DCIS]). A false-positive mammogram was defined as a study that led to further diagnostic workup that was not followed by a breast cancer diagnosis. The authors used a published estimate of 22% to determine the number of screen-positive women diagnosed with breast cancer who were likely to have received an overdiagnosis. Costs were defined as the total amount paid by the insurer for the claim related to the diagnosis.

Excluding screening cost, the average claims expenditure per false-positive mammogram was $852 and the average out-of-pocket expense was $200. The average cost of medical services for each invasive breast cancer diagnosed was $51,837 (out-of-pocket $3019). For DCIS, the average treatment cost was $12,369. One-third of women diagnosed with invasive breast cancer underwent total mastectomy. Using these estimates, the authors calculated that the overdiagnosis of invasive breast cancer and DCIS ($1.2 billion) and workup of false-positive mammograms ($2.8 billion) cost the U.S. health care system $4 billion each year.

REFERENCES
Macrosomia

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SYNOPSIS: Previous Alerts have touched on the relationship between big babies and big problems, such as birth injury, infant/childhood obesity, and diabetes. This special feature is designed to provide a more comprehensive look at the causes, risks, prediction, management, and prevention of macrosomia.

The terms large for gestational age (LGA) and macrosomia are interchangeable, but different thresholds have been used by different authors, including a birth weight or estimated fetal weight (EFW) of > 4000 g (8 lbs, 15 oz) or > 4500 g (9 lbs, 13 oz) at any time in pregnancy. Other definitions are based on gestational age, using the 95th or 97th percentile. As expected, many adverse perinatal outcomes correlate directly with the degree of macrosomia.

CAUSES

Genetic predisposition obviously plays a role in fetal/infant size, and it is common for parents of large stature, in the absence of other factors, to have large babies. However, the three major causes are obesity, diabetes, and post-term pregnancy — with the most likely culprit being obesity. Obesity is a major rising problem. Overall, more than one-third of women in the United States are obese and more than half of pregnant women are either overweight (body mass index [BMI] 25-30 kg/m²) or obese (BMI > 30 kg/m²). Also, in addition to a predilection for their larger babies to have downstream birth injuries, the offspring of obese women have higher rates of childhood obesity and later cardiovascular abnormalities, with the dye being cast long before birth.
Maternal diabetes affects various fetal organs in different ways. Maternal/fetal hyperglycemia and insulin resistance force the fetal pancreas to produce more insulin, a growth stimulator, and to store the extra glucose as glycogen in their larger livers. Also, lipogenic dysfunction leads to over-accumulation of fat in the subcutaneous tissues. All these macrosomic factors can lead, through resulting body to head disproportion, to birth injury. Add glucose intolerance to a clinical mix of an obese woman of short stature (with an inherently small pelvis) and you have the “perfect storm” for shoulder dystocia (SD).

In post-term pregnancy, there is more time for further growth of the fetus. Interestingly, while there is some slowing of overall fetal weight at term and into post-term, the size of the fetal abdomen (and with it, the shoulders) continue to increase linearly — another setup for SD. Nevertheless, this is becoming a less frequent cause of macrosomia and SD, because the fear today of stillbirth has led to a greater tendency to intervene before patients can become post-term. Therefore, this special feature will focus mostly on obesity with a secondary look at diabetes.

THE RISKS OF MACROSOMIA
Maternal risks of fetal macrosomia mostly are associated with delivery events. These include the risk to the pelvic floor after vaginal birth — resulting in later anal incontinence, stress urinary incontinence, and prolapse, with odds ratios for each of 2.2, 4.4, and 7.5, respectively. One prospective study showed that urinary stress incontinence was independently related to birth weight, episiotomy, and the size of the fetal head. Another study showed that in those with postpartum stress incontinence, 21% persisted after a vaginal delivery, while only 3% persisted in those having cesarean sections.

Infant injury can be traumatic or asphyxical. The incidence of SD in the overall population is 1.4%, but when birth weight exceeds 4500 g, the rate is 9-24%. When adding vacuum/forceps delivery to the mix, the rate is 23%, and with birth weights > 4750 g, the rate is 29%.

Shoulder dystocia can lead to brachial plexus injury, with a usual rate of 0.5-1.9 per thousand, rising 20-fold when infants weigh more than 4500 g. Permanent injury can occur in 10% of these infants. One retrospective study found a 20% risk of hypoxic central nervous system injuries at 6 months of age in infants with SD.

DIAGNOSIS OF FETAL MACROSOMIA
It is somewhat understandable that ultrasound estimates of fetal weight have been maligned since the often stated standard error is about 10% — meaning that an EFW of 4000 g carries a splay of between 3600 g and 4400 g. One study even suggested that the patient’s own estimate of fetal weight was better than ultrasound.

Although the literature is replete with formulas for EFW, the most commonly used one, plotted against gestational age, was constructed at sea level in 392 patients. It consists of measurements of the biparietal diameter (BPD), head circumference, abdominal circumference (AC), and femur length. Newer methods, adding 3-D reconstructions of the fetal thigh, have yielded better accuracy.

Since the precision of fetal weight estimates involves systematic error (the biometric formulas themselves) and random error (maternal variables and even altitude), some formulas have utilized a “customized” approach to take this into account. What is clear is that most formulas underestimate the EFW in LGA babies, and Melamed et al found that in 21 formulas studied, the average underestimation in large babies was -6.2%.

Taking into account all of the above variables in LGA fetuses, especially, Lindell et al derived a formula incorporating head, abdomen, femur length, and 3-D volumes of the fetal abdomen and thigh that identified 93% of fetuses whose weights were above 4500 g (when rates of SD rise appreciably) by using an EFW threshold of 4300 g. This seeming triumph was at a false-positive rate of 38%.

USING ULTRASOUND TO DETECT MACROSOMIA
It is clear that with forewarning one can avoid possible macrosomic disasters at birth, so various approaches have been put into play.

The AC alone as a screening tool. Since corpulent fetuses all have big abdomens, the AC has been noted to be as accurate as more complicated ultrasound formulas. Screening at 30-34 weeks can capture 70% of fetuses destined to be > 4000 g, with a false-positive rate of 25%. Interestingly, a more cumbersome multi-parameter formula added only 3% to the predictive accuracy.

A two encounter approach. This is a concept suggested by Campbell in a comprehensive review of the subject. A screening test is done at 30-34 weeks, followed by a 2-D/3-D scan targeted to macrosomia at 39 weeks in those identified to be LGA by the earlier scan. After initial screening, the higher prevalence of LGAs improves the positive predictive value appreciably.

Prediction of macrosomia at term with a single earlier EFW. The rationale here is that a careful EFW by a standard formula at 34-37 weeks (when there are ideal conditions for scanning) can be used to extrapolate forward to predict the fetal weight at term. This assumes that the fetus will grow along the same trajectory (in percentile). Best et al found it to be especially effective in predicting macrosomia (> 4000 g) in diabetics with a positive predictive value of 87% and an absolute error of 6.8%.

METHODS TO PREDICT SHOULDER DYSTOCIA
In 1982, Cohen et al tried to predict shoulder dystocia by the degree of discordance between the abdomen and the head. The authors found that in fetuses with EFW of > 3800 g, if the difference in average abdominal diameter (AD) — AC divided by 3.14, minus the BPD — exceeded 2.5 cm, there was a 33% chance of SD. If < 2.5 cm, none of the patients had SD. This finding was validated later by
another group who found almost identical results (SD in 25% of all patients and 38% in diabetics if the AD-BPD difference was > 2.5 cm and only 3.8% if < 2.5 cm).19

MANAGEMENT OPTIONS FOR PATIENTS WITH AN ULTRASOUND DIAGNOSIS OF MACROSOMIA

Cesarean section for those with EFW > 4500 g. Campbell makes the case for elective cesarean in this backdrop since a targeted scan at 39 weeks in high-risk pregnancies (obesity, diabetes, postdates, or earlier suggestion of macrosomia) will identify more than 90% of those fetuses weighing more than 4500 g if the EFW is > 4000 g.16 Choosing a cesarean section in this setting would virtually eliminate birth injury and reduce later maternal morbidity to < 3%. Although a cost/benefit analysis by Rouse et al20 strongly challenged this approach, another paper by Culligan et al in a urogynecology journal21 did suggest an economic benefit. Indeed, ACOG agrees with the approach of offering elective section, but only if the EFW is > 5000 g.6

Some authors are bullish on the use of elective cesarean section in macrosomia, based on increased rates of maternal and neonatal morbidity. An interesting slant is that a New Zealand survey showed that 21% of OB/GYNs and 42% of urogynecologists would choose elective cesarean section if their fetuses had EFWs > 4500 g.22 So, ask the proponents, why would our patients not be given the same opportunity?

A selective approach to route of delivery with macrosomia. Although proponents point to the risk of later maternal pelvic morbidity, they seem to slip over the immediate operative, and later repeat pregnancy complications, with cesarean section, which is not an innocuous procedure. My feeling is that if the EFW is between 4500 g and 5000 g in non-diabetics and there is no evidence of body to head disproportion, then the risk of SD is negligible if the patient labors spontaneously, has a normal labor curve, does not have a lengthened second stage, and does not need an instrumental delivery.

Induction of labor near term to pre-empt further growth. This approach to macrosomia has been validated in diabetics,23 but not in non-diabetics when EFWs are < 5000 g,24 and an oft-quoted review showed that the cesarean section rate doubled in those having induction, with no difference in any other outcome variables.

PREVENTION OF MACROSOMIA

First, it is important to point out that there is more to macrosomia than being big. The diagnosis is made simply by weight at birth or in utero EFW according to gestational age. Infant BMI and ponderal index give us an idea about weight distributed over length, but what is becoming clear is that anthropometric measurements of adiposity correlate best with childhood obesity, metabolic syndrome, and eventual diabetes. Work is in progress to use 3-D measurements of the abdomen and thigh as in-utero surrogates for adiposity.

LIMITING WEIGHT GAIN IN PREGNANCY

For years, there has been a laissez-faire approach to weight gain in pregnancy until the Institute of Medicine (IOM) came out with some stringent guidelines in 200925 based on patients’ pre-pregnant BMIs. Succinctly, recommended weight gain is 13-20 pounds for women with BMI > 25 kg/m², and 11-20 pounds for all obese women (BMI > 30 kg/m²). Studies conflict as to whether weight gain in pregnancy is more important than pre-pregnant weight, but it is clear that curtailing both will be of benefit to decrease adverse outcomes in children of obese mothers.

While one Florida study26 (previous Alert) suggested that weight gain in pregnancy had a greater effect on birth weight than pre-pregnant weight or diabetes, other studies have shown pre-pregnant weight to exert the greatest influence.27 Lifestyle interventions (diet and exercise) seem to have a less effect on birth weight in obese patients, while weight gain has its greatest effect in those mothers with normal starting weights.

PRE-PREGNANT WEIGHT

Clearly, weight reduction in obesity and in diabetes prior to pregnancy can give the patient a leg up on a prospective pregnancy. However, this apparently is not so easy to do. A recent NIH study showed that in 774 women studied, average weight gained in pregnancy was 32 pounds.28 One year later, 75% were heavier than their previous pre-pregnant weight — 47% were > 10 pounds over and 24.2% were more than 20 pounds over. This is why BMIs tend to stair-step upward with each pregnancy. Interestingly, in the same issue of the journal, another study from British Columbia showed that there was a very worrisome linear relationship between adverse pregnancy outcomes and increasing pre-pregnant BMI.29 This, coupled with an earlier study relating pre-pregnancy weight directly to longer-term consequences of macrosomia,30 such as childhood obesity and metabolic dysfunction, should get our attention.

PRE-CONCEPTUAL COUNSELING

This can have a major beneficial effect in the two conditions that can go hand in hand: diabetes (gestational and pre-gestational) and obesity. Peterson et al have calculated that by employing universal pre-conceptual counseling and screening for pre-gestational diabetes, and applying appropriate treatment and management, 8397 preterm deliveries, 3725 birth defects, and 1875 perinatal deaths could be averted per year.31 This would result in a saving of $4.3 billion over the lifetimes of the surviving children.

By applying (postpartum) the same principle in obese patients (again, representing at least one out of three women in the United States), huge health care savings could be accrued by optimizing conditions prior to their next pregnancies.

REFERENCES

CME QUESTIONS

1. The current iPLEDGE program requires the use of a secondary form of contraception (male condoms, diaphragm, cervical cap, or vaginal sponge) if an intrauterine device is selected as the primary form of contraception.
   a. True
   b. False

2. The estimate of cost associated with overdiagnosis of breast cancer is based on:
   a. the actual out-of-pocket expenses of women with advanced breast cancer.
   b. expenditure data from a major national U.S. health care insurance plan.
   c. the group of women with a true diagnosis of DCIS.
   d. women with a false-negative mammogram who died within 1 year from breast cancer.

3. Which of the following is not a major predisposing factor in macrosomia?
   a. Post-term pregnancy
   b. Diabetes — gestational or otherwise
   c. Obesity
   d. The size of either parent at the time of their births.