Question: I have a physician friend who believes that generic birth control pills are less efficacious than brand-name equivalents. He is fairly convinced of this, although he admits that it is based on several anecdotal experiences.

I have never heard of any evidence to suggest that this is true. I think he may be misled. This is frustrating because he insists that all patients at the abortion clinic he runs get brand-name prescriptions only, which can be unaffordable.

Is there any research that indicates for or against this idea?

Respondent 1: Generics have to be “bioequivalent,” which means they have to include the same amount of active medication as the branded formulations. For oral contraceptives (OC), the pharmaceutical company is considered to have reached bioequivalence if the amount of steroid in its formulation is within 20% of the amount of steroids in the branded OC. So theoretically, there could be 20% more or less active hormone in the generic pills than the branded OC. That being said, even within branded OCPs, from batch to batch, there only has to be agreement within 20%, so if someone is on the edge of needing more hormone and there is a batch that has 18% less hormone, they might be at increased risk for pregnancy.

Respondent 2: Generic medications need to demonstrate average serum equivalency of 80–125% over the month compared to the original medication. They do not have to demonstrate efficacy with separate studies. They are subject to the same requirements that the pills contain the stated amount of medication as brand-name medications, but with the carriers and other ingredients, serum levels can vary within that range. Different brands and generics may lead to varying serum levels, so problems can arise when you switch back and forth from different agents.

Efficacy studies do not find a difference, and we would expect missing pills to trump a small serum level difference. I, and the contraception experts I know, support using the pill that is most economical and easy to obtain for the patient. I also support giving a patient the pill she prefers if she has a preference.

1. Literature review

Over 75 million women worldwide utilize oral contraceptive pills (OCPs) for contraception [1]. In the United States, over 80% of women born after 1945 have used OCPs at some time in their lives [2]. Thus, OCPs are one of the most commonly prescribed medications and are, in fact, the most extensively studied medications in the history of medicine [1]. And yet, misconceptions about OCPs are common among patients as well as providers. The 50th anniversary of the OCP’s approval by the US Food and Drug Administration (FDA) provides an opportune time for clarifying one common misconception surrounding this well-utilized and effective contraceptive method — are generic OCPs as effective as their brand-name counterparts?

According to the FDA, generic and brand-name OCPs are considered clinically equivalent and thus are interchangeable [3]. Despite the fact that there are scant data in the literature to the contrary, this belief has been challenged [4–6]. Ansbacher [4,5] argues that differences between therapeutically equivalent generic and brand-name low-dose OCPs “with respect to the bioavailability of hormones may interfere with contraceptive efficacy and increase breakthrough bleeding.” He argues that substituting a therapeutically equivalent generic low-dose OCP could ultimately result in increased rates of unintended pregnancies since increased breakthrough bleeding is a common reason for OCP discontinuation [7–9] and studies have demonstrated that many women switch to a less-effective method or no method of contraception following OCP discontinuation [7]. Although portions of Ansbacher’s [4,5] argument can be supported [7–9], his argument is largely theoretical.

Despite the fact that regulations regarding bioequivalence have been in place for more than 20 years, controversies over bioequivalence continue to arise [10]. Many clinicians and patients remain uninformed regarding the scientific basis for establishing bioequivalence and the generic drug approval process in general. The passage of the Drug Price Competition and Patent Term Restoration Act in 1984 was designed to facilitate the entry of generic versions of brand-name drugs into the marketplace [11]. Since its passage, manufacturers of generic products no longer need to submit
separate clinical safety and efficacy studies, as noted by Respondent 2. The generic versions must demonstrate both therapeutic equivalence — meaning that it contains the same active ingredients, identical in strength and dosage, as the brand-name product — and bioequivalence — meaning that clinical trials demonstrate no significant difference in the rate and extent of absorption (similar pharmacokinetics) when compared to the brand-name product [10].

To demonstrate bioequivalence, the manufacturers must perform a crossover study of adequate power (usually 20–30 women) to compare the rate and extent of absorption of the active ingredients achieved after administration of both the generic and brand-name products to the same individuals under as identical conditions as possible [11]. Pharmacokinetic calculations of the area under the drug concentration—time curve (AUC) — indicative of the extent of absorption, the maximum concentration and the time to maximum concentration — are calculated based on these studies. Differences of less than 20% in the mean AUC between brand-name and therapeutically equivalent drugs are deemed acceptable [11]. In other words, the average blood level deviation of the generic product from the brand-name product must fall within the 90% confidence interval limits for the mean AUC — in the range of 80–125%, as mentioned by one of the respondents [12]. If these criteria are met, the FDA considers the generic product to be interchangeable with the brand-name product. No further clinical trials are necessary given that the safety and efficacy of the generic product are expected to be identical to the clinically tested and FDA-approved brand-name product [12].

In practice, the reported ranges of bioequivalence for generics are much narrower [12]. In the case of many formulations, the variability between the generic and brand-name products is no different than the variability found between different lots of the same brand-name drug [6]. Given the acceptable range of bioequivalence, skeptics have argued that switching from brand-name to generic OCPs might result in increased side effects [4,5]. However, the reported incidence of increased side effects should, in theory, be similar when switching between generic OCPs, between brand-name OCPs and generics, or between two batches of the same formulation made by the same manufacturer. Clinicians also note that patients complain of minor side effects whenever OCP brands are changed, even if the compounds are the same [6]. Many manufacturers also package their brand-name products differently when marketing them as generics; thus, the product is theoretically identical [12]. Therapeutically equivalent drugs may differ in their inert ingredients, packaging, color, shape, flavor, expiration time and labeling [11]. These differences may be especially important for OCPs because any confusion on the part of the patient upon switching products or delaying the start of a newly prescribed product may affect compliance and could increase the likelihood of an unintended pregnancy [4,5,12]. As mentioned above, the statistical methods used by the FDA to determine bioequivalence have been challenged. The FDA has taken a firm stance upholding the therapeutic equivalence and interchangeability of generic and brand-name products [3]. Their letter to health care practitioners regarding therapeutic equivalence of generic drugs notes that, in addition to tests performed prior to market entry, the FDA regularly assesses the quality of products in the marketplace and thoroughly researches and evaluates reports of alleged drug product nonequivalence. To date, there have been no documented examples of a generic product manufactured to meet its approved specifications that could not be used interchangeably with the corresponding brand-name drug. The letter also notes that patients may pay closer attention to their symptoms following substitution of one drug product for another, thereby resulting in a non-meaningful increase in reported symptoms at that time, which may ultimately result in anecdotal reports of decreased efficacy or increased toxicity. Upon investigation by the FDA, no problems attributed to substitution of one approved drug product for another have been observed [3].

The efficacy of OCPs requires proper use [9]. Different failure rates have been reported for various brands; however, as few head-to-head studies have been performed, there is no evidence that, with perfect use, different OCP products have different failure rates [7]. There are no clinical data either on differences in compliant use between brand-name and generic OCP users, although patients and clinicians both anecdotally report problems attributed to switching products [12]. Some of these problems may be the result of confusion due to different packaging as mentioned above. However, there are no evidence-based data to date evaluating these issues. There are no clinical data either on how patients’ perception of generic products affects adherence to treatment.

The cost of OCPs clearly has a major influence on access and adherence. The price differential between generic and brand-name products can be as much as 70% [12]. Studies have consistently found that increased copayments are associated with decreased use of prescription drugs [13]. In one large study evaluating treatment adherence based on drug class within a three-tier system, Shrank et al. [13] concluded that prescribing generic or preferred medications within a therapeutic class is associated with improvements in adherence to therapy. Patients who received generic medications were 62% more likely to achieve adequate adherence than with branded products (OR 1.62, 95% confidence interval 1.39–1.89).

Generic OCPs approved by the FDA that demonstrate therapeutic equivalence and bioequivalence should be considered clinically interchangeable with the brand-name products. There is no strong evidence to the contrary. The ACOG Committee Opinion on Brand Versus Generic Oral Contraceptives concludes that ACOG “supports patient or clinician requests for branded OCPs or continuation of the same generic or branded OCP if the request is based on clinical experience or concerns regarding packaging or...
Stephanie P. Sober  
Department of Obstetrics and Gynecology  
Pennsylvania Hospital  
Philadelphia, PA 19107, USA  
E-mail address: stephanie.sober1@uphs.upenn.edu

Courtney A. Schreiber  
Department of Obstetrics and Gynecology  
University of Pennsylvania School of Medicine  
Philadelphia, PA 19104, USA  
E-mail address: cschreiber@obgyn.upenn.edu

References


