Hormonal Contraception and Physiology: A Research-based Theory of Discontinuation Due to Side Effects

Virginia J. Vitzthum and Karin Ringheim

Side effects influence the acceptability and continuation of hormonal contraceptives. Counseling the client about the management of side effects is a principal approach advocated for increasing continuation. Evidence of a biological basis for variation in women’s tolerance of hormonal contraceptives argues, however, that greater attention should be given to altering the product rather than principally attempting to alter a woman’s ability to deal with the product. Discontinuation rates for hormonal contraceptives, largely attributable to side effects and health concerns, are high in nearly all less-developed countries for which Demographic and Health Survey data are available. Oral contraceptives appear to be particularly problematic for Latin American women, most notably in Bolivia. Clinical trials suggest substantial variation in the physiological response to exogenous hormones, and new evidence confirms the hypothesis that the normal hormonal profiles of Bolivian women are significantly lower than those of women in the United States. These findings suggest a need for more population-specific physiological research linked to analyses of the possible association between endogenous hormone differences and contraceptive continuation. Appropriately adjusting the level of the steroid delivered may benefit women’s health and improve the acceptability and continuation of hormonal contraceptives. (STUDIES IN FAMILY PLANNING 2005; 36[1]: 13–32)

Hormonal contraceptives are among the most effective reversible methods for preventing pregnancy (Hatcher et al. 1998). In addition to the familiar daily tablet containing some combination of synthetic estrogen and progestin (“the pill” or combined oral contraceptive), progestin-only pills (“the mini-pill”), injections, implants, and patches are available. These coitus-independent methods also confer several noncontraceptive benefits (Mishell 1993; Sherif 1999). Many women experience reductions in the physical and/or psychological discomfort associated with the menstrual cycle. Although some women experience reduced libido (Graham et al. 1995), others report enhanced sexual enjoyment, perhaps because of a diminished fear of pregnancy (Egarter et al. 1999; Ernst et al. 2002). Combined oral contraceptives can improve acne, hirsutism, and lipid levels, and may protect against osteoporosis, endometriosis, and rheumatoid arthritis. Particularly noteworthy, they substantially reduce the risks of pelvic inflammatory disease and, both during use and for several years afterward, ovarian and endometrial cancers. The totality of evidence to date also argues that current formulations of these contraceptives do not carry a substantial health risk for most women (Huezo 1998), and progestin-only contraceptives appear to have none of the serious, albeit rare, risks associated with combined oral contraceptives. Yet, despite the high contraceptive efficacy, safety, and additional benefits of hormonal contraceptives, discontinuation is surprisingly frequent among women who do not wish to become pregnant.

Acceptability research has consistently shown that women judge a contraceptive method primarily on the basis of its perceived safety, effectiveness, and convenience (WHO 1980; Hardon 1992 and 1994). Health concerns and experience or fear of side effects (resulting from past use or rumor) are the most commonly cited reasons for not practicing contraception or for relying on a less efficacious method (ESHRE Capri Workshop Group 2000). In less-developed countries for which Demographic and Health Survey (DHS) data are available, the experience of side effects is the leading predictor of discontinuation of hormonal methods (Ali and Cleland 1995; Blanc et al. 1999). Discontinuation is also higher for hor-
monal pills and injections than for the IUD (Ali and Cleland 1995). Thus, side effects, whether experienced or perceived, are central to the acceptability, use, and continuation of hormonal contraceptives. Discontinuation because of side effects often leads to unplanned pregnancies and, therefore, may be a primary precursor of induced abortion (Ringheim 1996). In examining factors that may contribute to induced abortion, Singh and Wulf (1994) noted that use of oral contraceptives appeared to be particularly problematic for women in Latin America and suggested that the reasons for high rates of discontinuation because of health problems should be further explored.

If the causes of the side effects of hormonal contraceptives were better understood and addressed, women would be more likely to choose them, to use them correctly, and to continue using them. Unwanted fertility and induced abortion would, thereby, be decreased, maternal mortality would be reduced, and women would accrue additional health benefits and improvements in their quality of life.

This article advances the argument that common side effects associated with hormonal contraceptives arise principally from biological variation among women and populations. DHS data reveal the contemporary extent of side effects associated with hormonal contraceptives among women in less-developed countries. Clinical and pharmacological investigations disclose the substantial unexplained variation in response to exogenous hormones among clients and populations. Anthropological studies of reproductive functioning in nonindustrialized populations confirm that levels of endogenous reproductive steroids are naturally lower than those among women in the United States. Our aim is to encourage further study into this physiological variation (which may range higher as well as lower than the level found among “typical” North American women) with an eye toward improving hormonal contraceptive acceptability. Of course, increased efforts to improve the quality of reproductive health services should not be abandoned in favor of improved contraceptive formulations, but efforts to reduce discontinuation rates through counseling on the management of side effects may saddle providers with an unrealistic goal. Such an approach is certainly a disservice to women if the biological etiology of side effects of the product they receive is taken inadequately into account.

Formulations and Side Effects

In milligrams, early formulations of the pill contained hormone doses that were several times higher than current levels. The different steroids currently in use, however, are not necessarily biologically equivalent by weight to early combined oral contraceptive compounds or to each other. A brief review of the development of hormonal contraceptive formulations affords a better understanding of the complex relationship between steroid dosages and side effects.

Approved by the US Federal Drug Administration in 1962, the original Searle combined oral contraceptive contained 150 mcg estrogen (mestranol) and 9.85 mg progestin (Tyrer 1999; Kaunitz 2004). By 1965, in response to serious complications (for example, thromboembolism) observed among a small proportion of users, steroid levels were substantially lowered (to 100 mcg mestranol and 2.5 mg progestin). In 1970, Wyeth introduced a pill with half the amount of mestranol (50 mcg) and 5 mg of progestin; “low-dose” combined oral contraceptives (30 or 35 mcg ethinyl estradiol, [EE]) followed in 1973. In fact, because only about 70 percent of a mestranol dose is biologically available, 35 mcg EE is equivalent to 50 mcg mestranol (Brody et al. 1989; Goldzieher and Brody 1990).

Several progestins have been developed since 1962, often classified as first (norethynodrel, norethisterone, norethindrone, ethynidiol diacetate), second (levonorgestrel, norgestrel, norgestimate), and third (desogestrel, gestodene) generation, based roughly upon their time of introduction and/or paired dosage of EE. This classification, however, is neither standardized nor particularly helpful (The Contraceptive Report 1999a). Rather, progestins are divisible into estranes (which include all those designated above as first generation; the biologically active compound is norethindrone) and gonanes (those designated above as second and third generation, each having a different biologically active compound).

Estranes and gonanes differ in three clinically relevant factors that affect contraceptive efficacy and cycle control: bioavailability, half-life, and binding affinity (see Figure 3 in The Contraception Report 1999b:14). An increase in either bioavailability (the amount of a drug detected in the blood after oral ingestion compared with intravenous administration) or binding affinity for progesterone receptors translates into the use of smaller doses for the same contraceptive effect. A longer half-life (the time necessary for the blood level to fall to 50 percent of its maximum) gives greater cycle control and greater contraceptive protection despite missed pills. Thus, contraceptive efficacy and propensity to side effects vary with the choice of progestin as well as with the absolute dosage. For example, gonanes offer better cycle control than do estranes (The Contraception Report 1999b), and gestodene appears to be superior to desogestrel (Rosenberg et al. 1996; Endrikat et al. 1995 and 1997).

In addition to dosage and choice of progestin, the route of delivery and sequence of steroid administration...
affect efficacy and the occurrence of side effects. The identical combined oral contraceptive administered vaginally has much lower side effects when it is taken orally, yet it has comparable efficacy (Zaiei et al. 2002). Biphasic and triphasic combined pills vary in the daily steroid dosages delivered so as to better mimic the ovarian cycle and thereby, in theory, reduce side effects. Combined oral contraceptive regimens can range from 21 to 84 days prior to a drug-free period of several days. Progestin-only pills must be taken daily within a narrow time window. Injections must be periodically renewed; implants deliver the steroid continuously.

The principal health-threatening side effects of combined pills are attributable to the estrogen component. These dose-dependent risks (especially diseases of the circulatory/cardiovascular system) have been substantially lowered by dosage reductions (Hatcher et al. 1998), but not eliminated (Tanis et al. 2001; Lidegaard and Kreiner 2002; Lidegaard et al. 2002). Estrogen-related, dose-dependent, nonlethal side effects include nausea and vomiting, headaches, breast tenderness, and late-cycle breakthrough bleeding\(^4\) (Rosenberg et al. 1995a; The Contraception Report 1997; Lawrence 1997; Hatcher et al. 1998; Hardon 1997). Breakthrough bleeding during the early part of the cycle suggests that the estrogen level (or estrogen–progestin ratio) may be too low (The Contraception Report 2004). Changes in menstrual bleeding (ranging from amenorrhea to heavier-than-usual flow) are both common and a common reason for discontinuation of combined oral contraceptives, even though clinical trials suggest that bleeding returns to more normal patterns over time (Rosenberg and Long 1992; Rosenberg et al. 1995a).

Progestin-only contraceptives are an important alternative for women who are breastfeeding, who cannot tolerate combined pills, or for whom combined pills are contraindicated. Although it was not introduced until 1973, a progestin-only pill was the original goal of contraceptive research in the 1950s (Perone 1994). An unintended contamination of norethynodrel with mestranol prompted the realization that the synergistic interaction of estrogen and progestin allows less of each, when combined, to suppress ovulation than would be the case if they were used individually (The Contraception Report 1997), thus hastening development of combined over progestin-only contraceptives. Today, progestin-only contraceptives are available in a broad array of delivery mechanisms (pill, injection, implant, patch, and the IUD).

Clearly, progestin-only contraceptives represent the lowest dose of estrogen possible, and hence their use is free of estrogen-associated health risks. The most common nonfatal side effects are changes in menstrual bleeding (amenorrhea, lighter- or heavier-than-normal bleeding, and breakthrough bleeding). Breakthrough bleeding has proved particularly challenging to the continued use of this form of contraceptive. Other reported side effects include nausea and vomiting, headaches, and breast tenderness, although the frequency and severity of these conditions appear to be much lower than they are with combined oral contraceptives (Hardon 1997). Progestins vary in their pharmacokinetics, whether they are delivered in synergistic combination with estrogen, as discussed above, or delivered alone. Progestins that are only offered without estrogen (for example, depot-medroxyprogesterone acetate, “Depo”) are not equivalent by weight to progestins in combined pills, and the side effects may vary accordingly. Even the side effects of a given dose of a specific progestin in a progestin-only contraceptive may differ from those that occur when it is delivered in a combined pill because of the interaction between the two steroids and the difficulty of attributing a nonfatal side effect to only one steroid or the other. The dosage sequence and mode of administration also affect contraceptive efficacy and concomitant side effects.

Further efforts to modify combined-pill formulations, balanced by continued caution (Djerassi 1992; Elstein 1994; Kaunitz and Ory 1997) regarding the potential drawbacks of dose reductions (loss of efficacy and breakthrough bleeding), have led to “lower-dose” or “ultra-low” combined pills (that is, 20 mcg and 25 mcg EE). Paired with estranes, trials of 20 mcg EE formulations were disappointing (see, for example, Sulak et al. 1999). Initial reports (Family Planning Digest 1973) suggested that the efficacy of these low-dose pills was poorer relative to other formulations, although subsequent clinical trials found their efficacy to be comparable (WHO 1982). Discontinuation rates, however, were higher as a result of bleeding disturbances, and in a study of follicular development (Grimes et al. 1994), reduced norethindrone doses were associated with a greater risk of developing ovarian structures >30 mm in size.\(^5\) These outcomes discouraged widespread use of lower-dose combined pills.

Pairing with gonanes has, however, produced much more satisfactory lower-estrogen-dose formulations (Foitherby and Caldwell 1994). A 12-country European trial found a 20 mcg EE/150 mcg desogestrel combined pill to be effective, safe, and well accepted; no serious side effects occurred, and bleeding was comparable to that of other low-dose pills (Lammers and op ten Berg 1991). In an evaluation of 20 mcg EE paired with either 75 mcg gestodene or 150 mcg desogestrel, none of the women ovulated or experienced any serious adverse effects (Fitzgerald et al. 1994). A vaginal ultrasonographic study concluded that 20 mcg EE/150 mcg desogestrel, compared with 35 mcg EE/250 mcg norgestimate, did not lead more often to ovarian follicles or cysts (Egarter et al. 1995).
More recently published results of several clinical trials in the United States (Archer et al. 1997 and 1999; Reisman et al. 1999; Rosenberg et al. 2000; LaGuardia et al. 2003; Poindexter et al. 2003) and Europe (Endrikat et al. 1995, 1997, 2001a, and 2001b; Akerlund 1997; Serfaty and Vree 1998) found that these formulations demonstrate acceptable cycle control and excellent contraceptive efficacy and safety, typically comparable to that of higher EE formulations. In some studies, lower-dose combined pill users were found to have lower rates of irregular bleeding, which may be related to the specific progestin in the combined oral contraceptive. Also, stricter compliance may be required for optimal cycle control for lower-dose than for low-dose combined pills (Rosenberg et al. 1996). Abdominal pain, which may indicate follicular growth and delayed atresia, was rarely or never reported by users of the lower-dose combined pill in these trials. In most studies, headache, nausea, and breast tenderness were lower with the use of lower-dose pills than with the use of higher EE formulations.

Some concern has been voiced that the benefits of lower-dose combined pills containing desogestrel or gestodene may be offset by a relatively greater risk of venous thromboembolism (VTE) compared with the risk from lower-dose combined oral contraceptives containing levonorgestrel. Several reports and counterreports have appeared since 1995, and this controversy is yet to be resolved (Hatcher et al. 1998; Kaunitz 2004). The risk of VTE, however, is lower for any of these formulations than it is during pregnancy (Huezo 1998). Moreover, myocardial infarction may be lower among users of desogestrel or gestodene relative to users of levonorgestrel or norgestimate, thus shifting the risk–benefit evaluation (Kaunitz 2004).

Today, the most widely used combined oral contraceptives contain 30 mcg or 35 mcg EE, less than one-fourth by weight of the original estrogen dosage of 150 mcg mestranol. With respect to bioavailability, a 35 mcg EE dose is about one-third that of the original formulation (Brody et al. 1989; Goldzieher and Brody 1990). By weight, the progestin component of current low-dose combined pills is no more than one-tenth that of the original formulations and, in some formulations, is as low as one-sixtieth (0.15–1.0 mg; Hatcher et al. 1998). Some gonanes may be as much as 20 times more potent than the estranes used in early formulations, however. Hence, with respect to potency, progestin doses in some combined pills may be as high as ever (Gerstman et al. 1991).

Of 68.5 million annual oral contraceptive prescriptions filled in the United States during 1998, 47 percent were for combined pills with 35 mcg EE, 43.4 percent contained 30 mcg EE, 8.2 percent contained 20 mcg EE, and 1.4 percent contained 50 mcg EE or mestranol (The Contraception Report 1999c). Upon introduction to the United States, lower-dose combined pills were generally seen as a second choice for those women who had proved to have poor tolerability of higher-dose formulations (Kaunitz and Ory 1997). Opinion is growing, however, that they can be recommended to first-time oral contraceptive users (The Contraception Report 1997 and 1999c). Lower-dose combined pills have a larger share of the market in Europe, where they have been available for much longer than in the United States and where physicians are less reluctant than doctors in the United States to prescribe them (Fotherby and Caldwell 1994). The United States Agency for International Development (USAID), a major supplier of oral contraceptives worldwide, distributes a combined pill containing 30 mcg EE/300 mcg norgestrel and a progestin-only pill (Spierer 2004).

In sum, the greatest reduction in the estrogen dose of combined pills had occurred by 1970 (50 mcg mestranol). Ethinyl estradiol formulations are approximately 100 percent (35 mcg), 86 percent (30 mcg), 71 percent (25 mcg), and 57 percent (20 mcg) biologically equivalent to 50 mcg mestranol. Currently available progestins differ greatly in their pharmacokinetics and are not equivalent by weight. The choice of compounds, the dosage, the sequence of administration, and the mode of delivery influence contraceptive efficacy and concomitant side effects. Depending upon the specific formulation, many women worldwide may be receiving combined pills with steroid dosages biologically equivalent to those commonly prescribed in 1970. Despite changes in formulations, contemporary hormonal contraceptive discontinuation rates attributable to side effects and health concerns are generally high in less-developed countries.

**Discontinuation Rates in Less-developed Countries**

*Survey results are the bones of any topic; the “flesh” comes from listening to people with direct experience.*

(Widyantoro 1994:24)

Some Demographic and Health Surveys (DHS 2004) document the extent of contraceptive discontinuation within the first 12 months of initiation and the reasons for stopping. Data on oral contraceptives are available for 18 less-developed countries; in cases of multiple national surveys, we selected the most recent for our analyses (see Table 1). Figure 1 shows the first-year discontinuation rate for oral contraceptives for these countries, regardless of the reason for stopping, and the discontinuation rate attributed to “side effects/health concerns.” These
rates refer to episodes of oral contraceptive use ("OC-episodes") initiated during a period of approximately five years prior to the survey (that is, a respondent may report on her multiple experiences during that time frame; see Blanc and colleagues [2002] for a description of the data-collection procedure). The reasons for discontinuation are modeled as competing risks (that is, they are multiple-decrement, or net, rates).

For 17 of these 18 countries (excluding Zimbabwe), from 33 percent to 73 percent of OC-episodes were discontinued within the first 12 months of initiation. Between 10 percent and 36 percent of all OC-episodes were reported to have ended because of side effects/health concerns; in most countries, side effects/health concerns constituted the most frequently cited reason for discontinuation. Excluding OC-episodes terminated because of the woman’s desire to become pregnant, in every surveyed country at least 30 percent of terminated OC-episodes were attributed to side effects/health concerns (as shown in Figure 2). In eight of the 18 surveys, side effects/health concerns were cited as the reason for discontinuance in at least 50 percent of the terminated OC-episodes.

The discontinuation patterns observed for oral contraceptives are also apparent in the DHS data on injectable contraceptives (Table 1).

Table 1  Rates of contraceptive discontinuation within first 12 months of initiation, by country and survey date, according to method and reason for discontinuation

<table>
<thead>
<tr>
<th>Country/survey date</th>
<th>Pill</th>
<th>Injectable</th>
<th>IUD</th>
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<tbody>
<tr>
<td></td>
<td>To become</td>
<td>To become</td>
<td>To become</td>
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<tr>
<td></td>
<td>pregnant</td>
<td>pregnant</td>
<td>pregnant</td>
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<td></td>
<td>Side effects,</td>
<td>Side effects,</td>
<td>Side effects,</td>
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<td></td>
<td>health concerns</td>
<td>health concerns</td>
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<tr>
<td></td>
<td>All reasons</td>
<td>All reasons</td>
<td>All reasons</td>
</tr>
<tr>
<td>Bangladesh 1999/2000</td>
<td>7.6</td>
<td>22.0</td>
<td>46.3</td>
</tr>
<tr>
<td>Bolivia 1994</td>
<td>4.4</td>
<td>36.0</td>
<td>58.9</td>
</tr>
<tr>
<td>Brazil 1996</td>
<td>5.0</td>
<td>11.8</td>
<td>44.8</td>
</tr>
<tr>
<td>Colombia 2000</td>
<td>7.0</td>
<td>17.0</td>
<td>49.7</td>
</tr>
<tr>
<td>Dominican Republic 1999</td>
<td>7.8</td>
<td>26.2</td>
<td>60.4</td>
</tr>
<tr>
<td>Egypt 2000</td>
<td>7.5</td>
<td>21.1</td>
<td>48.4</td>
</tr>
<tr>
<td>Guatemala 1998/99</td>
<td>8.0</td>
<td>28.1</td>
<td>51.4</td>
</tr>
<tr>
<td>Indonesia 1997</td>
<td>10.4</td>
<td>11.4</td>
<td>33.9</td>
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<tr>
<td>Jordan 1997</td>
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<td>67.9</td>
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<td>11.2</td>
<td>37.4</td>
</tr>
<tr>
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<td>18.6</td>
<td>49.2</td>
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<td>60.0</td>
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<td>Zimbabwe 1999</td>
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— = Not applicable.

Figure 1  Oral contraceptive discontinuation rates within first 12 months of use, 18 less-developed countries
able hormonal methods, available for 12 of the 18 countries listed in Table 1. Excluding episodes terminated because of a wish to become pregnant, side effects/health concerns were reported as the reason for stopping for 46 percent to 79 percent of the discontinued injection-episodes (see Figure 2). The median rate of discontinuation for these 12 surveys is 60 percent.

In comparison, within any country except Bangladesh and Morocco, the rate of discontinuation for the IUD (ranging from 9 percent to 34 percent across 14 countries) is less than half of that for hormonal contraceptives (as shown in Table 1). In every survey, at least 56 percent of the terminated IUD-episodes (excluding those that ended because of the woman’s wish to become pregnant) were reported to have ended because of side effects/health concerns, a pattern we discuss further below. The relatively lower rate of IUD termination that is, nevertheless, accompanied by a high attribution to side effects/health concerns illuminates the need for caution in interpretation of these survey data. Nonetheless, the DHS data show that discontinuation rates of hormonal contraceptives are generally high, and that side effects and health concerns are the major reason reported for discontinuation of hormonal methods among women in less-developed countries. Ali and Cleland (1995) reached comparable conclusions based on survey data. The relatively lower rates of IUD termination compared with termination of hormonal methods (for example, oral contraceptives). Hence, the longer-acting method would be biased toward a lower discontinuation rate. Analyses of the 1997 DHS data from Indonesia confirmed that method choice is endogenous to contraceptive discontinuation in that population (Steele and Curtis 2003). In addition, these analyses suggested that women who choose IUDs or implants rather than pills or injectables are, contrary to the prediction above, at a higher risk of abandoning use. Nevertheless, when this endogeneity is controlled for, discontinuation of IUDs or implants is still significantly lower than for pills or injectables (Steele and Curtis 2003). The analyses also indicated that older users are more likely than younger users to abandon contraceptive use. These observations cannot be extrapolated directly to other settings, but the authors noted that simpler analytical approaches that do not control for endogeneity “are unlikely to be wildly misleading . . . for descriptive purposes” (p. 20).

The analyses discussed above highlight the difficulties of making generalizations about the causes of contraceptive discontinuation, especially generalizations based on survey data. The relatively lower rates of IUD termination compared with termination of hormonal contraceptive use in any given country may reflect lower experience of side effects, user’s age, ease of discontinuation, access to health facilities, or family-size goals. Ali and Cleland (1995) found, however, that in the six DHS they analyzed, even among those who had achieved or exceeded their desired family size, the IUD was used for much longer durations than the pill (20 percent to 36 per-

Figure 2  Percentage of contraceptive episodes that were discontinued within first 12 months of use because of side effects/health concerns versus percentage of all episodes discontinued (excluding those episodes terminated because of the woman’s wish to become pregnant), by method type, 18 less-developed countries

Note: The graphed lines delineate the proportion of discontinued episodes that were terminated because of side effects/health concerns.
cent of pill users discontinued use within 12 months of acceptance, compared with 6 percent to 19 percent of IUD users. They also reported that “problems of availability and access [and also cost] were rarely mentioned” as a reason for discontinuation (p. 95). In addition, urban–rural differences in pill discontinuation (which might be expected if access affected continuation) were negligible in four of those six countries (Ali and Cleland 1995).

Among IUD users, the high rates of discontinuation attributed to side effects suggest that the side effects experienced are serious enough to warrant removal of the device and/or that this justification for wanting to have the device removed may attract the greatest attention from health providers. Based on in-depth interviews, Hull (1998) reported that Indonesian women had problems having IUDs and implants removed at health centers. In Thailand, women were told that implants would not be removed for minor side effects (Zimmerman et al. 1990). As we discuss below, what constitutes a “minor” side effect is a matter of personal experience and interpretation. Compared with IUD-episodes, a higher proportion of oral contraceptive and injection episodes are terminated because of the woman’s reported desire to become pregnant. This differential may occur principally because those women choosing the IUD have completed their families and have less desire to become pregnant again at the time they choose a method. As the analyses of Indonesian data (Steele and Curtis 2003) suggest, other factors may also play a role. For example, attributing discontinuation of oral contraceptive use to a desire to become pregnant may be one way that some women avoid being pressed to tolerate side effects that they find unacceptable.

Unfortunately, we know too little about the experience of contraceptive use from the perspective of the user (Hardon 1997). Without population-specific studies, it is difficult to add any flesh to the bones afforded by an examination of DHS data. As Blanc and her colleagues (2002) noted, however, it is logical to assume that women report the reason for discontinuing that is the most salient for them. While urging caution in interpretation, Ali and Cleland (1995:92) argue, “...there is no reason to believe that discontinuation probabilities calculated from [DHS] data are not broadly correct or that the large differences among methods and countries are not valid.” Therefore, we can reasonably conclude from the DHS data presented in Table 1 that side effects and health concerns constitute a major reason for hormonal contraceptive discontinuation in developing countries.

This conclusion is supported also by studies conducted in Brazil (Janowitz et al. 1986), Egypt (Trottier et al. 1994), New Zealand (Trlin and Perry 1982), and Thailand (Sunyavivat et al. 1983), all of which found the occurrence of side effects to be a major factor affecting oral contraceptive continuation. Although all of these reports are drawn from data gathered before 1990, when available dosages may have been higher, more recent studies continue to find that side effects are a major reported reason for cessation of oral contraceptive use. For example, in a survey conducted in rural Bangladesh, 53 percent of women discontinuing use of the pill did so because of side effects; women who experienced side effects were 1.4 times more likely to terminate use than were those who had not (Khan 2001). In a comparison of Bangladeshi oral contraceptive users, after six months, one-third of those on a low-dose regimen discontinued use while nearly half of those on a (formerly) standard higher dose had terminated use. Nausea and headache were the chief complaints leading to discontinuation (Akhter et al. 1996). Even for the lower-dose regime, 45 percent stopped using the method within 12 months of initiation, more than half attributing this decision to side effects and health concerns (Blanc et al. 1999).

Discontinuation rates obtained from clinical trials are typically much lower than those discussed above. The report of the ESHRE Capri Workshop Group (2000) specifically noted, however, that data from clinical trials are generally short-term and not representative. Enrolled subjects are typically committed to a fixed interval of use within the duration of the trial, agree to additional follow-up, accept an uncertain treatment allocation (in randomized clinical trials), and usually receive considerable attention by project staff motivated to maintain subjects’ participation. Exclusion and inclusion criteria with regard to age, medical and contraceptive history, current disease or illness, and use of medication are strictly defined (Oddens 1999). Participants in clinical trials are not typical users of oral contraceptives. Yet even within the constraints of clinical trials, side effects are a major reason for discontinuation among those who withdraw. During one 12-month clinical trial at five clinics in Costa Rica, Egypt, Mexico, Sri Lanka, and Yugoslavia (McLaurin and Dunson 1991), 26 percent of 1,602 women discontinued using oral contraceptives. Of discontinuers not wishing to become pregnant, 34 percent stopped because they experienced side effects. In a six-cycle trial in Thailand (Koetsawang et al. 1995), the total dropout rate was about 13 percent; side effects accounted for about half of the discontinuation rate among those reporting a reason for dropping out.

In short, the evidence suggests that the experience of side effects is a major reason for discontinuing use of hormonal contraceptives. Perhaps differences between the discontinuation rates observed in clinical trials and those of other users have contributed to the attitude that women’s reports of side effects are exaggerated or fan-
ciful. Because subjects in clinical trials are not representative of all women, however, inferences regarding rates of and reasons for discontinuation must be judicious. Acknowledging that among typical users the reported side effects are, in large measure, actually experienced is a critical step in meeting women’s contraceptive needs.

Minor by What Measure?

Good client–provider interaction has been associated with higher levels of oral contraceptive continuation (Cotton et al. 1992; Koenig et al. 1997; Blanc et al. 2002; RamaRao et al. 2003; RamaRao and Mohanam 2003). Women who were counseled on potential side effects—what to expect and how to cope with them should they occur—are more likely to continue with the method than those not so forewarned (Lei et al. 1996; Canto de Cetina et al. 2001; Sanogo et al. 2003). Thus, efforts to improve compliance and continuation of hormonal contraception have encouraged improvements in counseling to help clients learn to anticipate and manage side effects (Jain 1989; Bruce 1990; Rosenberg et al. 1995b and 1998; ESHRE Capri Workshop Group 2000; Yuzpe 2002). These and other advancements in the quality of care are important contributions to serving the clients’ health. A preferential emphasis on counseling assumes, however, that side effects associated with hormonal contraception are minimal and manageable.

The bulk of epidemiological evidence finds that the risks of potentially life-threatening side effects (for example, cardiovascular disease and cancer) attributable to hormonal contraceptive use are, in fact, minimal (Huezo 1998). Far less attention has been given, however, to evaluating the risks, severity, and impacts of nonfatal sequelae (for example, headache). These effects are consistently described in the literature as “minor” or “nuisance” factors, and some authors have gone so far as to ask “where’s the beef?” in terms of “real” side effects (Goldzieher and Zamah 1995). Researchers often attribute women’s beliefs about modern contraceptives to myth and hearsay rather than to experience (Djerassi 1992; Hardon 1992; Watkins 1998). Some have speculated that the research instruments examining contraceptive-use dynamics may exaggerate health concerns as a cause of discontinuation among women who may, in fact, have complex, multidimensional reasons for stopping (Phillips et al. 1990).

In sum, whether given credence or dismissed as imagined, nonfatal side effects are generally considered to be tolerable according to providers. Clients, however, may not experience such side effects as either minor or manageable. That substantial proportions of users elect to discontinue hormonal methods despite their high efficacy suggests that, for many women, the costs engendered by nonfatal side effects outweigh the benefits of these contraceptives.

The DHS do not collect data on the specific nature of the side effect or health concern that prompted respondents’ termination of hormonal contraceptive use. In smaller studies and clinical trials, women reported headaches, nausea, vomiting, changes in vaginal bleeding, mood changes, decreased libido, and breast tenderness as associated with hormonal method use (Hardon 1992 and 1997; Hatcher et al. 1998), but data are rarely collected on the frequency and severity of the side effect or its impact on well-being or quality of life. The failure to probe more deeply into why these side effects prompt discontinuation may reflect several implicit, and likely unsupported, assumptions regarding the severity, persistence, impact, and meaning of side effects in different sociocultural contexts. A growing body of evidence, principally from industrialized countries, suggests that the impacts of common ailments, similar to those associated with hormonal contraceptive use, have long been underappreciated. Seemingly minor afflictions can impose severe limitations on productivity, social relations, and the capacity to function normally in daily life.

Headaches, for example, affect the quality of an individual’s life and have measurable economic consequences. In a random survey of nearly 29,000 working adults in the United States, headache was the most common pain condition to result in lost production. Workers suffering from headache during a two-week period averaged a loss of 3.5 hours per week of productive work time, principally as a result of reduced performance rather than absenteeism (Stewart et al. 2003). Similarly, another study (Schwartz et al. 1997) found that among those workers having nonmigraine headaches, reduced performance accounted for the majority of lost productivity. In a study of college students in the United Kingdom, 21 percent reported having experienced headaches that had a negative impact on their quality of life (Kernick and Reinhold 2002). Particularly relevant to headache associated with hormonal contraception, the impact of a headache is not a straightforward reflection of its severity. Headache-associated disability and affective distress, in addition to pain density, are independent factors correlated with headache-impact measures (Holroyd et al. 1999). A study conducted in Spain revealed that headache chronicity had a greater impact on quality of life than did intensity of pain (Guitera et al. 2002).

Nausea and vomiting are also common side effects associated with hormonal methods, the impact of which has likely been underestimated. Studies among pregnant women find that nausea and vomiting symptoms are worse than generally believed, that their severity correlates with psychiatric morbidity, and that these symp-
toms have a profound impact on daily functioning and well-being (O’Brien and Naber 1992; Smith et al. 2000; Swallow et al. 2004). In the general population of the United States, dyspepsia (that is, nausea, sour stomach, indigestion) is common. Although it is associated with diminished quality of life and significant morbidity, it is underinvestigated (Majumdar et al. 2003).

Changes in vaginal bleeding are perhaps better recognized as a significant problem for women using hormonal contraceptives (Rosenberg and Long 1992; Hardon 1997). Maintaining acceptable bleeding patterns among users of hormonal contraceptives is one of the greatest challenges to the design of these methods, because of both the range of possible changes (amenorrhea; excessive and/or unpredictable flow) and the complexity of the underlying physiology. Early-cycle breakthrough bleeding or spotting typically results from inadequate estrogen dosage, whereas bleeding or spotting late in the cycle suggests an unduly high estrogen dose (The Contraception Report 2004). Clinicians in the United States make use of the timing of bleeding to adjust hormonal dosages appropriately to their clients’ needs, but relatively few providers in less-developed countries would have the means to make such accommodations for their clients. Most reports of hormonal contraceptive side effects do not distinguish the timing of breakthrough-bleeding events. In one of the few direct comparisons undertaken in the United States between 20 mcg EE and 35 mcg EE combined oral contraceptives (Rosenberg et al. 2000), users of the higher dose had a slightly lower prevalence of bleeding, but “those women that bled did so for a longer duration.” The authors draw attention to the lack of “clinical data that indicate whether duration, severity, or the simple occurrence of unscheduled bleeding is best correlated to user satisfaction” (Rosenberg et al. 2000:327).

Little is known about why changes in vaginal bleeding pose difficulties and how these may vary in different sociocultural contexts. For example, a lack of menstrual bleeding is often listed as a benefit of the use of some hormonal methods. In the Philippines, however, and perhaps throughout peninsular Southeast Asia, any reduction in menstrual flow is interpreted as a failure of the normal cleansing of a woman’s internal body, necessarily perceived to have negative consequences for health and well-being (Henry 2001). Among some couples, sexuality may be affected by changes in vaginal bleeding patterns. A study of urban Hispanic men and women found that vaginal bleeding and spotting were associated with substantial reductions in genital sexual behaviors (Davis et al. 2002). The prolonged and/or irregular bleeding associated with the use of some hormonal methods might well prompt discontinuation of use among women experiencing such disruptions in sexual intimacy. Likewise, decreased libido that has been reported with hormonal contraceptive use may prove disruptive to sexual relationships and trigger discontinuation.

Mood changes are also frequently reported with hormonal method use (Egarter et al. 1999). Depression, although often included among “minor” side effects of use alongside edema and headache (see, for example, Hirvonen et al. 1995), is nonetheless a serious side effect and one of the most commonly reported drug-induced psychiatric symptoms (Kendler et al. 1988).

Clearly, nonfatal side effects need not be insignificant. The magnitude of their significance for hormonal contraceptive users remains to be determined. The authors’ search of the published literature did not uncover any systematic study of the frequency, persistence, severity, and impacts of headache or nausea among typical hormonal method users. Only slightly more information is available regarding the consequences of changes in vaginal bleeding patterns or mood, especially depression and decreased libido, that can accompany use. If the impacts of these nonfatal side effects mirror those of similar ailments in the general population, it is not surprising that some women find hormonal contraceptives untenable, or even intolerable, in the context of daily work demands and personal relationships.

Counseling and education must remain important components of contraceptive services. These approaches, however, will not solve the problem of bringing what providers perceive as minor side effects into line with what women find to be major difficulties.

The Pharmacology of Hormonal Contraception: Acknowledging Variation

The degree of interpatient and interpopulation variation in drug bioavailability and plasma concentrations should not be underestimated, nor should the pharmacologic, pharmaceutical, and clinical differences among contraceptive steroids. (Goldzieher 1989:1,263)

More than 20 years ago, pharmacokinetic studies of the absorption, distribution, clearance, and excretion of hormonal contraceptives quickly revealed substantial interindividual and interpopulational responses to identical doses of exogenous hormones (WHO 1978; Fotherby et al. 1979 and 1981; Goldzieher et al. 1980a and 1980b; Stadel et al. 1980; Fotherby 1983). Recognizing the significance of these findings for the potential reduction of undesirable side effects by means of decreasing hormonal dosages, Goldzieher and colleagues (1980a) encouraged further studies to elucidate the causes of the pharmacokinetic variation. Stadel and colleagues (1980:258)
sought to ascertain whether this variation might be associated with differences in “physical, behavioral, or other characteristics” of women. Finding substantial unexplained variation, they called for further studies, noting that differences among women yet to be determined might underlie differences among hormonal method users in “risk for adverse reactions” (p. 260). In addition, two early studies in Mexico (Bassol et al. 1984) and Thailand (Fotherby et al. 1980) demonstrated, albeit with small samples, that hormonal dosages then in use were unnecessarily high for achieving desired contraceptive efficacy in these less-developed countries and recommended reevaluating, and possibly reducing, contraceptive dosages.

Despite these studies’ findings, few authors subsequently considered whether physiological differences among women and populations may play a role in the experience or severity of side effects of hormonal contraceptive use. Goldzieher and colleagues (1980a) suggested that populational differences in hepatic metabolism may be involved and later proposed that variability in plasma levels (as much as a fourfold difference among populations) in response to identical estrogen doses could be attributed to differences in first-pass effect (that is, in hepatic metabolism; see Goldzieher [1989]). Koetsawang (1984) hypothesized that differences in body build, nutrition, and drinking and smoking habits between women of Asian and western European heritages might influence the incidence of certain estrogen-related side effects. Thromboembolic disease among users of hormonal contraceptives, for example, is much lower in the former populations than in the latter. The Koetsawang study also suggested that the incidence of nausea may be higher among Asian women because their mean body weight is lower. In an earlier study, Talwar and Berger (1977) observed that heavier women generally experienced fewer estrogen-related side effects such as nausea, headache, menstrual cramps, and breast discomfort than did lighter women.

More recently, Bergink and colleagues (1990) presented evidence that differences in first-pass effects are unlikely to be responsible for variation in pharmacokinetic responses to endogenous hormones. Goldzieher and Brody (1990:2,119) restated the need for further research on the role of nutrition, intestinal bacterial flora, genetic differences in metabolism, and “other as yet undiscovered influences on the metabolism” of exogenous hormones.” Drawing on medical literature that proposes an association between fat consumption and elevated estrogen levels and on small studies suggesting interpopulational differences in levels of endogenous progesterone, Bentley (1996) proposed that dietary differences among populations may be responsible for variation in the metabolism of both endogenous and exogenous hormones. As other researchers had proposed earlier (for example, Goldzieher 1989) and have pointed out more recently (for example, Dickey 2002), Bentley suggested that adjustments in hormonal contraceptive formulations that reflected this variation might reduce side effects.

Studies of the newest formulations for combined oral contraceptives suggest that successful accommodation of natural biological variation among women and populations is possible and warranted. As discussed above, clinical trials in the United States and Europe of combined pills containing 20 or 25 mcg EE paired with a gonane have proved these formulations to be efficacious with good cycle control in samples of women ranging in age from 17 to 49 years. Ovarian function, however, varies with age (Yen et al. 1999). From menarche through a woman’s early 20s, and again from her late 30s through menopause, her endogenous steroid levels are lower than during her peak reproductive years. Therefore, a given low-dose combined pill likely would be more efficacious and produce less breakthrough bleeding (a principal side effect associated with lower estrogen doses) among older and younger women than among women in the mid-range of their reproductive years. The available evidence supports this hypothesis. Fitzgerald and colleagues (1999) reported that 20 mcg EE/75 mcg gestodene resulted in relatively greater ovarian suppression among older women. In a clinical trial conducted in the United States of 20 mcg EE/100 mcg levonorgestrel (Carr and DelConte 2002), women older than 35 experienced substantially lower rates of breakthrough bleeding and spotting than did the sample as a whole (aged 17–49 years).

The few studies of lower-dose formulations among non-US/non-European populations document equally favorable or better outcomes compared with those of higher EE dosages. In Thailand, a clinical study of 20 mcg EE/150 mcg desogestrel used for 12 months among 146 women reported no conceptions, few side effects, and very low rates of irregular bleeding (Jaisamrarn et al. 2001). In Latin America, clinical trials of 20 mcg EE paired with 100 mcg levonorgestrel (Sartoretto and Ortega-Recio 1974), 150 mcg desogestrel (Bassol et al. 2000), or 75 mcg gestodene (Bassol et al. 2003) all reported high contraceptive efficacy, good cycle control, and few if any adverse effects. Bassol et al. (2003:371) concluded, “the 20 mcg EE oral contraceptive could be administered in the first line to Latin American women.”

Although published documentation is rare, the experiences of women who have switched from one formulation to another offers additional support for the hypothesis that appropriately adjusting steroid formulations may reduce combined-pill nonlethal side effects and hence discontinuation rates. A European clinical trial
of 30 mcg EE/75 mcg gestodene found that dysmenorrhea (painful menstruation) virtually disappeared among those who had previously experienced it when they used a different combined oral contraceptive (Brill et al. 1991). A Dutch study found that women who switched to a low-dose combined pill had significantly improved psychosocial functioning after three months of use compared with the moods they experienced prior to switching (Deijen et al. 1992). In a study conducted in the United States, 89 percent of those switching from 30–35 mcg EE combined pills to a 25 mcg EE/triphasic (180–215–250 mcg) norgestimate combined pill reported that they were very or somewhat satisfied, and 73 percent planned to continue with the new formulation (Poindexter et al. 2003). In a study in Bangladesh (Salway et al. 1994), new users of a low-dose method (35 mcg EE/500 mcg nor- ethindrone) had higher continuation rates at all times following adoption than those of new users of a standard-dose combined pill (50 mcg EE/500 mcg norgestrel). Perhaps the most convincing evidence of the importance of prescribing suitable steroid dosages is the observed increase in side effects in a study of discontinuation among Filipino women after they changed to using a combined oral contraceptive containing higher levels of progestin and estrogen than those in the pills they had used previously (Dickey et al. 1973).

The latest evidence suggests that when paired with newer progestins, estrogen doses can even be successfully reduced to as little as 15 mcg EE by using novel modes of administration or changing the administration sequence (EJCRHC 1999; Sullivan et al. 1999; van der Mooren et al. 1999; Fruzzetti et al. 2001; Roumen et al. 2001; Sitruk-Ware et al. 2003; Brincat et al. 2003). Of course, not all attempts to reduce steroid dosages have proved equally satisfactory. A study of the use of 20 mcg EE/50 mcg gestodene among 22 English and Austrian women demonstrated that this formulation failed to inhibit ovulation adequately compared with 20 mcg EE/75 mcg gestodene (Ludicke et al. 2001). The question arises, however, whether the lower formulation might have proved more effective among women in less-developed countries. Two studies of low-dose combined pills among Asian women in Malaysia (30 mcg EE/150 mcg desogestrel [Ismail 1994]) and Thailand (30 mcg EE paired with 150 mcg desogestrel or 75 mcg gestodene [Koetsawang et al. 1995]) and a study conducted in Mexico (30 mcg EE/75 mcg gestodene [Garza-Flores et al. 1994]) reported lower incidences of irregular bleeding compared with Caucasian women using these same formulations.

In sum, “fears that further lowering the estrogen dose [from 30 mcg] might compromise contraceptive reliability appear to have been unfounded” (Endrikat et al. 1997:131; Bassol et al. 2003). Despite more than 20 years of research documenting substantial interindividual and interpopulational differences in the pharmacokinetics of exogenous hormones, and despite calls to investigate these differences and their significance for the etiology of side effects, scant attention has been paid to these hypotheses. Pharmacokinetic studies have not focused on women’s individual levels of natural circulating hormones and whether variations in these levels may cause women to experience hormonal contraceptives differently, nor have investigations focused on whether differences occur across populations in the mean levels of circulating hormones that may be associated with the experience of side effects. Rather, the assumption generally is made that species-wide minimal levels of reproductive steroids are necessary for conception to occur and that all fecund women have levels of endogenous hormones above this minimum. New evidence, discussed below, demonstrates otherwise.

**Studies of Reproductive Hormones in Nonindustrialized Populations**

For a variety of reasons, measurements of reproductive steroids have typically been restricted to the laboratory study of relatively few subjects willing to give blood. Despite the small samples, findings from the earliest studies suggested significant interpopulational variation in reproductive steroids (for example, see Briggs and Briggs 1972), but it was difficult to expand this work more widely (see van der Walt et al. [1977] for a notable exception). However, the development of methods for measuring steroids in saliva, found to be well correlated with serum steroid levels (Malamud and Tabak 1993), has greatly expanded our ability to evaluate ovarian functioning in nonclinical settings (Seaton and Riad-Fahmy 1980; Ellisson 1988; Lipson and Ellisson 1989). Salivary sample collection is quick, easy, noninvasive, and acceptable even where cultural reservations exist about blood-sample collection; it does not require a coldchain (rapid refrigeration or freezing) and can be performed repeatedly throughout the day and/or every day throughout a cycle.

Despite the advantages of salivary assays, pituitary hormones (for example, luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) cannot be measured in saliva. Of the ovarian steroids, measurement of estradiol in saliva has proved difficult and expensive, but progesterone is relatively easier to assay. In the course of the menstrual cycle, progesterone is low and flat during the follicular (preovulatory) phase; it begins to rise at about the time of ovulation, peaking midway through the luteal (postovulatory) phase. If conception occurs, progesterone continues to rise from mid-luteal levels.
throughout gestation, peaking at birth. Without conception, progesterone and estrogen fall to basal levels at about the beginning of the next menses, thus initiating another cycle of follicle growth (stimulated by FSH) and ovulation (Yen et al. 1999).

The normal biological stimulus for ovulation is the midcycle surge in LH secretion. Via negative feedback, the rise in endogenous progesterone that occurs with conception and implantation suppresses the LH surge and, hence, prevents another ovulation during the current pregnancy (Yen et al. 1999). Estrogen, also at a relatively high level during pregnancy, exerts an inhibitory effect on FSH. In effect, hormonal contraception prevents follicular development and ovulation by mimicking these relatively high levels of endogenous steroids. Metaphorically, the body is tricked into responding as if the woman is pregnant (Rivera et al. 1999). The balance that must be achieved in contraceptive design is dosages of progesterin and estrogen sufficiently high to suppress ovulation yet low enough to avoid side effects. Thus, if significant variation exists among women and populations in the levels of endogenous steroids that are normally sufficient to suppress ovulation, a repertoire of hormonal contraceptives that more closely mimic that variation would reduce side effects while maintaining contraceptive efficacy.

In the late 1980s and early 1990s, studies of salivary progesterone in samples from agricultural populations in several countries—Bolivia (Vitzthum et al. 1994 and 2000), Nepal (Panter-Brick et al. 1993), Poland (Jasienska and Ellison 1993), and Zaire (Ellison et al. 1989)—suggested that levels of this steroid are far lower than those typically seen among women from Boston (Lipson and Ellison 1992). In fact, the average progesterone level in some of the agricultural populations was so low that many of the women would have been considered infecund had they been observed in a clinical setting in the United States. Hence, these lower levels of progesterone were considered indicative of subfecundity, perhaps because of a failure to ovulate rather than reflecting normal ovarian function in that agricultural population. If this were to be the case, these lower levels would not be an appropriate basis for designing hormonal contraceptive dosages.

Although theories were put forward to explain the observed lower steroid levels (Ellison 1990; Vitzthum 1990 and 1997), methodological limitations of the studies may have been responsible for the purported differences among populations. The samples were small, often comprised a high proportion of women at younger and older ages (when subfecundity is the norm), and did not always exclude anovulatory cycles. Moreover, the cross-sectional selection of currently cycling study participants in natural fertility populations, where fecund women are more likely to be pregnant or lactating, may have biased sample composition toward women of lower fecundity than the population’s norm. Finally, whether ovulation and conception could occur at these lower levels of progesterone was not known.

**REPA: A Longitudinal Study of Natural Progesterone Levels**

Correcting these limitations and ascertaining the significance of lower levels of reproductive steroids required a longitudinal study that measured progesterone levels among women representing different stages of the reproductive cycle while simultaneously testing for conceptions and subsequent pregnancy progression. To this end, Project REPA (Reproduction and Ecology in Provincia Aroma) was begun in 1995 in the Bolivian altiplano in a group of rural Aymara agropastoral communities (Vitzthum et al. 1998 and 2004).

Representing approximately 80 percent of the potential pool, 316 women aged 19–40 (only nine were either younger than 22 or older than 36), reporting stable sexual unions and no contraceptive use, were recruited. For all menstruating women, saliva samples were collected every other day throughout the menstrual cycle, and urine samples were collected for the detection of human chorionic gonadotropin (hCG), indicative of conception. Women were followed for up to six cycles or until conception occurred. All conceptions were followed until the birth of the child or through four weeks after fetal loss.

For comparison, two samples of urban Bolivian women—one comprising very poor women (urban-p, n = 30) and the other, better-off women (urban-b, n = 31)—were also recruited in La Paz, each woman providing salivary samples for two complete cycles (Vitzthum et al. 2002). Unlike samples used for previous cross-sectional studies, all of these women were between 23 and 35 years of age and reported regular menstrual cycling, no pregnancy or breastfeeding for at least the previous six months, no hormonal contraceptive use or other medications, and no noticeable weight change during that same period. A comparative sample of women living in Chicago, aged 23–39, having regular menstrual cycles from 25 to 35 days in length, and attempting to conceive, were also followed for collection of daily salivary samples and the regular collection of urine to detect conceptions (Lu et al. 1999). Exclusion criteria for the Chicago sample were: outside the normal body-mass index limits according to the Metropolitan Life Insurance tables, medication for chronic illnesses, use of oral contraceptives within the last three months, lactating within the last six months, evidence
of infertility, or presence of sexually transmitted diseases. All salivary samples from Bolivia and Chicago (n=11,000) were assayed by the same techniques in the same laboratory (Lu et al. 1999).

Figure 3 displays the average progesterone profiles for ovulatory cycles from these four samples (Vitzthum et al. 2002 and 2004), each of which has the postovulation rise, peak, and fall of progesterone described above. An index that summarizes the profile is mean-peak-luteal (mPL) progesterone, defined as \( \left[ \frac{1}{\text{days}} \sum \text{progesterone from } x \text{ to } y \right] \times (y-x) \), where \( x \) and \( y \) are the day of peak progesterone \( \pm 2.5 \) days, respectively. The Chicago sample has the greatest rise in progesterone (mean and standard error of the mean for mPL = 336 ± 29.1 pmol/L), a level similar to that observed among Boston women (Lipson and Ellison 1992). The three Bolivian samples are statistically comparable (mPL urban-p = 232 ± 14.0 pmol/L; mPL urban-b = 208 ± 16.9 pmol/L; mPL rural = 237 ± 7.5 pmol/L) and significantly lower than the Chicago sample (P < 0.0001). These findings suggest that lower progesterone levels, and perhaps levels of other reproductive steroids, are the norm for at least these Bolivian populations and perhaps for the populations of other less-developed countries. These data also suggest that, rather than representing a "normal" hormonal profile, the elevated levels seen among women in the United States may represent the high end of natural interpopulation variation in human reproductive steroids, a point made by all of the investigators conducting the earlier cross-sectional studies.

Figure 4 confirms that conception and subsequent implantation (taking place about eight to ten days after ovulation) occur among rural Bolivian women at relatively lower progesterone levels (63 percent and 42 percent, respectively) than among Chicago women (Vitzthum et al. 2004). Moreover, within each sample of women, a close match is found between the mean levels of progesterone in conception and nonconception ovulatory cycles at about the midpoint of the luteal phase; that is, within the same population, the progesterone profiles in Figure 3 are no lower than those levels observed in conception cycles.

In sum, these data confirm that progesterone levels are naturally lower among Bolivian than among North American women and suggest that reproductive steroids may also be lower among women in other less-developed countries. The REPA study unequivocally demonstrates that the endogenous progesterone levels necessary to suppress ovulation during pregnancy are relatively lower among the Bolivian women studied. This finding supports the hypothesis that for these and similar women, comparable contraceptive efficacy may be obtainable with hormonal contraceptive steroid dosages lower than those found in the most commonly prescribed combined-pill formulations. Use of formulations with lower
dosages would result in less risk of side effects and, perhaps, greater compliance and continuance, with all their attendant benefits.

Implications

Collectively, several lines of evidence argue for the necessity of evaluating directly the relationship between natural variation in endogenous reproductive steroids and the experience of nonfatal side effects associated with the use of hormonal contraceptives.

The impact of side effects on hormonal method use, in several populations at least, is apparent. DHS data, supported by other studies, demonstrate that discontinuation rates for hormonal methods are high and that health problems and the experience or fear of side effects are major factors in discontinuation among women in less-developed countries. The extent and impact of nonfatal side effects remain unknown among those who continue hormonal contraceptive use, some of whom may be sufficiently motivated to avoid an unwanted pregnancy despite negative experiences. This Hobson’s choice may place an untenable burden on both providers and clients to “manage” side effects. Inferring from assessments of similar ailments, side effects associated with hormonal contraceptive use may have a significantly negative impact on quality of life, including productivity and social relations. For women in less-developed countries, who often have demanding workloads and limited access to even rudimentary remedies such as aspirin, the consequences of hormonal contraceptive use may be difficult to manage.

Physiological evidence lends support to the hypothesis of a biological etiology for nonfatal side effects. Pharmacokinetic analyses reveal substantial interindividual and interpopulational variation in response to the administration of exogenous hormones. Project REPA’s longitudinal study of levels of endogenous progesterone among women at conception and throughout gestation confirms that the level of this steroid is naturally lower among Bolivian than among North American women. Whether such variation holds for women in other less-developed countries remains to be determined. The cross-sectional studies discussed above, though methodologically flawed, suggest this possibility. Furthermore, the potential causes of this variation (arguably, evolutionary adaptation to nutritional and workload stress during growth and development [Vitzthum 1990, 1997, and 2001]) are common in many less-developed countries. Therefore, relatively lower levels of progesterone, and perhaps other reproductive steroids, may be the norm among these women. If biological variation is the principal reason that hormonal contraceptive users have markedly different experiences of side effects, high discontinuation rates are unlikely to be ameliorated by counseling.

Population-level data reveal a high rate of discontinuation attributed to side effects among Bolivian users of oral contraceptives, a predictable response to use if the dosages of exogenous hormones these women receive are inappropriately high relative to their typical levels of endogenous hormone. According to the 1994 Bolivia DHS (the 1998 Bolivia DHS did not collect reasons for discontinuation), the 12-month discontinuation rate for oral contraceptives was 59 percent, of which nearly 61 percent was attributed to side effects and health concerns. During Vitzthum’s periods of fieldwork in Bolivia (from 1989 to the present), both women and health-care workers complained about problems with side effects of the pill. Such negative experiences with oral contraceptives among the 13 percent of Bolivian women who have ever used them may also contribute to the low rate of use of this method (4 percent) among currently married women. The plurality of users (22 percent) rely on substantially less-effective periodic abstinence (BDHS 1998). For Bolivian women, the health consequences of reliance on a less-effective method, coupled with low use and high discontinuation of effective methods, include an unwanted total fertility rate of nearly two births per woman, the highest among 15 countries in a recent DHS comparative analysis (Blanc et al. 1999). Blanc and her colleagues (1999) estimated that in the absence of method failure or discontinuation, total unwanted fertility could be reduced by 54 percent.

Although many gaps remain in our understanding, current evidence is sufficiently compelling to warrant additional investigation into both interindividual and interpopulational variation in endogenous steroids and into whether such variation is associated with higher rates of hormonal contraceptive side effects and discontinuation. The required study would examine endogenous levels of reproductive steroids among individual women before the initiation of hormonal contraception, measure the pharmacokinetics of exogenous hormones, monitor the occurrence of side effects, and ascertain whether a relationship exists among individuals between endogenous hormone levels and the experience and severity of side effects.

Although an ideal contraceptive may be an impossible goal (Elstein and Furniss 1996), nonetheless, clearly, one pill does not suit all women. Even within industrialized populations, practice guidelines dictate that selection of a specific oral contraceptive for an individual varies depending upon the client’s past use, experience of side effects, and medical history (Burkman 1997). For any woman anywhere, the most suitable contraceptive
reflects a set of tradeoffs. Some women may prefer a hormonal contraceptive that produces few side effects even if its efficacy is less than that of another method. Others may prefer bleeding irregularities to headaches. Still others may be willing to tolerate any side effect so long as the risk of pregnancy is as low as can be had without recourse to sterilization. The decision regarding the right balance among these tradeoffs must rest with the user. Understandably, faced with limited resources and the needs of many women, some policymakers and health-care providers may conclude that the hormonal contraceptives having the greatest efficacy are to be preferred. An individual woman, experiencing the impact of exogenous steroids on her body and her quality of life, may disagree. A perfectly efficacious contraceptive, if misused or discontinued because of unacceptable side effects, will achieve neither personal nor policy goals. The authors’ intention here is not to advocate lower-dose hormonal contraceptives for all women; for some, such a reduction might carry an unacceptable increase in the risk of becoming pregnant. Rather, we are proposing that dosages that are a closer match to a woman’s endogenous steroid levels would result in fewer side effects and hence greater compliance and continuation, thereby increasing the concomitant benefits of hormonal contraceptive use.

With further evidence in support of the hypothesis that variation in endogenous steroids is a significant factor affecting the experience of side effects associated with hormonal contraceptives, pharmaceutical manufacturers may be able to tailor dosages more closely to the typical endogenous hormonal profile of a given population, thereby enhancing contraceptive acceptability without reducing its efficacy. From a user’s perspective, quality of life would be enhanced and method satisfaction improved by a superior product with less likelihood of producing side effects. Greater satisfaction would be reflected in higher contraceptive continuation that, in turn, would lead to fewer unintended pregnancies and induced abortions. Service providers would spend less time addressing method dissatisfaction and method switching. Manufacturers would gain a larger market. Improvements of hormonal contraceptives that reflect individual and populational biological variation would have beneficial outcomes for all concerned.

Notes

1 First-generation progestins were classified by some as second generation when paired with <50 mcg EE (The Contraception Report 1999a).

2 Norgestimate has been variously classified as either second or third generation (The Contraception Report 1999a).

3 Some controversy has arisen regarding the significance of relative binding affinity for comparing the contraceptive pharmacology of the progestins (Fotherby and Caldwell 1994).

4 Much remains to be learned about the nature and causes of bleeding changes resulting from hormonal contraceptive use. Most studies do not distinguish between late- and early-cycle breakthrough bleeding, although the clinical approaches to the two types are diametrically opposed (The Contraception Report 2004).

5 An international expert panel defined ovarian cysts as only those structures >35 mm and persistent for more than four weeks (Contraception 1992).

6 A new study (Holt et al. 2005) of women in the United States finds that the risk of pregnancy among consistent users of the pill is more than doubled for women with a body mass index (BMI = weight in kg/height in meters squared) greater than 27.3, compared with those with a BMI below this threshold. The reasons for the increased risk are unknown, but it may be that endogenous hormone levels are naturally higher among women of greater weight-for-height, and hence standard contraceptive dosages are less likely to suppress ovulation. Compared with the United States population, in less-developed countries a higher proportion of the population has relatively low weight-for-height. Therefore, standard oral contraceptive dosages may be unduly high for some women.

7 Only progesterone levels in ovulatory cycles should be compared. If nonovulatory cycles are included in the comparison, progesterone levels among poorer urban Bolivian women are even lower than among women in the other samples.

8 Evaluation of a woman’s endogenous hormonal profile before she begins use of a hormonal contraceptive would be of great value. Simple tests of this type are not available, however. All such tests require a laboratory assay of some bodily fluid (saliva, blood, or urine). Moreover, the daily fluctuation of hormones over the cycle coupled with pulsatile release of endogenous hormones means that several assays would be required to characterize a woman’s hormonal profile. In general, within a population, younger and older women, shorter women, thinner women, and women with shorter periods of menstrual bleeding are likely to have relatively lower progesterone levels. Reliable inferences cannot be made, however, about an individual on the basis of these attributes. For example, within every population, men are, on average, taller than women. Because of the substantial overlap in height between the two sexes, however, the sex of an individual cannot be inferred from height.

References


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