A recent publication in the influential *British Medical Journal* (BMJ) using the Danish National Registry databases reported an increased risk of venous thrombosis (VT) in women using the combination contraceptive ring and patch, and suggested that the risk may also be increased among users of the etonogestrel implant [1]. While an increased risk of VT is well established for women using combined hormonal methods, in this database study, users of the ring and patch were noted to have double the risk of VT compared to users of a low-dose levonorgestrel (LNG) pill. In 2009, the same research group using similar methodology reported a twofold increase in VT risk among users of drospirenone-containing combined oral contraceptives (OCs) relative to LNG pills [2]. This created a ripple effect that bounced off our shores and led to FDA hearings that resulted in media attention and a change in labeling for these products. How should we communicate this new information about the ring and patch to patients and other health care providers?

Scientific debate is messy but ultimately healthy for patient care. Unfortunately, the medical literature has rapidly moved from an exclusive currency of scientific exchange and clinical advancement used by researchers and clinicians to a source for the lead story on the evening news or as ammunition for litigation. Before most clinicians have a chance to read and discuss an important new manuscript, the results are on the front page of daily papers and on electronic blogs. Chances are your first office patient read the report on her iPhone while you were still finishing morning rounds.

The communication of risk and benefit is a core component of health care counseling. One of the most important rules of practice is to “first do no harm.” But without balance, that tenet might lead us on a risk-averse trajectory where it becomes impossible to “do good.” The safety bar for contraception is higher than that for most other treatments in medicine, as healthy women engage in the use of therapy to avoid the real and potential negative consequences of an unintended pregnancy. This higher bar has important implications because nonuse of contraception and use of methods with lower effectiveness expose sexually active women to the inherent risks of pregnancy. Rarely is the prevention of health and social consequences of unintended pregnancy taken into account as a benefit of contraception in the discussion of risk. We have not seen a case where a woman was considered too medically fragile to use hormonal contraception but an acceptable risk for pregnancy.

For healthy women, the mortality risks of contraception are very low; about 1.5/100,000 woman-years for combined OC users and 0.01/100,000 woman-years (1 in 10 million) for women using an intrauterine device [3]. To put this risk into perspective, the chance of death with pregnancy is about 12/100,000 woman-years [4], and the chance for death due to a motor vehicle accident is 17 (ages 25–44 years) to 26 (ages 15–24 years) per 100,000 woman-years [5]. These numbers are easy to discuss and compare as they point out absolute risk and share a common denominator. Discussing the risks associated with common activities can help communicate that the risk associated with contraception is in fact very low, particularly in young otherwise healthy women. Since the use of hormones is a common concern, it is also helpful to point out that the overall risk of death is lower among current and past users of OCs compared with nonusers [6].

Media accounts rarely report absolute risk and focus instead on relative measures of risk. Attributable risk (AR) is an acceptable way of communicating this information as it provides an estimate of the absolute number of events that a treatment will cause or prevent. Unfortunately, AR is less widely reported than risk ratios or odds ratios. News sources will typically sport headlines like “Dietary treatment results in 20% decrease in X cancer” or “New drug doubles the risk of Y cancer.” But, a 20% decrease or a twofold (200%) increase in a condition may or may not be clinically meaningful, particularly if other important benefits or risks are associated with the treatment. If you double the risk of a
rare event, the likelihood of the event is still rare. If that does not make intuitive sense, we will sell you our secret to increase your chance of winning the lottery by 200% (buy two more lottery tickets!).

Using the example of the Danish Database study, compared to nonusers of hormonal contraceptives, the risk of confirmed VT attributable to use of the vaginal ring was 5.7 per 10,000 woman-years of exposure (the incidence of VT in nonusers was 2.1/10,000 woman-years compared with 7.8/10,000 woman-years in ring users). However, when we compare ring users to users of the LNG pill, the attributable risk drops to 1.5/10,000 woman-years (incidence 6.2/10,000 woman-years in the LNG pill). In other words, fewer than 2 additional cases of VT occurred in 10,000 women per year using the ring instead of a low-dose LNG pill. How do we communicate that risk? One approach is to consider that double the risk of a rare event is still a rare event. While it is well established that combined hormonal contraception is associated with an increase in the risk of VT, the absolute risk of an event remains small in most otherwise healthy young users [7]. However, the baseline risk is higher in obese women and in those with inherited thrombophilias. Moreover, the database study design cannot inform us about the relative or absolute risks in these subpopulations. The importance of the interaction with obesity must be emphasized since the proportion of obese women is growing in our population.

Clinicians and the public are frequently confused when studies published in high-quality journals present conflicting results. This inconsistency undermines the public’s confidence in science and in our clinical opinions. Sorting out the literature can be confusing even for experienced clinicians, particularly when we are evaluating factors that contribute to the development of rare disease. To interpret the literature, we must understand the strength and limitations of different study designs. The power of the Danish database is that a large sample size can be created by linking past prescription data with subsequent events in a “retrospective” prospective design. These studies are sometimes called TROHOC (spells COHORT backwards). Unfortunately, this is not a true prospective design as the investigator generally cannot collect essential baseline characteristics of the cohorts needed to adjust for important confounders and risk modifiers. For the interaction between VT risk and hormonal contraception, many key sources of bias have been identified, the most important being the underdiagnosis of VT; no information on important venous thromboembolism risk factors such as smoking, body mass index and family history of VT; and invalid control of duration of use [7,8]. Since the risk of VT is highest in the first 6 months after starting a combined hormonal method, these limitations become significant handicaps in database studies [9]. Also, many clinicians view a new product as potentially safer, and this can adversely affect the incidence of events as providers switch less healthy individuals to these newer methods. These and other deficiencies in the newest Danish study have been described in detail in a series of “rapid responses” (electronic letters to the editor) concerning the manuscript available at the BMJ Web site [10].

Only a true prospective study designed with careful attention to details can overcome these biases. Fortunately, large well-designed multinational prospective studies evaluating VT risk have been completed. The first (European Active Surveillance Study) enrolled subjects in Europe and showed no increased risk of VT with drospirenone pills compared to LNG pills [9]. While full data from a similar large study evaluating this risk in the United States (International Active Surveillance Study) [11] have not yet been published, interim results presented to the FDA hearing last December revealed no increase in the relative risk of VT for drospirenone pills compared to other combined OCs [12] and are consistent with the earlier published results from the prospective Ingenix study in the United States [13]. Most recently, data from another large prospective cohort study carried out in the United States and five European countries (Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing) presented at the 2012 annual clinical meeting of the American Congress of Obstetricians and Gynecologists demonstrated no increased risk of VT with the vaginal ring compared to combined OCs [14]. These prospective studies effectively trump the results of the database studies.

Although a large-scale randomized study would be the best way to definitively answer this question, this design would be extremely expensive and require years to complete. So, prospective cohort studies provide the highest quality of evidence on uncommon and rare side effects associated with hormonal contraception. The results of database studies can be useful when no better data are available, but should be weighted below those of well-designed and sufficiently powered prospective studies.

The last Danish database study paper led to FDA hearings and a labeling change for drospirenone pills. While the new package insert is actually helpful, as it presents results from the database and prospective studies, it will be up to clinicians to take the time to evaluate and communicate this information. No one can possibly keep up-to-date with all the literature, so clinicians need a healthy understanding of the principles of clinical epidemiology to guide their practice. The World Health Organization and the Centers for Disease Control have published guidelines that establish eligibility criteria that are regularly updated for the use of contraception in women with medical conditions [15].

Communication of risks and benefits is an essential part of health care delivery. As health care providers, we have the responsibility to interpret the science for our patients. Like all important clinical tasks, this requires training and a commitment to continuing education. To meet this need, the Association of Reproductive Health Professionals is sponsoring a new continuing medical education visiting faculty program, Risk Made Real: A Case-Based Approach to Addressing Risk in Contraception. The goal of this program is to provide health care providers and their patients with the
knowledge and practical tools they need to appropriately contextualize and understand the risks and benefits of all forms of contraception. The program will be introduced at Reproductive Health 2012 in New Orleans and will be available as a training tool through the Association of Reproductive Health Professionals.

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