Progestin-Only Oral Contraception:
A Comprehensive Review

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# Abbreviations

## Exogenous Hormones

### Progestins

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<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>CA</td>
<td>chlormadinone acetate</td>
</tr>
<tr>
<td>DMPA</td>
<td>depot medroxyprogesterone acetate (Depo-Provera®)</td>
</tr>
<tr>
<td>DG</td>
<td>desogestrel</td>
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<tr>
<td>ED</td>
<td>ethynodiol diacetate</td>
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<tr>
<td>LNG</td>
<td>levonorgestrel</td>
</tr>
<tr>
<td>LYN</td>
<td>lynestrenol</td>
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<tr>
<td>MPA</td>
<td>medroxyprogesterone acetate</td>
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<tr>
<td>MA</td>
<td>megestrol acetate</td>
</tr>
<tr>
<td>NA</td>
<td>norethindrone acetate</td>
</tr>
<tr>
<td>NET</td>
<td>norethindrone/norethisterone</td>
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<tr>
<td>NEL</td>
<td>norethynodrel</td>
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<tr>
<td>NG</td>
<td>norgestrel</td>
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<tr>
<td>QA</td>
<td>quingestanol acetate</td>
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### Estrogens

<table>
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<th>Abbreviation</th>
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<tr>
<td>EE</td>
<td>ethinyl estradiol</td>
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<td>ME</td>
<td>mestranol</td>
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### Other

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CIN</td>
<td>cervical intraepithelial neoplasia</td>
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<tr>
<td>COC</td>
<td>combined oral contraceptives</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>EP</td>
<td>ectopic pregnancy</td>
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<tr>
<td>FSH</td>
<td>follicle stimulating hormone</td>
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<td>hCG</td>
<td>human chorionic gonadotropin</td>
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<tr>
<td>HDL</td>
<td>high density lipoprotein</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HL</td>
<td>hepatic lipase</td>
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<tr>
<td>HRT</td>
<td>hormone replacement therapy</td>
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<tr>
<td>IUD</td>
<td>intrauterine (contraceptive) device</td>
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<tr>
<td>LDL</td>
<td>low density lipoprotein</td>
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<tr>
<td>LH</td>
<td>leutinizing hormone</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>OC</td>
<td>oral contraceptive</td>
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<td>OR</td>
<td>odds ratio</td>
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<td>PID</td>
<td>pelvic inflammatory disease</td>
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<tr>
<td>POP</td>
<td>progestin-only pill (oral contraceptive)</td>
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<td>RR</td>
<td>relative risk</td>
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<td>SHBG</td>
<td>sex hormone binding globulins</td>
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<td>STD</td>
<td>sexually transmitted disease</td>
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<td>TBG</td>
<td>thyroid binding globulin</td>
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<td>TSH</td>
<td>thyroid stimulating hormone</td>
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<td>T₃</td>
<td>triiodothyronine</td>
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<tr>
<td>T₄</td>
<td>thyroxine</td>
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<tr>
<td>VLDL</td>
<td>very low density lipoprotein</td>
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<td>Acronym</td>
<td>Full Name</td>
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<tr>
<td>ACOG</td>
<td>American College of Obstetrics &amp; Gynecology</td>
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<tr>
<td>INTRAH</td>
<td>Program for International Training in Health</td>
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<td>IPPF</td>
<td>International Planned Parenthood Federation</td>
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<td>OFPA</td>
<td>Oxford Family Planning Association</td>
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<tr>
<td>PPFA</td>
<td>Planned Parenthood Federation of America</td>
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<tr>
<td>RCGP</td>
<td>Royal College of General Practitioners</td>
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<tr>
<td>U.S. AID</td>
<td>U.S. Agency for International Development</td>
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<td>U.S. FDA</td>
<td>U.S. Food and Drug Administration</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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I. INTRODUCTION

A. Usage of Progestin-Only Pills

The purpose of this review is to provide the background for package insert labeling of progestin-only oral contraceptives in the United States. Current labeling for oral contraceptives (OCs) does not distinguish between combined OCs (COCs) and progestin-only pills (POPs), and it is based on information about combined OCs. It thus does not accurately reflect the risks and benefits of POPs. This review focuses on the two POP formulations currently marketed in the United States: norgestrel (NG) 0.075 mg and norethindrone (NET) 0.35 mg.¹

Progestin-only pills are particularly suited for women who have contraindications to the estrogen in combined oral contraceptives, for breastfeeding mothers, and for older women. POPs not only lack the estrogen component of COCs but also have a lower dose of progestin² and thus have sometimes been called "minipills;" they therefore may also be the method of choice for women who simply wish to minimize their total hormone intake below that of the already-low doses in COCs. POPs are clearly the preferred type of formulation for breastfeeding mothers who desire oral contraception (see Section XI), because progestins do not inhibit milk production (which estrogens have been shown to do) and because the dose of hormone that is transmitted to the infant through breast milk is less than with COCs. The primary disadvantages of the POPs are that (1) high efficacy is achieved only by careful compliance in taking the pills (Section IV) and (2) abnormal patterns of

¹The norgestrel formulation is available as Ovrette from Wyeth-Ayerst Laboratories, and the norethindrone formulation is sold as Micronor by Ortho Pharmaceutical Corporation and as Nor-QD by Syntex Laboratories.

²Low-dose combined OCs, with 0.03-0.035 mg ethinyl estradiol (EE) or 0.05 mg mestranol (ME), typically contain 0.30 mg NG or 0.5-1.0 mg NET.
vaginal bleeding are common (Section X). These factors may be of less concern to breastfeeding women and to older women, because in both of these situations fecundity is lower and changes in bleeding patterns are less unexpected. POPs are particularly advantageous for women over age 35 who smoke, because of the lack of thrombolic effects associated with progestins. (See Sections V and VI.)

The prevalence of POP use varies widely among countries, in part because of varying levels of awareness about their advantages and disadvantages. According to sales data from pharmaceutical companies, 15% of OC sales in Sweden are for POPs, compared to 6% in Finland and 3% in France. In Great Britain, the percentage of oral contraceptive users who take pills containing only progestin has increased steadily from less than 1% in the early 1970s to 7.5% in 1993; the sales of combined OCs have also increased in this time period, so the absolute number of POP users has risen substantially (Thorogood & Vessey, BJFP, 1990). The percentage of British OC users who had POPs prescribed in 1987 also rose with age, from less than 10% among women under age 30 to about 20% at ages 30-39 and half of OC users ages 40-54.


In the United States, POPs are only a small part of the OC market, with less than 1% of OC users taking POPs (Forrest, 1990; Piper & Kennedy, 1987). Pharmaceutical sales figures for 1993 put the current rate at 0.2%. Yet, where providers are familiar with prescribing POPs, prevalence may be
much higher; for example, one third of OC acceptors at Grady Memorial Hospital Family Planning Clinic in Atlanta were using POPs in 1988, most often because of estrogen-related side effects or contraindications to use of COCs (Hatcher et al., 1988).

Future trends in POP use in the U.S. may be influenced by the changing age distribution of women and the availability of other progestin-only methods. Recent projections indicate that during the next two decades increasingly larger percentages of U.S. women will be in the upper end of the reproductive age span (Trussell & Vaughan, 1992). The contraceptive choices of these older women in the future is uncertain, but will presumably be affected by such factors as the 1989 removal of the upper age limit for combined OC use by the U.S. Food and Drug Administration (U.S. FDA), the trend toward delayed childbearing and sterilization, and public perceptions about the risks and benefits of oral contraception (Trussell & Vaughan, 1992). Experience in other countries such as Great Britain (Thorogood & Vessey, BJFP, 1990) suggests that these increasing numbers of older women may be more likely than younger women to select POPs. The impact on POP use of the recent availability in this country of other progestin-only methods, such as NORPLANT® and Depo-Provera® is uncertain; these other progestin-only methods might either be used by women who would otherwise have used POPs, or they might attract more attention to progestin-only contraception and thus result in a greater number of POP users.

The contraceptive potential of synthetic progestins was first recognized in the 1950s (Edgren, I J Fertil, 1991, p. 16; Speroff & Darney, 1992). The first oral contraceptive studied was norethynodrel

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3NORPLANT® is the registered trademark of the Population Council for subdermal levonorgestrel implants.

4Depo-Provera® is the registered trademark of Upjohn Pharmaceuticals for a sterile aqueous suspension of medroxyprogesterone acetate, which is administered by injection. The generic abbreviation is DMPA.
(NEL) given daily for 20 days, followed by a break for withdrawal bleeding. This initial compound was found to be contaminated with estrogen; when purification techniques reduced the estrogen content, rates of breakthrough bleeding increased and so it was decided to add a fixed amount of estrogen. Thus, the first commercially available OC, marketed in 1960, was norethynodrel 9.85 mg plus mestranol 0.150 mg. Meanwhile, investigation continued on development of progestins that could be administered continuously. In 1966, Mexican researchers reported that chlormadinone acetate (CA), an antiestrogenic progestin, could be an effective contraceptive, despite the fact that it did not always inhibit ovulation (Martinez-Manautou et al., 1966). Norethisterone (now called norethindrone; NET) 0.35 mg was approved for contraceptive purposes in 1973 and norgestrel 0.075 was approved in 1974. Unlike combined OCs, for which the doses have steadily declined over the years, these already low doses for POPs have not been altered substantially.

B. Methodology of this Review

The information available on many issues regarding these two POPs is very limited; therefore, data will also be considered for other formulations of POPs marketed elsewhere, other modes of administering these two progestins (e.g., NORPLANT® levonorgestrel implants), and combined pills with varying levels of these two progestins -- despite some uncertainty about the relevance of some of this information. Furthermore, risks of combined OCs will be evaluated to determine whether they can be related specifically to either the estrogen or the progestin component. Finally, only minimal attention will be given to data on exogenous progestin (or progesterone) use by postmenopausal women, because of the very different underlying hormonal levels and requirements of these older women.
Several summaries of the POP literature have been published recently (Chi et al., 1992; Chi, Contrac, 1993, p. 1; Chi, Adv Contr, 1993; Fotherby, book, 1989; Fraser, 1991; Guillebaud, book, 1993; Hatcher et al., 1994; Huezo and Briggs, 1992; INTRAH, 1993), but none is sufficiently comprehensive to provide the necessary background for labeling purposes. Several authorities have also recently issued revised guidelines, including the International Planned Parenthood Federation (IPPF) (Huezo & Briggs, 1992), the Program for International Training in Health of the University of North Carolina School of Medicine (INTRAH, 1993), and the 1994 Contraceptive Technology clinical text (Hatcher et al.). These guidelines are summarized in Appendices A-E. Our recommendations are as consistent with these as is feasible.

A comprehensive review of progestin-only pills was published in 1975, as a Population Report monograph (Rinehart, 1975), and covers the period of most intensive research on POPs; that monograph has 233 references, most of which are not re-examined for the present review, with the Population Report itself instead generally cited for the pre-1975 literature.

These various POP reviews and clinical guidelines, as well as reviews on specific medical topics (such as breast cancer, sexually transmitted diseases, etc.) in relation to OCs in general, have been invaluable in providing citations to be examined for the present review. Computerized literature searches (including MEDLINE and POPLINE) have also been conducted, but they are of limited utility; because POPs do not have a distinct key word, it is only possible to search on "progestins," which yields studies of progestins for purposes other than contraception, and also studies of progestin implants and injectables for contraception. Another difficulty has been that it is often not possible to determine from the title of an article on OCs whether or not POPs are included or whether the COC
dosage of progestins has been evaluated. The reviewers of this manuscript, acknowledged elsewhere, have also provided us with important citations specific to POPs.

Our goal has been to cite the primary sources for virtually all research specific to POPs since 1975. Many of the studies have important limitations with regard to study methodology -- most notably, small sample sizes and lack of control for potential confounding factors. Although a few studies either randomized women among the study groups or statistically controlled for confounding in the analysis, most studies did not. This shortcoming is particularly problematic for studies of POPs because they are preferentially used by older women, breastfeeding mothers, or women with underlying medical conditions that may be contraindications to combined OC use (Chi, Adv Contr, 1993); similarly, examination of dosage levels in combined OCs is confounded by the fact that older women often tend to continue with the higher dose pills that they were prescribed initially (Van de Carr et al., 1983). No attempt has been made to critically evaluate each article cited, but sample sizes are generally presented, randomized trials have been identified as such, and important information about the study population (particularly the breastfeeding status) has been noted.

Summary statements are given in boldface type at the end of each section of this paper. The types of studies that support each statement are indicated, using the following scheme, which is adapted from a U.S. Preventive Services Task Force Review (1989):

I. Evidence obtained from at least one well-designed randomized clinical trial

II. Evidence obtained from one or more of the following types of studies:

- Well-designed controlled trials without randomization
- Well-designed cohort or case-control analytic studies
III. Opinions of respected authorities, based on clinical experience, descriptive studies, laboratory analyses, or reports of expert committees. (Note that III is listed only if there are virtually no studies in Categories I and II.)

In addition, the types of hormonal contraceptives that were examined in these studies are indicated, according to the following hierarchy:

A. NET or NG/LNG progestin-only OCs, or other POPs that are metabolized to NET
B. Other modes of administration of LNG (NORPLANT®, vaginal rings, IUDs)
C. Other progestins (other POPs, Depo-Provera®)
D. Combined OCs

The methodology of this review has adhered as closely as possible to several recent commentaries on review articles (Milne and Chambers, 1993; Mulrow, 1987; Oxman and Guyatt, 1988; U.S. Preventive Services Task Force, 1989).
II. MODE OF ACTION

The current package labeling for progestin-only oral contraceptives (POPs) states that "the primary mechanism through which [brand-name] prevents conception is not known, but progestogen-only contraceptives are known to alter the cervical mucus, exert a progestational effect on the endometrium, interfere with implantation, and, in some patients, suppress ovulation." In their review of the literature, Li & Newton (1992) describe 5 modes of action of these progestins, as follows:

1) suppression of ovulation in about half of cases;
2) suppression of midcycle peaks of LH and FSH;
3) production of 'hostile, blocked' mucus, resulting in poor sperm penetration;
4) reduction in the number and size of endometrial glands and inhibition of progesterone receptor synthesis in the endometrium, preventing implantation;
5) reduction in the activity of the cilia in the fallopian tube.

POPs appear to prevent conception through various combinations of these mechanisms, with great inter-individual and intra-individual variation. Mills (1987) best describes the process as a "desynchronization of the normal menstrual cycle." This phenomenon was illustrated most dramatically in a Swedish study by Kim-Bjorklund and colleagues (Contrac, 1991), which compared serum hormone assays and biopsy specimens of the endometrium, fallopian tube and corpus luteum from women scheduled for surgical sterilization, 35 of whom were administered 0.30 milligrams (mg) norethisterone (NET) daily for three months and 10 who were untreated. They found no correlation among the responses of the various target organs, suggesting that these organs react to progestins independently of each other, thus enhancing their contraceptive effect. This is in line with reports from this same group of investigators a decade earlier that found no relationship between ovulation,
bleeding patterns, and gonadotropin production for users of NET 0.30 mg (Diczfalusy & Johannisson, 1984; Johannisson et al., 1982; Landgren et al., 1979; Landgren, Lager, & Diczfalusy, 1981).

A. Ovulation Prevention

Ovarian response to POPs varies widely among individuals. For example, Landgren and Diczfalusy (1980) report that the percentage of cycles in which ovulation occurs ranges from 14 to 84% in various studies of norethindrone (NET).

The Swedish researchers (Landgren et al., 1979; Landgren & Diczfalusy, 1980; Kim-Bjorklund et al., Contrac, 1991) summarize four characteristic and distinctly different types of ovarian reaction to the POP as follows: group A -- no sign of follicular or luteal activity as evidenced by low estradiol and progesterone levels; group B -- marked cyclic follicular activity but no luteal function; group C -- normal follicular activity, but reduced (insufficient) luteal activity; and group D -- estradiol and progesterone profiles indistinguishable from normally menstruating women or their own pretreatment cycles. Group D was considered the most likely to become pregnant (Landgren, Lager, & Diczfalusy, 1981). In their most recent study, Kim-Bjorklund et al. (Contrac, 1991) reported that only 10 of the 35 NET 0.30 users (29%) had a well-developed corpus luteum compatible with normal ovulation, (Group D), based on steroid assays. Three had completely suppressed ovulation (i.e., no luteal activity), 10 had follicular activity only, and 12 had follicular activity followed by insufficient luteal function. Histologic changes seen on biopsy supported these hormonal classification regarding the presence and function of the corpus luteum. The study a decade earlier (Landgren, Lager, & Diczfalusy, 1981) found that 8 women, of 21 in the study, displayed estradiol and progesterone profiles indicative of ovulation (as well as other indices of luteal function) during both the second and
sixth month of NET 0.30 mg administration and no woman appeared to ovulate at just one of the two measurement points. Although there were steady decreases in several indices of luteal function for these 8 women, these parameters all remained within normal ovulatory limits. That study also documented higher pretreatment levels of 17-hydroxyprogesterone in the eight women who ovulated, extending the previous observation that women with a relatively long luteal phase and relatively high luteal activity before NET administration were more likely to have "ovulatory-like" steroid profiles while taking POPs.

An early study of chlormadinone acetate 0.5 mg used culdoscopic visualization to determine that ovulation was prevented in 15 to 40% of cycles in 24 women (Martinez-Manautou et al., BMJ, 1967). A 1973 study by Coutinho et al. used electronic monitoring and found MA did not interfere with ovulation in 8 of 10 cases. Oberti et al. (1974) reported ovulation in about 60% of 33 subjects taking one of 4 progestins (retroprogesterone, ethynodiol diacetate, norgestrienone, clogestone) using light and electron microscopy. Tayob et al. (1985), using ultrasonography, found that only six of 21 women (29%) who were taking any of three POPs (levonorgestrel 0.03 mg, norethindrone 0.35 mg, ethynodiol diacetate 0.50 mg) appeared to ovulate normally.

The experience with NORPLANT® contraceptive implants also indicates that even those women who ovulate do not have normal endocrine cycles. Among the 55% of subjects in a NORPLANT® study who were ovulatory, some form of dysfunction was found: diminished gonadotropin (LH and FSH) surge, luteal phase insufficiency (low progesterone levels and shortened luteal phase), and abnormal estradiol profiles (Faundes et al., Fertil Steril, 1991). Using ultrasound, Shaaban et al. (1993) report evidence of a luteal phase defect with low midcycle peaks of FSH, LH, and EE, acting as a secondary safeguard against pregnancy by slowing the ovum’s progress through
the fallopian tubes and preventing the endometrium from preparing properly for implantation. In addition to the possible effects of luteal insufficiency, the normal maturation of the ovum may have been impaired. In an earlier study of NORPLANT® users by the same team, there was no change in the estradiol curve despite the depressed LH and FSH levels, but there was a distinctive corpus luteum (Alvarez et al., 1986). Also Brache and colleagues (1990) found that the percentage of 88 NORPLANT® users' cycles with plasma progesterone levels indicative of luteal activity (3 mg/ml) increased dramatically from less than 25% in the first year to 75% by the fifth year -- despite the fact that LNG concentrations decline very slowly after the first few weeks post-insertion. The fact that the pregnancy rate does not increase during the official 5 year lifetime of NORPLANT®, despite the increase in presumed ovulation, is further evidence that other mechanisms play a role in the contraceptive mode of action (Faundes et al., Fertil Steril, 1991).

From a clinical perspective it would be of interest to know which POP users are ovulating. The clinical texts by Fotherby (book, 1989), Guillebaud (1993) and Hatcher et al. (1994) state that lack of a regular bleeding cycle may indicate inhibition of ovulation. However, the data on this point are sparse and conflicting. The Swedish researchers found no correlation between ovulation status and the number of days of bleeding among 24 women taking 0.30 mg NET daily (Johanissen et al., 1982; Landgren, Lager, & Diczfausz, 1981). In an earlier study of 0.35 mg NET Moghissi et al. (1973) noted that "breakthrough bleeding" occurred only when ovulation was suppressed, but the sample size was only 5; 3 women ovulated, of whom 2 had bleeding.

This issue has also been explored for users of progestins administered continuously, by implants or vaginal rings. Even among regularly menstruating NORPLANT® users only about half had ovulatory cycles and these cycles all evidenced some dysfunction (Alvarez et al., 1986; Faundes et
al., Fertil Steril, 1991; Shoupe et al., 1991). This was supported by data on NORPLANT® users from Olsson et al. (BJFP, 1990) who used ultrasound to examine 15 women in their Swedish study and determined that "those with apparently normal menstrual cycles do not apparently ovulate." On the other hand, Shoupe et al. (1991) in their study of NORPLANT® found it was those with regular bleeding patterns who were at highest risk for method failure, with a 17% 5-year cumulative pregnancy rate for women with regular cycles compared with 4% for those with irregular cycles and 0% in users with amenorrhea.

Landgren and colleagues found that, unlike women in their POP study (Johanisson et al., 1982; Landgren, Lager & Diczfaluzy, 1981), suppressed ovulation was associated with a higher frequency of intermenstrual bleeding among users of vaginal rings releasing either NET (Landgren, Oriowo & Diczfalusy, 1981) or LNG (Landgren et al., 1982).

Some of the variation in these findings may be due to real differences in these small samples; other explanations may be statistical artifact, or differences in definitions of bleeding parameters, or the prior menstrual status of the women in the studies.

B. Suppression of Midcycle Gonadotropin Peaks

Progestin-only pills affect hypothalamic-pituitary function, with marked reduction in the midcycle peaks of luteinizing hormone (LH) and follicle stimulating hormones (FSH) and with variable suppression of basal levels of these hormones (Li and Newton, 1992). There is some evidence of variation in response by type and dose of progestin.
Dericks-Tan et al. (1992) compared 6 women using desogestrel (DG) 0.125 mg with 16 women on 2 combined OC formulations during days 4 and 20 of a single cycle. They found LH secretions to be unaffected by DG but a reduced FSH level after 20 days compared to control cycles. They proposed that the lack of effect of DG on LH and FSH function suggests that the ovulation inhibition of progestins is through direct action on the ovary, by disrupting gonadotropin receptor formation, rather than inhibiting ovarian function at the central hypothalmic/pituitary level as do estrogens. These findings corroborate those of Kim-Bjorklund et al. (Contrace, 1991) that the target organs seem to react independently.

Pituitary gonadotropin levels were also assessed as part of the set of studies of NET 0.30 mg by Landgren and colleagues (1979). During most of the second month, FSH and LH levels after NET administration were generally unaffected, but the peak levels of both FSH and LH were much lower than in the pretreatment control cycle. The FSH and LH patterns did not vary when evaluated according to ovarian response, with "bizarre" patterns of FSH and LH in women both with and without steroid patterns indicative of ovulation (Landgren, Lager & Diczfalusy, 1981). Even in those women with estradiol and progestin profiles suggestive of ovulation, preovulatory FSH levels and the LH peak were below normal, and in some ovulatory women there was virtually no FSH or LH surge (Landgren et al., 1979). The authors concluded that "ovarian suppression by the NET minipill is unrelated to the degree of inhibition of FSH and LH secretion." They also found that women with low basal LH levels in the pretreatment cycle are more likely to have suppressed ovulation once NET administration begins.

The research on NORPLANT® (e.g., Alvarez et al., 1986; Faundes et al., 1991; Olsson et al., 1990) shows similar patterns, with reduced LH and FSH peaks.
C. Changes in Cervical Mucus

Although alteration of the cervical mucus is not the single most important mode of action of progestin-only contraceptives, it is the most immediately protective. In women who are not using hormonal contraception, cervical mucus viscosity varies dramatically throughout the menstrual cycle, depending on the relative levels of estrogen and progesterone. During the pre-ovulatory and mid-cycle periods, under estrogen dominance, cervical mucus becomes increasingly watery, clear, alkaline, and favorable for sperm penetration. Then, during the post-ovulatory phase, with increasing progesterone levels, the cervical mucus becomes scanty, thick, opaque, and unfavorable for sperm penetration; it also contains increasing numbers of leukocytes. The amount of mucus may vary from 600-700 mg at mid-cycle to <50 mg at other times (Schumacher, 1988).

Progestin-only contraceptives cause what is sometimes described as a "hostile" cervical mucus, that reduces the likelihood of sperm penetration. Specifically, the progestin-only pill greatly reduces the volume of cervical mucus produced at mid-cycle, increases its viscosity and cell content, and alters its molecular structure (Chretien et al., 1980; Martinez-Manautou et al., BMJ, 1967; Moghissi et al., 1973). The effect is a "blocked" mucus, which has high siliac acid cross-linking, low spinnbarkeit and poor ferning. Martinez-Manautou et al. (BMJ, 1967) found this to result in little or no sperm penetration in 70-80% of cases. Even in the rare cases when penetration does occur, sperm motility is reduced (Kesseru-Koos, 1971; Moghissi et al., 1973; Roland, 1970; Ruiz-Velasco et al., 1974; Schumacher, 1988). For example, Kesseru-Koos (1971) found that, although there were no sperm in the cervical canal of either the 50 women treated with LNG 0.03 mg or controls, in the uterine cavity there also was almost a total absence of sperm for the treated group but sperm were present in 18 of
the 19 controls. Spona et al. (1993) particularly note the importance of the fact that the cervical mucus effects occur at much lower doses of progestins than do the other modes of action.

Chretien et al. (1980) used a scanning electron microscope to determine sperm penetration of cervical mucus under the influence of norgestrienone 0.35 mg in cervical mucus samples from 8 women at 24, 36 and 48 hours after taking their last pill (on days 13, 14, 15 of the menstrual cycle). Among these POP users, they found "drastic" midcycle thickening of the mucus, giving it an appearance typical of the late luteal phase. They demonstrated the immobilizing effect of such dense mucus on sperm and measured the duration of the effectiveness after discontinuing the pills on day 13 of the cycle. At 24 hours the cervical mucus was still extremely dense in all samples, a few had some local loosening at 36 hours, and by 48 hours, the local loosening was comparatively frequent (in fact, 3 of 8 samples had completely loosened).

Early studies showed the changes in cervical mucus associated with the POP reached their peak 3-4 hours after a pill was ingested (Wright et al., 1970) and the possibility of sperm penetration remained low for 16-19 hours. Kesseru-Koos (1971) found that the arrest of sperm migration occurred within 30 minutes of administration of natural progesterone, and was a little slower with LNG administration. Kesseru-Koos (1971) also found the oral progestins (LNG 0.03 mg) prevented any sperm from entering the cervical canal for 24 hours and the uterine cavity for 3 days. However, sperm penetration has been found to return to almost pre-treatment levels by 22-24 hours after ingestion of MA 0.50 mg or 0.25 mg (Lebech, 1969) in vivo and by Cox (1968) in vitro. Cox (1968) found the highest level of protection to be 5-10 hours after ingestion of the MA 0.50 mg. It is important that the cervical mucus block continues to be maintained even after intercourse has occurred because, although
the median life of sperm is one day (Royston, 1982) to three days (Schumacher, 1988), sperm can live for up to six days (WHO, 1983).

Data on postcoital tests among users of 4 types of POPs have been reported by Mears et al. (1969). Of the 4 types tested, norethisterone acetate 0.30 mg was found to have the most pronounced anti-fertility effect on the cervical mucus, with the 3 other progestins (NG 0.05 mg, MA 0.25 mg, and CA 0.50 mg) all found to have a small percentage of users whose cervical mucus remained receptive to sperm penetration.

In conclusion, the effect of progestins on cervical mucus is the most immediate but shortest lived level of protection provided by POPs, thereby serving as the first line of defense but offering full protection for less than 24 hours.

D. Changes in the Endometrium

The variety of effects of POPs on the endometrium are evidenced in variations in bleeding patterns. In fact, Mears et al. (1969) and Vessey et al. (1972) speculated that changes produced in the endometrium by POPs may be more significant than those in the cervical mucus. The progestins appear to interfere with the cyclic development of the uterine lining, making it unsuitable to receive the fertilized ovum.

The more recent research by Kim-Bjorklund and colleagues (Contrac, 1991) found that, of the 35 NET 0.30 mg users, only 3 had normal secretory activity of the endometrium; 3 others had atrophy, 9 had suppressed proliferation, 8 had proliferation, and 12 had irregular secretory activity. There was
no correlation of endometrial histology with other histology or steroid hormone levels. Their team concluded that: "The corpus luteum and the endometrium react to exogenous progestogens independently of each other."

In an earlier study by the same Swedish group, endometrial biopsies of 24 women taking NET 0.30 mg also documented that the proliferative activity of the endometrium was suppressed, compared to pre-treatment cycles (Johannisson et al., 1982). The only endometrial pattern that was different for subjects with and without intermenstrual bleeding was that the endometrial glandular diameter was significantly greater for women exhibiting intermenstrual bleeding.

In Vessey's (1972) randomized trial of four POPs, a sample of 25 women underwent endometrial biopsies, with differences in results among the progestins. Although most biopsies indicated proliferative changes early in the cycle, the timing of secretory changes varied. Norethisterone [norethindrone] acetate 0.3 mg and norgestrel 0.075 mg had greater effects on the endometrium, with better menstrual cycle control, compared to megestrol acetate 0.7 mg and chlormadinone acetate 0.5 mg. (See Section X.) In contrast, the lack of estrogenic activity for NG, with strong antiestrogenic activity, results in more rapid breakdown of the endometrium and shorter cycle lengths than NET. The earlier study by these same investigators (Mears et al., 1969) included a larger number of biopsies (N=89), with similar results.

Examining 5 women taking norethindrone 0.35 mg, Moghissi et al. (1973) found the endometrial morphology altered, showing a mixed phase endometrium. Another early study also found that most of the 25 women taking ethynodiol diacetate at various doses had inactive endometrium on biopsy (Ruiz-Velasco et al., 1974). This study also assessed uterine contractility,
noting a decrease in frequency of contractions and an increase in their intensity throughout the cycle, compared to pre-treatment observations.

A morphometric study of biopsies obtained at hysterectomy has quantified the effect of NET 0.35 mg and LNG 30 mcg on endometrial blood vessels (Hourihan et al., 1986). The number of arteries in the region of the endometrial/myometrial junction was decreased, while the total number of veins and the number of dilated veins in the functional endometrium were increased for both groups of POP users, compared to women not taking any hormonal preparations. These dilated veins, which were often found directly below the surface, may result in increased venous drainage into the endometrium and thereby account for the irregular bleeding complications associated with POPs.

The findings of Hourihan et al. (1986) were recently supported by the first study to use immunohistochemical methods to evaluate endometrial vascular density across different stages of the menstrual cycle (Rogers et al., 1993). That study, conducted in Australia and Indonesia, found endometrial vascularity not related to bleeding patterns in NORPLANT® users, suggesting that progestins administered long-term act differentially on the different types of endometrial blood vessels, increasing capillaries and veins and reducing arterioles. Unlike the normal menstrual cycle, microvascular density did not correlate with estrogen concentrations, bleeding patterns or endometrial histology. The control mechanisms are still not understood. Furthermore, as Fotherby (book, 1989) points out, the extent to which the changes in the endometrium would prevent implantation of the blastocyst is unclear, particularly since the normal endometrial requirements for implantation at the cellular level are not known.
E. Changes in the Fallopian Tube

The evidence for changes in the fallopian tube is not as clearcut as for the endometrium. However, the reviews by Fotherby (book, 1989) and Li & Newton (1992) conclude that progestins reduce the number of cilia on the tubal epithelium, as well as the intensity and frequency of cilia action, thus slowing the rate of ovum transport. For example, in one half of patients using a continuous 0.35 mg dose of megestrol acetate, tubal motility was depressed during a four week cycle (Coutinho et al., 1973). Two other studies also report that low-dose progestins can produce changes in the action of the fallopian tubes that in turn exert an effect on ovum transport, fertilization, and possibly sperm capacitation as well as sperm migration (Oberti et al., 1974; Zanartu, Pupkin et al., 1968). A more recent study (Kim-Bjorklund et al., Contrac, 1991) found no differences between the tubal epithelium of NET 0.30 mg users and that of women who were not using hormonal contraception but did not rule out the possibility of such tubal changes. One important reason for a further understanding of these changes is that they help explain why ectopic pregnancies are higher for POP users than COC users. (See Section IV.)

F. Clinical Implications

These multiple mechanisms of contraceptive effect -- suppressing ovulation, smoothing FSH and LH peaks, making the cervical mucus unfavorable to sperm penetration, and altering the endometrium to prevent implantation, as well as slowing movement of the ovum through the fallopian tubes -- have been studied one or two at a time, but data are not available on their total synergistic

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5Five of Oberti et al.'s (1974) 19 cases were postpartum lactating, non-menstruating women which may have affected their findings. All of the other studies reported in this section were presumable conducted among non-breastfeeding women.
effect. This limited knowledge about the mode of action of POPs is problematic in terms of
developing instructions for POP users about when to start or switch to POPs, and what action to take
when pills are not taken on schedule. (See Section XII.) Nonetheless, the data do provide some
guidance on these issues.

Because ovulation is not suppressed consistently, even when the pill is taken as scheduled,
these multiple "desynchronized" contraceptive mechanisms must be taken into account. The mucus
effect develops so quickly after the first pill is ingested that no additional contraceptive precautions are
necessary when a woman begins POPs early in her menstrual period. However, because the potential
for sperm penetration of the cervical mucus is close to pre-treatment levels 24 hours after a pill is
taken when a POP is missed or delayed, the effects on the gonadotrophin peaks, the fallopian tubes
and endometrium become more important by preventing ovum transport and implantation. The
slowed movement of the ovum through the fallopian tubes is presumably responsible for the
occurrence of ectopic pregnancies. (See Section IV.)

The implications of the bleeding patterns of POP users are not yet clear, with some studies
reporting that bleeding patterns were most regular in women who ovulate, others not. The suppression
of proliferation in the endometrium likewise may or may not be associated with intermenstrual
bleeding.

CONCLUSION: Progestin-only pills desynchronize the normal menstrual cycle, acting to
prevent conception in several independent ways. They prevent ovulation about half the time,
smooth the midcycle LH and FSH peaks, slow the movement of the ovum through the fallopian
tubes, thicken the cervical mucus to prevent sperm penetration, and prevent implantation in the endometrium. The significance of intermenstrual bleeding while on POPs has not been determined. (Types of evidence: I A, B; II A, B, C, D.)
III. PHARMACOLOGY

Norgestrel (NG) and norethindrone (NET), the progestins used in progestin-only oral contraceptives, are both structurally-related to 19-nortestosterone (Edgren, in press); norgestrel is in the gonane class and norethindrone is an estrone. Levonorgestrel (LNG)\(^6\), the active enantiomer of the racemic compound norgestrel, is also marketed as a POP outside of the United States, at a dosage of 0.03 mg. Ethynodiol diacetate and lynestrenol, used as POPs in other countries, are metabolized to norethindrone (Edgren, in press; Fotherby, in press; Odlind et al., 1979; Stanczyk & Roy, 1990).

There are also three relatively new 19-nortestosterone gonane progestins that are being used in COCs, but not yet in POPs: gestodene, desogestrel, and norgestimate (Edgren, in press; Fotherby, in press; IOM, 1991). Medroxyprogesterone acetate, administered as the injectable DMPA or Depo-Provera\(^8\), is derived from 17 alpha-hydroxyprogesterone and belongs to the pregnane class of progestins.

A. Pharmacokinetics

Current understanding of the pharmacokinetics and pharmacodynamics of progestin-only oral contraceptives is somewhat limited because of the complexity of the subject and the paucity of relevant data (Fotherby, in press; Stanczyk & Roy, 1990). It is apparent that there are some differences among the various progestins. There are both inter-individual and intra-individual differences among women and most studies involve only a small number of women, making it difficult to predict the pharmacodynamic responses of individual POP users. Assessment of pharmacokinetics is also complicated by the fact that, in many studies, blood levels are assessed after a

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\(^6\)In the past, norgestrel was sometimes referred to as dl-norgestrel and levonorgestrel was d-norgestrel.
single dose, a situation which may be quite different from the more clinically-relevant steady-state conditions. The pharmacokinetics of synthetic progestins can vary depending on route of administration and whether the progestin is given alone or in combination with estrogen. Finally, animal studies are of little relevance to humans because of differences in absorption and metabolic clearance among various species.

Serum steroid levels peak about two hours after oral administration of progestins, followed by rapid absorption, distribution and elimination, as displayed in Figure 1. The pattern is similar for NET and NG/LNG, although LNG is eliminated more slowly. A recent comprehensive review by Fotherby (in press), that included both progestin alone and progestin plus estrogen, gives the mean elimination half-life of LNG as 16 hours, compared to 7 hours for NET. The absolute serum steroid levels are higher for NET, reflecting its higher dosage level necessitated by its lower progestational potency (as discussed in the next section). However, the differences between the two progestins in serum levels are not as great as would be anticipated based on dosage alone, because of differences between the two steroids in bioavailability. LNG is virtually 100 percent bioavailable when given orally, while the bioavailability of NET is about 60 percent (47-73% in various studies) because during first pass through the intestines and liver some of the NET is inactivated (Back et al., II, 1978; Fotherby, in press; Goebelsman, book, 1986; Goldzieher, AJOG, 1989; Humpel et al., 1978).

The various routes of administration of progestins produce differing hormone profiles. For example, the fact that there are immediate first pass effects of the liver on progestins given orally, but not when they are administered as an injectable or implant, indicates differences in absorption and circulation. Route of administration also affects fluctuations over time of steroid concentrations in the blood; with daily oral administration there are large fluctuations each day, whereas with implants,
IUDs, and vaginal rings the steroid levels are fairly constant. The NORPLANT® contraception implants result in mean levonorgestrel levels of 1-2 ng/ml after 24 hours, declining to 0.25-0.4 ng/ml by six months and averaging 0.3 ng/ml thereafter for 5-6 years (Population Council, 1990). The labeling for these implants notes the "considerable" variation among users in LNG concentrations "as a function of individual metabolism and body weight." The text of the labeling goes on to say, "Because of the range of variability in blood levels and variation in individual response, blood levels alone are not predictive of the risk of pregnancy in an individual woman." Mean LNG levels in women with an LNG-releasing IUD have been reported to be 0.36 nmol/l (Barbosa et al., 1990), which converts to 0.11 ng/ml. For vaginal devices releasing progestins, peak levels are also reached by 24 hours after insertion, followed by a very slow decline; for devices releasing 0.20 mcg/24 hours, serum NET levels decline slightly from 0.26 ng/ml at 24 hours to 0.23 ng/ml at three months (Landgren et al., Contrace, 1981, p. 29); and for vaginal devices releasing LNG 0.02 mg/day the steady-state serum level was 0.2-0.3 ng/ml (Landgren et al., 1982). For all three of these alternative delivery modes, steady-state levels are intermediate between the peak and trough levels of POP users, as reviewed above.

There are very few studies of the pharmacokinetics of POPs and most of these include only a small number of subjects. Fotherby's review (in press) lists five studies of NET given alone at contraceptive doses (with 3-16 women per study) and only two such studies of NG/LNG (with 3 subjects in one study and 5 in the other). The patterns displayed in Figure 1 are representative of

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5The studies of NET listed by Fotherby (in press) are Odlind et al. (1979), Nygren et al. (1974), Saxena et al. (1977), Stanczyk et al. (1978) and Prasad et al. (1979); the two studies of NG/LNG are Weiner et al. (oral admin., 1976) and Brenner et al. (1977). In one of the studies of NET (Saxena et al., 1977) the women were all lactating. Several other reports of breastfeeding women also present limited data on serum levels of NET (Toddywalla et al., 1980) and LNG (Bertrabet et al., 1987; Nilsson et al., AJOG, 1977; Shikary et al., 1987; Toddywalla et al., 1980).
those found in these studies, although absolute levels are affected to some extent by differences in methodology.

It is difficult to anticipate the pharmacokinetics of POPs in individual women because of the large variations among women, and even in the same woman over time. For example, in the studies of NET 0.35 mg, the range of individual peak concentrations was 4.7-14.8 ng/ml among the 16 subjects in one study (Prasad et al., 1979), 2.1-5.1 ng/ml in another study (N=5) (Saxena et al., 1977), and about 3-6 ng/ml in a third (N=12) (Stanczyk et al., 1978). Two studies of a slightly lower dosage of NET (0.30 mg) found peak concentrations of 3-5 ng/ml (N=2) (Nygren et al., 1974) and 1.5-8.0 ng/ml (N=5) (Odlind et al., 1979). Similarly, in one of the studies of NG/LNG, the range of peak LNG concentrations was 0.9 to 2.0 ng/ml (LNG 0.03 mg) (N=5) (Weiner et al., Contrac, 1976, p. 563) and in the other it was 1.5 to 1.9 (NG 0.075 mg) (N=3) (Brenner et al., 1977).

Of particular importance for contraceptive purposes is whether the lowest steroid level reached by an individual remains above the level required for contraceptive purposes -- but that contraceptive level presumably also varies among individuals and even among target organs within the same individual because of differences in pharmacodynamic responsiveness. The concentrations at 24 hours after pill ingestion (i.e., when the next pill should be taken) were 0.2-0.9 ng/ml in one study of NET 0.35 mg (Saxena et al., 1977), 0.3-0.4 ng/ml in another (Stanczyk et al., 1978), and up to 1.6 ng/ml in a third such study (Prasad et al., 1979). In one of the studies of NET 0.3 mg, the 24-hour levels were 0.06-0.3 ng/ml (Odlind et al., 1979). Twenty-four hour LNG levels were 0.05-0.14 ng/ml in a study of LNG 0.03 mg (Weiner et al., Contrac, 1976, p. 563) and 0.2-0.5 ng/ml in a study of NG 0.075 mg (Brenner et al., 1977).
Continued decline beyond 24 hours for women who are late in taking their next pill is an additional concern, which most studies have not addressed. The limited available data beyond 24 hours suggest that levels range from undetectable to levels similar to those found at 24 hours. In the study of LNG 0.03 mg, the 48-hour levels were 0.03-0.07 ng/ml and the 72-hour levels were all 0.03 (Weiner et al., Contrac, 1976, p. 563). In one of the studies of NET 0.3 mg, the 36-hour measurements were 0.05-0.1 ng/ml (Odlind et al., 1979).

The time courses of the distribution phase and, particularly, of the elimination phase also vary considerably among studies and among individuals in the same study. The peak serum concentration was reached within about two hours for most, but not all, women (Brenner et al., 1977; Nygren et al., 1974; Prasad et al., 1979; Saxena et al., 1977; Stanczyk et al., 1978; Weiner et al., Contrac, 1976, p. 563). The half-life of elimination averaged 8.2 hours in a study of NET, with a range among individuals of 1.5-23.6 (Prasad et al., 1979); the mean was about 9 hours in another such study (Nygren et al., 1974) and 7.9 hours in a third study of NET (Odlind et al., 1979). In a report on NG 0.03 mg, the half-life of elimination averaged 13.7 hours, with a range of 8.0-23.2 hours (Weiner et al., Contrac, 1976, p. 563).

The data presented in the above five paragraphs are all from studies of NET or NG/LNG given alone, by mouth, at contraceptive doses. Other studies have examined higher doses of progestins alone, but these generally involve subjects other than women seeking routine contraception -- for example, oophorectomized women, women requiring postcoital contraception, and even men (Fotherby, AJOG, 1990, p. 323).
There are also numerous pharmacokinetic studies in which these progestins are given in combination with estrogen; because COCs involve both higher doses of progestin and interactions of the two steroids, caution must be taken when applying these data to consideration of progestin-only OCs. Administration of progestin with estrogen, rather than alone, affects many aspects of progestin pharmacokinetics. One of the most notable differences is that combined OC users have a rise in plasma progestin level over time, whereas there is no such increase among women taking progestins alone (Kuhnz et al., Contrac, 1992, p. 443; Kuhnz et al., Contrac, 1992, p. 455; Song et al., 1989; Weiner et al., Contrac, 1976, p. 563); thus, under steady-state conditions, identical doses of progestins will be associated with lower serum progestin levels for women taking only a progestin compared to women who are simultaneously taking estrogen. The lower progestin dosage of POPs, together with the lower serum levels that result from the same dose when given without estrogen, produce serum progestin levels that are typically much lower for POP users than for COC users (Brenner et al., 1977; Stanczyk et al., 1978; Weiner et al., Contrac, 1976, p. 563).

An understanding of the role played by serum binding is critical to understanding progestin pharmacokinetics. Progestins form strong bonds with sex hormone binding globulin (SHBG) and weaker bonds with albumin (Fotherby et al., in press). The relative binding affinity to SHBG is stronger for LNG than for NET and thus a greater proportion of LNG is bound to SHBG (Fotherby, in press; Goebelsman, book, 1986); this may be one reason that elimination rates are somewhat slower for LNG compared to NET. Among the newer progestins, gestodene has an even higher affinity for SHBG than does LNG, whereas the affinity of desogestrel is just slightly higher than that of NET (Fotherby, in press); MPA has no measurable affinity for SHBG (Fotherby, in press). Because estrogen stimulates production of SHBG, co-administration of estrogen with NET or NG/LNG increases the SHBG concentration, thus permitting more progestin to bind with SHBG (Fotherby, in
press; Goebelsman, book, 1986; Shenfield & Griffin, 1991); higher doses of estrogen are generally associated with higher levels of SHBG, whereas progestin dose is negatively correlated with SHBG concentration (Fotherby, 1988). The higher serum levels and longer half-life of elimination for progestins when co-administered with estrogen rather than alone are due in part to this sequence of increased SHBG associated with estrogen, increased binding to SHBG, and reduced progestin clearance (Fotherby, 1990, AJOG, p. 323). SHBG is thus at least partly responsible for many of the differences discussed above, including differences between NET and LNG, differences between progestins alone and progestins administered with estrogens, differences between single-dose and steady-state administration, and both inter-and intra-individual variation.

A recent study in China evaluated both steroid and SHBG concentrations during one month of administration of four different hormonal formulations (LNG 0.15 mg alone, LNG 0.15 mg + EE 0.03 mg, NET 0.60 mg + EE 0.035 mg, and NET 1.0 mg + EE 0.035 mg) (Song et al., 1989). Although the dosage of LNG alone was five times the dosage used in POPs, it is the same as the LNG dose in COCs and thus more readily permits comparisons within the study. Among women taking LNG alone (N=6), LNG levels declined somewhat after the first few days of treatment. In contrast, levels increased throughout the month in all three of the COC groups, so that toward the end of the month the levels were about three times as high as they had been earlier; for the COC containing LNG, they were three times as high as for LNG alone, despite the identical LNG dosage. The SHBG concentration for the LNG-only group declined steadily, so that by the end of the treatment period it was less than half of the baseline level, whereas for the LNG-COC group an initial small decline was followed by a rise to baseline; for both of the NET-COC groups SHBG increased steadily to three times the baseline level. By eight days after cessation of treatment, SHBG levels had not yet returned to normal for the three groups that had shown changes from baseline.
Reports from Germany have also evaluated differences in steroid and SHBG concentrations between the higher dose of LNG (0.15 mg) alone and LNG 0.15 plus EE 0.03 mg; in addition, they compared the effects of a single dose with one to three months of administration (Kuhnz et al., Contrac, 1992, p. 443; Kuhnz et al., Contrac, 1992, p. 455). Among women taking LNG alone (N=12), the patterns of LNG concentrations over 24 hours were very similar for the single-dose and steady-state phases of the study. However, for users of the COC, both peak and trough serum levels of LNG were several times higher at the end of each treatment cycle than after only one dose. With the achievement of steady-state conditions on day five, in the LNG-only group the LNG trough levels declined over the cycle to about half of the day-five level, and SHBG levels followed a similar time course; users of LNG plus EE had steady increases in both LNG and SHBG concentrations throughout the treatment cycle. For women taking LNG alone, the decrease in SHBG resulted in a declining percentage of LNG that was bound to SHBG, an increase in the percentage that was bound to albumin, and a slight increase in the already-low percentage of free steroid. The German researchers performed a computer simulation of steady-state LNG levels, based on the single-dose levels and changing SHBG concentrations reported above. The results indicate that these two factors are predictive of the actual steady-state levels for users of LNG alone but not for users of the LNG combined OC, for whom other factors (such as changes in SHBG binding capacity or changes in hepatic metabolism of LNG) also play a role.

A third study, in Finland, measured SHBG levels (but not steroid levels) for various formulations of contraceptive steroids (Kauppinen-Makelin et al., 1992). SHBG concentrations were reduced during administration of LNG 0.15 mg alone, but increased above baseline with LNG 0.15 mg plus EE 0.03 mg and with a sequential OC containing these two steroids. This study is thus in agreement with the above studies for POPs; the pattern among COC users is more consistent with that
reported by Kuhnz et al. (Contrac, 1992, p. 455) than Song et al. (1989). It has previously been noted by Fotherby (AJOG, 1990, p. 323) that there are inconsistencies in the results of SHBG concentrations among studies of COCs, due in part to differences in steroid formulation and in study methodology, with changes over time ranging from small decreases to large increases. However, the limited data on POPs, reviewed above, support the conclusion that POPs are generally associated with small decreases in SHBG concentrations.

In many NORPLANT\textsuperscript{\textregistered} users, SHBG levels decline rapidly in the week following implant insertion, then rise somewhat thereafter but remain below the pre-insertion levels (Speroff & Darney, 1992). Individual variations in the pattern of SHBG are thought to be responsible for some of the individual variation in plasma LNG levels among NORPLANT\textsuperscript{\textregistered} users. Strong correlation between SHGB and LNG levels among NORPLANT\textsuperscript{\textregistered} users has been reported by Affandi et al. (1987) and Weiner and Johansson (1976). The NORPLANT\textsuperscript{\textregistered} labeling notes that one reason for the rapid decline in steroid levels during the first month after insertion is the reduction in SHBG.

There appear to be numerous factors that are responsible for the inter- and intra-individual differences in progestin pharmacokinetics. Clearly, genetic differences in metabolism account for some of the differences among individuals, but not among different measurement points for the same individuals. For norethindrone, but not for NG/LNG, individual variation in the first-pass effects of the liver plays an important role. Although this indicates that there might be greater inter-individual variation in plasma steroid concentration for NET than for LNG (Goldzieher, AJOG, 1989), the stronger affinity of LNG for SHBG suggests that variations in SHBG levels could have a greater effect on free circulating steroid levels for LNG than for NET. Thus, there is considerable variation for both of these progestins.
Other factors that can affect an individual's drug metabolism include diet, weight, alcohol use, and smoking (Fotherby, AJOG, 1990, p. 2153), as well as co-administration of other drugs (which is discussed in Section IX of this paper). Although there has been research on the influence of diet and nutrition on the clinical pharmacokinetics of various drugs, there has been little study of their effect on contraceptive steroids. For example, absorption of some lipid-soluble drugs is increased by a high-fat diet, and pharmacokinetics of lipid-soluble drugs may be altered in obese people, but it is not known if these relationships pertain specifically to lipid-soluble steroids (Fotherby, AJOG, 1990, p. 2153).

Alteration in SHBG levels appears to be a primary mechanism by which diet affects the unbound biologically active portion of progestins, as SHBG is inversely related to body weight (Goebelsman, book, 1986) and is higher for persons eating low-fat and vegetarian diets (Fotherby, AJOG, 1990, p. 2153).

Information on the effect of diet and weight on serum steroid levels for OC users is conflicting. An Indian study of NET 0.35 mg found that women who were better nourished (as assessed by anthropometry) actually had higher steroid levels and a slower half-life of elimination (Prasad et al., 1979). Another study in India, involving two NG/LNG COCs, found similar results, while two studies that have examined this relationship for NET COCs found no correlation between body size and pharmacokinetics (Fotherby et al., 1979; Prasad et al., 1981). One of these latter studies (Prasad et al., 1981) also found no significant differences when lactovegetarian and nonvegetarian women were compared. Furthermore, a recent carefully controlled clinical trial, in which diet was standardized and smoking was forbidden, nonetheless found large differences in plasma NET (and EE) levels, both within and between individuals, following administration of single doses of combined OCs (NET 1 mg, plus either mestranol 0.05 mg or EE 0.035 mg) (Brody et al., 1989). Interestingly, these investigators, as well as others (Fotherby, 1983; Kiriwat & Fotherby, 1983., Shi et al., 1987), also
determined that there was no correlation between the rates at which progestin and estrogen are metabolized, based on relative steroid levels.

Studies of the early versions of NORPLANT® clearly showed that heavier women had lower plasma steroid levels, were more likely to be ovulatory, and had higher pregnancy rates (Population Council, 1990; Sivin, 1988). These differences appear to be due to differences in dilution volumes and/or in drug metabolism, because the LNG release rate from the implants does not vary by weight (Sivin, 1988). It should be noted that this problem of higher pregnancy rates among heavier women does not occur with the currently-marketed implants, which use a different type of tubing (Sivin, 1988).

Cigarette smoking could potentially affect steroid metabolism because it is known to increase the metabolic rate for some drugs, by stimulating hepatic microsomal enzymes (Back & Orme, in press; Kanarkowski et al., 1988). However, the limited data on contraceptive steroids indicate that smoking status does not affect the pharmacokinetics of LNG, at least in COCs (Crawford et al., 1981; Kanarkowski et al., 1988).

Because many metabolic processes display circadian differences, it is also important to consider whether the time of day that OCs are taken affects their pharmacokinetics. No studies have addressed this issue for POPs. A randomized cross-over trial of a combined OC (NET 1 mg + EE 0.05 mg) found no differences in numerous pharmacokinetic parameters when comparing morning and evening pill-taking (Kiriwat & Fotherby, 1983).
Finally, there are dramatic differences among species in metabolism of contraceptive steroids (Humpel, 1989). For example, norgestrel must be given at a higher mg/kg body weight basis in rats than in humans to produce the equivalent plasma drug levels (i.e., norgestrel has much lower oral bioavailability in rats) (Jordan, 1992). A comparison of humans and rhesus monkeys indicated that the peak levels of NET were lower in the monkeys, per kg of body weight, and the peak was maintained for a longer period of time (Nygren et al., 1974). Fotherby states in his 1986 review of species differences in metabolism of contraceptive steroids that "no species would appear to be suitable as a model for human studies". Therefore, animal data are used only minimally in this review.

B. Pharmacodynamics and Potency

Synthetic progestins have a broad range of pharmacological properties, as a result of their binding not only to progesterone receptors but also to estrogen, testosterone, and corticoid receptors (Edgren, in press). Thus, they not only have progestational effects on various target organs, but also have estrogenic, androgenic, and glucocorticoid or mineralcorticoid effects. Norethindrone and norgestrel, the two progestins marketed as POPs in the United States, have similar biological effects; they both display progestational, androgenic, and anti-estrogenic effects; they both lack glucocorticoid effects; and most studies demonstrate no estrogenic effects (except for long-term animal studies of norethindrone) (Edgren, in press). In contrast, synthetic estrogens bind only to estrogen receptors and thus act very much like natural estrogens.

Biosynthesis of progesterone and estrogen receptors is, in turn, affected by the presence of these steroids (Edgren, in press). Both progesterone and estrogen receptor formation is stimulated by estrogen. Conversely, synthetic progestins inhibit estrogen receptor biosynthesis.
Quantifying the strengths of these pharmacologic effects (i.e., the potencies) is fraught with difficulties (Edgren, in press; Goldzieher, book, 1989; Goldzieher, AJOG, 1989; Swyer & Little, 1968). Perhaps the biggest problem is that such quantification is usually based on animal bioassays or, occasionally, on in vitro analysis of human tissue, so that applicability of the results to humans in vivo is uncertain. As with the steroid levels, there are also numerous technical problems, such as inter-laboratory variations in protocols and differences in statistical interpretation of the dose-response curves (Edgren, in press). Thus, laboratory data can provide only relative potency comparisons, for specific biologic effects, and ideally such comparisons should be made only with data from the same laboratory, using the same experimental and statistical procedures.

A review by Dorflinger (1985) concluded that norgestrel has five to ten times the progestational potency of norethindrone and that norethindrone is approximately equivalent in progestational potency to norethindrone acetate and ethynodiol diacetate, both of which are metabolized to norethindrone. The progestational potency of synthetic progestins has generally been assessed in humans by examining effects on the endometrium -- either indirectly, using the delay of menses test, or directly, by examining subnuclear vacuolization as evidence of the secretory transformation of the glands in the endometrium; in vitro assessment of human endometrial explants has also been performed recently. Progestational bioassays have also been performed in animals, including examination of the glandular proliferation of rabbit uterine epithelium and the maintenance of pregnancy in rabbits (Edgren, in press). For contraceptive purposes, relative effects on ovulation-inhibition and cervical mucus changes (as well as endometrial effects) are also important measures of potency (Swyer & Little, 1968). Researchers have recently evaluated the binding of various progestins to the progesterone receptor in human breast tumor cell cultures, with the finding that levonorgestrel
has 2 to 7 times the progestational potency of norethindrone (Bergink et al., 1983; Kloosterboer, et al., 1988).

Although there are some differences in study results using these various types of assessment methods, as well as differences among studies using the same method, other reviewers have also concluded that norgestrel is several times more potent a progestin than norethindrone (Phillips et al., 1987; King & Whitehead, 1986). These rankings are reflected in dosage levels of current POPs, with NET being given at a dosage of about five times that of NG (0.35 mg NET vs. 0.075 mg NG). Levonorgestrel, the active enantiomer of norgestrel, comprises half of the racemic compound, and therefore levonorgestrel is twice as potent as norgestrel; LNG is available as a POP outside of the United States at a dosage of 0.03 mg, about half the stated dosage of NG formulations. Thus, the inherent differences in progestational potency have been accounted for in determining the contraceptive dosage, and so the clinical progestational effect of the various POP formulations is approximately the same (Speroff & Darney, 1992).

Although there is some consensus among recent studies of progestational potency, these relative rankings are somewhat different from those presented two decades ago by Greenblatt (1967). Greenblatt reported, based on the delay of menses test, that norgestrel is 30 times as potent as norethindrone (rather than 5 to 10 times) and that ethynodiol diacetate is 15 times as potent as norethindrone (rather than equipotent). Greenblatt's conclusions have been widely cited, but they have also been criticized by numerous researchers (Armstrong, 1986; Dickey & Stone, 1976; Dorflinger, 1985; Edgren & Sturtevant, 1976; Edgren, 1978; Edgren, in press).
These discrepancies have implications for studies which correlate various physiological outcomes with the progestational potency of OCs because several of these studies have based their analysis of progestin potency on Greenblatt's now-outdated review. The most notable example of this problem is research on breast cancer etiology (Armstrong, 1986; Pike et al., Lancet, 1983, p. 926; Swyer, 1983), in which analyses of progestational potency of COCs based on Greenblatt's review and on more recent data found different results (see Section VII.) A 1985 report that simultaneously classified COCs by estrogenic and progestational potency (Covington et al., 1985) was also based in part on Greenblatt's 1967 findings, with COCs containing ED 1 mg and NG 0.5 mg being inappropriately classified together with COCs containing NET 10 mg as "high" progestin potency. Despite this erroneous classification, the Covington report has been used as the basis for the progestational potency rankings in recent epidemiologic studies (Gerstman et al., 1990; Piper & Kennedy, 1987).

Whether norgestrel and norethindrone have estrogenic activity remains uncertain. Very recently it has been reported that several 19-nortestosterone progestins (including both NET and NG) exert estrogenic effects through the estrogen receptor of breast cancer cells in culture (Jordan et al., 1993). In contrast, another study which quantified the relative affinity of various steroids for binding to estrogen receptors in human breast tumor cells indicated virtually no estrogenic activity for either NET or LNG (Bergink et al., 1983). The other available evidence for NG/LNG indicates no estrogenic effects (Edgren, in press; Stanczyk & Roy, 1990). Regarding NET, recent laboratory studies and limited data on postmenopausal women suggest that this progestin may be partially converted to ethinyl estradiol (Fotherby, in press), and long-term animal studies of NET also suggest some estrogenic activity (Edgren, in press; Stanczyk & Roy, 1990).
Both the nortestosterone progestins and the acetoxyprogesterones have antiestrogenic activity, which means that they compete with estrogen for estrogen binding sites and they inhibit estrogen receptor biosynthesis (Edgren, in press). This activity has been quantified in rodents by examining reversal of estrogen-induced changes in vaginal smears or uterine growth (Edgren, in press). The antiestrogenic effects of progestins are responsible for one of the primary modes of action of POPs, that of inhibiting the normal mid-cycle changes in cervical mucus (as described in Section II). (Edgren, in press). Antiestrogenic activity also counteracts the tendency of estrogens to stimulate SHBG production, which explains some of the differences in SHBG levels among hormonal contraceptive steroids (Fotherby, in press).

Norgestrel and norethindrone both display androgenic effects, with norgestrel being particularly potent in this respect (Edgren, in press). Progestins can act as androgens either directly or indirectly, by displacing endogenous androgens from SHBG (IOM, 1991). These androgenic effects have been demonstrated in the laboratory in several ways: affinity for rat prostatic androgen receptors; ability to stimulate ventral prostate growth in immature castrated rats; and affinity for human SHBG in vitro (McGuire et al., 1990). In animal studies, levonorgestrel was found to be the most androgenic of several synthetic progestins, while norethindrone had very little androgenic activity (Phillips et al., 1987). LNG has also been found to have a higher binding affinity for androgen receptors in human breast tumor cell cultures than NET (Bergink et al., 1983; Kloosterboer et al., 1988). The effects of progestins on lipid metabolism (which will be discussed more fully in Section V) can also be interpreted as markers of androgenic potency, as androgens tend to lower HDL-cholesterol levels (Dorflinger, 1985; Edgren, in press; McGuire et al., 1990); these metabolic effects suggest that norgestrel has five to ten times the androgenic potency of norethindrone (Dorflinger, 1985). Thus, as
with progestational potency, the two types of POPs have similar androgenic potency because of the higher dosage levels of NET compared to NG/LNG.

The new progestins are purported to lack the androgenic effects of the parent compound (levonorgestrel) because they do not appear to affect circulating levels of HDL-cholesterol, but laboratory studies find varying degrees of androgenic activity (Edgren, in press). One study computed a "selectivity index," the ratio of the relative binding affinity for the progesterone receptor to that of the androgen receptor (Kloosterboer et al., 1988). The selectivity indices for desogestrel and gestodene were much higher than for levonorgestrel and norethindrone; this means that, at the same progestational bioavailability, desogestrel and gestodene would have less androgenic effect than LNG and NET. Whether or not these new progestins have important clinical advantages remains to be demonstrated (Goldzieher, book, 1989; Speroff & Darney, 1992).

Finally, although the acetoxyprogesterones (such as medroxyprogesterone acetate) bind to corticoid receptors and thus exhibit gluco- or mineralcorticoid effects, the 19-nortestosterones do not (Edgren, in press). Desogestrel also binds to the corticoid receptor.

The various types of potencies of the progestins must be considered simultaneously because one may affect another, but this is difficult to do. Similarly, when progestins are given together with estrogens the potencies of both steroids must be considered, but it is often not known whether the combined effects are synergistic, antagonistic or simply additive. Most notably, in one of the methods for assessing progestational potency — the delay of menses test — estrogen increases the potency of progestins, with the effect of estrogen varying for different progestins (Swyer & Little, 1968; Swyer, 1982). Similarly, because of the estrogenic activity of some progestins, the delay of menses test is
problematic even for progestins alone, but this is not the case for the subnuclear vacuolization test of progestational potency (Dickey & Stone, 1976; Dickey, 1979).

Most of the above discussion of the various potencies of progestins focuses on the reproductive system—specifically, on binding of progestins to the different types of receptors in various reproductive organs. Progestational, estrogenic, antiestrogenic and androgenic effects can all vary depending on the target organ, and so it is difficult to postulate a dose-dependent effect of NET or NG/LNG on other organ systems based on data from the reproductive organs (Edgren, 1978; Edgren & Sturtevant, 1976). Goldzieher (book, 1989) lists more than two dozen specific activities of progestational compounds. One example of the difficulties inherent in extrapolating from one pharmacodynamic response to another is the finding that SHBG and ceruloplasmin levels do not both respond the same way to various contraceptive steroid formulations, despite the fact that they are both proteins of hepatic origin (Song et al., 1989).

C. Clinical Implications

It is apparent from this review that norgestrel and norethindrone are similar in many pharmacokinetic aspects. Although norgestrel has more potent progestogenic and androgenic effects, it is given at a lower dose than norethindrone for contraceptive purposes, so the actual potencies of the two progestins when administered as POPs are similar. Both of these progestins also have antiestrogenic action. And both POPs are associated with large variations among individuals in steroid metabolism, making it difficult to predict individual pharmacodynamic responses. NET and NG differ in one important aspect of pharmacokinetics, that of elimination half-life; because NG is eliminated
more slowly, it can be hypothesized that it would be less likely to result in "subtherapeutic" blood levels (Goldzieher, book, 1989), which is of particular concern when a woman takes her pill late.

There are greater differences between these two progestins and other types of progestins, such as medroxyprogesterone acetate. There are also major differences in some aspects of the pharmacokinetics of NG and NET when they are given alone compared to being given with estrogen, because of both the higher dose of progestin and the interactions of the progestin and the estrogen in the COC, mediated in part by differing interrelationships with SHBG. Finally, there are differences by route of administration in terms of the patterns of serum levels -- although, because NORPLANT® involves the same progestin (LNG) as one of the POPs and the steroid levels are of approximately the same order of magnitude as POPs, clinical data can be extrapolated from NORPLANT® more reliably than from COCs and from other progestins.

Therefore, this review focuses on orally-administered norgestrel/levonorgestrel and norethindrone and indicates clinical differences between these progestins where applicable. Information on lynestrenol and ethynodiol diacetate pills is also considered, as norethindrone is their active metabolite. Data on these progestins administered by other routes (particularly LNG implants) is also utilized. However, data on other progestins administered by other routes (notably DMPA) is deemed to be of little clinical relevance to users of orally-administered norgestrel and norethindrone and therefore is excluded from discussion of most issues. Similarly, studies of combined oral contraceptives are not presented in detail, except for issues about which the relative effects of progestin and estrogen may be informative.
IV. EFFICACY AND PREGNANCY OUTCOMES

A. Pregnancy Rates

The current oral contraception labeling includes a table that gives the "lowest expected" failure rate for progestin-only pills as 0.5 percent, compared with 0.1 percent for combined OCs. This table is from Trussell & Kost (1987), who define the "lowest expected" failure rate as the expected rate of failure "among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly)." It represents the authors' best guess of the percentage of couples expected to experience an accidental pregnancy during the first year if they do not stop using the method for any other reason. The table was updated in a paper by Trussell et al. (1990) but these two lowest expected failure rates did not change. (See Table 1 for a comparison of failure rates by method; Table 2 contains studies of POP pregnancy rates.)

The "lowest reported" failure rate for POP users is 1.1% and for COC users is 0.5% (Trussell et al., 1990). (See Table 1.) This is defined as "the lowest reported percentage who experienced an accidental pregnancy during the first year following initiation of use (not necessarily for the first time) if they did not stop use for any other reason."

"Typical" failure rates cannot be computed separately for POPs and COCs, because these rates are based on data from surveys which did not differentiate between the two types of OCs (Table 1). The "typical" rate for pill users, most of whom are COC users, is 3% (Trussell et al., 1987). Trussell

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6Hatcher et al.'s 1994 edition of Contraceptive Technology replaces the term "lowest expected" with "during perfect use".
personal communication, 1993) and others therefore informally place the typical failure rate for POPs at closer to 5%. The "typical" failure rate is defined as follows: "Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they did not stop use for any other reason."

First year failure rates can generally be assumed to be higher than those of longer term users, both because new users are learning how to take their oral contraceptives correctly and because those who have problems using the pills comfortably, correctly, and effectively tend to drop out early. About 25% of all U.S. pill users discontinue in the first year (Trussell & Kost, 1987; Grady et al., 1989).

Other estimates of the failure rates for oral contraceptives in the general population of the U.S. have been higher, and are considered by some experts (Jones & Forrest, 1992; Harlap et al., 1991) to be closer to 5-8% than to the 3% cited by Trussell & Kost (1987). This is because Trussell & Kost's rates were based on married women only and did not take into account unreported abortions (Jones & Forrest, 1992). Trussell (letter, 1993) in return argues that the Harlap et al. failure rates are too high because contraceptive failures leading to live births are overreported, thus cancelling the effect of the underreporting of abortion. Trussell also argues that "single women using OCs may actually have lower failure rates because they have sex less often."

When compared to other contraceptive methods, the POP's lowest expected first year failure rate of 0.5 per 100 users is only slightly higher than the 0.3 for DMPA and 0.1 for COCs. It is also lower than that of the IUD (0.8-2.0) or any of the barrier methods. NORPLANT®'s failure rate (0.04) is the lowest of all the methods (Trussell et al., 1990).
If we assume the failure rate of POPs to be about 5% in typical use (Trussell et al., 1990), the rate for POPs exceeds the 3% estimate for COCs by 2%. The typical POP failure rate exceeds those for the long-acting reversible methods by a greater margin, since theirs remain the same as their lowest expected rates: DMPA, 0.3 per 100 and NORPLANT®, 0.04. However, compared to nonhormonal methods, the typical failure rate of POPs is identical to that of IUDs and much lower than those of the barrier methods, which range from 12% (condoms) to almost 30% (the sponge for parous women).

(See Table 1.)

In addition to the methodological difficulties inherent in comparisons of failure rates among contraceptive methods (Trussell & Kost, 1987), POP failure rates are affected by the fact that they are used preferentially by older women and breastfeeding women. A recent analysis of data from the Oxford Family Planning Association (OFPA) cohort study found that the failure rate for POP users declined from 2.0 per 100 woman-years of use at ages 25-34 to 1.1 at 35-39, and only 0.3 at 40-44 (Vessey et al., BJFP, 1990). The overall failure rate in that study was 0.8, but this rate was skewed by the older age of this sample, with half of the women being over 40 at the time of this most recent analysis. It was not possible to control directly for breastfeeding because there was no recorded information on infant feeding; however, the above results were obtained by excluding all use in the year following delivery to ensure exclusion of most breastfeeding women. Re-calculation of failure rates without excluding these postpartum women produced similar results. Guillebaud (book, 1993) uses data from this study to conclude that a woman over 40 taking the POP has the same chance of conceiving as a 25-year-old taking the combined pill.
Another study that compared failure rates by age was carried out using clinic records in Scotland (Bisset et al., 1990). The failure rate declined with age, from 1.7 per 100 woman-years among women less than 25 and 1.4 at ages 25-34 to 0.5 at 35-44 and 0.0 at 45 and older.

Table 2 presents the results of numerous studies of pregnancies among POP users. There is considerable variation in inclusion criteria, especially postpartum and breastfeeding status, age and whether switchers or only new users are included -- all of which affect the pregnancy rates. Furthermore, some papers report a Pearl Index of efficacy while others use life table rates. Although some studies report pregnancy rates for more than one formulation of POPs, these do not necessarily represent true differences between the pills themselves. Small sample sizes and lack of control for differences among the women taking the various progestins also account for some of the variation; for example, in one study the percentage of breastfeeding women was different among the formulations (Bisset et al., 1990).

The only study that randomly allocated POPs with different progestins, as well as COCs, found higher failure rates for NET 0.35 mg than for LNG 0.03 mg (WHO, Contrac, 1982). The life table pregnancy rates were 13.2 and 9.5 per 100 women, respectively, at one year and 19.6 and 9.5 at two years; the two-year rates were significantly different between the two progestins. The two-year rates for both POPs were similar to the rate of 12.9 per 100 women for one of the combined OCs (mestranol 0.05 mg plus norethindrone 1 mg), but the failure rate for norethindrone was significantly higher than the rate of 4.5 for the other COC (EE 0.30 mg plus LNG 150 mcg).

Reports of failure rates with progestins administered by several routes have indicated that pregnancy is more likely among women with a higher body weight. This trend is suggested by the
data on POPs from the Oxford Family Planning Association, which reports the lowest failure rate of 0.5 for the lightest women (less than 112 pounds) and the highest rate of 1.3 for the heaviest women (greater than 155 pounds or 70 kg) (Vessey et al., BJFP, 1990). The tendency to higher pregnancy rates among heavier women using POPs was also noted two decades ago, when a report by Vessey and colleagues (1972) indicated that the mean pre-treatment weight of the women who became pregnant during POP use was 3-5 kg greater than for those who did not become pregnant. Studies of NORPLANT® contraceptive implants (Sivin, 1988) and LNG vaginal rings (WHO, Contrac, 1990) have also found significantly increasing pregnancy rates with extreme body weight (≥70 kg).

Several reports of pregnancy rates have focused exclusively on breastfeeding women. A study in Argentina found a 6-month lifetable pregnancy rate of 0.5 per 100 women for both users of NG 0.075 mg and the nonhormonal contraceptive comparison group (Moggia et al., 1991). Another study in the same clinical practice found 9-month life table pregnancy rates of 3.9 per 100 women among users of LNG 0.03 mg, compared to 1.9 among IUD users, and 22.8 among users of barrier contraceptive methods (McCann et al., 1989). The pregnancy rate for POP users was statistically similar to that of IUD users, but significantly lower than that of the other nonhormonal subgroup. In both of these studies POP use began within one week postpartum and in both studies the pregnancies occurred toward the end of the follow-up period, when the contraceptive protection provided by lactation was waning. In a multicenter study of breastfeeding women, NG 0.075 mg was begun up to six months postpartum by 4,088 women, of whom 3,714 returned for at least one follow-up visit (Dunson et al., 1993). The authors computed an 11-month life table failure rate of 1.2 per 100 women. The investigators attributed 15 of the 20 pregnancies in the first six months of the study to

7The newer, less dense NORPLANT® SYSTEM tubing has reduced this problem (Sivin et al., 1988).
method failures, but most of those occurring in months 7-12 (10 of the 14 pregnancies) were attributed to user failure.

Other issues that may affect the efficacy of POPs include drug interactions (see Section IX), correct use of the method (see below) and possibly vomiting and diarrhea. Vomiting might reduce POP effectiveness in some cases, if it eliminates a series of recently swallowed pills, thereby having the same effect as not swallowing them in the first place. Severe diarrhea may also reduce the effectiveness of POPs, since steroids are partly absorbed through the intestinal wall (Back & Orme, in press; Orme, 1982; Fotherby, AJOG, 1990; Guillebaud, book, 1993). Sparrow (1987, 1989) and Shenfield (1986) are convinced that diarrhea can reduce OC efficacy. Sparrow (1989) records 42 cases (26%) of diarrhea-associated OC failure in one retrospective analysis of clinical records and 46 (33%) in another (Sparrow, 1987) but does not specify COC vs. POP users. However, women who have had an ileostomy or bowel resection do not have reduced absorption, according to Back and Orme (in press).

CONCLUSION: Pregnancy rates for women using POPs are slightly higher than the rates for women using COCs, especially for heavier women and for women who do not take the pills exactly on schedule. Typical failure rates are also higher for POPs than for long-term methods such as NORPLANT® contraceptive implants, and injectables. However, the typical pregnancy rates are the same as for IUDs and lower than for other immediately reversible contraceptive methods. Finally, the groups for whom POPs are most likely to be recommended for safety reasons (older women and those who are breastfeeding) have reduced fecundity. There are not enough data to support or refute the relationship between diarrhea and absorption. (Types of evidence: I A, C, D; II A, C, D.)
B. Compliance and Efficacy

Medication compliance has been defined in a variety of ways. For purposes of this paper, oral contraceptive compliance (or adherence) can be defined as "the use of a contraceptive method in a consistent and ongoing manner for the prevention of pregnancy" (Jay et al., 1989). As with other medications, this definition is not meant to imply that poor OC compliance is necessarily the fault of the user. It also does not assume that the clinician, pharmacist and/or manufacturer have provided the user with complete, correct or easily understood information about how to use the method effectively (Potter, 1991).

The factors that influence correct and effective use of the method include the personal characteristics of the user, the characteristics of the method itself, and those of the service system providing the method. User characteristics include sociodemographic factors such as age, education, parity, socioeconomic status and general social circumstances, as well as knowledge of correct use. Method characteristics include the hormones used, doses, and also the packaging and cost. Finally, service system characteristics include access, counseling provided at initiation and follow-up, whether written materials are provided, and whether additional back-up contraception is provided for emergencies (Potter, 1991, 1992).

Knowledge of how to use POPs correctly is essential. A small retrospective study of COC users in the U.K. (Brook & Smith, 1991) found that half of the women in their study did not know any of the factors that might reduce efficacy, including missed pills or certain drugs. A U.S. study (Emans et al., 1987) found that most of their inner-city teen clients did not read the instructions; 16% of COC users became pregnant in their first year of use.
Turning to progestin-only pills specifically, we can assume that, although correct use of progestin-only pills is not the only determinant of the effectiveness of the method, it is a primary contributor. The more pill-taking deviates from the prescribed regimen, the more likely the user is to become pregnant. Data on the relationship between progestin-only pill compliance and efficacy are scarce. (See Table 2.)

Quantifying the effect of non-compliance on efficacy rates is difficult for several reasons. Not all clinical trials report compliance data or failure rates attributable to incorrect use; furthermore, some studies (e.g., Dunson et al., 1993) drop poor compliers from the analysis. Also, it is the participants who experience problems with the method who are most likely to drop out of their own accord. Finally, the percentage of failures attributable to poor compliance is probably higher in the general population than in the small number of clinical studies that include compliance data (Harlap et al., 1991). The rates in these studies are based on self-report, generally using diary cards, by selected participants who are likely to receive careful counseling when they start the method, as well as on-going monitoring.

As discussed previously, the POPs rely on a very low dose of a single hormone and therefore do not always prevent ovulation, increasing the chance of method and user failure. The kinds of errors that constitute a threat to efficacy include: 1) taking a pill more than 24 hours after the last one; 2) missing any number of pills; and 3) not using a back-up contraceptive method when pills are late or missed, when they are vomited, or when taking certain drugs, such as anticonvulsants, antifungals and certain antibiotics. (See Section IX.) In general, consensus has been reached on the need for back-up contraception when even a single pill is more than 3 hours late, but whether the back-up should be used for 48 hours or 7 days has not been settled. (See Section XII.)
In a selected group of 17 studies (10 of which were previously reported by Trussell & Kost, 1987; Trussell et al., 1990), the failures attributed to the user varied from none (Vessey et al., 1972; Broome & Fotherby, 1990); to one-fourth (Vessey et al., BJFP, 1985; 1990); to one-third (Lawson, 1982; Postlethwaite, 1979); about half (Board, 1971; Jubhari et al., 1974; Hawkins & Benster, 1977); to two-thirds (Korba & Paulson, 1974; WHO, Contrac, 1982; Shroff et al., 1987; and Bissett et al., 1990) to over 90% (Martinez-Manautou et al., BMJ, 1967; Moggia et al., 1991). (See Table 2.) However, method and user failure rates from these studies are difficult to compare for a variety of reasons. Furthermore, there have been various changes over time in packaging from loose pills to blister packs, after the 1967 study by Martinez-Manautou (BMJ) noted the need for a reminder system.

The definitions of "user failure" (i.e., poor compliance) are not always provided in the literature, and those that are given vary from one late pill (Bisset et al., 1990, 1992; Shroff et al., 1987) to 2 or more missed pills in a cycle (Dunson et al., 1993). Some include drug interactions or diarrhea as user failure (Postlethwaite, 1979; Bisset et al., 1990, 1992), while others only include pill omissions without use of a back-up method (Shroff et al., 1987). In many cases, the specific non-compliance behavior is not stated. For example, the specific types of errors are described in only half of the cases in one study (Vessey et al., BJFP, 1985, 1990) and in 8 of the 17 studies reported here, no explanation of specific compliance errors was provided.

Only 3 of the studies with compliance data were conducted in the U.S. (Board, 1971; Korba & Paulson, 1974; Nelson, 1973). Among the general population of pill users in the U.S., the relationship between failure and compliance is especially difficult to measure in POP users because the number of women using POPs in this country make up less than 1% of the oral contraceptive market (Weber, 1987).
The low percentage of POP users, in the U.S. especially, also makes it difficult to generalize the proportion of failures due to poor compliance from these studies to the general population.

Again, most of the 17 studies reported in Table 2 are carefully monitored studies of selected populations, each with different entry criteria, some dropping poor compliers, and each with a different definition of poor compliance. Some of the studies include only postpartum women (Hawkins & Benster, 1977; Dunson et al., 1993; McCann et al., 1989; Moggia et al., 1991); some have a mix of postpartum and other users (Nelson, 1973; Lawson, 1982); some postpartum samples include no breastfeeders (Broome & Fotherby, 1990) while others include only breastfeeders (Dunson et al., 1993; McCann et al., 1989; Moggia et al., 1991). Age groups also vary. As discussed earlier, the significant proportion of the POP users who are either breastfeeding or are older, less fertile users, may artificially inflate the efficacy rates for more fertile pill users since the ages and breastfeeding status are not clarified in much of the reported data.

CONCLUSION: POP failures are due more often to user error than method failure. Characteristics of the user, the method and the service system interact to increase or decrease these errors. (See Section XII for a detailed discussion of specific problems.) (Types of evidence: II A, C, D; III A, D.)

C. Ectopic Pregnancies

Pregnancies that occur among users of POPs are more likely to be ectopic than are pregnancies among users of most other contraceptive methods -- although this statement does not necessarily imply that the actual rate of ectopic pregnancies is higher. While the causes of ectopic pregnancies (EP) in
general are uncertain, delay in ovum transport is hypothesized to be a factor. Because reduction in the activity of the fallopian tube cilia may be one of the modes of action of POPs (see Section II), changes in tubal motility that interfere with ovum transport could be the primary mechanism responsible for EP changes among POP users (Li & Newton, 1992). Electrophysiologic evaluation of the oviduct lends credence to this relationship; women who have naturally low progesterone levels also have electrophysiologic characteristics associated with poor ovum transport (Pulkkinen & Jaakkola, 1989), suggesting that the low progesterone levels in POP users (see Section II) could have similar associations.

In the U.S., the incidence of ectopic pregnancy (EP) has increased over the past two decades, from 4.5 EPs per 1000 reported pregnancies in 1970 to 16.8 in 1987 (Nederlof, 1990). Factors contributing to the trend may be: 1) increased rates of STDs and PID, with consequent tubal damage; 2) later childbearing; and 3) the increased use of modern contraceptives, and specifically, progestin-only methods (Franks et al., 1990; Li & Newton, 1992). Although all contraceptive methods, including POPs, prevent ectopic pregnancies by reducing the chance of conception, the degree of protection that a method provides against EP depends on the degree to which it prevents ovulation, conception and implantation, and on correct use of the method. In one of the earliest studies, Smith et al. (1974) reported that 4% of the pregnancies in their study of POP users were extrauterine and so hypothesized that POPs are better at preventing uterine than extrauterine implantation. This may be because, while the POP-induced endometrial changes prevent implantation there, the reduction in fallopian tube activity may slow ovum transport enough to cause implantation before the ovum reaches the endometrium (Li & Newton, 1992).
Because pregnancy is uncommon among users of POPs and because ectopic pregnancy is a small subset of these pregnancies, precise figures on the risk of ectopic pregnancies among POP users are difficult to obtain (Li & Newton, 1992). (Table 3 provides ectopic pregnancy rates from several studies.) A 1977 review of 18 studies, using 9 different types of POPs (Tatum & Schmidt, 1977), reported that 6% of all pregnancies among POP users were ectopic. This was significantly higher than would be expected in the normal population of pregnant women who conceived without using contraception, but there were differences among the various progestins (1.4% of pregnancies for NG/LNG and 8% for NET), and these percentages are based on very small numbers (1 and 3 ectopic pregnancies, respectively). These percentages reflect the number of EPs in relation to the number of pregnancies; they do not reflect the actual rate of occurrence of ectopic pregnancy with respect to woman-years of experience with POPs.

The likelihood of an ectopic pregnancy depends on both the pregnancy rate and the proportion of pregnancies that are ectopic. Franks and colleagues (1990) have computed the likelihood of ectopic pregnancy among users of various contraceptive methods (other than POPs) by multiplying (1) the "lowest expected" pregnancy rate from the comprehensive review by Trussell & Kost (1987) and (2) the proportion of pregnancies that are ectopic, obtained from various studies of specific contraceptive methods. We have modified their methodology to instead use the "typical" pregnancy rates, from Trussell's more recent paper (Trussell et al., 1990). We have also added POPs to the contraceptive methods considered, using data on the proportion of ectopic pregnancies from the large study of pregnancies among POP users conducted by Bisset et al. (1990); 2 of the 21 pregnancies were ectopic, for a proportion of 0.095, which is intermediate between the proportions of ectopic pregnancy used by Franks et al. for tubal sterilization (0.159) and IUD (0.051). Applying this proportion to the typical annual failure rate for POPs of 5% (or 50 per 1000 woman-years) produces an estimated ectopic
pregnancy incidence of 4.75 per 1000 woman-years for POPs. This incidence is similar to the incidence among women not using any contraception, although it is higher than for users of other contraceptive methods.

The studies of EP among POP users are, for the most part, retrospective, with small samples and no comparison groups; and even those studies that are prospective do not have controls. (See Table 3.) There has been only one double blind clinical trial comparing POPs and COCs, conducted by WHO (Contrac, 1982). However, the results of all these studies do point in the same direction and rates are fairly consistent across studies. In the 1970s, several small retrospective studies found unexpectedly high proportions of EP among POP users (Bergsjo, 1974; Bonnar, Lancet, 1974; Rantakyla, 1977). Then, a study of 238 EPs in two Finnish hospitals (Liukko et al., 1977) found significant differences in EP rates by type of progestin among 30 POP users. They compared POP sales figures with the number of EPs and found that lynestrenol had a significantly lower risk than other progestins (0.1 per 1000 woman-years of use for LYN 0.5 mg, 3 for LNG 0.03 mg and 4 for NET 0.30 mg.) Also based on sales data, a study of 1973-1977 Norwegian data on EP among POP and IUD users (Ulstein & Sandvei, 1980) found an annual ectopic pregnancy rate of 1.3 per 1000 woman-years. They did not specify the types of progestins or IUDs but found EP rates to be twice as high in the IUD group (0.24).

The only randomized clinical trial (WHO, Contrac, 1982) reported 2 ectopics out of 22 pregnancies among POP users, or 0.9 per 1000 woman-years, but no ectopics among the COC users. A recent study in Zimbabwe also compared the risk of EP in women using either POPs or COCs (De Muylder, 1991). It found a rate of 3 ectopic pregnancies per 1000 woman-years of use for unspecified POPs and 0.5 for COC users (based on 10 and 3 EPs, respectively).
Finally, EP rates vary by age and gravidity as well as race, socioeconomic status, sexual habits and infections, "... all of which should be taken into account before the incidence of EP can be realistically attributed to a specific contraceptive method" (Tatum & Schmidt, 1977). However, because EPs represent such a small subset of POP users, it is virtually impossible to control for these factors in analysis.

NORPLANT® has an estimated EP rate of 1.3 per 1000 woman-years of use, based on 5000 participants in clinical trials (Population Council, 1990). This is similar to the EP rate in the general U.S. population (including both contraceptive users and non-users) of 16.8 per 1000 woman-years (Nederlof, 1990). The NORPLANT® data suggest that the rate of EP may increase with duration of use and increased weight of the user.

There is some controversy as to whether a history of EPs should be considered a contraindication against POP use. Probably most clinicians would agree with Li & Newton (1992) in recommending combined OCs as the more appropriate choice of hormonal contraception for patients with a history of EP when possible. The issue is less clear in those situations where POPs would be the hormonal method of choice. Among several major clinical guidelines, none recommends previous EPs as an absolute contraindication. The Medical and Service Delivery Guidelines for Family Planning of the International Planned Parenthood Federation (IPPF) deem previous ectopic pregnancy to be a relative contraindication for POP use, suggesting that close medical supervision is advisable (Huezo & Briggs, 1992). Guillebaud (book, 1993) adds that history of ectopic pregnancy should be a stronger relative contraindication for a nulliparous woman than for an older multiparous woman because of concern about preserving future fertility potential. The INTRAH (1993) Guidelines note that POPs do not prevent ectopic pregnancy as effectively as they prevent intrauterine pregnancy, but do not advise
against POP use by a woman with a history of ectopic pregnancy. Goldzieher (book, 1989), Hatcher et al. (1994) and Speroff & Darney (1992) do not include previous EPs as a contraindication to POP use. (Appendix A.)

However, as Chi noted in his 1993 (Contrac) review of the literature, there is almost unanimous agreement that there be suspicion of EP when a patient using POPS develops symptoms such as abdominal or pelvic discomfort, unexplained vaginal bleeding or amenorrhea. Hatcher et al. (1994) specify sudden, intense pain or cramping in the lower abdomen, usually on one side; irregular bleeding or spotting with pain when period is late or especially light; and fainting or dizziness as warning signs of ectopic pregnancy.

CONCLUSION: Although approximately 10 percent of the pregnancies among POP users implant at an extrauterine site, the incidence of ectopic pregnancies is similar to that for women not using any contraceptive methods. Nonetheless, a history of EP need not be considered a contraindication to POP use. However, the POP label should emphasize the need to be alert to symptoms of EP. (Types of evidence: I A, C; II A, B, C, D.)

D. Outcome of Pregnancies Conceived While Using POPs

In the 1970s, concerns were raised about the dangers of fetal exposure to POPs and other steroids. Further research, using carefully controlled studies, has found no such relationship.

Several factors are involved in whether or not a specific agent is teratogenic in humans: the specific agent and its dosage, when the fetus is exposed, and the genetic susceptibility of mother and
infant. It is during embryonic weeks 3-8 that the embryo is most susceptible. After that period, except for brain and gonadal tissue, it would be growth rather than formation that would be affected (WHO, 1981; Wilson & Brent, 1981; Simpson & Phillips, 1990).

Several reviews of the literature (WHO, 1981; Wilson & Brent, 1981; Bracken, Ob/Gyn, 1990; Simpson & Phillips, 1990) agree that those studies finding significant rates of malformations due to exogenous progestins (and to steroids in general) have methodological problems that call their results into question. The relevant literature on the effect of steroids on congenital malformations is of three types: 1) a limited number of articles that deal directly with accidental use of oral contraceptives during pregnancy; 2) the research on use of OCs "around the time of conception"; and 3) articles on the use of progestins during early pregnancy as a pregnancy test or to prevent abortion (although the administration of these progestins is for a brief period and is given in higher doses than that used in POPs for contraception).

Preconceptual administration of sex steroids was previously thought to possibly result in an abnormal endometrium that might be responsible for an increase in abnormal development, according to Wilson & Brent (1981). However, there is no scientific support for the induction of teratogenesis from preconceptual exposure to sex steroids (WHO, 1981; Wilson & Brent, 1981; Simpson & Phillips, 1990). Also, Simpson & Phillips (1990) note that it is important to keep in mind that the only estrogen implicated as a teratogen, diethylstilbestrol, is not contained in oral contraceptives. Therefore, pooling data on exposure to progestin-only and combined oral contraceptives can provide useful information in evaluating risks to the fetus. The WHO (1981) review specifically notes the lack of data on progestin-only methods.
The detailed review of the literature by Simpson & Phillips (1990) examined 18 major prospective studies evaluating the effects of progestin exposure during pregnancy, and determined that the doses received were not teratogenic. They conclude that hormonal contraception is not associated with increased risk of any of the following birth defects: cardiac anomalies, limb reduction deformities, hypospadias (abnormal development of male genitalia), neural tube defects and hydrocephalus, esophageal atresia, polydactyly, congenital abnormalities as a group, chromosomal abnormalities, or gene mutations. The lack of effect on risk for cardiac malformations, the largest single type of congenital defect, has been directly acknowledged by the U.S. Food and Drug Administration (Simpson & Phillips, 1990).

In doing a simple count of the prospective studies of progestin exposure during pregnancy reported in Simpson & Phillips (1990), only 5 of the 18 reported a statistically significant percentage of excess anomalies; of those, all were conducted in the 1970s. There was no pattern to the anomalies found, and each study had methodological problems, although in all cases there was a slightly higher rate of anomalies in the progestin-exposed group, albeit quite small and not of statistical significance. However, of all 18 studies, only three used matched controls (Savolainen et al., 1981; Varma & Morsman, 1982; Michaelis et al., 1983) and the kinds of progestins and exposure times varied.

The conclusions of Simpson & Phillips (1990) are further strengthened by a meta-analysis of 12 prospective cohort studies which examined major malformations, cardiac defects, and limb reduction defects among those exposed to any use of oral contraception before or early in pregnancy (Bracken, Ob/Gyn, 1990). This analysis increased the statistical power of otherwise inconclusive studies in order to detect any significant effects of OC exposure early in pregnancy; no such effects were found. The review also found no effects of exposure to OCs before pregnancy. The overall relative risk of
malformations in those exposed to OCs was 0.99 for cardiac defects; and for limb reduction defects, the relative risk was just 1.04. Bracken notes that it is especially reassuring when the results of so many studies involving different populations agree on the lack of increased risk for OCs.

A comprehensive review of the literature (Wilson & Brent, 1981) also concluded that "the use of exogenous hormones during human pregnancy has not been proven to cause developmental abnormality in nongenital organs and tissues." That review found "no consistent type, pattern, or range of defects," but, on the contrary, noted that the "reports emphasized associations with different defects or patterns." Although they did not consider the data sufficient to allow a definitive conclusion, they described the risk of such abnormalities as being substantially below the spontaneous risk, and possibly not causal. However, when high doses of progestins were used for threatened abortion, masculinization of female genitalia was found to occur; this use of progestins has been discontinued.

As suggested above, the individual studies included in these reviews have numerous methodological problems and differing definitions, populations, denominators and purposes. Estimates are unstable due to the small numbers of exposed women and the low rates of teratogenicity. Among the issues are retrospective vs. prospective cohort studies, type and dosage of progestin and length of exposure, what other drugs are being taken, whether the control group is similar, and whether cases had experienced previous pregnancies with malformations. The earliest reported studies did find associations, but with widely, almost randomly, varying types of effects. The authors of the individual reports themselves frequently noted the possibility that their results were statistical artifacts.
For example, in one case-control study (Lammer & Cordero, 1986), only 36 of the 1091 infants exposed to exogenous steroids in the first trimester of pregnancy were exposed to contraceptive progestins and no significant rates of malformation were found in that group. In the report of another study, concern was expressed about the statistical validity of its own findings of a small relationship between exogenous progestins and malformations that both seemed to increase with mother's age and affect boys more than girls (Janerich et al., 1980). The authors noted that when the relative risk is less than double, it is often difficult to distinguish between cause and confounding by other factors.

Another example of the confounding effects of other variables is in a study of 1370 malformed infants (and 2968 controls) that stratified on specific estrogens and progestins in OCs taken around the time of conception (1 year prior to 4 months after conception) (Bracken et al., 1978.) No overall relationship (odds ratio = 0.94) between OC exposure and malformations was found. However, in that sample, heavy smokers who also used hormonal contraception were 13 times more likely to have a baby with a malformation than non-smoking, non-hormonal contraceptors. A third study that raised the issue of confounding was one that showed a marginal relationship between exogenous steroid exposure and congenital heart disease in offspring of 390 mothers, compared with 1254 normal births (Rothman et al., 1979). In that study, the authors found that exposure to other drugs, such as antibiotics, anticonvulsants, anti-nausea agents, insulin, and codeine, was reported more frequently by mothers of malformed infants than was exposure to the hormones.

Reanalysis of other earlier studies (such as Wiseman & Dodd-Smith's 1984 re-analysis of Heinonen et al.'s 1976 data on cardiac lesions) or later studies by the same researchers (Harlap et al., 1985 vs. Harlap et al., 1975) also did not substantiate previous findings, as the need for stricter definitions of type and timing of exposure were understood and applied.
There are even fewer studies on the long-term developmental consequences for infants of POP use during pregnancy than on the immediate teratogenic effects. One study of 19 infants of at least one year whose mothers used POPs (Ravn, 1975) found no subsequent complications. Two long-term follow-up studies of the growth and development of offspring of former combined OC users also found no significant association between OC use prior to conception and infant outcomes. One of these studies, of 177 infants, found no correlations with physical growth, hematological outcomes or psychometric scores up to the age of 3 (Magidor et al., 1984). However, the number of children still being followed at age 3 was too small to provide the needed power to detect differences if they existed. The other study (Ortiz-Perez et al., 1979) does show a non-significant trend toward lower IQ score for offspring of former OC users, which they felt warranted further study. However, that study is not clear about the timing of the OC use "prior to conception" or other potential confounders.

It should be noted that clinical trials of NORPLANT® also found no evidence of teratogenicity for LNG administered by implants (Population Council, 1990).

Based on the findings of these studies, it is unlikely that fetal abnormalities or developmental lags will occur because of accidental use of POPs during pregnancy, nor is there an hypothesized biological mechanism for such an effect. However, clinical guidelines recommend ruling out any suspected pregnancy before initiating use of POPs, not only because contraception is not needed then but also to prevent any concern about the possibility of abnormalities or any confusion about the timing of conception (ACOG, 1993). (See Appendix A.)

CONCLUSION: There is no evidence of increased risk of teratogenic effects with progestin-only oral contraceptives taken either pre-conceptionally or during early pregnancy. While this
conclusion is reassuring to women who accidentally become pregnant while taking POPs, it is nonetheless prudent to rule out suspected pregnancy before initiating any hormonal contraceptive use. (Types of evidence: II A, B, C, D; III A, B, D.)

E. Fertility Following POP Discontinuation

In the normal population of the U.S. (and the U.K.), approximately 25% of women will conceive within one month of unprotected intercourse, 60-70% within 6 months, 80-90% within 12 months and 90-95% within 24 months (Fraser & Weisberg, 1982). Because progestin-only OCs cause less suppression of ovulation and of hypothalamic-pituitary-ovarian function than the combined pill, they should produce less delay, if any at all, in the return to fertility after ceasing contraception (Fraser & Weisberg, 1982). There are no large scale studies of return to fertility in former POP users but data from several small studies indicate no effect. A study by Eckstein et al. (1972) found that of 6 users of NG 0.075 mg who stopped use to conceive, all succeeded within 6 months (2 of them within the first month). Another study (Lawson, 1982) found that of 43 women who had discontinued NET 0.35 mg, a majority became pregnant within 3 months, 10 took longer than 6 months, with the rest in between; there was no relation between length of time to achieve pregnancy and the length of treatment. Finally, the Oxford Family Planning Association study (Vessey et al., 1985) found return to fertility of 83 POP users was not significantly different from that of diaphragm users.

Similarly, the Population Council (1990) reports that studies of NORPLANT® users have shown a rapid return to fertility. After a year or more of use, the post-removal pregnancy rate is similar to rates following discontinuation of IUDs or among women who have not recently used contraceptives (Affandi et al., 1987). Ismail et al. (1987) found return to ovulation in 8 of 10 NORPLANT® users
after 3 weeks and Konje et al. (1992) reported that all of the 17 women they examined were ovulating. Full return to fertility was most rapid in those who had regular cycles while using NORPLANT®; cervical mucus remained hostile in a few women "for some time", possibly suggesting a luteal phase deficiency. Diaz (1987) reported that 49% of 90 women had conceived by 3 months and 86% by 12 months after removal of the implants, compared with 69% and 89% of a control group by 7 weeks after their implant removal.

CONCLUSION: Although data on return to fertility after use of POPs are sparse, there does not appear to be a significant delay following discontinuation. POPs prevent ovulation in only about half of cycles during use and so normal ovulation can be expected to resume readily after discontinuation. Although POPs have less residual effect on resumption of ovulation than do COCs, it is possible that in some women the POPs may continue to have some short-term effect on other mechanisms of action even after full return to ovulation. (Types of evidence: II A, B, C.)
V. METABOLIC EFFECTS

The very low progestin dosage in POPs suggests that any metabolic effects would be very small. Thus, as will be discussed in Section VI, it is very unlikely that POPs are associated with an increase in cardiovascular disease (CVD).

A. Lipid Metabolism

The results of several studies of lipid metabolism among users of POPs are presented in Table 4. In general, these findings indicate very little effect on lipid metabolism. The levels of total cholesterol are unchanged in all of the studies. Similarly, none of the studies that measured high density lipoprotein (HDL), low density lipoprotein (LDL), or very low density lipoprotein (VLDL) found any effects of POPs. There was some evidence of a small decrease in HDL cholesterol. This HDL decrease was most apparent in the randomized clinical trials by Kauppinen-Makelin et al. (1992), in which LNG was given at a dose five times that of the usual POP dose. This latter study also reported the expected increase in hepatic lipase (HL), suggestive of catabolism of HDL, but not the corresponding change in apolipoprotein A-I. The other study that measured apolipoproteins was cross-sectional in design; it found no effects on apolipoprotein B (associated with LDL metabolism) and significantly lower levels of apolipoprotein A-I and A-II for users of POPs containing NET or ED, but not LNG (Godsland et al., NEJM, 1990). In addition, HDL levels were lower in some, but not all, study groups. Finally, some studies have also found decreases in triglycerides, while others found no significant changes. There were no consistent differences between POPs containing NG/LNG and NET.
Although there have been numerous studies of the relationship of combined OCs with serum lipids and lipoproteins, considerable controversy remains due to differences in pill formulations and to the complexities of accurate measurement of lipoprotein subfractions (Crook et al., 1988; Fotherby, BJFP, 1990). Furthermore, extrapolating the COC results to POPs is complicated by the fact that progestins have effects on lipid metabolism that are opposite those of estrogens (Crook et al., 1988; Dorflinger, 1985; Krauss & Burkman, 1992). Most studies of combined OCs have found no change in total cholesterol or LDL cholesterol, but HDL cholesterol may be increased, decreased, or unaffected, depending on the specific COC formulation. All types of COCs appear to increase serum triglycerides. Several studies of COC users have shown a relationship of higher progestin dose with decreased total HDL and HDL₂ cholesterol and, to a lesser extent, with increased LDL cholesterol; there is some suggestion of greater effects by LNG than NET, although the opposing effect of estrogen ameliorates these relationships (Godsland et al., NEJM, 1990; Krauss & Burkman, 1992; Mishell 1989; Tikkanen & Nikkila, 1986; WHO, Contraceptives, 1988). A Consensus Development Meeting regarding metabolic aspects of OCs related to cardiovascular diseases (Skouby, 1990) concluded:

Oral contraceptives induce changes in lipid and lipoprotein metabolism, and these changes are dose dependent and can be related to both estrogen and progestin.

The effects of progestins on lipoprotein metabolism appear to be related to the androgenicity of progestins, with stimulation of hepatic lipase accelerating the clearance of HDL and thus lowering HDL levels (Krauss & Burkman, 1992). Therefore, the more androgenic levonorgestrel has a greater potential effect on lipid levels than does norethindrone (Ball et al., 1991; Crook et al., 1988; Dorflinger, 1985; Krauss & Burkman, 1992). However, because the relative androgenicity of LNG and NET is similar to their relative progestogenic effect (Dorflinger, 1985) and because the relative progestogenic activity has been accounted for in the POP dosage levels, the marketed LNG and NET POPs would actually be expected to have similar effects on lipids. This is shown most conclusively in
the randomized clinical trial of NET 0.35 mg and LNG 0.03, by Ball et al. (1991), which found no significant differences between the two POPs in any of the lipid parameters after 6 months.

Studies of NORPLANT® subdermal LNG implants have found that HDL₂ levels were lowered in the only study in which they were measured, but that total HDL was increased in some studies and decreased in others, according to a review by Population Council (1990). Total cholesterol was decreased in all studies and the ratio of total cholesterol to HDL was not significantly increased in any studies. Part of the differences among studies is attributable to variations in the time periods covered by the reports (Otubu et al., 1993). Recent studies that have evaluated NORPLANT® throughout the full five years of use demonstrated that there were initial decreases in total cholesterol, HDL, LDL, and triglycerides, but all of these parameters returned to pre-insertion levels by the end of five years (Singh et al., Contrace, 1992, p. 141; Singh et al., Contrace, 1992, p. 463). The labeling for NORPLANT® states that LNG: decreases total cholesterol, LDL, and triglyceride levels; variously produces increases and decreases in HDL levels; and results in no statistically significant increase in the ratio of total cholesterol to HDL-cholesterol. The conclusion in the labeling is: "Although lipoprotein levels were altered in several clinical studies with the NORPLANT® SYSTEM, the long-term clinical effects of these changes have not been determined." As a precaution, the labeling recommends that women with hyperlipidemias who use NORPLANT® be carefully monitored.

Consideration of whether POPs are appropriate for women with dyslipidemia requires extrapolation from studies of lipid effects on women without lipid abnormalities and from evaluation of COCs (Knopp et al., 1993). The recommendation to use any OC depends on the level of lipid abnormality, the woman's age, and the presence of other cardiovascular disease risk factors. A recent review (Knopp et al., 1993) of contraception and dyslipidemia concludes:

Progestin-only contraception is probably preferable in the presence of overt hypertriglyceridemia to avoid estrogen-induced increases in triglycerides. Because data are insufficient regarding older women who use oral or implantable progestin-only preparations, monitoring of dyslipidemic patients who are given such agents is recommended.

IPPF Guidelines conclude that POPs have a "negligible" effect on lipid metabolism (Huezo & Briggs, 1992). INTRAH (1993) Guidelines state that progestin-only contraceptives have no significant effect on cholesterol.

CONCLUSION: POPs have only negligible effects on lipid metabolism. There is a suggestion of decreases in HDL and HDL_{2} cholesterol (as well as increases in hepatic lipase and decreases in apolipoproteins A-I and A-II), but these changes are very small and not found in all studies. LDL cholesterol levels are not affected by POP use. POPs may be appropriate for women with lipid abnormalities, depending on the severity of the abnormality, successful management of the dyslipidemia, and proper monitoring. (Types of evidence: I A; II A, B, C, D.)

B. Carbohydrate Metabolism and Diabetes

Research findings on the relationships between POPs and carbohydrate metabolism are mixed, as displayed in Table 4. Most assessments indicate no effect, but there is a suggestion of slight deterioration in glucose tolerance and elevated plasma insulin concentrations. These adverse effects
appear to be somewhat more likely with NG/LNG than with NET, even at the POP dosages. Earlier data also indicated that POPs have minimal effects on carbohydrate metabolism (Rinehart, 1975).

The limited evidence on POP use among women with diabetes mellitus indicates that this is an acceptable method for diabetic women. In one study, diabetic women taking 0.35 mg NET did not require an increase in their insulin dose and experienced no change in their retinopathy (Steel & Duncan, 1981). A randomized cross-over study among diabetic women of a POP and a COC, each containing lynestrenol (which is converted to NET), found that use of LYN 0.5 mg alone did not change the insulin requirement, blood glucose, or body weight, but that during use of the COC (LYN 2.5 + EE 0.05) insulin requirements were increased (Radberg et al., 1982; see Table 4). Because of the increased risk of pregnancy complications among diabetic women, it is particularly important that they use effective contraception (Elkind-Hirsch & Goldzieher, in press; Mestman & Schmidt-Sarosi, 1993). It has been suggested that diabetic women usually have excellent POP compliance because they take their pill at the same time as they take their daily dose of insulin (Guillebaud, book, 1993; Steel & Duncan, 1981). Thus, whether a diabetic woman who desires hormonal contraception should use a POP, a low-dose COC, or a progestin implant depends in part on her personal preference, as well as the results of careful monitoring, according to a recent discussion of contraception options for women with diabetes mellitus (Mestman & Schmidt-Sarosi, 1993).

Regarding combined OCs, research indicates that abnormal glucose tolerance test results are related to progestin dose (especially for NG/LNG) and that estrogen does not affect carbohydrate metabolism (Mishell, 1989; Perlman et al., 1985; Spellacy, 1982; Gaspard & Lefebvre, 1990). The Consensus Development Committee (Skouby, 1990) concludes, as follows:
The progestogen component is mainly responsible for the effects of OCs on carbohydrate metabolism, but the estrogen may modulate the influence. The magnitude of the impact on glucose metabolism depends on the type of progestogen and also on the doses of a given steroid.

Two reviews of COC experience (Elkind-Hirsch & Goldzieher, in press; Gaspard & Lefebvre, 1990) state that current use is associated with an increased risk of impaired glucose tolerance, primarily with increased insulin levels maintaining normal glucose levels. These alterations are particularly pronounced with higher doses of progestins and among women who are older, obese, or have a history of gestational diabetes or a family history of diabetes mellitus. The mechanism for this effect appears to be impaired binding of insulin to its receptor. Current use of lower progestin-dose COCs carries only a small elevation in risk of impaired glucose tolerance, even among women with previous gestational diabetes. Furthermore, there is no evidence for a sustained elevated risk, with no difference in the likelihood of diabetes mellitus in ever users compared to nonusers. Thus, both reviews conclude that, while small changes in various parameters of glucose metabolism can be measured in OC users, these changes are unlikely to be of clinical significance.

The Population Council (1990) review reports small initial increases in serum glucose concentration among NORPLANT® users, but these levels do not increase further with duration of use. Recent 5-year follow-up studies by Singh and colleagues (Contrac, 1992, p. 141; Contrac, 1992, p. 463) indicate no significant changes in carbohydrate metabolism. Konje et al. (1991) report changes in some parameters of carbohydrate metabolism, peaking at 12-18 months after implant insertion, but all changes remained within the normal limits. No data on use of NORPLANT® by women with diabetes are available, because initial studies specifically excluded these women (as well as women with other chronic health conditions) (Mestman & Schmidt-Sarosi, 1993). The NORPLANT® labeling reports no significant changes in mean serum glucose levels after insertion, but recommends that diabetic and pre-diabetic implant users should be carefully observed.
The INTRAH Guidelines note that current progestin-only methods have no significant effect on development of diabetes (INTRAH, 1993). IPPF recommends POPs for diabetic women who wish to use OCs (Huezo & Briggs, 1992).

CONCLUSION: Most studies of the effects of POPs on carbohydrate metabolism report only small alterations that are probably not clinically important. This is true even for diabetic women, for whom POPs are an acceptable method of contraception. (Types of evidence: I A, D; II A, B, D.)

C. Coagulation Factors

Progestin-only oral contraceptives have generally been found to have little effect on various parameters of coagulation activity (Fotherby, BJFP, 1989). However, most studies have been small, have looked at only short-term exposure, and have each investigated only a few hematological factors; furthermore, they were generally performed in the 1960s and 1970s, and thus did not use recent laboratory methods (Beller, in press; Fotherby, BJFP, 1989).

The small randomized clinical trial of NET 0.35 mg and LNG 0.03 mg by Ball et al. (1991), described in Table 4, recently examined several coagulation factors. There was no significant effect on fibrinogen and plasminogen, although there was a tendency toward a decline in both. Several other factors (Factor VIIc, Factor X, and antithrombin III) were unchanged in new users but fell among women switching from COCs to POPs, reflecting the removal of estrogen. In contrast, another study found that use of a POP containing lynestrenol 0.5 mg was associated with a decrease in antithrombin III levels, similar to that of a COC in the same study, with levels significantly lower than for
nonhormonal controls (Bounameaux et al., 1978). A report from Finland of three POPs (analyzed as a
group) found no effect on antiaggregatory prostacyclin or proaggregatory thromboxane A2, as assessed
by plasma levels of their metabolites, and a decreased ability of the platelets to release thromboxane
B2 during spontaneous clotting (Ylikorkala et al., 1982). A review of early data also noted that POPs
have less effect than COCs on coagulation factors, or no adverse effect at all (Rinehart, 1975).
Among these early studies is research by Howie and colleagues (1970), which indicated that ED 1.0
mg had no effect on the following assessments of coagulation and fibrinolysis: antithrombin,
antiplasmin, fibrinogen, thrombin clotting time, one-stage prothrombin time, kaolin partial
thromboplastin time, Factor II, Factor V, Factor VIII, and plasminogen; in comparison, many of these
parameters were significantly affected by a combined OC and by estrogen alone.

Meaningful quantification of coagulation factors is difficult because of the nature of the
coaulation cascade, in which one coagulation factor activates the next, and simultaneously stimulates
inhibitory factors. Furthermore, concentrations of such factors as fibrinogen, factor VIII, factor VII/X
and antithrombin III have very broad ranges (Beller, in press). Finally, no causal relationship between
increased levels of individual clotting factors and thrombosis has been established. Nonetheless, early
studies showing some evidence of adverse changes in both the blood coagulation and fibrinolytic
systems with combined OC use led to concern about potential increased risk of thrombosis. The
Consensus Development Committee (Skouby, 1990) stated the following:

Oral contraceptives induce alterations in hemostasis variables.... It is conceivable that these
effects are estrogen mediated because they have not been demonstrated in progestogen-only
preparations. There is a dose-dependent relationship in the case of estrogen, although in
combination pills, the progestogens might exert a modifying effect.

Reviews of NORPLANT® research have concluded that, although studies have produced
inconsistent results regarding clotting factors (Population Council, 1990), in general, the blood
coagulation system appears to be unchanged (Davies & Newton, 1991). Recent reports from 5 years of follow-up of women using NORPLANT® and NORPLANT®-2 indicate the following: decrease in Factors II, V, and VII; reduction in fibrinolytic activity; increased platelet numbers; and accelerated platelet aggregation (Singh et al., Contrace, 1992, p. 203; Singh et al., 1993). Factor X was significantly increased for users of NORPLANT® but not for NORPLANT®-2 in these studies by Singh and colleagues. Shabaan et al. (1984) have compared numerous coagulation parameters for NORPLANT® and COC users (ME 0.05 mg + NET 1.0 mg; EE 0.03 mg + LNG 0.15 mg). They concluded: "The results demonstrate, with marked contrast, that the implants had less pronounced effects on the blood coagulation system than did the combined pills used in this study."

Similarly, DMPA does not affect the coagulation and fibrinolytic enzyme systems (Beller, in press).

IPPF Guidelines state that POPs have "no effect on coagulation factors and therefore no risk of venous thrombosis" (Huezo & Briggs, 1992). Similarly, INTRAH (1993) Guidelines advise POPs for women over 35 who smoke heavily (and are thus at increased risk of thrombosis) but who do not want to use a non-hormonal method.

CONCLUSION: POPs appear to have little or no effect on coagulation factors. They may therefore be particularly appropriate for women who wish to use oral contraceptives but who are at increased risk of thrombosis, including older women who are smokers. (Types of evidence: I A; II A, B, C, D.)
D. **Blood Pressure**

Most studies of progestin-only oral contraception find no increase in blood pressure measurements or prevalence of hypertension. Some investigators report a decrease in blood pressure, but this may result from the well-known phenomenon of regression to the mean in longitudinal assessment of blood pressure, resulting in part from lessened anxiety of patients on repeat examinations. The randomized clinical trial by Ball and colleagues (1991) found declines in both mean systolic and mean diastolic pressures for NET 0.35 mg and LNG 0.03 mg, with somewhat greater declines for LNG but no significant differences in the two groups at 6 months. In the randomized cross-over trial conducted among diabetic women by Radberg et al. (1982), there were no significant differences in blood pressure measurements between LYN 0.5 mg alone and LYN 2.5 mg plus EE 0.05 mg.

Observational studies have produced similar results. A study comparing several contraceptive groups revealed that, after two years, mean blood pressure had not increased among POP users; there was a suggestion of some decrease for the three POP groups (NET 0.35 mg, NG 0.075 mg, ED 0.50 mg) and the nonhormonal control groups in systolic and/or diastolic blood pressure, but significant increases for both low-estrogen-dose COC groups (LNG 0.15 mg + EE 0.03 mg; ED 2.0 + EE 0.03) (Wilson et al., 1984). Because the women taking POPs were older and more likely to be smokers, the analysis was repeated for the subset of women who were age 21 to 30 and non-smokers, with similar results. A report of another comparative study also indicates no increase in mean blood pressure or incidence of hypertension (blood pressure >140/90 mm Hg) for either of two POP groups (NG 0.075 mg, ED 0.25 mg) or for IUD users, but increases for high dose OC users (ME 0.1 mg + ED 1.0 mg) (Spellacy & Birk, 1972); elevated blood pressure was significantly less common for NG users than for
IUD users. A comparison among three POPs found significant decreases in mean systolic and diastolic blood pressures for NET (0.35 mg), a significant increase in systolic blood pressure for chlormadinone acetate (0.5 mg) and no significant changes for megestrol acetate (0.5 mg) (Hawkins & Benster, 1977). Finally, a ten-year follow-up study of NET 0.35 mg found no trends in either systolic or diastolic blood pressure (Lawson, 1982).

It is uncertain whether the increase in blood pressure reported for some combined OC users is the result of the estrogen or progestin components. A recent multicenter randomized clinical trial of COCs containing either 0.03 or 0.05 mg EE (with LNG 0.25 mg), sponsored by WHO (Contrac, 1989, p. 147), found no significant differences in blood pressure measurements or the life-table probability of developing hypertension within one year. Comparison of the higher estrogen dose COC groups in this study with IUD users revealed significantly higher mean blood pressures and rates of hypertension for COC users (WHO, Contrac, 1989, p. 129). Thus, there appears to be a vasopressor effect of combined OCs, but no dose-response relationship for estrogen.

Several data sets have been analyzed to examine whether there is a dose-response relationship of higher blood pressure with increasing progestin dose in COCs. The study by Meade and colleagues (1980) that examined various endpoints in relation to progestin dose, based on reports to the Committee on Safety of Medicine, found no association of dose of either LNG or NA with hypertension. Similarly, a clinical study by Meade et al. (1977) did not document a dose-response effect for either LNG or NET on systolic or diastolic blood pressure measurements. In the Walnut Creek Contraceptive Drug Study, mean blood pressure readings were similar for various doses of norethindrone and norethynodrel; in addition, blood pressure was similar for the various types of progestins, which also included norgestrel (Fisch et al., 1974). In contrast, analysis of the Royal
College of General Practitioners (RCGP, Lancet, 1977, p. 624) Oral Contraception Study showed a dose-response relationship of hypertension with increasing progestin dose in COCs containing EE 0.05 mg (8.2% for norethindrone acetate 1 mg, 12.3% for NA 3 mg, and 13.9% for NA 4 mg).

No significant changes in blood pressure have been found following NORPLANT® insertion (Davies & Newton, 1991; ICCR, 1978). Nonetheless, elevated blood pressure is given in the NORPLANT® labeling among the warnings that are based on combined OC experience. Although it states that there were no statistically significant trends in blood pressure in clinical trials of these implants, physicians should be "aware of the possibility" of elevated blood pressure with NORPLANT®.

Both IPPF and INTRAH Guidelines state that not only do POPs not have an effect on blood pressure, but POPs should be used by hypertensive women who prefer oral contraception (Huezo & Briggs, 1992; INTRAH, 1993). Hatcher and colleagues (1994) concur with this recommendation. A 1993 review of contraception for women with cardiovascular disorders adds that progestin-only formulations are particularly advantageous for hypertensive women who are older, who smoke, or who have hypertension that is difficult to control (Sullivan & Lobo, 1993).

CONCLUSION: It can thus be concluded that POPs do not increase the prevalence of hypertension. Furthermore, for women who are hypertensive, POPs are preferable to COCs. (Types of evidence: I A, D; II A, B, D.)
VI. CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is rare among premenopausal women. Because a large number of premenopausal women take OCs, this fact suggests that any absolute increased risk among OC users is quite small. This low incidence of CVD also makes it difficult to evaluate the risk associated with specific pill formulations -- which is particularly true for POPs, as they are taken by a very small percentage of the OC users. The small increase in risk of CVD that is associated with COC use is dose-related; thus the very low dose of progestins in POPs is unlikely to impact CVD risk. Furthermore, most of the increased risk for COC users is due to the thrombotic effects of estrogens, and POPs have no effect on coagulation factors.

A. Progestins and Cardiovascular Disease

Only two studies have evaluated the risk of cardiovascular disease with POPs. A Danish case-control study found no association of POPs use with cerebral thromboembolic episodes (OR 0.9, 95% confidence interval 0.4-2.4, after exclusion of women with predisposing conditions and controlling for age, smoking, and education) (Lidegaard, 1993). Analysis of COC users in this study revealed a dose-response effect of increasing risk with increasing estrogen dose; progestin type and dose in COCs was not considered.

A recent case-control study of fatal myocardial infarction (MI) in England and Wales found that cases were less likely than controls to have been current users of POPs, although the numbers were very small (Thorogood et al., 1991). Comparison of the 3 cases (1.9%) and 12 controls (3.9%) who used POPs to non-users of any OCs results in an odds ratio of 0.54, but this calculation does not
consider the effect of cigarette smoking, and age was controlled only by 5-year age matching of cases and controls. Similar analysis by the same researchers regarding fatal stroke did not produce separate counts for POPs (Thorogood et al., 1992). Among COC users, the results suggested a small increase in risk of subarachnoid hemorrhage and a larger increase in risk of occlusive stroke and fatal MI, with some indication of a dose-response relationship for estrogen.

Two large case series have produced figures for the prevalence of various cardiovascular diseases among POP users, but with no comparison groups. In the Oxford Family Planning Association (OFPA) prospective study, there were 2 women with venous thromboembolism and 2 who had strokes (one subarachnoid hemorrhage and one non-thrombotic stroke during 3303 woman-years of POP use) (Vessey et al., 1985). Among 2,202 women in the United States and Puerto Rico who accumulated 29,006 woman-months of taking NG 0.075 mg, the only CVD was 1 case of post-traumatic thrombophlebitis (Korba & Paulson, 1974). On a related point, another clinical report noted that 15 women with thrombophlebitis were administered POPs and had no adverse effects (Hawkins & Benster, 1977).

Several researchers have considered whether there is a dose-response relationship of progestin dosage in combined OCs with CVD. A recent review by Stergachis (1992) concludes that the limited available data on progestin dose indicate an increased risk of cerebrovascular disease (stroke) with increasing progestin dose, but no association for MI or venous thromboembolism. However, caution should be taken in interpreting these relative potency analyses, particularly if they involve different progestins and did not simultaneously consider estrogen dose. (See Section III.) A recent Consensus Development Committee on OCs and CVD (Skouby, 1990) cautions:
Whether particular formulations or progestogens have qualitative advantages or disadvantages merits further study. Estrogens and progestogens interact at many levels, and in epidemiologic studies of users of combined OCs, it is difficult to assign a risk to either component separately. Moreover, it is physiologically unsound to do so.

Data from the Royal College of General Practitioners (RCGP) cohort study have been analyzed to consider the relationship between COCs of various progestin dosages, at the same estrogen dosage, with arterial disease (Kay, 1982). The rates of "any arterial disease" and the rates of specific arterial diseases (ischemic heart disease, cerebrovascular disease, and peripheral vascular disease) generally increased with increasing dosage of NA, from 1 mg to 3 mg and 4 mg (in combination with 0.05 mg EE) and with increasing LNG dosage from 0.15 mg to 0.25 mg (in combination with 0.03 mg EE), controlling for age, parity, and smoking; the trends for "any arterial disease" reached statistical significance for both progestins, as did the trend for cerebrovascular disease among NET users. (However, it should be noted that the higher NA doses are no longer in widespread use.) In a nested case-control study of the RCGP data, multivariate analysis of the risk factors for acute MI indicates that the risk is elevated for current OC users only among smokers (Croft & Hannaford, 1989); smoking had a strong independent effect, and other significant risk factors were hypertension, toxemia of pregnancy and diabetes mellitus.

A nested case-control study of myocardial infarction and angina pectoris in relation to COCs has also been carried out within the OFPA cohort study (Mant et al., 1987). POP users were included with the < 0.05 mg estrogen COC users for the "low dose" groups, in which there was only one case of angina and no cases of MI among current users. There was no statistically significant association with MI or angina for either low or high OC dosage, in part because of small numbers. The authors note that consideration of progestin dosage was also precluded by the small number of cases. Smoking increased the risk of both MI and angina, in a dose-response fashion.
Cohort analysis of mortality among women enrolled in the OFPA Study considered different formulations of OCs separately, but no significant relationships appeared, due in part to the small number of cases (18 deaths due to ischemic heart disease and 10 due to cerebrovascular disease) (Vessey et al., BMJ, 1989). Rates of both ischemic heart disease and cerebrovascular disease were elevated for OC users, but the results were not statistically significant. Users of COCs containing 0.05 mg estrogen contributed 70.2% of the women-years and POP users contributed only 10.0% of the person-years to the denominator of the rate calculations.

Meade and colleagues (1980) analyzed reports of cardiovascular events to the Committee on Safety of Medicine (of the United Kingdom) in relation to progestin dosage of combined OCs. Among users of COCs containing EE 0.05 mg with various doses (1.0-4.0 mg) of norethindrone acetate (NA), the risk of both fatal and non-fatal stroke or ischemic heart disease increased with dose of NA. A similar pattern for non-fatal stroke was found for comparisons of LNG 0.15 mg and LNG 0.25 mg, in combination with EE 0.03 mg, but the numbers of users were smaller. Reports of venous events (fatal and non-fatal) were not associated with progestin dose, supporting the conclusion that progestins are not related to any COC-induced increase in risk from thromboembolic disease. There was also no association of progestin dose with reported hypertension. However, underreporting and other potential biases associated with use of this type of data set suggest caution in interpreting the results (Hawkins & Elder, 1980).

A retrospective cohort study of Medicaid records in Michigan evaluated the risk of deep venous thromboembolism in relationship to both progestogenic and estrogenic potency (Gerstman et al., 1990). Unfortunately, the progestin potency rating was based in part on the rankings of Greenblatt (1967), which are not completely accurate (as discussed in Section III). Gertsman and colleagues reported no
difference in the incidence of deep venous thromboembolism by progestin potency, but significant increases for intermediate and high estrogen dose.

For two decades, it has been recognized that use of combined oral contraceptives can increase the risk of certain cardiovascular diseases (Gaspard & Lefebvre, 1990; Godsland et al., 1992; Grimes, 1992; Harlap et al., AGI, 1991; Mishell, 1989; Stergachis, 1992). The elevated risk among current OC users is greater for thromboembolism and for cerebral vascular disease than for other types of CVD. While the estrogen component of COCs is presumably responsible for most of this increased risk, the progestin component may also contribute, particularly in high doses. In more recent studies, reduction in the dosage levels of both hormones has been accompanied by a lower risk of CVD for COC users (Croft & Hannaford, 1989; Hirvonen & Idanpaan-Heikkila, 1990; Mant et al., 1987; Porter et al., 1985; Vessey et al., 1984). Other factors that have contributed to the lower risk found in recent research include multivariate control for confounding factors, better screening of potential users, and greater diagnostic accuracy (Skouby, 1990; Sturtevant, 1989, 1991). Epidemiologic research has also shown that smoking markedly increases the CVD risk and that, particularly among older women, smoking may act synergistically with COC use to increase this risk. Although the risk of CVD increases with age, there is now sufficient information regarding the minimal effect of COC use among older women in the absence of smoking to permit the FDA to remove its upper age limit on COC use (Kaeser, 1989).

Because migraine headaches are of vascular origin, there is potential for some concern regarding use of combined OCs. However, a recent review notes very little evidence of an increased risk of stroke for women with migraine (either for OC users or non-users) (Mattson & Rebar, 1993). The authors advise careful monitoring of women with migraine headaches who choose to use COCs and
immediate discontinuation if focal neurologic symptoms or more severe headaches occur. They note that data on use of progestin-only contraceptives are limited. For women whose migraine headaches cluster around the time of menses, the decline in estrogen levels may precipitate the attack and thus Mattson and Rebar (1993) suggest that "continuous progestin contraception may be of benefit for this sub-group of patients."

Although circulatory and cardiovascular problems were occasionally the stated reason for termination of NORPLANT® use, there were few women for whom these reasons were given, and it is not clear whether the problems were actually related to the implants (Sivin, 1988).

B. Progestins, Metabolic Changes, and Cardiovascular Disease

Because of the paucity of information regarding the risk of CVD associated with POP use, it is necessary to also consider the potential effects of any POP-related metabolic changes on CVD risk. It is widely acknowledged that the increased risk of CVD among OC users is primarily related to thrombosis, not atherosclerosis (Gaspard & Lefebvre, 1990; Grimes, 1992; Mishell, 1989; Speroff & Darney, 1992; Stergachis, 1992). Several lines of reasoning lead to the conclusion that there is no long-term effect of COCs on atherosclerosis. One reason is that past use of COCs is not associated with an increased risk of CVD, based on recent analysis of the Nurses' Health Study and a concurrent meta-analysis of other studies (Stampfer et al., 1990). Another reason for this conclusion is that there is a stronger dose-response relationship between estrogen and thromboembolic diseases than for other CVDs (Meade et al., 1980; Gerstman et al., 1990; Speroff & Darney 1992; Vessey, et al., 1984). In addition, among monkeys fed an atherogenic diet, those given OCs actually had slightly less
atherosclerosis (despite lower HDL levels) than those given placebos (Clarkson et al., 1990). The recent Consensus Development Committee (Skouby, 1990) concluded the following:

Because the risk of MI is apparent in current users, disappears on cessation of use, and is not associated with duration of use, there is no epidemiologic support for the hypothesis that risk of cardiovascular diseases is of atherogenic origin.

The Consensus Development Committee (Skouby, 1990) went on to say:

Whether the elevated insulin levels in OC users are associated with increased risk of coronary heart disease cannot be determined at this time.... Although the lipid changes are quite definite, there is no evidence that they are related to atherogenesis in OC users.

Therefore, although changes in lipid and carbohydrate metabolism, as well as blood pressure, could theoretically affect CVD risk, it is primarily the changes in the coagulation system that are of concern. The estrogen in COCs is known to decrease the levels of antithrombin III and increase the levels of several clotting factors, suggesting an adverse impact on coagulation which could lead to an increased risk of MI, thrombotic stroke, and venous thromboembolism (Gaspard & Lefebvre, 1990; Harlap et al., 1991; Mishell, 1989; Stampfer et al., 1990; Stergachis, 1992).

In contrast, metabolic effects of POPs are minor, as reviewed in Section V. Most importantly, progestin-only pills do not appear to have any effect on blood coagulation factors, and thus it cannot be postulated that they would affect the risk of thrombosis-related cardiovascular diseases. POPs also do not have any measurable effects on the CVD risk factors of altered lipid metabolism or hypertension. It is only in the area of carbohydrate metabolism that POPs produce some alterations, but these changes are very small at the low dose of progestins given in POPs and therefore are unlikely to be of clinical relevance (Speroff & Darney, 1992).
It should be noted that considerably less is known about the relationship between altered metabolism and CVD in women than in men. A recent analysis of the Lipid Research Clinics Prevalence Study found that the association of low high density lipoprotein (HDL) and high low density lipoprotein (LDL) levels with CVD death was stronger for men than for women and that, in women, low HDL cholesterol has a stronger effect than does high LDL cholesterol (Jacobs et al., 1990). A 1992 editorial, accompanying detailed analyses of the CVD literature, concludes "there is no association between high blood cholesterol and cardiovascular deaths in women" (Hulley et al., 1992). In reviewing the clinical implications of data on HDL, Gordon & Rifkind (1989) concluded that, although exogenous estrogen tends to increase HDL and exogenous progestin to decrease HDL, endogenous estrogen is not a major factor in male: female differences (Gordon & Rifkind, 1989). Similarly, reviewing the effect of gender, Godsland et al. (1987) argue that the commonly accepted belief that sex differences in lipoproteins and CVD are due to endogenous sex hormones may not be true.

Several clinically-oriented reviews have recently considered the contraceptive options for women with a personal or family history of CVD or with other CVD risk factors. Although low-dose combined OCs may be acceptable for asymptomatic women with family histories of thromboembolism, they are not recommended for women who themselves have a personal history of venous thrombus disease (Comp & Zacur, 1993). POPs may therefore be preferable for women with a history of thrombosis (Goldzieher, book, 1989) or with conditions such as mitral valve prolapse, which may increase the risk of thrombosis (Sullivan & Lobo, 1993). As discussed in the previous section, POPs may also be more appropriate for women with dyslipidemia, especially hypertriglyceridemia (Knopp et al., 1993), with diabetes (Mestman & Schmidt-Sorosi, 1993), and with hypertension (Sullivan & Lobo, 1993). Speroff & Darney's (1992) A Clinical Guide for Contraception also states that:
The minipill is a good choice in situations where estrogen is contraindicated, such as patients with serious medical conditions (diabetes with vascular disease, severe systemic lupus erythematosus, cardiovascular disease).... No impact can be measured on the coagulation system. The minipill can probably be used in women with previous episodes of thrombosis, but the package insert in the United States carries the same precautions and warnings that combined oral contraceptives carry. This is not appropriate in view of the absence of estrogen and the lower dose of progestin.

The 1994 edition of *Contraceptive Technology* states that there is no evidence of an increased CVD risk associated with POPs, but that they should be used cautiously and with careful monitoring in women with CVD (Hatcher et al., 1994). These guidelines advise against NORPLANT® insertion for women with active thrombophlebitis or pulmonary emboli, yet removal of the implants is not considered mandatory if their conditions develop during NORPLANT® use. They add that, "Women with a past history of thromboembolic or cardiovascular disease can probably use low-dose progestin-only methods... safely."

The labeling for NORPLANT® lists active thrombophlebitis or thromboembolic disorders as a contraindication. It also specifies that users who develop these conditions should have their implants removed. However, the discussion of thromboembolic disorders and other vascular problems (including cerebrovascular disorders and myocardial infarction) is presented under the heading of warnings based on combined OCs; the text acknowledges that these are primarily estrogen-related conditions and that there are no data on their occurrence among NORPLANT® users. The labeling also notes that the increased CVD risk associated with COC use among smokers is "believed to be an estrogen-related effect." It goes on to say that "women who use the NORPLANT® SYSTEM should be advised not to smoke", but this warning is not presented in the same prominently-displayed "boxed" format as for COCs.
As noted in Section V, both the IPPF and INTRAH Guidelines conclude that POPs have virtually no effect on lipid metabolism, carbohydrate metabolism, coagulation factors, and hypertension (Huezo & Briggs, 1992; INTRAH, 1993). Although IPPF considers cerebrovascular or coronary artery disease to be absolute contra-indications to POP use (Huezo & Briggs, 1992), the recent INTRAH Guidelines state that POPs may be a reasonable choice for women with active or past history of these conditions who would not use other effective methods (INTRAH, 1993). The rationale for this latter statement is that POPs are safer for such women than pregnancy, and safer than use of COCs. INTRAH (1993) also recommends POPs for women with a history of migraine headaches.

The INTRAH Guidelines add that POPs would be preferable to COCs for older women who smoke heavily, as does Guillebaud (book, 1993). Similarly, POPs are recommended for hypertensive women who smoke (Sullivan & Lobo, 1993).

CONCLUSION: POPs do not appear to increase the risk of cardiovascular disease. The increased risk of CVD associated with combined OCs is primarily related to the effect of estrogens on the thrombogenic mechanism, and progestins do not have clinically important effects on thrombogenesis. Other risk factors for CVD (hypertension and alterations in lipid and carbohydrate metabolism) are affected only minimally, if at all, by progestins at the low doses in POPs. Furthermore, POPs are preferable to COCs for women with pre-existing CVD or with CVD risk factors, including older women who are cigarette smokers. POPs are also recommended for women with migraine (vascular) headaches. (Types of evidence: II A, D.)
VII. CANCER

There is very little information available on the risk of cancer among users of progestin-only OCs, primarily because both POP use and most cancers are relatively rare, making it difficult to find sufficient numbers of women for epidemiologic studies. This section therefore focuses on the largest studies and on studies in countries where POP use is most common, in order to maximize the likelihood that POP users will be included. Information on the relative effect of various formulations of COCs is also included, as well as data from studies of NORPLANT®.

It has been noted that there are no particular groups of women who should be advised not to take OCs because of increased cancer risk (Skegg, 1991) (unlike for MI, in which women who smoke or have other CVD risk factors are told not to take combined OCs because of increased MI risk, as reviewed in Section VI). Regarding women who already have cancer, effective contraception is important because pregnancy could raise concerns about effects of cancer therapy on the fetus and possible increased aggressiveness of some cancers (Herbst & Berek, 1993). In their recent review of this issue, Herbst and Berek (1993) conclude that COCs or progestin implants are acceptable contraceptive methods (except for women with breast cancer); presumably POPs would be, as well.

A. Endometrial Cancer

Only two studies of the relationship between oral contraceptive use and endometrial cancer have tabulated POP users, and in both of these studies the number of POP users was very small. In the Cancer and Steroid Hormones (CASH) study, conducted by the U.S. Centers for Disease Control, only one case and six controls had used POPs exclusively, resulting in a crude odds ratio (OR) of 0.6 (95%
confidence interval or CI: 0.1-5.0) (CASH, JAMA, 1987). The WHO Collaborative Study of Neoplasia and Steroid Contraception (WHO, 1988), conducted in several countries, found no cases and only 2 controls who had used POPs exclusively. Therefore, inferences about POPs must be made from knowledge about combined and sequential OCs, other risk factors, and biologic mechanisms. Together, this information indicates that estrogen "unopposed" by progestin plays an important causal role (Pike et al., 1993), thus suggesting that POPs would not be expected to increase the risk and could perhaps decrease the risk.

Numerous epidemiologic studies have uniformly shown that combined OCs have a strong protective effect against endometrial cancer, which continues for at least 15 years after pill cessation (Edgren, I J Fert, 1991, p. 37; Grimes, 1992; Harlap et al., AGI, 1991; Prentice & Thomas, 1987; Schlesselman, 1991; Stergachis, 1992; WHO, Tech Rep, 1992). Several analyses have considered the relative estrogen and progestin potency of the COCs, but the results are inconsistent, in part because of difficulties in accurately quantifying potency (as reviewed in Section III).

The original report of the WHO Collaborative Study regarding endometrial cancer (WHO, 1988) found an odds ratio (or estimated relative risk; RR) of 0.53 for COCs. A more recent analysis of this case-control study by Rosenblatt and colleagues (1991) which focused on the composition of COCs specifically excluded POP users. These researchers classified the progestins in COCs according to the subnuclear vacuolization method, then multiplied the potency score by the dose. The lowest risk was found among COC users taking higher dose progestins, among both high estrogen and low estrogen pills. Because of small numbers in each group when COCs were classified simultaneously by both steroids, subsequent analysis ignored estrogen dose and compared all high-strength progestin preparations to all low-strength progestin preparations; this analysis found a significantly greater
protective effect for high progestin dose pills (OR=0.13 for high progestin dose and 0.64 for low progestin dose). The risk was lowered even for women who took high progestin doses for less than two years, and this reduced risk continued for more than 10 years after pill discontinuation.

In the CASH study the relative risk of endometrial cancer associated with ever-use of COCs was 0.6, and this protective effect persisted for at least 15 years (CASH, JAMA, 1987). The risk was reduced for each of the 8 most common COC formulations, with the age-adjusted relative risks ranging from 0.2 to 0.7 and with no apparent pattern by dosage; included among these formulations were the lower dose COCs that are now most commonly prescribed. Similarly, analyses of risk based on "milligram-months" of exposure to either estrogen or progestin found no dose-response effect.

Three earlier studies also examined endometrial cancer risk in relation to COC formulation (Henderson et al., Br J Ca, 1983, p. 749; Hulka et al., 1982; Weiss & Sayvetz, 1980). Two of the three reports concluded that there was a greater protective effect with "progestogen-predominant" preparations than with "estrogen-predominant" preparations (Hulka et al., 1982; Weiss & Sayvetz, 1980). However, the number of OC users in the various categories was quite small, reflecting the low overall prevalence of OC use in the 1960s and early 1970s.

Concern about the possibility of increased endometrial cancer risk associated with sequential OCs (Henderson et al., Br J Ca, 1983, p. 749; Weiss & Sayvetz, 1980) was responsible for their removal from the market in 1976 (Huggins & Zucker, 1987). Because estrogen is given alone for the first two weeks of sequential OC administration, an increased risk would fit with the "unopposed estrogen" etiologic hypothesis, as would the fact that an elevated risk was found primarily with one specific preparation in which the estrogen-progestin ratio was highest (CASH, JAMA, 1987; Weiss & Sayvetz,
The summary OR for sequential OCs, combining the small numbers from the three studies, is 2.0 (Prentice & Thomas, 1987).

The estrogen dependence of endometrial cancer is also demonstrated among women receiving estrogen alone for many years as a postmenopausal hormone replacement therapy (HRT) (Jick et al., 1993). The addition of progestin (usually MPA) to postmenopausal estrogen therapy greatly reduces the risk associated with estrogen alone, bringing the endometrial cancer incidence among HRT users down close to the spontaneous incidence (Jick et al., 1993; Schlesselman, 1991). Similarly, several other risk factors (such as obesity, nulliparity, and early menopause) suggest that endogenous estrogenic stimulation without adequate cyclical progesterone plays a causal role in endometrial cancer (Schlesselman, 1991; WHO, Tech Rep, 1992).

The biological basis for the "unopposed estrogen" hypothesis is that estrogen stimulates endometrial cell division, while progesterone or synthetic progestins block that effect (Jordan et al., 1993; King, 1991; Pike et al., 1993). During the normal menstrual cycle, the endometrial cell mitotic rate is highest in the early follicular phase, during which serum estradiol levels are increasing while progesterone levels remain low. When progesterone levels increase during the luteal phase, endometrial cell proliferation ceases, despite continued elevation of estradiol. In normal mammalian physiology, the primary function for progesterone is preparation of the uterus for implantation, which is primarily a differentiating function, but which also involves some proliferative activity (Clarke & Sutherland, 1990). Progestins induce glandular epithelial secretory activity and decidual transformation of stromal fibroblasts; these terminally differentiated cells can no longer proliferate and are shed if implantation does not occur.
In addition, the sensitivity of the endometrium to both estrogen and progestin is reflected in observations of estrogen and progestin receptors (Clarke & Sutherland, 1990; King, 1991; Pike et al., 1993). These receptors are found in various types of uterine tissue (endometrial, stromal, and myometrial smooth muscle cells), and it is known that most steroid hormone action is mediated via specific receptors. Progestins have been shown to down-regulate estrogen receptors in all of these tissues (as well as to increase estrogen metabolism). There is also considerable cyclic variation in receptor levels, with receptor expression being much greater in the follicular (estrogen-dominant) phase of the menstrual cycle. Thus, estrogen receptor expression is greatest during that phase of the menstrual cycle with the greatest endometrial cell proliferation.

Both *in vivo* and *in vitro* studies indicate that progestin inhibits epithelial cell proliferation, in neoplastic as well as normal tissue. Thus, progestins are sometimes used in the treatment of endometrial carcinoma (Clarke & Sutherland, 1990; Jordan et al., 1993). Specifically, progestins have been found to reverse endometrial hyperplasia and cause regression of endometrial carcinoma (Schlesselman, 1991).

This information on progestin’s inhibitory effect on endometrial cell proliferation indicates that it must be the progestin rather than the estrogen that is responsible for the protective effect of COCs, suggesting that POPs would also have a protective effect. Adding to this protection is the fact that POP users take progestin every day, and thus would not have any time when endogenous estrogen is unopposed. In contrast, combined OC users receive both estrogen and progestin for three weeks but are exposed to unopposed endogenous estrogen (albeit at low levels) during the week in which they are not taking OCs (Pike et al., 1993). As reviewed in Section II, although the endometrial effects of POPs vary somewhat among individuals, the overall result is reduced proliferation.
DMPA use has also been found to have a strong protective effect on endometrial cancer, at least as strong as for COCs, according to the WHO Collaborative Study of Neoplasia and Steroid Contraceptives (I J Ca, 1991, p. 186). Although DMPA reportedly increased the risk of endometrial cancer in monkeys, these carcinomas developed in cells of a type not found in humans (Klitsch, 1993).

Carcinoma is presented in the NORPLANT® labeling under the heading of "warnings based on experience with combination (progestin plus estrogen) oral contraceptives." The following text is included in that section:

Evidence indicates that combination oral contraceptives may decrease the risk of... endometrial cancer. Irregular bleeding patterns associated with the NORPLANT® SYSTEM could mask symptoms of... endometrial cancer.

The IPPF Guidelines state that "uterine malignancies" are an absolute contraindication for POP use (Huezo & Briggs, 1992), but the rationale for this recommendation is unclear. The INTRAH (1993) Guidelines do not list endometrial cancer as a contraindication or precaution. However, undiagnosed abnormal genital bleeding could be an indication of the presence of endometrial cancer (or could have many other causes, as presented in Section VIII), and thus is considered to be a temporary contraindication.

CONCLUSION: There are virtually no data on protection against endometrial cancer among POP users, but based on knowledge about the effects of COCs (and post-menopausal hormone replacement therapy) there is no reason to postulate an adverse effect of POPs and there may be a modest protective effect of the progestin. Abnormal vaginal bleeding is a temporary contraindication until endometrial cancer and other pathological causes have been ruled out.
For women with endometrial cancer whose uteri remain intact, POPs are an acceptable contraceptive method. (Types of evidence: II A, C, D.)

B. Ovarian Cancer

As with endometrial cancer, only the large multicenter CASH and WHO studies of ovarian cancer have reported the prevalence of POP use, and the numbers are very small. In the CASH study 1 case and 8 controls had used a POP exclusively (CASH, NEJM, 1987). No cases included in the WHO study had used only POPs and the number of POP users among controls was not reported (WHO, I J Epid, 1989, p. 538). Thus, again, an understanding of any possible association with POPs must be derived from analysis of data on COCs and consideration of the biological mechanisms.

Combined OCs have a strong protective effect against ovarian cancer (Edgren, I J Fert, 1991, p. 37; Hankinson et al., 1992; Prentice & Thomas, 1987; Stanford, 1991; Whittemore et al., Am J Epid, 1992, p. 1184). A recent meta-analysis computed a summary odds ratio of 0.64 (95% CI: 0.57-0.73) for ever-use of COCs (Hankinson et al., 1992). A collaborative analysis of 12 U.S. case-control studies similarly found odds ratios of 0.70 (0.52-0.94) for hospital studies and 0.66 (0.55-0.78) for population-based studies (Whittemore et al., Am J Epid, 1992, p. 1184). Grimes (1992) has commented that this is "the most important non-contraceptive health benefit" of COCs, because ovarian cancer is the most frequent cause of death associated with gynecologic malignancy.

One of the few reports regarding possible differential effects of various COC formulations is from the large CASH (NEJM, 1987) study. A reduction in ovarian cancer risk was demonstrated for all 11 of the preparations analyzed, including those with the lowest dosages, and there was no pattern with
either estrogen or progestin type or dose. A case-control study by Cramer et al. (1982) also found no significant differences among the various types of estrogen and progestins, although they were not able to evaluate dosage. Sequential OCs have been shown consistently to have a protective effect (Stanford, 1991).

Two hypothetical mechanisms for this protective effect of OCs have been proposed (Hankinson et al., 1992; Whitemore et al., Am J Epid, 1992, p. 1212). One hypothesis is that elevated ovarian cancer risk is related to "incessant ovulation," which is supported by the fact that OC use, pregnancy, and lactation are all protective. However, analysis of the months of ovulation suppression by each of these three factors indicates that they do not provide equal protection from ovarian cancer (Gwinn et al., 1990; Risch et al., 1983; Whitemore et al., Am J Epid, 1992, p. 1212), suggesting that prevention of ovulation may not be the only protective mechanism. Because ovulation is not always suppressed by POPs (as discussed in Section II), reduction in risk of ovarian cancer by POPs would not be expected to be as strong for POPs as for COCs, based on the purported ovulation suppression mechanism (King, 1991). The other proposed mechanism is that the lower plasma gonadotropin levels in COC users are responsible for the lower risk of ovarian cancer. Hankinson et al. (1992) speculate that because the newer low dose COCs do not suppress gonadotropin levels as much as do the high dose COCs, they will not provide as great a protective effect; presumably this also applies to POPs, with an even lower dose of progestin and no estrogen.

Although both progesterone and estrogen receptors are found in ovarian cancer cells, it is not generally believed that sex steroids have a direct hormonal effect on the surface epithelial cells from which ovarian tumors arise (King, 1991).
The fact that postmenopausal estrogen therapy does not affect the risk of ovarian cancer (Whittemore et al., Am J Epid, 1992, p. 1212) suggests that it is the progestin component, rather than the estrogen component, of COCs that is responsible for their protective effect. This lack of a relationship with hormone replacement therapy also argues against the gonadotropin hypothesis (Whittemore et al., Am J Epid, 1992, p. 1212). However, risk factors for postmenopausal women may not be the same as for premenopausal women because of differences in endogenous estrogen and progesterone levels.

The NORPLANT® labeling states that, as with endometrial cancer, the available evidence is based on combined OCs, which are associated with a decreased risk of ovarian cancer.

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives (WHO, I J Ca, 1991, p. 191) has shown that the risk of ovarian cancer is similar for users and non-users of DMPA. The authors suggest that the absence of an expected protective effect may have been due to the following factors: the fact that most DMPA users had also used COCs, making it difficult to evaluate the effect of DMPA alone; the use of DMPA primarily by parous women for whom considerable protection has already been provided by their parity, again making it less likely that there would be additional protective effect by DMPA; and the low statistical power of the study.

A clinical review of gynecologic cancers and contraception states that "no data exist to indicate that any form of contraception is contraindicated" for women with ovarian cancer (Herbst & Berek, 1993). The INTRAH (1993) Guidelines do not include women with ovarian cancer among those who should avoid POP use. In contrast, the IPPF Guidelines list ovarian malignancies as absolute contraindications to POP use (Huezo & Briggs, 1992).
CONCLUSION: POPs presumably have less of a protective effect than COCs in relation to ovarian cancer, although there may be a modest degree of protection. There is no reason to believe they would increase the risk nor are POPs necessarily contraindicated for women with ovarian cancer. (Types of evidence: II C, D.)

C. Cervical Cancer

No studies have provided data on cervical cancer risk among POP users, and very few analyses of COCs have considered the effect of the various OC formulations. Whether cervical cancer is related to OC use, in general, remains unclear because of the numerous methodological problems in studying this association. These problems include the following: (1) confounding by sexual behavior, smoking, and other factors; (2) use of an inappropriate comparison group (particularly women who have used barrier contraceptive methods, which protect against cervical cancer); (3) misclassification with regard to cervical cancer presence or absence; and (4) detection bias resulting from OC users receiving Pap smears more regularly (Swan & Petitti, 1982). It is also possible that different results could be seen in studies of pre-invasive cervical intraepithelial neoplasia (CIN) than in studies of invasive cancer, either because of differential effects of screening or diverse biological effects of OCs on the two stages of disease (Irwin et al., 1988; WHO, Tech Rep, 1992).

Most, but not all, studies find a small elevation in cervical cancer risk associated with long-term OC use (WHO, Tech Rep, 1992). A recent modeling analysis of the overall effect of long-term OC use on reproductive cancers selected 1.2 as the most reasonable relative risk for cervical cancer incidence at age 15-49, declining to 1.0 thereafter (Coker et al., 1993). This would result in an additional 67 cancers per 100,000 OC users in the U.S., a number which is more than counterbalanced
by the reduction in ovarian and endometrial cancer. Another similar analysis considered the most likely relative risks to be 2.0 under age 45, 1.5 at ages 45-54, and 1.0 after age 55, but the authors cautioned that "our likely-case assumption about cervical cancer is the least firm" among the four reproductive cancers evaluated (Petitti & Porterfield, 1992).

The report of the WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1985) regarding invasive cervical cancer does not present data on POPs (unlike their reports on ovarian and endometrial cancer), but instead simply states that two percent of cases and three percent of controls used OCs other than combined OCs, which presumably includes sequential as well as progestin-only pills. The WHO analysis also does not stratify by formulation of COCs.

In a large multicenter study of invasive cervical cancer conducted in the U.S. by the National Cancer Institute (Brinton et al., 1986), possible variation in risk by pill formulation was examined in several ways, most of which did not show differential effects; the only exception was estrogen "potency," for which a higher relative risk was found for higher "potency." In contrast, a study in Australia found that risk of carcinoma-in-situ increased with the lifetime dose of progestin and of estrogen (Brock et al., 1989); the authors remarked that there was a strong statistical correlation between dosages of the two steroids. Finally, the 1983 analysis of the Oxford Family Planning Association cohort study by Vessey and colleagues found no differences in risk associated with specific estrogens or progestins or with dosage; however, they were unable to control for sexual behavior, and the numbers of women with each stage of cervical neoplasia were quite small (Vessey et al., Lancet, 1983).
Information about possible biologic mechanisms involved in an etiologic link between OCs and cervical cancer has only recently begun to emerge (Brinton, 1991; King, 1991; Stendahl & Rogo, 1990). It is well-recognized that both estrogen and progestins influence the normal cervix in diverse ways. For example, in laboratory rodents estrogen induces hyperplasia and cornification of the luminal layers, while progestins inhibit these effects (Edgren, I J Fertil, 1991, p. 37). The presence of both progestin and estrogen receptors in cervical mucus has been documented. Finally, OCs may affect cervical cancer risk indirectly, by stimulating human papilloma virus, which is currently believed to be the agent most likely to be responsible for neoplastic development.

The NORPLANT® labeling concludes the following:

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In spite of many studies of the relationship between combination oral contraceptive use and cervical cancer, a cause-and-effect relationship has not been established. Irregular bleeding patterns associated with the NORPLANT® SYSTEM could mask symptoms of cervical cancer.

The WHO Study of DMPA found a non-significant relative risk of 1.1 for invasive cervical cancer (WHO, Contrac, 1992).

A clinical review of contraception and gynecologic cancers emphasizes the need for annual Pap smear screening of women who use OCs, particularly for more than five years (Herbst & Berek, 1993). Although they note concern about a possible role for OCs in progression of dysplasia to invasive carcinoma, they make no specific recommendation regarding use of COCs or progestin-only contraceptives by women with dysplasia.
According to IPPF procedures, women with a history of non-cancerous abnormal Pap smear may elect to use POPs, if follow-up Pap smears are obtained (Huezo & Briggs, 1992). These IPPF Guidelines consider cervical malignancies to be absolute contraindications, but the INTRAH (1993) Guidelines do not.

CONCLUSION: There is no information about cervical cancer risk among POP users and very little data about risk among COC users in relation to progestin dose. POP users with abnormal Pap smears should have frequently repeated Pap smears. (Types of evidence: II C, D.)

D. Breast Cancer

A recent comprehensive review of exogenous progestins and breast cancer (Stanford & Thomas, 1993) cites five studies that examined POP users separately from COC users. None of these studies found an elevated risk of breast cancer, with odds ratios (or estimated relative risks) close to 1.0 and 95% confidence intervals that all included the null value. The two studies that evaluated the duration of POP use suggest a protective effect that increases with duration. Although the numbers of POP users in these five studies are small, the consistent findings of no effect are encouraging.

The most detailed analysis of POP use, with the largest number of POP users, is the UK National Case-Control Study (1989) of breast cancer among women age 35 or younger. Included were 123 cases and 116 controls who had used POPs, resulting in a crude odds ratio of 1.07 and an adjusted odds ratio of 1.00. Whether or not the woman had ever breastfed was one of several variables controlled for in multivariate analysis; this was the only one of the five studies to consider breastfeeding in the analysis. There was a marginally significant trend of protection with longer
duration of POP use (OR = 1.35 for 1-12 months, 0.73 for 13-24 months, and 0.59 for 25+ months). Among combined OC users in the study, the opposite trend was found, with breast cancer risk increasing with longer duration of use, particularly among users of COCs containing 0.05 mg or more of estrogen. There was no relationship of breast cancer risk with progestin type or dose.

The other study that evaluated duration of use was much smaller (only 28 cases and 29 controls had used POPs), and age was the only variable controlled in the analysis (Ewertz, 1992). This Danish case-control study of women less than age 60 found an odds ratio of 0.99 (95% confidence interval 0.6-1.7) for ever-use of POPs. POP use for less than five years was associated with an odds ratio of 1.31 (95% C.I. 0.7-2.6), compared to 0.65 (0.3-1.5) for five or more years of use. As with the British study, long-term users of higher dose combined OCs appeared to be at elevated risk of breast cancer, but the author notes that few women had yet had the opportunity to use lower dose COCs for extended periods of time.

Another British case-control study was conducted by Vessey and colleagues (Br J Ca, 1983, p. 455) among women up to age 50. It included 33 cases and 29 controls who had used POPs, for a crude odds ratio of 1.11 (95% C.I. 0.7-1.8) A similar lack of association was reported for COC use.

A report from France also presented an adjusted odds ratio of 1.1 for breast cancer, in women up to age 55. However, this OR was based on only 9 cases and 10 controls who had used POPs and thus the 95% confidence interval was quite broad (0.4-2.7) (Clavel et al., 1991). The multivariate odds ratio for combined OC use was 1.5; however, because there was no association with various characteristics of COC use (such as duration of use or age at first use) the authors note that the
elevated risk could be partially the result of information bias, as the data were collected in the mid-
1980s when recognition of a possible risk associated with COC use was emerging.

The fifth POP study cited by Stanford and Thomas (1993) was conducted by the CASH (1986)
breast cancer study group. They computed an adjusted odds ratio of 1.3, based on an unspecified
number of POP users up to age 55. Among COC users the odds ratio was exactly 1.0, with
remarkably little variation by progestin or estrogen type and dose.

Two other studies have reported very small numbers of POP users. A report of the multinational
WHO Collaborative Study of Neoplasia and Steroid Contraceptives (Br J Ca, 1990), which included
women up to age 55, notes that only 1.0 percent of cases and 0.6 percent of controls had used
"continuous" OCs (POPs) exclusively. McPherson et al. (1987) counted two cases and no controls in
their case-control study of breast cancer.

Considerable controversy surrounds the issue of whether combined OCs alter the risk of breast
cancer, and one aspect of this controversy is whether high progestin COCs, in particular, increase the
risk. A decade ago Pike and colleagues (Lancet, 1983, p. 926) reported that COCs with higher
progestin potency were associated with increased breast cancer risk among young women who had
used COCs before age 25 for an extended time. However, their classification of progestin potency has
been criticized (Armstrong, 1986; Sturtevant, 1984; Swyer, 1983) because it was based on Greenblatt’s
(1967) outdated review of delay of menses research. Greenblatt had stated that norgestrel has 30 times
the progestational potency of norethindrone, whereas more recent data, based on both endometrial and
breast tissue response, indicate that norgestrel is actually 5-10 times as potent. (See Section III.)
Subsequently, the breast cancer data from the CASH Study were reanalyzed according to Pike's classification, and users of "high progestin potency" COCs were not found to have an increased breast cancer risk (Stadel et al., 1985). Other case-control studies have also found no elevated risk for users of pills designated by Pike as "high progestin potency" (McPherson et al., 1983; Miller et al., 1986). In addition, analyses of progestin type and dose categorized in various other ways have not demonstrated any differences in breast cancer risk (although it should be noted that in general there was low statistical power for these subgroup analyses). These other studies include: the UK National Case Control Study (1989), the WHO Collaborative Study (Thomas et al., 1992) and the CASH (1986) study, all described above; both cohort (Kay & Hannaford, 1988) and nested case-control (Vessey et al., Br J Ca, 1989) analyses of the RCGP cohort study; and other case-control studies (Miller et al., 1989; Ravnihar et al., 1988).

Several comprehensive reviews and meta-analyses have recently assessed the possible role of COCs in breast cancer etiology (Edgren, I J Fert, 1991, p. 37; IOM, 1991; Kelsey & Berkowitz, 1988; Romieu et al., 1990; Schlesselman, 1989; Thomas, Contrace, 1991, p. 597; Stanford & Thomas, 1993). Additionally, two groups have produced models that give the hypothetical incidence of breast and other reproductive cancers, using relative risks for breast cancer associated with OC use that are slightly different. Coker and colleagues (1993) set the relative risk of breast cancer at 1.2 for ages 15-49 and 1.0 at age 50 and older, while Petitti and Porterfield (1992) use an RR of 1.7 for ages 15-44 and 1.0 at age 45 and older. A committee advising the U.S. Food and Drug Administration has concluded that "the overall risk of breast cancer in relation to oral contraceptive use is approximately 1.0" and that "the existing data do not support a change in prescribing patterns" (Johnson, 1989). The U.S. Institute of Medicine (1991) and the World Health Organization (WHO, Tech Rep, 1992) concur with this overall assessment.
If there is an elevation in risk of premenopausal breast cancer with long-term OC use, it appears to be greatest for use before the first full-term pregnancy (Edgren, I J Fert, 1991, p. 37; Kelsey & Berkowitz, 1988; Romieu et al., 1990; Thomas, Contrac, 1991, p. 597). Only limited attention has been given to the effect of COC use late in reproductive life, but there is some suggestion of increased breast cancer risk associated with use near the time of menopause which merits further analysis (Kelsey & Berkowitz, 1988; Malone et al., 1993; Thomas, Contrac, 1991, p. 597; WHO, Tech Rep, 1992).

Not only may age at OC use affect the relationship between OC use and breast cancer, but a recent analysis of the CASH study has also found variations by age at cancer diagnosis (Wingo et al., 1991). Although ever-use of OCs slightly increased the risk of breast cancer among women age 20-34 at diagnosis, there was no association for women age 35-44 and a small decrease in risk for women age 45-54. Three other studies have also shown a very modest protective effect of COC use in relation to breast cancer at older ages of diagnosis, but not at younger ages (McPherson et al., 1987; Paul et al., I J Ca, 1990; Vessey et al., Br J Ca, 1989). Most studies to date have focused on premenopausal breast cancer because older women have not had the opportunity for long-term exposure to OCs; thus, any relationship of OCs with postmenopausal breast cancer remains largely unexplored. Because the vast majority of breast cancer cases occur after age 45, the limited data suggesting no effect of OC use on breast cancer at later ages, and possibly even a protective effect, are quite reassuring.

It has recently been observed (Herbst & Berek, 1993) that this relationship with age at diagnosis is analogous to the situation with regard to pregnancy. Although it is widely recognized that
pregnancies decrease the risk of breast cancer at older ages, pregnancies actually increase the risk of breast cancer diagnosis before about 40-45 years of age (Kelsey et al., 1993).

The small sample size of studies assessing the relationship between progestin-only pills and breast cancer has precluded consideration of age at POP use and age at cancer diagnosis. It is imperative that future analyses of POP use and breast cancer risk consider these factors, particularly given the fact that older age is sometimes considered to be an indication for selection of POPs. In addition, further attention should be paid to the confounding effect of breastfeeding, because breastfeeding may have a modest protective effect for breast cancer (Kelsey et al., 1993) and it is also one of the primary indications for POP use (as presented in Section XI). Whether a woman has ever breastfed should be considered in the analysis, as well as such other parameters of breastfeeding as total duration (Harlap, 1991).

In their comprehensive review of progestins and breast cancer, Staffa and colleagues (1992) cite numerous hypotheses about the possible biological mechanisms for such a relationship, but suggest three of these as being most strongly supported by the available data. The first of these, termed the progestinic hypothesis, states that progestins stimulate deoxyribonucleic acid (DNA) synthesis, increasing mitotic activity in breast epithelial cells and thus increasing breast cancer risk. The other two hypotheses instead suggest a protective role for progestins in opposing the stimulatory effect of estrogens. According to the luteal insufficiency hypothesis, inadequate levels of progesterone during the luteal phase would allow unopposed estrogen to cause proliferation of breast tissue. Similarly, the estrogen window hypothesis proposes that there are two time periods, at the beginning and at the end of the reproductive life span, when low progesterone levels would allow unopposed estrogen to act on breast tissue. Recent research that unites the first of these hypotheses with the other two suggests that
progestins stimulate only one round of cell replication, followed by differentiation, whereas estrogen induces multiple replications (Clarke & Sutherland, 1990; Staffa et al., 1992).

The primary physiologic role of progesterone is to stimulate lobuloalveolar development in preparation for milk production (Clarke & Sutherland, 1990; Staffa et al., 1992). Although estrogen is responsible for proliferation of the breast epithelial tissue, progesterone does not have an inhibitory effect on this proliferation and may have a stimulatory effect. Because the vast majority of invasive breast cancers are of epithelial origin (Schlesselman, 1989), it is the action of progestins on epithelial cells that is of greatest concern. There is considerably less evidence for breast tissue than for the endometrium regarding the mechanism by which progesterone acts at the cellular level. As Clarke and Sutherland (1990) note:

It is abundantly clear that the effects of progesterone on cell proliferation in general, and on estrogen-mediated cell proliferation in particular, are diverse. They vary among the different cell types of the uterus and mammary gland within a single animal, in the same cell types in different species, and even between species in the various physiological states characterizing the female reproductive cycle.

The dominant action of nortestosterone progestins in regard to breast tissue appears to be synergism with estrogen to enhance cell proliferation (King, 1991; McGonigle & Huggins, 1991; Pike et al., 1993; Stanford & Thomas, 1993). This is part of a set of complex interactions in which estrogen increases the level of progesterone receptors in normal breast epithelial cells, thus increasing tissue responsiveness to progestins, while progesterone reduces the level of estrogen receptors. The fact that mitotic activity of breast epithelial cells is higher during the progesterone-dominant luteal phase than in the follicular phase of the normal menstrual cycle lends credence to the idea that progestins increase proliferation of these cells (Anderson et al., 1989; Stanford & Thomas, 1993).
Anderson et al. (1989) have assessed the effect of current use of various OC formulations on the proliferative status of normal breast epithelium, using biopsy tissue from benign lesions and controlling for the effects of parity, time since menarche and menstrual cycle phase. Proliferation, as quantified by the thymidine labeling index, was higher for current OC users than non-users among nulliparous, but not parous, women. Therefore, analysis of the effect of pill formulation was restricted to nulliparous women. Among nulliparas, proliferation was greater for the 14 POP users (progestin type and dose unspecified) than for the 73 women taking COCs or the 36 women taking triphasic OCs. In evaluating COC dosage, LNG was considered to have 8 times the progestational potency of norethindrone; although this potency classification was admittedly based on endometrial data, it is in line with other data, including breast cells in vitro, as discussed in Section III. There was a statistically significant effect of estrogen dose (after adjusting for progestin dose), but the effect of progestin dose (after adjusting for estrogen dose) was smaller and not statistically significant. Anderson et al. (1989) conclude that, "Our limited data on the progestin-only formulation do not indicate that its effect on the breast will be less than combined or triphasic OC."

Estrogen receptor levels in breast epithelial tissue are much lower in combined OC users than in the normal menstrual cycle, and progesterone receptor levels are slightly lower (Pike et al., 1993). Further complicating an understanding of breast cancer etiology, breast cells have receptors for numerous hormones other than estrogen and progesterone, and several types of growth factors can be produced within the breast (IOM, 1991). In order to ascertain how OCs could produce malignant transformation of breast cells, it is necessary to also know how these other hormones and growth factors affect the cells.
There may be differences between normal and neoplastic tissue; although progestins increase cellular proliferation in normal breast epithelium (in combination with estrogen), they can be inhibitory for growth of mammary tumors (King, 1991). Estrogen clearly stimulates the growth of established breast cancer cells but data on progestins are contradictory (King, 1991). Some types of studies have shown that progestins have weak inhibitory effects. However, recent research has demonstrated that several 19-nortestosterone derivatives (including NET and NG) stimulate the growth of estrogen receptor-positive (but not estrogen receptor-negative) breast cancer cells in culture, as proliferative response increases with progestin dose (Jordan et al., 1993). In another study, human breast epithelial cells were exposed to NG and NET, a proliferative response was demonstrated only for the malignant cells; in contrast, exposure to EE alone or in combination with progestin produced a response among normal and atypical cells as well (Longman & Buehring, 1987). Progestin down-regulation of estrogen receptors has also been shown for human breast cancer cells, but not for normal breast cells (Clarke & Sutherland, 1990). Furthermore, animal studies have shown that contraceptive hormones inhibit carcinogenesis if given before administration of a cancer-initiating agent, but stimulate cell proliferation after initiation (King, 1991). It should also be noted that high doses of progestins have been used to treat advanced breast cancer, with some success (Clarke & Sutherland, 1990; Jordan et al., 1993; McGonigle & Huggins, 1991).

Breast and endometrial tissue appear to differ in many ways in their response to both endogenous and exogenous steroids (Clarke & Sutherland, 1990; King, 1991; Malone et al., 1993; McGonigle & Huggins, 1991; Pike et al., 1993). While breast epithelial cell proliferation is greater during the progesterone-dominant luteal phase, endometrial proliferation is greater during the estrogen-dominant follicular phase. There is also a difference in cyclic expression of receptors, with no cyclic variation in progesterone receptors in breast tissue and very little variation in estrogen receptors, but marked
variation in endometrial tissue; furthermore, estrogen receptor expression in the breast is greater during
the menstrual cycle phase with the least cell proliferative activity, which is again the reverse of the
dermatial pattern. In addition, the hormone sensitivity of endometrial tissue does not vary with age,
whereas breast epithelium of young women is clearly more sensitive than that of older women.
Furthermore, it has not been demonstrated that progestins play the same role in down-regulating
estrogen receptors in the normal breast tissue as for the endometrium, and the cellular mechanisms that
mediate the protective effect of progestins on endometrial cancer do not occur in preliminary studies of
breast tissue. Finally, the epidemiologic data on cancer risk associated with OCs present a very
different picture regarding the relationship with OCs for these two sites; while endometrial cancer risk
is clearly reduced in OC users, no such protective effect has been shown for breast cancer.

Many of the complexities of the pharmacokinetics of progestins (as reviewed in Section III) are
also relevant to the consideration of whether POPs could affect breast cancer risk. For example, the
large variation in blood levels of OC steroids makes it difficult to assess the relative actions of OC
doses on the breast (IOM, 1991). There is also considerable interindividual variation in breast cell
proliferation, and no studies have been conducted to relate serum hormone concentrations with breast
cell division rates (Pike et al., 1993).

Further complicating an understanding of the biologic mechanisms that could be responsible for
any association between POPs and breast cancer is the variability among POP users in their serum
levels of endogenous estrogen and progesterone (as discussed in Section II). Both epidemiologic and
laboratory data suggest that higher levels of endogenous estrogen, combined with higher levels of
endogenous progesterone, play a causal role in breast cancer (Pike et al., 1993).
Considerable animal research has documented that progestins alone, as well as estrogens alone and estrogens combined with progestins, can be mammary carcinogens, although many studies find no such effects (IOM, 1991; King, 1991). In much of this research, effects were found only at doses that are many multiples of the human contraceptive dose. Furthermore, results vary among species and even among strains within species, raising questions about the relevancy of this research to humans. The findings also vary by progestin, with DMPA, but not levonorgestrel, being mammary carcinogens in beagle dogs, for example. The 1967 application to the U.S. FDA to market DMPA was denied at least in part because progestins cause both benign and malignant mammary tumors in beagle dogs (Jordan, 1992; Klitsch, 1993); the requirement for use of the beagle in toxicology and carcinogenicity testing of contraceptive hormones has since been eliminated, although testing is still mandated in rats, mice, and monkeys (Jordan, 1992). After 25 years of use in other countries, the U.S. FDA approved DMPA for contraceptive purposes in 1992 (Klitsch, 1993).

Both epidemiologic and laboratory studies have also compared the effects of the 17-alpha-hydroxyprogesterone progestins (e.g., MPA) and the 19-nortestosterone progestins. A recent analysis of the formulations of COCs in the WHO Collaborative Study indicated that both classes of progestins had similarly little effect on breast cancer risk (Thomas et al., 1992). Bergink and colleagues (1983) found that the specificity of MPA for the progesterone receptor in breast tumor cell cultures was intermediate between that of NET and LNG. Jordan et al. (1993) recently reported that although both NET and LNG stimulated the growth of estrogen receptor-positive breast cancer cells in vitro, MPA did not.

Epidemiologic research on a possible relationship between breast cancer and DMPA use is somewhat limited, with small sample sizes and various methodological weaknesses (Stanford &
Thomas, 1993). The two largest studies indicate no overall effect but suggest a possible elevation in risk associated with long-term DMPA use before age 25 (Paul et al., 1989; WHO, DMPA and Breast Cancer, 1991).

No epidemiologic data are available on breast cancer risk in relation to NORPLANT® (Stanford & Thomas, 1993). The NORPLANT® labeling includes the following statement:

Recent evidence in the literature suggests that use of combination oral contraceptives is not associated with an increased risk of developing breast cancer in the overall population of users. The Cancer and Steroid Hormone (CASH) study also showed no latent effect on the risk of breast cancer for at least a decade following long-term use. However, some of these same recent studies have shown an increased relative risk of breast cancer in certain subgroups of combination oral-contraceptive users, although no consistent pattern of findings has been identified. This information should be kept in mind when prescribing NORPLANT®.... In spite of many studies of the relationship between combination oral-contraceptive use and breast... cancer(s), a cause-and-effect relationship has not been established.

The review by Herbst and Berek (1993) states that it is general medical practice not to give estrogens to women with a history of breast cancer, but that there are no data to support either giving such medication or withholding it. They suggest that OCs not be given to women who currently have breast cancer. Regarding progestin-only contraception, they note that very little is known about the relationship with breast cancer, but they make no clinical recommendation regarding its use by women with current or past breast cancer.

IPPF considers malignancies of the breast to be an absolute contraindication to POP use (Huezo & Briggs, 1992). INTRAH lists known or suspected malignancy of the breast as a relative contraindication, not because POPs are believed to cause breast cancer but because hormonal treatment can cause lumps to grow; however, they advise that POP use may continue while a breast lump is
being evaluated if a woman will not use a reliable non-hormonal method in the interim (INTRAH, 1993).

CONCLUSION: Although further research is needed on the interrelationships of progestin use, age, and breastfeeding, the current data do not suggest an elevated risk of breast cancer among POP users. The small increase in risk for long-term use of COCs and DMPA by young women could also exist for POP users, but there is no reason to expect a greater effect of POPs. However, women with breast cancer should not use POPs. (Types of evidence: II A, C, D.)

E. Other Cancers

Several other types of cancer have also been suspected of being related to combined OC use. The currently available data do not suggest a link with the following neoplasias: colorectal, kidney and gallbladder cancer; pituitary tumors; and malignant melanoma (Edgren, I J Fert, 1991, p. 37; Green, 1991; Harlap et al., 1991; Milne & Vessey, 1991; Prentice & Thomas, 1987; WHO, Tech Rep, 1992). Of these, only gallbladder cancer merited the attention of the WHO Collaborative Study of Neoplasia and Steroid Contraceptives (Thomas, Contrac, 1991, p. 695; WHO, I J Epid, 1989, p. 309); although the small number of OC users in the study precluded assessment of OC formulations, no association was found for OC use overall.

Regarding liver cancer, the relationship with COCs appears to vary considerably among populations (Rosenberg, 1991; WHO, Tech Rep, 1992). In countries with a relatively high incidence of liver cancer (primarily hepatocellular carcinoma), chronic infection with the hepatitis B virus is the primary causal factor, whereas other factors are more important in low-risk populations. Studies in the
United States, the United Kingdom, and Italy have all found strong associations of liver cancer with long durations of COC use (Prentice & Thomas, 1987; WHO, Tech Rep, 1992). In the largest of these studies (which had only 26 cases), the age-adjusted relative risk was 4.4 for 8 or more years of COC use, and when women who had markers of hepatitis B virus were excluded, the RR increased to 7.2. Neither COC formulation nor use of POPs was specifically analyzed. In another of these studies it was noted that 1 case and 10 controls had used progestins for non-contraceptive purposes (Forman et al., 1986). The summary RR for COC use, based on four papers, has been computed as 2.6 for ever-use and 9.6 for long-term use (variously defined as more than 5 or 8 years) (Prentice, 1991). Despite the high relative risk, because the disease is extremely rare, the number of additional cases that could be expected are quite small: about 1 death per 100,000 long-term users per year among women under age 35 or 2 deaths for women aged 35-44 (Harlap et al., 1991).

In contrast, the limited research in high-risk populations has found no connection between use of OCs and liver cancer (WHO, Tech Rep, 1992). For example, the WHO Collaborative Study (I J Ca, 1989, p. 182) reported an estimated relative risk close to unity and no trends in risk with duration of use (although it should be noted that there were very few long-term OC users). There was also no variation with dose of estrogen. Similarly, the WHO Study (I J Ca, 1991, p. 187) found no association of liver cancer with DMPA use.

Progestin receptors have not been found in liver tissue, but androgen receptors have been identified and synthetic progestins have been shown to bind to the androgen receptors in the liver, as well as other tissues (King, 1991). Estrogen is believed to have less of a promotional effect on hepatic neoplasia than does androgen. One hypothesis is that these liver tumors result from vascular changes
associated with COCs (Prentice & Thomas, 1987), which would suggest that POPs would not have a causal relationship.

CONCLUSION: There are no data on progestin-only OCs in relation to liver, colorectal, kidney or gallbladder cancers, pituitary tumors, or malignant melanoma. However, there is no reason to expect a clinically significant increased risk. (Type of evidence: II D.)
VIII. OTHER MEDICAL CONSIDERATIONS

A. **Persistent Ovarian Follicles**

A British study performed serial pelvic ultrasound examinations and found functional ovarian cysts in half of the POP users (12 of 21 women who used 3 types of POPs), compared to only 4 of 21 controls (Tayob et al., 1985). Seven of the POP users with cysts had abdominal pain, which was generally mild, but which sometimes required analgesics; none of the non-users with cysts had pain. Tabulation of functional ovarian cysts in the Oxford Family Planning Association Study by contraceptive method revealed that cysts were much more common in POP users than in COC users (Vessey et al., 1987).

Ultrasonography of IUD users has shown a higher rate of ovarian cyst development with LNG-releasing IUDs compared to copper IUDs, as well as a higher mean follicular diameter of those cysts (Barbosa et al., 1990).

Leroy and colleagues (1992) state that ovarian "cyst" is an inappropriate term because it suggests a pathologic condition, leading to surgical intervention. Mishell (1992) concurs, recommending that these small fluid-filled structures in the ovary be termed "persistent follicles." These structures are generally too small to be palpable, but can be seen by ultrasonography; they usually do not require surgery. Mishell states that they are "not uncommon" among women on "low dose hormonal contraceptive therapy," because, "the preovulatory LH peak is either inhibited directly or the contraceptive steroids block the positive feedback of the preovulatory estradiol peak produced by the follicle."
If these follicles are not symptomatic, POP use need not be discontinued and no intervention is necessary; the cysts will usually regress spontaneously. POP users presenting with abdominal pain should be carefully evaluated to determine whether the pain is related to ovarian cysts, ectopic pregnancy, or other causes. There have been cases reported of POP users with ovarian cysts who have been subjected to unnecessary surgery (Tayob et al., 1985). If painful follicles persist, POP discontinuation may be indicated (Hatcher et al., 1994).

NORPLANT® users also have a much higher frequency of ovarian cysts than do normally cycling women (Speroff & Darney, 1992). This is apparently due to the variable effects of low-dose LNG on FSH and LH levels. Development of these cysts does not usually necessitate implant removal. The NORPLANT® labeling comments that these enlarged follicles are the result of delayed follicular atresia among users in whom follicular development occurs. In most women these enlarged follicles will spontaneously disappear, although rarely they may twist or rupture, causing abdominal pain and sometimes requiring surgical intervention, according to the labeling.

The IPPF Guidelines consider functional ovarian cysts to be a relative contraindication, necessitating close medical supervision (Huezo & Briggs, 1992). The INTRAH Guidelines do not list ovarian cysts as a contraindication.

CONCLUSION: Although persistent ovarian follicles are common among POP users, they are not generally of clinical importance. If they are painful, the woman may wish to discontinue POPs. There is no reason for history of ovarian cysts to be a contraindication to POP use unless the cysts have been painful or required surgical intervention. (Types of evidence: II A, B, C.)
B. **Sexually Transmitted Diseases**

In the only study of sexually transmitted diseases (STDs) and OCs that analyzed POP users separately, a relative risk of 0.9 (95% CI: 0.2-3.4) was estimated for the relationship with acute initial episodes of pelvic inflammatory disease (PID) (Panser & Phipps, 1991). This was based on only 3 cases and 11 controls, and it did not consider length of use. Analysis of combined OC use in the same dataset indicated a protective effect for all estrogen dosages, with a greater effect among those women who had been taking their pills for at least 12 months.

A National Institutes of Health Expert Committee on Pelvic Inflammatory Disease (1991) has concluded that combined OCs may provide some protection against pelvic inflammatory disease, but they provide no protection against (and perhaps even increase the risk of) lower reproductive tract infections. The protection against upper reproductive tract infections may operate through several mechanisms, including the following: (1) thickened cervical mucus, providing a physical barrier to bacterial penetration; (2) atrophy of the endometrium, decreasing the medium for bacterial growth, and, perhaps; (3) decreased fallopian tube contractility, which could reduce the propulsion of bacteria into the peritoneum (Cates & Stone, 1992; McGregor & Hammill, 1993; NIH Expert Committee, 1991; Panser & Phipps, 1991; Speroff & Darney, 1992). All of these actions of COCs are also part of the mode of action for POPs, with the effect of POPs on cervical mucus being particularly pronounced, and so it can be expected that POPs could also exert a modest protective effect on PID.

The possible increased risk of lower genital tract infections, particularly cervical chlamydial and gonorrhea infection, may be attributable to the expanded zone of cervical ectropion that results from COC use, as the endocervical epithelial cells are the primary sites for attachment and infection for
Chlamydia trachomatis and Neisseria gonorrhoeae (Cates & Stone, 1992; Harlap et al., 1991; McGregor & Hammill, 1993; NIH Expert Committee, 1991; Roddy, 1993). Because cervical ectropion is primarily an estrogenic effect (Paavonen et al., 1990), it would not be a factor for POP users. In addition, progesterone has been reported to depress the growth of N. gonorrhoeae in the laboratory (McGregor & Hammill, 1993). On the other hand, in animal studies progesterone promotes the growth of C. trachomatis, speeds its ascent into the upper reproductive tract, and prolongs the persistence of the infection (McGregor & Hammill, 1993).

Most studies have found no relationship between OC use and infection with the human immunodeficiency virus (HIV), although some research suggests an increased risk (Cates & Stone, 1992; McGregor & Hammill, 1993). These conflicting, but worrisome, findings reflect the multifactorial nature of HIV infection and the numerous methodological difficulties in the studies reported to date. The only study of a progestin-only contraceptive, conducted among Thai prostitutes, found an elevated risk among users of DMPA, after controlling for other variables (Rehle et al., 1992). The authors suggest as a potential mechanism an antiestrogenic effect on the vaginal mucosa which could make the mucosa more atrophic and susceptible to tears during intercourse, thus providing a route for HIV transmission. In contrast, a potentially protective effect is indicated by a cell culture study which showed that progesterone inhibits HIV replication (Cavett et al., 1991).

The changes in bleeding patterns associated with POPs could theoretically affect the likelihood of both upper reproductive tract infection and HIV transmission (McGregor & Hammill, 1993; Speroff & Darney, 1992). Women who have decreased menstrual flow may have less retrograde flow of potentially contaminated menstrual blood and semen and also have a reduced amount of culture medium to support growth of pathogenic organisms; in addition, their sexual partners would have less
risk of exposure to HIV. Conversely, women who have increased menstrual flow while taking POPs could have increased risks of exposure, as could their sexual partners.

Limited support for a protective effect of progestins on the risk of PID comes from studies of progestin-releasing IUDs. A randomized clinical trial demonstrated a significantly lower rate of discontinuation due to PID for an IUD that released 0.02 mg LNG daily compared to a copper-releasing IUD (Toivonen et al., 1991). Another study examined histologic specimens that were obtained when IUD users were sterilized; salpingitis was not observed in any of the 22 wearers of the Progestasert IUD, but was common among users of various other types of IUDs (Soderstrom, 1983). In contrast, analysis of data from the Women’s Health Study found a modest elevation in PID risk associated with the Progestasert; the authors speculated that this could be a result of the requirement for frequent removal and re-insertion of this type of IUD, which increases the possibility of insertion-related infection (Lee et al., 1983).

A recent review by Cates and Stone (1992) evaluates the risks of gonorrhea infection and unplanned pregnancy associated with various contraceptive methods. They conclude that the risk of cervical gonorrhea is neither increased nor decreased for users of COCs, injectable hormonal contraception or hormonal implants, compared to users of no contraceptive method. For maximum protection against unwanted pregnancy, the methods of choice are hormonal contraceptives, IUDs or sterilization. Couples who are not mutually exclusive sexual partners should also use a barrier method for protection against STDs.

The INTRAH Guidelines state that POPs provide some protection against pelvic inflammatory disease, but that they do not protect against most STDs, including HIV (INTRAH, 1993). HIV
positivity is not a contraindication to POP use, according to IPPF Guidelines, although the partner should use a condom for protection against HIV transmission (Huezo & Briggs, 1992).

CONCLUSION: The risk of lower reproductive tract infections is unlikely to be affected by POP use, and the risk of PID may be decreased. Whether there is any association between HIV infection and POP use is unknown. For couples who are not mutually exclusive sex partners, condoms and/or other barrier methods should be used in addition to POPs in order to minimize STD transmission. (Types of evidence: II A, C, D; III A.)

C. Abnormal Vaginal Bleeding

Abnormal vaginal or genital tract bleeding prior to POP use is considered a contraindication for use of POPs (as well as any other hormones), at least until the reason for the bleeding is determined (Guillebaud, book, 1993; Hatcher et al., 1994). This is because the irregular bleeding that may result from POP use can obscure a diagnosis. In the labeling for NORPLANT® undiagnosed abnormal genital bleeding is also listed as a contraindication.

The INTRAH Guidelines note that undiagnosed abnormal vaginal bleeding may be caused by the following conditions: intrauterine or ectopic pregnancy; breastfeeding; pelvic inflammatory disease; endometrial, ovarian or cervical cancer; early or premenopause; hypo- or hyper-thyroidism; fibroids; or other gynecological problems. Although none of these conditions is actually worsened by POP use, "Since initiating the use of POPs is likely to cause irregular bleeding in many women, it would be optimal to determine the cause of the bleeding and to treat any serious problems before she starts to use POPs if she can use another reliable method in the meantime" (INTRAH, 1993).
CONCLUSION: POPs should not be prescribed for women with abnormal vaginal bleeding until a definitive diagnosis has been made and then only if no contraindication exists. (Types of evidence: III A, D.)

D. Uterine Fibroids

Uterine fibroids (leiomyomas) were detected during POP use in 15 of the 2,202 women (0.7%) using NG 0.075 mg in the case series reported by Korba and Paulson (1974). A case-control analysis of the Oxford Family Planning Association Study indicates that combined OCs reduce the risk of uterine fibroids, with a statistically significant reduction in risk with increasing duration of use (Ross et al., 1986). The OFPA data also suggest a dose-response effect for progestins, with greater protection by pills with a higher progestin dose (at a constant estrogen dose). Multivariate analysis determined that several other variables (parity, menopausal status, weight, and cigarette smoking) have the same relationship with uterine fibroids as with endometrial cancer. These risk factors suggest a causal role for "unopposed" estrogen in development of both of these conditions -- and thus a possible protective role for progestins.

A review by Huggins and Zucker (1987) states that, although estrogen is related to growth of existing leiomyomas, the limited available data on low estrogen dose COCs do not support a hypothesis for a stimulative effect. They conclude that uterine fibroids should not be a contraindication to low estrogen dose COCs.

CONCLUSION: Uterine fibroids should not be considered a contraindication to POP use. (Types of evidence: II A, D.)
E. Gestational Trophoblastic Disease

Whether or not steroidal contraception should be used by women who have recently had a hydatidiform mole has been the subject of some controversy (Cunningham et al., 1989; Curry et al., 1989). It is clear that prevention of pregnancy for at least one year is extremely important and that OCs are very effective. A further argument in favor of combined OCs (and, to a lesser extent, POPs) is that they suppress luteinizing hormone, which can cross-react with some of the tests for human chorionic gonadotropin (hCG) used for determining whether molar tissue persists.

A retrospective analysis by Stone and colleagues, reported in 1976, indicated that women who used oral contraception after evacuation of a hydatidiform mole were more likely to develop a trophoblastic tumor than non-users. Furthermore, among women who did not develop postmolar trophoblastic disease, hCG levels fell more slowly in OC users, suggesting that OC steroids stimulate secretion of hCG by trophoblastic tissue and thus lead to unnecessary chemotherapy. However, numerous studies since then have failed to confirm these findings (Berkowitz et al., 1981; Curry et al., 1989; Dei Cas et al., 1991). Notably, a prospective randomized clinical trial conducted by the Gynecologic Oncology Group compared a COC (EE 0.05 mg + NG 0.5 mg) with barrier contraceptives (Curry et al., 1989). There were no significant differences between the two groups in the incidence of postmolar trophoblastic disease or in the time for regression of hCG levels to normal; however, barrier method users were twice as likely to become pregnant. In another retrospective study, the risk of developing a postmolar gestational trophoblastic tumor was significantly less in women using OCs than in women using either barrier methods or no contraception (Dei Cas et al., 1991). Multivariate analysis indicated that contraceptive type was the most important predictor. There was no difference in risk of tumor development by OC estrogen dose.
Two other groups of researchers compared users of DMPA, COCs, and non-hormonal contraception who had recently had gestational trophoblastic disease (Eddy et al., 1983; Goldberg et al., 1987). There was no difference among these contraceptive groups in the percentage who developed postmolar trophoblastic disease in either study.

A laboratory study has directly addressed the issue of whether oral contraceptive steroids increase the rate of hCG secretion by trophoblastic cells (Gal et al., 1981). *In vitro* analysis found no effect of NA or EE, either alone or in combination. Similarly, progesterone does not affect hCG production by choriocarcinoma culture, although it inhibits hCG levels in cultures of normal placenta (Maruo et al., 1986; Wilson et al., 1980).

Regarding the initial development of a hydatidiform mole, OC use does not appear to be a risk factor (Bracken, 1987). In fact, because OCs prevent pregnancy they thereby prevent the occurrence of these moles (Prentice & Thomas, 1987).

CONCLUSION: There does not seem to be any reason why women with gestational trophoblastic disease should not use POPs. In fact, the importance of pregnancy prevention indicates that an effective contraceptive method such as the POP should be selected. (Types of evidence: I D; II C, D; III A.)

F. Benign Breast Disease

Most investigations into the relationship between oral contraceptive use and benign breast disease indicate a protective effect of current use that increases with duration of use (Huggins & Zucker, 1987;
Prentice & Thomas, 1987; WHO Scientific Group, 1992). Analyses of both the OFPA and RCGP Studies revealed the lowest risk at the highest progestin dose, controlling for estrogen dose (Brinton et al., 1981; RCGP, Lancet, 1977, p. 624). Although this relationship was not demonstrated in a case-control study in Connecticut (Berkowitz et al., 1984), this U.S. study had very few current users, and the large number of pill formulations necessitated assignment of progestin potency based on their relative effects on lipid metabolism. Two of these studies specifically noted that there were too few users of POPs for meaningful analysis (Berkowitz et al., 1984; Brinton et al., 1981).

Benign breast disease has been noted rarely in prospective studies of POP users. Among 2,202 women who used NG 0.075 mg for 29,006 woman-months, benign breast masses were found for 25 (1.1% or 0.86 per 1000 woman-months) (Korba & Paulson, 1974). During one year of POP use, breast fibroadenoma was detected for 2 of 100 women using NET 0.35 mg (1.0%), 1 of 182 women using CA 0.5 mg (0.5%), and 1 of 174 women using MA 0.5 mg (0.6%) (Hawkins & Benster, 1977). Bisset et al. (1992) reported that 0.5% of 1042 women using various POPs had benign or malignant breast pathology. Finally, breast lumps were detected in 3 of the 518 women using either POPs or COCs in a study by WHO (Contrac, 1982).

The term "benign breast disease" encompasses numerous pathologic conditions. Classification of these benign epithelial breast changes has been inconsistent, which makes it difficult to accurately portray their relationship with malignant conditions (Bodian, 1993; McGonigle & Huggins, 1991). As reviewed by Bodian (1993), several recent investigations, all of which used the same classification system, have found that nonproliferative breast disease is associated with little or no elevation in breast cancer risk; proliferative disease without atypia modestly increases the risk, while the greatest risk was
exhibited by women who had atypical hyperplasia. This latter category comprises only a small subset of those with benign breast disease (Huggins & Zucker, 1987).

Whether POPs affect the risk of breast cancer among women in general has been reviewed in Section VII. It is also important to consider whether there is a link between POP use and breast cancer specifically among women with benign breast disease. This is difficult to discern because of the apparent beneficial effect of progestins on benign breast disease, discussed above, as well as because of the different types of benign disease. Many of the studies of combined OCs have not distinguished between OC use before and after diagnosis of benign breast disease; experts have recently argued that the only appropriate methodology for analyzing the breast cancer-OC relationship among women with benign disease is to restrict the analysis to women who had benign disease prior to OC initiation (Stadel & Schlesselman, 1986; McGonigle & Huggins, 1991; Thomas, 1991). Studies that have restricted their analyses appropriately have not demonstrated an increased breast cancer risk among this subgroup of women (Malone et al., 1993; Thomas, 1991). None of these studies has considered either POPs or the progestin dose in COCs as part of their subgroup analyses, but the lack of effect for COCs is reassuring.

CONCLUSION: POPs may have a protective effect on benign breast disease, because progestins appear to be responsible for the well-documented protective effect of combined OCs. Although the interrelationships among OC use, benign breast disease, and breast cancer are not completely understood, current evidence indicates that benign breast disease should not be considered a contraindication to POP use. (Types of evidence: II A, D.)
G. **Liver Disease**

Liver function is affected in numerous ways by estrogen and, to a lesser extent, by progestins (Speroff & Darney, 1992). For example, in a large clinical series of NG 0.075 mg, among more than 600 women on whom liver function tests were performed, there were no significant differences between the values before and during POP use for various liver function tests (Korba & Paulson, 1974); there were also no clinical symptoms of liver disease. Similar results were reported among 556 women using 3 types of POPs by Hawkins and Benster (1977), who further noted that 23 of these women had a history of liver disease but experienced no deterioration in liver function during POP use. A review of the early data on POP concluded that POPs have less effect than COCs or none at all on liver function (Rinehart, 1975).

In correspondence regarding POPs and liver disease, Orme (1993) has stated that there is less concern about progestins than estrogens in women with liver disease, and that metabolic conversion of progestins to estrogens occurs at low levels, if at all. Furthermore, he does not believe that failure to metabolize progestins would be a problem, unless the liver disease is so severe that the woman would not be in need of contraception. He concludes that "I would therefore agree that progestin-only methods are a reasonable choice for women with liver disease." Guillebaud (book, 1993) concurs that progestins alone have little effect on hepatic secretion of plasma proteins.

Combined OCs are associated with liver adenomas; the risk increases with both duration of use and higher dosage levels (Prentice, 1991; Rosenberg, 1991; Speroff & Darney, 1992; Wilhelm et al., 1992; WHO, Tech Rep, 1992). The mechanism appears to be slowed metabolism of ethinyl estradiol to the weaker estrone, resulting in increased estrogenic activity in the liver and the potential for
initiation of hepatic tumors (Wilhelm et al., 1992). Although these rare tumors are benign, they may rupture and cause death by intra-abdominal hemorrhage. It does not appear likely that they would be associated with low-dose progestins alone.

Considerable research on NORPLANT® contraceptive implants has documented "no clinically important unfavorable changes" in liver function (and also no such changes in kidney, adrenal, or thyroid function) (Population Council, 1990). Another review noted no consistent changes in liver function among NORPLANT® users, again commenting that the changes sometimes found with COCs are attributable to the estrogen component (Davies and Newton, 1991). Nonetheless, acute liver disease, as well as benign or malignant liver tumors, are given as contraindications to NORPLANT® use in the labeling. Hepatic tumors are subsequently discussed under the heading of warnings based on combined OC experience, where it is stated that, "the contribution of the progestin component of OCs... is not known." It is also suggested that implants be removed if jaundice develops, because steroid hormones may be poorly metabolized in patients with impaired liver function. Recent studies have found that bilirubin is significantly elevated, compared to pretreatment levels, throughout the 5 years of NORPLANT® use, although all women remained within normal limits and there were no significant changes in other liver function tests (Singh et al., Contrac, 1992, p. 141; Singh et al., Contrac, 1992, p. 463).

The IPPF Guidelines state that POPs have "very little effect on liver function," but that POPs should not be provided to women with "acute liver disease, such as infectious hepatitis, until liver function tests are normal" (Huezo & Briggs, 1992). The INTRAH Guidelines indicate that there is no evidence that POPs cause liver tumors or liver disease (INTRAH, 1993). While acknowledging that progestins may affect liver function to some extent, they point out that the effect of progestins is less
than that of estrogens and therefore conclude that, for women who will not accept an effective non-hormonal contraceptive method, "progestin-only methods are not likely to clinically worsen liver disease and would be safer than pregnancy" (INTRAH, 1993).

CONCLUSION: POPs have little or no effect on liver function or on development of liver adenomas. Liver disease is not considered to be a contraindication to POP use. (Types of evidence: II A, B, D; III A.)

H. Gallbladder Disease

A recent methodologic review and meta-analysis of studies regarding the association between OC use and gallbladder disease produced a pooled odds ratio of 1.36 (95% confidence interval = 1.15-1.62) for ever use of OCs (Thijs & Knipschild, 1993). Only the RCGP study considered different dosages of progestins, at the same estrogen dose, with no differences detected (RCGP, 1982). That study, as well as two others (Layde et al., 1982; Strom et al., 1986), found a small increase in risk with increasing estrogen dose. The overall association is weaker in the more recent studies, in which users of lower dose pills presumably comprise a greater percentage of the study subjects, but it is unclear whether lower dosages are responsible for this phenomenon or whether there are other explanations (such as improved study methodology or publication bias).

The data suggest that, rather than increasing the lifetime incidence of gallbladder disease, COCs may instead accelerate the development of disease in previously asymptomatic women (Prentice & Thomas, 1987; RCGP, 1982; Speroff & Darney, 1992). The mechanism appears to be an estrogen-mediated increase in the cholesterol concentration of bile (RCGP, 1982; Speroff & Darney, 1992).
Other risk factors, such as obesity and cigarette smoking, are consistent with an estrogenic etiology (Layde et al., 1982; RCGP, 1982; Strom et al., 1986).

The NORPLANT® labeling acknowledges that the risk of gallbladder disease is "minimal" with combined OCs at low doses and that the risk with progestin-only methods is unknown.


CONCLUSION: Based on the small increased risk for COC use and the apparent dose response relationship, it appears unlikely that POPs increase the risk of gallbladder disease. (Types of evidence: II D; III A.)

I. Inflammatory Bowel Disease

Although several researchers have reported that inflammatory bowel disease is more common among current COC users, it is unclear whether this represents an etiologic relationship. In cohort analysis of both the RCGP and OFPA Studies, the incidence of ulcerative colitis and of Crohn's disease were higher among current users than among never or former users, after adjustment for smoking and other factors, but these results were not statistically significant (Logan & Kay, 1989; Vessey et al., BMJ, 1986). The relative risks were somewhat higher for Crohn's disease than for ulcerative colitis in the RCGP Study (Logan & Kay, 1989), but in the OFPA Study the relative risk was higher (and of borderline statistical significance) for ulcerative colitis (Vessey et al., BMJ, 1986).
The numbers of cases were too small to permit consideration of OC formulations. Cigarette smoking was associated with a decreased risk of ulcerative colitis and an increased risk of Crohn's disease in both data sets. A recent case-control study conducted in North Carolina found an increased risk among current OC users for Crohn's disease, but not for ulcerative colitis (Sandler et al., 1992). Smoking and OC use were found to have a synergistic effect, such that the risk of Crohn's disease was significantly elevated for OC users who were current smokers, but there was no increased risk associated with OC use among former smokers or never-smokers.

The biologic mechanism for any possible relationship is unclear. It has been suggested that microvascular gastrointestinal infarction could be involved in Crohn's disease, which is corroborated by the interaction of smoking and OC use suggestive of thrombogenic effects (Sandler et al., 1992). This would imply that any relationship with combined OCs is the result of the estrogen component and thus that POPs are unlikely to affect the risk.

CONCLUSION: Inflammatory bowel disease need not be of concern for POP use. (Type of evidence: II D.)

J. Endocrine Dysfunction

The three endocrine conditions that have the greatest potential to interact with steroid contraception are thyroid dysfunction, prolactinomas, and polycystic ovarian syndrome, according to a recent review by Loriaux and Wild (1993). Of these, disorders of thyroid function are the most common. Oral contraceptives have no effect on thyroid disease, and so Loriaux and Wild (1993) state that there would be no effect expected from progestin-only implants; presumably this conclusion
would also apply to POPs. An early review of POPs noted no change in thyroid function (Rinehart, 1975). Studies of NORPLANT® users have also found no significant changes in various parameters of thyroid function from pretreatment levels (Diaz et al., 1989; Olsson et al., 1986) and no significant difference between women using NORPLANT® and Copper-T IUDs (Diaz et al., 1989). Neither study found significant effects on thyroid stimulating hormone or triiodothyronine (T₃); thyroxin (T₄) was shown by Olsson et al. (1986) to decrease with NORPLANT® use, but Diaz et al. (1989) found no effect.

Regarding prolactinomas, the only concern expressed is the potential for estrogen to stimulate prolactin secretion (Loriaux & Wild, 1993). However, it does not appear that OCs are associated with the subsequent development of these pituitary tumors (Loriaux & Wild, 1993; WHO, Tech Rep, 1992) or that use of OCs affects preexisting prolactinomas (Loriaux & Wild, 1993).

Finally, polycystic ovarian syndrome is characterized by androgen excess, and thus the preferred OCs would be the highest estrogen-to-progestin ratios (Louriaux & Wild, 1993). The androgenic activity of progestin-only implants (and, by extension, POPs) could potentially aggravate the hyperandrogenicity of women with polycystic ovary disease.

CONCLUSION: Women with thyroid dysfunction or prolactinomas can use POPs, but women with polycystic ovarian syndrome should not. (Types of evidence: II A, D; III B.)
K. Epilepsy

Epilepsy occurs in approximately one percent of the population, including women of childbearing years (Mattson & Rebar, 1993). Research indicates that both endogenous progesterone and exogenous progestins can reduce neuronal excitability and the occurrence of seizures, as reviewed by Mattson and Rebar (1993). Women with epilepsy require highly effective contraception because of the teratogenic effect of antiepileptic drugs, as well as the increased potential for pregnancy complications (Mattson & Rebar, 1993). Unfortunately, the enzyme-inducing action of most antiepileptic drugs results in reduced serum levels of serum hormones, as discussed in Section IX. Thus, POPs are not recommended for women with epilepsy because of their low progestin dose.

CONCLUSION: Although progestins may reduce the occurrence of epileptic seizures, POPs are not recommended for women with epilepsy because most antiepileptic medications reduce POP efficacy. (Types of evidence: II A, D; III A, B, D.)

L. Bone Density

Very little research has examined the effects of progestin-only contraceptives on calcium metabolism and bone density in women. One such study evaluated the effect of long-term use of lynestrenol 5 mg as a contraceptive (Dequeker et al., 1977), although this is 10 times the current POP dose for this progestin. Bone mass was significantly greater in users than in non-users matched for age and sex. Another group of researchers examined 30 women who had used DMPA for more than five years (Cundy et al., 1991). Average bone density in the lumbar spine and in the femoral neck
was somewhat lower among DMPA users. However, there were numerous methodological weaknesses in the study, and MPA is a different class of progestins than those used in POPs.

Although there is a large body of evidence regarding the effects of combined OCs, the results are conflicting, with some studies finding a beneficial effect on bone mass while others indicated no effect (Fortney et al., 1994; Mehta, 1993). It is clear that administration of estrogen replacement therapy does reduce the rate of bone loss that normally accompanies cessation of ovarian function. The relevance of this observation on postmenopausal hormonal replacement therapy to OC use is uncertain, not only because OCs are used by women whose ovaries would normally be functioning but also because of differences in hormonal formulation; hormone replacement therapy (HRT) involves natural estrogens, rather than the synthetic estrogens used in COCs, and medroxyprogesterone acetate (a C-21 progestin) is the preferred progestin for HRT, whereas the progestins used in both COCs and POPs are usually C-19 progestins. Several lines of reasoning support a causal relationship between low blood estrogen levels and bone loss, among both premenopausal and postmenopausal women (Mehta, 1993). Variable suppression of endogenous estrogen levels by progestin-only contraceptive methods (Speroff & Darney, 1992) make it difficult to predict their effect on bone mass.

A biologic role of progestins in bone turnover is suggested by recent laboratory studies. Receptors for progesterone as well as estrogen have been found in osteoblast culture lines of bone (Eriksen et al., 1988; Komm et al., 1988). Furthermore, a recent study has documented that several nortestosterone derivatives (including norethindrone and norgestrel) stimulate the growth of estrogen receptor-positive breast cancer cells, while MPA did not have that effect, suggesting that the 19-nor progestins could exert beneficial estrogenic effects such as bone preservation if a similar effect is observed in bone cells (Jordan et al., 1993).
CONCLUSION: The relationship between POP use and bone density remains unclear, but there is unlikely to be an adverse effect. (Types of evidence: II A, C, D.)

M. Sickle Cell Disease

There have been no studies of POPs and sickle cell disease, but research on other progestin-only contraceptives and on COCs suggest a beneficial effect. In a report of NORPLANT® users with sickle cell disease, there were no clinically or statistically significant group changes in numerous hematologic or biochemical parameters, nor were there any substantial changes for any individuals (Ladipo et al., 1993). When DMPA was assessed in a cross-over trial, painful sickle cell crises were less frequent during the DMPA phase than during the placebo phase, and red cell survival was improved (DeCeulaer et al., 1982). Progesterone and testosterone have both been shown in vitro to inhibit sickling by stabilizing the membrane of the erythrocyte (Isaacs & Hayhoe, 1967).

Unpublished studies of women with sickle cell disease (Lutcher, 1976; Lutcher et al., 1981) indicate no significant differences for combined OC users compared to non-users in terms of coagulation studies, blood viscosity measurements, or the incidence or severity of painful sickle cell crises. A recent review of hematological disorders and reproductive health comments that there is no scientific justification for considering sickle cell disease to be a contraindication to OC use (Howard & Tuck, 1993). The reviewers also pointed out that pregnant women with sickle cell disease, as well as their infants, have increased rates of morbidity and mortality, indicating a special need for effective contraception in women with sickle cell disease. It has been estimated that in populations with a high prevalence of sickle cell disease and a high rate of maternal mortality, increased use of effective contraception could substantially reduce the number of maternal deaths (Klufio et al., 1985).
IPPF Guidelines specify that POPs may be used by women who are sickle cell disease carriers (Huezo & Briggs, 1992). INTRAH Guidelines also suggest that POPs may be particularly appropriate for women with sickle cell disease because progestins may "stabilize the membrane of the red blood cell, preventing sickling and sickle cell crises" (INTRAH, 1993).

CONCLUSION: There is no reason for sickle cell disease to be a contraindication to POP use, and, in fact, POPs may have a beneficial inhibitory effect on sickle cell crises. (Types of evidence: I C; II B, C, D.)

N. Ocular Effects

Much of the literature on ocular/ophthalmic problems related to oral contraceptive use is made up of retrospective case reports published before 1970, when hormone dosages were much higher. (See Connell & Kelman, 1968; Li & Fu, 1988; Petursson et al., 1981.) In addition none of the literature is concerned with a progestin-only treatment, except a 1950 German study of the effect of natural progesterone on reducing the intraocular pressure of glaucoma (Meyer et al., 1966). Another study also found a slight reduction in intraocular pressure among combined pill users, but hesitated to attribute this to one hormone or the other (Meyer et al., 1966). However, it is the estrogens and not the progestins that have been shown to have a negative effect on the eye (Petursson et al., 1981). A single exception was a study of a case of ischemic papillopathy in a Depo-Provera® user in China, activated immediately after her second and again after her third injection (Li & Fu, 1988). The authors of that study stated that:

Although ocular complications caused by contraceptives are entirely attributable to estrogen and progestin-induced thrombotic disorders have not been reported, ischemic papillopathy seen in our patient may be considered an ocular complication on the use of Depo-Provera®

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The initial hormonal burst was apparently responsible for this problem with DMPA and is not directly relevant to the effects of the steady, low doses of progestins received in the POPs.

Petursson et al. (1981) reviewed cases from the National Registry of Drug-Induced Ocular Effects for 1976-1980, finding only 82 cases of ocular-vascular disorders and 69 neuro-ophthalmic disorders possibly linked to combined OCs in that 5-year period. He also counted 7 cases of difficulty wearing contact lenses, a small but unstated number of disturbances in color vision (retinopathy) in diabetics, as well as a similarly small number of cases of possibly accelerated retinitis pigmentosa. He concluded that OCs were not a significant factor in ocular problems. Prospective studies (Connell & Kelman, 1968; DeVries et al., 1978; Faust & Tyler, 1966), retrospective studies (Connell & Kelman, 1968; Li & Fu, 1988), and reviews of the literature (Connell & Kelman, 1968; Petursson et al., 1981) uniformly report no association between combined OCs and ocular problems.

Of the prospective studies, two from the 1960s examined eye problems in general. One study of 212 patients using various high dose combined OCs failed to reveal any eye pathology in detailed ophthalmic examinations (Faust & Tyler, 1966). The second study similarly reported no significant differences in the rate of eye problems between 184 OC users and 361 non-OC users (Connell & Kelman, 1968). Both studies, however, noted the need for larger samples to measure the rarer conditions. The third prospective study (DeVries et al., 1978) found no statistically significant difference in the ability to wear contact lenses between 199 women using OCs and either 242 women not on OCs or 76 male controls.

The NORPLANT® labeling states:

Retinal thrombosis is associated with OC use and is believed to be related to the estrogen component. However, NORPLANT® SYSTEM capsules should be removed if there is an
unexplained partial or complete vision loss; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Undertake appropriate diagnostic and therapeutic measures immediately.

The NORPLANT® labeling also notes that "contact lens wearers who develop visual changes or changes in lens tolerance should be assessed."

CONCLUSION: There seems to be no significant negative effect of POPs on any condition of the eye. Nevertheless, any eye problems or discomforts beginning after POP initiation should be reported. (Types of evidence: II A, C, D.)

O. Surgery

Because of concerns about potential aggravation of the risk of postoperative thromboembolism, discontinuation of combined OCs prior to elective surgery is sometimes recommended. These recommendations have been questioned in terms of prophylactic necessity with regard to thrombosis, risk of pregnancy, and practicality (Beller, in press). Furthermore, because postoperative thromboembolism is an estrogenic effect of COCs, discontinuation of POPs need not be considered. In fact, Hatcher and colleagues (1994) say that surgery is one of the indications for use of progestin-only contraception (including POPs).

The NORPLANT® labeling suggests that removal be considered for women who will be immobilized for a prolonged time, due to surgery or illness. However, no rationale for this recommendation is given.
CONCLUSION: Because POPs do not have the estrogen-related potential for thrombotic effects that may be associated with combined OCs, there is no reason for a POP user to discontinue if she is immobilized after an accident or if she requires surgery. (Types of evidence: III A, D.)

P. Overdosage

Regarding overdosage, the current package labeling for COCs and POPs states the following:

Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health care provider or pharmacist.

The NORPLANT® labeling suggests that overdosage could cause fluid retention and uterine bleeding irregularities.

CONCLUSION: Presumably the current labeling statement about lack of serious effects from overdosage would apply to the lower dose progestin-only OCs. (Type of evidence: III D.)
IX. INTERACTIONS WITH DRUGS AND LABORATORY TESTS

A. Drug Interactions

Pharmacological interactions between oral contraceptives and other compounds may take the form of the other drug impairing the efficacy of the oral contraceptive or of the OC's interfering with the metabolism of the other drug. The effect of other drugs on OCs is the issue of concern here. Specific drugs that may interfere with the efficacy of progestin-only oral contraceptives include several anticonvulsants and rifampicin (a treatment for tuberculosis and leprosy). Some broad spectrum antibiotics may have significant interactions with combined oral contraceptives but not with POPs, as they reduce only the bioavailability of EE. Also there is no evidence that smoking alters OC pharmacokinetics (Back & Orme, in press). Finally, inter-individual variations in the pharmacokinetics of OCs are probably the greater factors in any interactions (Fotherby, AJOG, 1990, p. 2153).

For the first decade of their use, oral contraceptives contained such relatively large doses of steroids that it was unusual for other drugs to reduce the efficacy of the OCs to a level where contraceptive failure might occur. Since the 1970's, with the advent of the lower dose OCs, a number of drugs have been reported to reduce OC efficacy (Orme, 1982). The pharmacokinetic interactions that may occur between contraceptive steroids and other drugs occur with: 1) absorption, 2) serum protein binding, and 3) hepatic metabolism (Fotherby, AJOG, 1990, p. 2153). Evidence suggests that some anticonvulsant, antibiotic and antibacterial drugs may reduce OC efficacy. However, the incidence of serious interactions is low. Fotherby (AJOG, 1990, p. 2153) notes that:

Even where there is a possibility of an interaction, probably in under 5% of women will the interaction occur to such an extent that there is a decrease in the efficacy of the OCs, thereby leading to the risk of pregnancy.
Fotherby (AJOG, 1190, p. 2153) further states that serious interactions would probably occur only in those women who are fast metabolizers of steroids, and therefore have low serum concentrations of contraceptive steroids, and in those women whose liver enzyme systems are particularly susceptible to induction. In addition, these effects are primarily on the estrogenic component of OCs.

Szoka and Edgren (1988) reviewed the adverse drug experience database of Syntex, which is based on both published reports and adverse experiences reported directly to Syntex. They found that of 453 cases involving possible interference with the efficacy of combined OCs, the interaction resulted in pregnancy in one-third of cases and manifested as menstrual disturbances in two-thirds. Szoka and Edgren found that there were also 270 women in the database who were simultaneously taking OCs and other medications with no adverse effects; these women without problems comprised about half of the subjects in 8 clinical studies of women taking OCs with other drugs.

Anticonvulsant Drugs:

Although clinical study has provided scientific evidence of worsening of seizures in epileptic women who use COCs, due to the estrogens, slight improvement has occurred in some cases due to the progestins (Mattson et al., 1986). However, the main concern here is the reverse effect, the fact that OC failure rates are higher in women taking enzyme-inducing antiepileptic drugs.

Levels of sex steroids can be diminished through hepatic enzyme induction by anticonvulsants. Because of the teratogenicity of antiepileptic drugs, failure of contraception is a serious issue (Mattson & Rebar, 1993). Anticonvulsants, as enzyme-inducing agents, stimulate production of SHBG, thus binding OC steroids to the SHBG at a higher than expected level, and thereby decreasing circulating
free synthetic steroids (Back et al., BJCP, 1979; Back et al., 1980; Crawford et al., 1990; Orme, 1982). For example, Crawford et al. (1990) found that the plasma concentration for LNG in a combined OC was reduced by the enzyme-inducing action of both premytoin and carbamazapine. Baciewicz (1985) has suggested that the hepatic enzyme-inducing effect of the antiepileptic drugs might render the OC ineffective by increasing the hydroxylation of both the estrogen and progestin.

A combination of hepatic enzyme-induction and the increase in plasma concentrations of SHBG makes less of the hormone available for pharmacological action (Orme, 1982), although this may be countered to some extent by the tendency of progestins to lower SHBG levels. (See Section III.) The specific isoenzyme action of the anticonvulsant drugs on EE is understood, but no data are available regarding which isoenzymes are involved in progestin metabolism (Back & Orme, in press). Hepatic enzyme-inducing anticonvulsants and sedatives that can reduce POP effectiveness include phenobarbital, phenytoin, and carbamazepine; whereas sodium valproate, which is not an enzyme-inducer, does not (Back & Orme, in press; Mattson et al., 1986; Mattson & Rebar, 1993).

NORPLANT® contraceptive implant users taking phenytoin or carbamazepine also have been reported to have increased metabolism and clearance of LNG and thus decreased contraceptive effectiveness (Odlind & Olsson, 1986; Population Council, 1990). The NORPLANT® labeling warns of possible reduced efficacy with these drugs. A case study of a 26-year old woman on phenytoin who had NORPLANT® implants inserted (Odlind & Olsson, 1986) exemplifies the problem. During combined phenytoin/LNG therapy, plasma LNG levels were well below those expected for a healthy NORPLANT® user. After discontinuing phenytoin, there was a marked increase in LNG levels and the regular ovulatory cycles experienced while on the phenytoin became irregular, with no signs of ovulation.
In the past, women were advised not to use OCs if they were taking anticonvulsants because of their interactive effect; however, that restriction is no longer applied when estrogen doses can be increased (Back & Orme, in press; Crawford et al., 1990; Guillebaud, book, 1993; Mattson et al., 1986; Orme, 1982). Combined pills, but not POPs, can therefore be considered as contraceptive options for those women. Increasing the progestin doses of a progestin-only pill in the same way is not generally recommended as this can cause even higher rates of irregular bleeding than in the general population of POP users (Mattson et al., 1986).

CONCLUSION: Progestin-only oral contraceptives are not generally recommended for women using enzyme-inducing anticonvulsant medications because of increased rates of irregular bleeding. (Types of evidence: II A, B, C, D.)

Antibiotics:

The interaction of antibiotics with OCs is the most controversial of the drug interactions. Ampicillin, erythromycin, and tetracycline seem to have no real systematic relationship with OC failure in careful clinical studies, but they frequently appear in the statistics on contraceptive failures (e.g., Dossetter, 1975; Proudfit, 1981; Sparrow, 1987, 1989; Kovacs et al., 1989). For example, Kovacs and colleagues reported that 23% of the pregnancies among 209 COC users had used antibiotics in their last two cycles before conception, with one-third of those having used amoxicillin. Sparrow also reported 23% of 163 failures (1987), then 34% of 136 failures (1989), to be associated with antibiotics. However, both authors specified that they found no such association in the few progestin-only pill users in their studies. In addition, clinical pharmacokinetic studies have been
"singularly unsuccessful in demonstrating any consistent effect of antibiotics on plasma concentrations of contraceptive steroids" (Back & Orme, in press).

Neely et al. (1991) comment that the OC label warning about possible contraceptive failure while taking doxycycline initially resulted from a single case report. Numerous other reviewers of the literature also point out the fact that most negative opinion about antibiotics is based on the anecdotal data, unsupported by formal studies, with documentation that is minimal and contradictory (Angle et al., 1991; Back & Orme, 1990; Back & Orme, in press; Goldzieher, book, 1989; Shenfield & Griffin, 1991).

It may be that certain individuals are at greater risk of an interaction between OCs and antibiotics, although this possibility seems to focus primarily on the bioavailability of estrogen in the gut wall and liver, a large recirculation of EE, and a gut microflora particularly susceptible to the antibiotic being used (Back & Orme, in press; Orme, 1982). Baciewicz (1985) theorizes that the antibiotics effects on the intestinal flora can interfere with reabsorption of the steroids, leading to escape ovulation. Another hypothesis is that antibiotics induce hepatic microsomal enzymes, which accelerate estrogen metabolism, resulting in subtherapeutic blood estrogen levels. However, both Baciewicz (1985) and Fotherby (AJOG, 1990, p. 2153) point out that neither of these actions is likely to affect progestin-only pills.

More specifically, enzyme-inducing antibiotics, such as rifampicin, could reduce the effectiveness of POPs, while other antibiotics would not (Angle et al., 1991; Back & Orme, 1990; Goldzieher, book, 1989; Guillebaud, 1993; Shenfield & Griffin, 1991). Some other antibiotics, such as tetracycline, doxycycline, and penicillin (or ampicillin), seem to increase breakthrough bleeding in some cases,
apparently due to reduction in blood levels of the progestin, but again documentation is minimal and

Studies of the interaction between progestins in combined OCs with broad-spectrum antibiotics
clearly support the position that most antibiotics interact with the estrogens and not the progestins.
Grimmer et al. (1983) reported that, by 1983, at least 38 cases of OC failure had been reported to the
U.K. Committee on Safety of Medicines in women also taking antibiotics (not including rifampicin).
The most commonly implicated drug was ampicillin, followed by cotrimoxazole. The authors found in
their own research that LNG levels did not change significantly, although EE levels did increase in
women on combined OCs and with the two broad spectrum antibiotics.

Previously, 11 subjects taking ED 1 mg plus EE 0.50 mg were studied during 2 consecutive
menstrual cycles in a double-blind study of ampicillin 250 mg use (Friedman et al., 1980). Similarly,
no increase in breakthrough bleeding, no significant difference in serum FSH or LH, and no difference
in progesterone levels were found in the ampicillin cycles, although EE did increase in some cases.
Finally, in another study, neither ampicillin 500 mg (6 women) or methonidazole (10 women) therapy
altered the ‘peak’ of 24-hour plasma levels for NET 1 mg or EE 0.30 mg in a combined low-dose pill
(Joshi et al., 1980, p. 643). Progesterone levels were in the anovulatory range in all ampicillin treated
cycles.

Despite these findings, because of concern that certain individuals may be more susceptible than
others to drug interactions and because the anecdotal data still raises concern (Editorial, BMJ, 1990),
the clinical guidelines that discuss drug interactions with POPs (Huezo & Briggs, 1992; INTRAH,
1993) recommend that women who are taking any of the enzyme-inducing drugs use alternative or
CONCLUSION: Although the research in this area is not definitive, there does not appear to be any significant effect of broad-spectrum antibiotics on POP protection. Pharmacokinetic studies can find no relationship, and even the anecdotal data that has implicated the combined OCs have found no association for progestin-only pills because the action of concern appears to involve the estrogen component. (Types of evidence: II A, D.)

Rifampicin:

Rifampicin is an antibiotic most often used to treat tuberculosis patients. Menstrual abnormalities and pregnancy have occurred in tuberculosis patients treated simultaneously with OCs and rifampicin, a hepatic enzyme-inducer. Reimers and Jezek (1971) reported increased breakthrough bleeding with rifampicin. Back et al. (EJCP, 1979) and Back et al. (1980) demonstrated an effect of the antituberculin treatment on NET as well as on EE blood levels. They studied 9 women during and one month after rifampicin treatment and found the rifampicin caused a significant decrease in plasma levels of NET 1 mg (combined with EE 0.50 mg.) Joshi et al. (Contrace, 1980, p. 617) confirm the earlier study by Back et al. (EJCP, 1979) that rifampicin reduces NET levels. In the Joshi study, rifampicin treatment caused a statistically significant reduction of the plasma NET levels as well as the AUC of NET in 9 women receiving low dose OCs with NET 1 mg and EE 0.30 mg. Two of 7 regularly menstruating women showed a premenstrual rise of plasma progesterone levels suggesting an ovulatory cycle and 3 experienced menstrual irregularities. A matched group of 8 women on other
antitubercular therapy showed no changes in plasma levels. All were anovulatory and only one had menstrual irregularities.

CONCLUSION: The likelihood of increased breakthrough bleeding, lower progestin levels and possible reduced effectiveness of the progestin-only OC suggests a switch to other means of birth control if rifampicin is being taken for treatment of tuberculosis. (Types of evidence: II A, D.)

Griseofulvin:

Griseofulvin, an oral anti-fungal medication, has been shown to induce liver enzymes, although Back and Orme (in press, 1990) do not consider the evidence in humans to be convincing. Shenfield and Griffin (1991) and D'Arcy (1986) recommend use of OCs and griseofulvin with caution. All three papers based their conclusions primarily on a single report of 22 cases of possible reduced OC effectiveness due to use of griseofulvin in the United Kingdom and the Netherlands (van Dijke & Weber, 1984). Back and Orme (in press) note that a single case has been reported more recently. Szoka and Edgren (1988) report no failures of OCs among griseofulvin users in the Syntex database through 1985. Although there is no clearcut evidence of a major enzyme-inducing effect, one of the concerns about taking OCs and griseofulvin at the same time is the increased breakthrough bleeding caused by the antifungal medication, especially in the first couple of months (Back & Orme, in press). Goldzieher (book, 1989) specifically recommends a higher dose of combined OCs with griseofulvin use to reduce breakthrough bleeding.
CONCLUSION: Although there is no strong evidence of a major hepatic enzyme-inducing effect in humans, POPs probably should not be the contraceptive of choice for long-term users of griseofulvin, not because of reduced effectiveness but because of increased menstrual irregularities. (Types of evidence: II A, D; III A, D.)

Vitamin C and Paracetamol:

Vitamin C (ascorbic acid) and paracetamol (acetaminophen) have been found to increase the bioavailability of EE, particularly in the gut wall. No such effect has been found for progestins (Back & Orme, 1990).

CONCLUSION: Vitamin C and paracetamol do not interact with POPs. (Types of evidence: II A, D.)

OVERALL CONCLUSIONS: Users of progestin-only pills should probably not take any hepatic enzyme-inducing drugs, such as most anticonvulsants or rifampicin. Antibiotics, however, are almost certainly not an issue. Nevertheless, like all OC users, POP users require monitoring of their bleeding patterns anytime they are taking other drugs as well as the contraceptive. For women whose bleeding patterns have stabilized, unexpected bleeding when taking other medications could indicate that serum steroid levels have been reduced. Particular care should be given to women who are taking multiple other drugs at the same time as POPs. (Types of evidence: II A, C, D; III A, C, D.)
B. Interactions with Laboratory Tests

Information about possible effects of POPs on laboratory test results is sparse. Similarly, most of the discussions about lab test interactions with COCs do not consider which steroid is responsible.

A 1974 review of the literature by Miale and Kent listed 100 clinical laboratory tests as significantly affected by combined oral contraceptives. In only two cases were the effects cited as being particularly due to the progestins, included complement-reactive protein (serum) and hematocrit, with platelet aggregation cited as a combined effect of the estrogen and progestin. Five years later, The Medical Letter (1979) listed 38 tests significantly affected by combined OCs, without specifying estrogen vs. progestin effects. Both sources noted the importance to the test results of the specific hormones used, their dosage and length of therapy.

A few clinical texts and guidelines list potential interactions of POPs with various lab tests, but these sources do not necessarily agree with each other or with the metabolic data. For example, Covington (1989) specifies:

Laboratory test results of hepatic function, coagulation tests (increase in prothrombin, factors VII, VIII, IX and X), thyroid, metyrapone test and endocrine functions may be affected by progestins or estrogens.

Dickey (1993) does not include clotting factors and prothrombin in his table on affected lab tests, but specifies that the "serum is increased" by progestins in the following tests: fibrinolysis, hematocrit, insulin, insulin resistance, nitrogen, and cholesterol ratios; and that "serum is decreased" in several other tests: alpha amino nitrogen, complement reactive protein, HDL cholesterol, leutinizing hormone, and triglycerides. Neither Covington (1989) nor Dickey (1993) provide discussion or specific documentation for their guidelines.
According to the COC labeling, "certain endocrine and liver function tests and blood components may be affected by oral contraceptives." Without noting whether or not these changes are in the clinically significant range, the labeling goes on to list 7 categories of tests that may be so affected:

- Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

- Increased thyroid binding globulin (TGB) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 is unaltered.

- Other binding proteins may be elevated in serum.

- Sex steroids binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

- Triglycerides may be increased.

- Glucose tolerance may be decreased.

- Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

Without saying that they are clinically significant, the NORPLANT® labeling states only that:

- SHBG concentrations are decreased.

- Thyroxine concentrations may be slightly decreased and triiodothyronine uptake increased.

Several modifications in the current OC labeling would appear to be appropriate for POPs, based on the discussions of lipid and carbohydrate metabolism in Section V and the comments of several experts, including Dorflinger (personal communication, 1993); Edgren (personal communication, 1993); Goldzieher (letters, 1993, 1994); Grubb (letter, 1993); Mishell (letters, July 1993, December 1993); Nash (letter, 1994); Orme (letter, 1994); Speroff (letter, 1993); and Weber (letter, 1993).
Lipid Effects:

Studies of metabolic effects show little effect of progestins on lipid levels. (See Section V.) In the 8 studies summarized in Table 4 most lipid levels (total cholesterol, HDL_{3}, HDL, LDL, and triglycerides) were unchanged by progestin-only contraceptives. Some, but not all, studies of HDL, HDL_{2} and triglycerides found significant changes in these parameters.

Based on the published and unpublished studies of NORPLANT® and NORPLANT®-2, Nash (letter, 1994) estimates that the LNG in the implants reduces total cholesterol by about 10%, HDL cholesterol by about 15%, and triglycerides, 25%; the total cholesterol/HDL ratio is variably increased and decreased.

Glucose/Insulin Levels:

Blood glucose and insulin levels show more variation than do the lipid levels, although most assessments indicate no effect of POP use, as shown on Table 4. Thus, the conclusion in Section V is that there is no clinically significant effect, overall, of POPs on carbohydrate metabolism. Nonetheless, clinicians should be alert to the possibility that, for an individual POP user, glucose tolerance tests and other assessments of carbohydrate metabolism could be affected by POPs.

Coagulation Effects:

Progestin-only oral contraceptives have generally been found to have little or no effect on various parameters of coagulation activity, as reviewed in Section V. Blood coagulation appears to be
similarly unchanged in NORPLANT® studies although results are not consistent (Section V). As noted by Beller (in press), many of the coagulation factors have very broad ranges. There does not appear to be an overall adverse effect of POPs on coagulation but one of the many things to be considered by a clinician in evaluating tests of the blood coagulation system is POP use because of the possibility of modest effects on individual women.

**Thyroid Function:**

The NORPLANT® labeling states that thyroid tests may be affected by the LNG, specifying that thyroxine concentrations may be slightly decreased and triiodothyronine uptake increased. However, neither of the two NORPLANT® studies reviewed in Section VIII (Diaz et al., 1989; Olsson et al., 1986) showed an effect on triiodothyronine (T₃) and only one (Olsson et al., 1986) showed a decrease in thyronine (T₄); neither found thyroid stimulating (TSH) to be affected.

**Sex Hormone Binding Globulins (SHBG):**

Sex hormone binding globulins (SHBG) are increased by estrogens, but decreased by progestins. (See Section III.) Thus, the COC labeling lists SHBG as being increased, but the NORPLANT® labeling states that SHBG concentrations are decreased.

**Serum Folate Levels:**

Serum folate levels may be slightly depressed by OC therapy, according to the COC labeling, which hypothesizes that this may be of clinical significance if a woman becomes pregnant shortly after
discontinuing OCs. However, as Goldzieher (letter, 1993) points out, this problem is hypothetical and has not been raised in the research literature on OC users, even in countries where nutrition is poor. The problem is also not mentioned in any other guidelines regarding laboratory test interactions. A study of the effect of DSG 0.15 mg plus EE 0.03 mg found no difference in serum folate levels of treated vs. untreated women (Steegers-Theunissen et al., 1992).

Clinical Implications:

The available information on the interactions of progestins with various laboratory tests suggests that, although there are often measurable, inconsistent, interactions in many of the tests, they do not have clinical significance overall. Of the seven interactions listed in the COC labeling, only one appears to have a sufficiently strong trend in any direction to be worth noting, and that one test is for SHBG.

It is interesting to note that, although the NORPLANT® labeling discusses changes in lipid and carbohydrate metabolism in other sections, it does not include them under laboratory test interactions, also suggesting that the interactions are not clinically significant. Of the two interactions specified in the NORPLANT® labeling, POPs clearly affect SHBG, but effects on thyroid function are uncertain.

CONCLUSIONS: Changes in laboratory test results are not clinically significant for the general population of POP users. Although values in the various laboratory tests listed in either the combined OC or NORPLANT® labeling may occasionally be affected by POPs in individual users, only for SHBG are the effects found uniformly. Most of the interactions of concern in
laboratory tests are caused by the estrogens in combined pills. Thus, the POP labeling should state the following regarding laboratory test interactions:

a. Sex hormone binding globulin (SHBG) is often decreased in POP users.

b. Tests of lipid metabolism are occasionally affected by POP use. HDL, HDL₂, and apolipoprotein A-I and A-II may be decreased; hepatic lipase may be increased; there is no effect on total cholesterol, HDL₃, LDL, and VLDL.

c. There may be slight deterioration in glucose tolerance, with increases in plasma insulin.

d. There is a possibility of alteration in tests of thyroid function, particularly a decrease in thyroxine (T₄).

e. There are no effects of POPs on coagulation parameters or folate levels.

(Types of evidence: Ic; II A, B, C, D; III A.)
X. COMMON SIDE EFFECTS

Menstrual cycle disruption is the predominant complaint among POP users. Headaches, weight gain and breast tenderness are also cited as common side effects of POPs (Appendix C).

Determination of the prevalence of medical conditions that are truly attributable to the POP is extremely difficult (Chi, Adv Contr, 1993). The biggest problem is that many of the studies do not have any comparative data. Although some studies include a comparison group, the groups are not usually randomized. A few studies instead present comparisons with POP users’ experience, but the time frames are not always of the same duration (and sometimes not even specified), nor is the woman’s previous contraceptive method considered. Recall bias may also be an issue, with women being more likely to notice and report conditions when they are taking any medication. Another concern is that neither the lists of side effects nor the manner in which women were queried about side effects is standardized among researchers.

Furthermore, some of the literature cites only those side effects that led to discontinuation, while other reports present all of the symptoms experienced. The denominator used for computing the rates also varies. The percentage of women experiencing side effects is usually based on the number of women admitted to the study, although occasionally it is calculated as the percentage of women who were observed at specific follow-up points. The percentage of women who discontinue because of side effects is also usually based on the number of women who enroll in the study, but is preferably computed as a life-table rate because both length of observation and discontinuation for other reasons should also be considered simultaneously. Sometimes all that is presented is the proportion of reasons for discontinuation among the women who discontinue, rather than among the entire study population.
In many studies, high loss-to-follow-up rates make it difficult to interpret the reported results. Finally, age differences, as well as inclusion of breastfeeding women in some studies, have important effects on both types and rates of side effects experienced.

Given these methodological problems, it is not surprising that the studies of side effects presented in Tables 5-7 indicate widely varying experiences. Added to these differences in study methodology are true differences among individuals in blood steroid level (as reviewed in Section III), in pharmacodynamic responsiveness, and thus in actual side effects.

A. Menstrual Side Effects

Changes in menstrual patterns, including short cycles, amenorrhea, and spotting or breakthrough bleeding, are the major disadvantage of POPs (Hatcher et al., 1994; Speroff & Darney, 1992). Of particular concern to users is the variability of menstrual cycle lengths during POP use.

Table 5 summarizes the results of studies of menstrual side effects among POP users. The nature of the bleeding disturbances is difficult to describe concisely because of differences among the studies in how the questions were asked and in how the data were analyzed and presented. There are also wide variations in the proportion of POP users who report menstrual side effects and who choose to discontinue the POP because of these side effects, within both breastfeeding and nonbreastfeeding study groups. It appears that both frequent bleeding (variously defined as short cycles and/or breakthrough bleeding) and amenorrhea occur, with frequent bleeding being more common.
In the three randomly allocated studies that included both POPs and COCs (Paulsen et al., 1974; Vessey et al., 1972; WHO, Contrace, 1982), it is clear that menstrual disturbances were greater among users of POPs than COCs. Although in one of these studies (Vessey et al., 1972) the COC was not part of the random allocation, all three studies followed-up both POP and COC users simultaneously, under the same study protocol, with menstrual diary cards used to record data on bleeding episodes. The following parameters were more prevalent among POP users than COC users in these randomized, double-blind studies: irregular bleeding, frequent bleeding, prolonged bleeding, infrequent bleeding, and amenorrhea. Of course, one of the features of COCs is that they generally provide "artificial" cycle regularity, so these studies do not necessarily indicate that these problems would be more common in POP users than in women using nonhormonal contraception.

Belsey and WHO (Contrace, 1988, p. 181) have recently applied uniform analytic methodology to data that were collected on menstrual diary cards as part of several WHO randomized trials of various contraceptive methods (including the above study of POPs and COCs). Ten indices of bleeding patterns were computed, for successive 90-day reference periods, and these indices were combined to identify six bleeding pattern subgroups. The percentage of women falling into these six subgroups varied considerably over time and among the contraceptive groups (COCs, LNG-releasing vaginal ring, and DMPA, in addition to POPs). During the first 90 days of method use, about 10% of POP users were found to have frequent bleeding (defined as more than 5 bleeding or spotting episodes in 90 days), which was a higher percentage than for the other contraceptive methods. Conversely, infrequent bleeding (less than 3 bleeding episodes) was less common for POP users than for vaginal ring and DMPA users, but more common than for COC users. Irregular bleeding (in women with 3-5 cycles) among POP users was also less common than among vaginal ring and DMPA users, but more common than among COC users. The prevalence of prolonged bleeding (1 or more bleeding/spotting
episodes lasting 14 days or more) among POP users was similar to that among vaginal ring users, higher than among COC users, and much lower than among DMPA users. No women taking POPs had amenorrhea for any of the 90-day reference periods; very few women using COCs or vaginal rings had amenorrhea, but complete absence of bleeding was common in the DMPA group. Two-thirds of POP users had none of the above bleeding disturbances, compared to about 90% of women in the COC group, half of those in the vaginal ring group, and only 10% in the DMPA group. The mean length of each bleeding/spotting episode was somewhat greater for POPs than for COCs which, together with more frequent episodes, resulted in a higher total number of bleeding/spotting days for COC users and shorter intervals between bleeding episodes.

More than 10 percent of women in most studies discontinued POP use in the first year because of menstrual disturbances, with as many as 25 percent discontinuing for this reason in three studies (Table 5). Discontinuation depends both on the magnitude of the menstrual irregularity and on the willingness of the user to tolerate the disturbance (which in turn depends on counseling, as well as any other concerns that the woman may have about POP use). A report of the WHO (Contrac, 1982) study on POPs noted that, despite the similarity between the two study sites in percentages of women with various disturbances, women at one site were more than twice as likely as women at the other site to discontinue POP use because of menstrual changes. Hatcher et al. (1994) advise that: "The success of a program offering... progestin-only pills... hinges on counseling women in advance about the menstrual changes...."

Nonetheless, discontinuation of hormonal contraception because of menstrual disturbances usually reflects the woman's actual experience with vaginal bleeding, as disclosed by Belsey and colleagues (Contrac, 1988, p. 207) in their analysis of data from WHO clinical trials. They compared the stated
reasons for discontinuation with actual bleeding patterns, as recorded on menstrual diary cards. POP users who were lost-to-follow-up, who discontinued for non-medical reasons, or who discontinued for medical reasons other than bleeding disruption all had bleeding patterns during POP use that were similar to those of women who remained in the study. In contrast, POP users who stated reasons for discontinuation were various bleeding disturbances did in fact have bleeding patterns that were reflective of the specific type of disturbance cited at discontinuation. Women who discontinued POP use because of amenorrhea had fewer bleeding/spotting days (median of 8 days in 3 months) than other POP users. Those who discontinued because of heavier bleeding had both more frequent bleeding (5 episodes in 3 months) and a greater number of bleeding/spotting days (31 out of 90 days). Among those who discontinued because of longer bleeding episodes, the median length of the longest episode was 13.5 days and the median length of the longest bleeding-free interval was only 17 days. POP users who discontinued because of irregular bleeding had the most bleeding episodes (6 in 3 months) and the shortest bleeding-free intervals, although their bleeding episodes actually occurred on a fairly regular basis (with only a small variation in the length of the bleeding-free interval). Among women with bleeding disturbances, DMPA users were less likely to discontinue compared to women using POPs, COCs, or LNG-releasing vaginal rings. The researchers attributed this difference to better counseling of DMPA users at the time of method initiation, since DMPA is widely recognized as causing menstrual disruption; they conclude that "prepared for such disturbances, their perseverance was remarkable."

Data on menstrual cramps are sparse. In one study, users of NET or LNG had slightly less cramping than prior to POP use (Ball et al., 1991), while in another study dysmenorrhea during LNG use was similar to the pretreatment month (Apelo & Veloso, 1973). Use of NET was reported by McQuarrie et al. (1972) to be associated with a decrease in dysmenorrhea in 47% of cycles and with
an increase in only 7%. In another comparison, users of ED were found to have more cramps than did COC users (Paulsen et al., 1974). A report concerning a large series of NG users indicated that 5% of POP users had menstrual cramps, but there was no reliable comparison provided (Korba & Paulson, 1974). In only two studies was dysmenorrhea a reason for discontinuation of POP use, and then only for very few women (Table 6). It appears that dysmenorrhea is not a major complaint among POP users.

Premenstrual tension was noted occasionally in a few studies (Table 5). McQuarrie et al. (1972) reported that, among 318 women using NET 0.35 mg, premenstrual tension increased in only 5.4% of cycles but decreased in 57.4% of cycles. Although no other papers presented any systematic comparisons, premenstrual tension does not seem to be increased dramatically by POP use.

Goldzieher (book, 1989) postulates that the longer half-life and greater bioavailability of LNG compared with NET (Section III) should be associated with less of a problem with bleeding irregularities, at least for combined OCs. However, the data presented in Table 5 suggest no consistent differences in bleeding patterns for these two progestins administered as POPs. In the two randomized trials of more than one progestin, Vessey et al. (1972) found the greatest disruption for NG and the least for norethisterone acetate, whereas WHO (Contrac, 1982) reported similar rates of bleeding problems for LNG and NET. In the studies which included more than one type of POP but without random allocation, it is difficult to interpret the results because of numerous factors that could have affected the type of pill being prescribed. This problem is illustrated in the report by Bisset et al. (1992) which indicated that menstrual disturbances were most common with norgestrel 0.075 mg and least common with levonorgestrel 0.03 mg. However, these two preparations are almost identical pharmacologically, since LNG is the active component of the racemic compound NG; thus,
presumably, it is selection factors rather than pharmacologic factors that are responsible for these differences.

One reason that menstrual disturbances are of concern to POP users is that bleeding patterns for some women become quite variable and unpredictable. The variation among women and the variation for each woman from one month to another are shown clearly in Table 5 for the study by Broome and Fotherby (1990), in which only 39% of POP users had "mostly" regular cycles. Another study demonstrated this by analyzing the range of cycle lengths for individual women, reporting that the number of days' difference between the shortest and longest cycle for each woman was a median of 24 for NG users (Vessey et al., 1972). Belsey and colleagues (Contrac, 1988, p. 181) reported the median range of bleeding-free interval lengths to be 14-16 days.

Whether or not menstrual disturbances decrease with time for women using POPs is unclear. Several reports (Apelo & Veloso, 1973; Korba & Paulson, 1974; Lawson, 1982; McCann et al., 1989; West, 1983; WHO, Contrac, 1982) have noted that the percentage of users with various complaints was lower in later cycles, while others reported no consistent changes over time (Mears et al., 1969; Vessey et al., 1972). One of the studies (McCann et al., 1989) that did detect changes over time had enrolled only breastfeeding women, suggesting that some of the change over time could be attributable to postpartum changes.

Another difficulty in interpreting comparisons of menstrual problems over time is that those women who have problems are more likely to stop taking POPs, leaving a group of women for whom POPs are less problematic. This is documented in the analysis by Apelo and Veloso (1973), which found that among women who had stayed on POPs for at least 12 months, the problem of short cycles
and/or intermenstrual bleeding was somewhat less common in the second 6 months (25.1%) than in the first 6 months (32.5%); this problem was most frequent among the other women in the study who had discontinued POP use within the first year (35.7%). Thus, it seems that although there is some amelioration of menstrual disturbances with time, these problems persist for many POP users.

It is necessary to look at breastfeeding women separately because their vaginal bleeding patterns are affected by their postpartum status and by their breastfeeding patterns, as discussed in Section XI. Intermenstrual bleeding and amenorrhea were commonly reported among breastfeeding women using POPs, although discontinuation of POPs use because of menstrual problems was relatively rare (Table 5). Whereas in many studies of non-breastfeeding women more than 10 percent of POP users discontinue because of abnormal bleeding, less than 5 percent do so in all of the studies of breastfeeding women. Because women often cease using POPs when they stop breastfeeding, "cessation of breastfeeding" would be expected to be a more common reason given for discontinuation of POPs among breastfeeding women, whereas "menstrual side-effects" would be of greater importance among non-breastfeeding women (Chi, Adv Contr, 1993). Postpartum women may also be more tolerant of unusual bleeding patterns, particularly if they are breastfeeding, because they do not expect to immediately resume regular cycles after delivery. A postpartum study which included both breastfeeding and non-breastfeeding POP users demonstrated that those who breastfed longer were more likely to have amenorrhea, while those who had stopped breastfeeding were more likely to have irregular bleeding (West, 1983).

Similarly, the age of POP users is another factor that should be considered when evaluating the relative effects of various contraceptive methods on bleeding patterns. Older women, for whom POPs are particularly appropriate, may be more likely to have menstrual irregularities associated with
approaching menopause, but they may also be more willing to tolerate such irregularities while taking POPs because they view changing bleeding patterns as part of the physiologic process. In the large review of clinical experience by Bisset and colleagues (1992), older women were much less likely to discontinue POPs because of problems with cycle control (10.5% among women >45, compared to 19.5% among women <25 years old).

Some authors (Fotherby, book, 1989; Guillebaud, book, 1993; Hatcher et al., 1994) state that missed menstrual periods may be an indication that the POP is preventing ovulation, although the evidence about the relationship between missed periods and ovulation is contradictory, as presented in Section II. Hatcher and colleagues (1994) extend this observation to suggest that POP users who have quite regular bleeding may be presumed to ovulate and thus may want to consider routine use of a back-up contraceptive method. Because of the uncertainty regarding this physiological relationship and because POPs have multiple modes of action, this additional contraceptive protection does not seem warranted, and it is also somewhat impractical.

Apelo and Veloso (1973) noted that the menstrual cycles of heavier women (≥ 110 pounds) were longer than the cycles of lighter women (≤ 90 pounds); heavier women were more than twice as likely to have cycles of 25-32 days, whereas lighter women were twice as likely to have cycles of less than 21 days. This may be related to the observation presented in Section III that heavier women using an early version of NORPLANT® had lower plasma steroid levels and were more likely to be ovulatory.

Among women using NORPLANT®, as well as POP users, abnormal bleeding patterns are the most commonly reported side effect and the most frequent medical reason for discontinuation of method use (Croxatto, 1993; Davies & Newton, 1991; ICCR, 1978; Population Council, 1990; Speroff
Darney, 1992; Sivin, 1988). Despite these menstrual irregularities, the total amount of blood lost
does not usually increase, nor does the prevalence of anemia rise (Croxatto, 1993; Davies & Newton,
1991; ICCR, 1978; Population Council, 1990; Speroff & Darney, 1992; Sivin, 1988). As with POPs,
NORPLANT® use by breastfeeding women is associated with fewer bleeding problems than use by
non-postpartum women (Croxatto, 1993). It is interesting that at one clinic there was a significantly
greater discontinuation rate for NORPLANT® when the method was first introduced, compared to
seven years later (whereas IUD discontinuation rates were unchanged); this difference was attributed to
greater confidence and experience with NORPLANT® among both the clinic staff and the target
population of potential users (Alvarez-Sanchez et al., 1988). The labeling for NORPLANT® states that
the following menstrual cycle problems are "associated with" use of the implants: many bleeding days
or prolonged bleeding, spotting, amenorrhea, irregular onset of bleeding, frequent bleeding onsets, and
scanty bleeding.

DMPA use is also associated with irregular menstrual bleeding (Hatcher et al., 1994; Speroff &
Darney, 1992). Amenorrhea is common among women who have used DMPA for long periods of
time. DMPA users have quite unpredictable patterns, with infrequent but prolonged bleeding episodes,
and an increasing prevalence of amenorrhea over time (Belsey & WHO, 1988). According to the
analysis of WHO data described above, disruption of bleeding patterns with DMPA is much more
common than with POPs (Belsey & WHO, 1988).

The INTRAH Guidelines conclude that POPs commonly cause amenorrhea, irregular periods, or
prolonged or heavy bleeding, but they may also decrease menstrual cramps and, for some women,
decrease the amount of bleeding and thus decrease anemia (INTRAH, 1993). The IPPF Guidelines
urge discussion of irregular bleeding and amenorrhea as possible side effects of POPs when counseling women about their contraceptive choices (Huezo & Briggs, 1992).

CONCLUSION: Menstrual irregularities are common among women taking POPs. Proper counseling will help to alleviate users' concerns. Some women will have less bleeding overall during POP use than previously and thus are less likely to be anemic. (Types of evidence: I A, D; II A, B, C, D.)

B. Non-menstrual Side Effects

Since POPs could not have the estrogen-related side effects of COCs, they may be better tolerated by women who have had estrogen-related problems with the combined pill; the lower dose of progestins in POPs should also produce a lower incidence of progestin-related side effects. Unfortunately, the COC literature is not clear regarding which side effects are associated with estrogen and which with progestin. Among the common medical conditions that are sometimes thought to be side effects of COCs, Hatcher and colleagues (1994) consider nausea to be attributable to estrogen, while headaches and breast tenderness can be the result of either the estrogen or the progestin. They suggest that the androgenic activity of the progestins is responsible for the following complaints: increased appetite and weight gain; depression, fatigue and tiredness; decreased libido; acne and oily skin; and hirsutism. The reader is referred to Section III for a detailed presentation of the problems associated with determining pharmacokinetic potency of progestins and the resulting pharmacodynamic effects.
Numerous studies have recorded information about various conditions and complaints reported by women taking POPs (Tables 6 and 7). As noted above, it is difficult to ascertain what proportion of these conditions are attributable to POP use, and thus should be considered true side effects, and what proportion are simply the background prevalence of these conditions. This problem was documented two decades ago by Goldzieher and co-workers (Fertil Steril, 1971) in a placebo-controlled double-blind crossover study of four OC formulations (2 COCs, a sequential pill, and a POP containing chlormadinone acetate 0.5 mg). The study design permitted comparisons of each OC with the following: pretreatment period, the same women taking other OCs, and placebo treatment. Nausea (and, to a lesser extent, vomiting) was correlated with estrogen dosage, but none of the following symptoms were associated with OC use: breast tenderness, headache, nervousness, depression, and weight gain or loss. The researchers concluded that, "the true incidence of drug-related complaints is far lower than indicated by the usual uncontrolled investigation."

Table 6 presents information on POP discontinuation attributable to non-menstrual side effects. As discussed above in the section on menstrual side effects, discontinuation is an indication of levels of side effects that cannot be tolerated, but this incorporates both the severity of the side effect and the ability of the woman to tolerate the side effect. The discontinuation rate for all non-menstrual side effects combined was less than 10 percent in most studies; it was also generally less than the discontinuation rate associated with menstrual disturbances. The randomized study by Vessey et al. (1972) reports discontinuation rates due to non-menstrual side effects of 0.6-1.5 per 100 woman years for the various POPs and a similarly low rate for the COC (1.6). In the WHO (Contraception, 1982) clinical trial, two-year discontinuation rates due to gastrointestinal side effects were highest for one of the COCs but lowest for the other COC and intermediate for the two POPs (6.7 for NET and 8.0 for LNG). For central nervous system discontinuations, the rates were again intermediate for the two
NET and 5.8 for LNG), but the pattern of rates for the two COCs was reversed. The most commonly-reported side effects responsible for discontinuation were headaches, breast discomfort, dizziness, nausea, psychological complaints, and weight gain. Acne, hirsutism, and decreased libido were reported infrequently.

Table 7 gives the percentage of women who reported various medical conditions while taking POPs. The list of most common complaints is the same as the list of side effects responsible for discontinuation. In the randomized trial in Yugoslavia (Vessey et al., 1972), the percentages of users reporting any non-menstrual side effects were fairly similar for the four POPs (28-38%) and the COC (27%). Only two studies (both in breastfeeding women) compared the prevalence of various symptoms at specific times during POP use to the prevalence during the month before POP use began (Apelo & Veloso, 1973; Dunson et al., 1993). In both studies, headaches, nausea, and dizziness were reported somewhat more frequently by women while taking POPs than prior to POP use. The prevalence of breast tenderness was similar before and during treatment; however, that condition could more likely be attributed to the fact that the women were breastfeeding than to POP use. Finally, only one of these two studies asked about psychological complaints, finding that nervousness, tension, and/or irritability were less common during POP use than in the prior month. Although one other study reported the frequency of various medical conditions before POP use began, the time period for the before-treatment prevalence was not specified (Korba & Paulson, 1974); the percentages are so much higher than for the treatment months that the women may have been asked if they had "ever" had those conditions.

In several of the papers the prevalence of side effects was displayed for multiple months, demonstrating considerable fluctuation from one month to the next, but with no consistent pattern of
increasing or decreasing prevalence over time. Finally, when Apelo and Veloso (1973) compared POP users who continued for 12 months to those who discontinued use, there was no difference in the rates of the various side effects.

Most headaches are of nonvascular origin, resulting from tension or muscle contraction; these are not believed to be related to OC steroids (Mattson & Rebar, 1993). The literature with respect to vascular (migraine) headaches and OCs is limited and conflicting, but any possible association is presumably with the estrogen component of the COC. (See Section VI.)

In a compendium of the data relating combined OCs with depression and other psychiatric problems, Prentice and Thomas (1987) conclude that the small increase of symptoms noted in some, but not all, studies is more likely to be due to underlying differences in the women selecting OCs than to the hormones themselves. This conclusion is supported (for both POPs and COCs) by the clinical trial by Goldzieher et al. (1971) described above.

Small percentages of women indicated that they experienced weight gain while taking POPs (Table 7), and some users discontinued for this reason (Table 6). However, in one study of slender postpartum Filipino women loss of weight was instead the reason for discontinuation (Apelo & Veloso, 1973). Several studies have weighed women before and during treatment, with no consistent findings of weight gain. Several of these reports note small increases in mean weight, but the studies had no nonhormonal comparison groups (Ball et al., 1991; Korba & Paulson, 1974; Spellacy et al., 1981; Vessey et al., 1972). Another study (Spellacy & Birk, 1972) reported a smaller mean increase in weight for women taking NG 0.075 mg than for IUD users. And three studies found that an equal proportion of POP users gained and lost weight (Hawkins & Benster, 1977; Lawson, 1982; McQuarrie
et al., 1972). Among women with insulin-dependent diabetes, a case series (Steel & Duncan, 1981) and a randomized crossover trial (Radberg et al., 1982) both found no apparent effect of POPs on body weight. Speroff and Darney (1992) comment that although the androgenic activity of progestins could potentially stimulate an increase in appetite, this is unlikely to have a clinical effect because of the low steroid levels. Hatcher et al. (1994) add that weight gain is more likely to be due to increased appetite than fluid retention.

The total discontinuation rate gives an overall impression of the acceptability of contraceptive methods (at that time, in that population, in those clinical settings). The pattern was not consistent among the three randomized clinical trials. In one study the total (one-year) discontinuation rate was higher for the POP (65%) than for the COC (51%) (Paulsen et al., 1974). The report by Vessey and colleagues (1972) also indicates higher total discontinuation rates for the POPs than for the COC, but among the four POPs the rates range from 38 per 100 woman years to 53, with the lowest POP rate being similar to that for the COC (34 per 100 woman years). The WHO study (Contrac, 1982) found total discontinuation rates for the four pill formulations (two POPs and two COCs) to be statistically similar (52.6-61.0 per 100 woman years at one year and 70.5-76.5 at two years).

Guillebaud (book, 1993) suggests that while switching to another POP in hopes of reducing either menstrual or non-menstrual side effects is an option, there is no evidence regarding which progestin might have less problems, and therefore continuing with the same POP, after appropriate counseling, would also be reasonable. In the large clinical series by Bisset et al. (1992), some women had amelioration of their menstrual side effects when they were switched to a different POP.
There is considerable variation among NORPLANT® users in reported side effects both among populations and among individuals within populations (Davies & Newton, 1991; Sivin, 1988; Speroff & Darney, 1992). Headache is the most common non-menstrual medical reason for termination; headache was more common among NORPLANT® users than among copper-IUD users in one study but not in another. Depression, anxiety and mood changes were common reasons for termination of NORPLANT® use in some populations but not others; in a comparison with IUD users, implant users were less likely to report increased nervousness and depression since contraceptive initiation (ICCR, 1978). Although weight change was also one of the most commonly reported reasons for NORPLANT® removal, studies that assessed weight change quantitatively found no significant difference between users and controls. Other commonly reported side effects are breast tenderness and acne, although, at least for acne, IUD users report a similar prevalence (ICCR, 1978). The NORPLANT® labeling concludes:

Controlled clinical studies suggest that the following adverse reactions occurring during the first year are probably associated with NORPLANT® SYSTEM use: headache; nervousness; nausea; dizziness; adnexal enlargement; dermatitis; acne; change of appetite; mastalgia; weight gain; and hirsutism, hypertrichosis, and scalp-hair loss.... In addition, the following adverse reactions have been reported with a frequency of 5% or greater during the first year and possibly may be related to NORPLANT® SYSTEM use: breast discharge; cervicitis; musculoskeletal pain; abdominal discomfort; leukorrhea; and vaginitis.

Among DMPA users, breast tenderness, weight gain and depression are the predominant complaints (Speroff & Darney, 1992). Weight gain appears to be more common among DMPA users than among women using LNG progestin methods (Hatcher et al., 1994).

Hatcher et al. (1994) state that POPs cause less depression, fewer premenstrual syndrome symptoms, and less decrease in libido than combined OCs. They recommend that women who have developed severe headaches or hypertension while taking COCs should instead use POPs. They also point out that women who are considering NORPLANT® use but for whom there are specific concerns
about side effects or metabolic changes may wish to first take LNG POPs for several months as a "suitability test" before undergoing implant insertion. Speroff & Darney (1992) suggest POPs for women who report diminished libido with combined OCs. They also recommend POPs for women who have complained of gastrointestinal upset, breast tenderness, and headaches while using COCs. And they note that acne may be associated with POP use because of the androgenic activity, which decreases the SHBG levels and permits an increase in free steroid levels of both LNG and testosterone (unlike COCs, in which the effect of progestins on SHBG are countered by the effect of estrogens).

The INTRAH Guidelines list the following as "occasional conditions (which may or may not be related to POP use)": headaches, mood changes or nervousness, weight gain or weight loss, breast tenderness, nausea, dizziness, dermatitis or acne, and, rarely, hirsutism (INTRAH, 1993). However, they also suggest that POPs may be particularly appropriate for women who have had "estrogen-related side effects from combined oral contraceptives, including vascular headaches (migraines), nausea, high blood pressure or breast tenderness." Similarly, the IPPF Guidelines recommend POPs for women who have had migraine syndrome, experienced focal migraine, or developed other estrogen-related complications while using a COC (Huezo & Briggs, 1992). IPPF also advises counseling of prospective POP users about breast tenderness and headaches as possible side effects.

CONCLUSION: Numerous conditions have been cited as possible side effects of POPs, but the limitations of study methodology make it impossible to ascertain whether POPs actually play a causal role. Non-menstrual side effects are clearly much less common than menstrual disruption. It appears that the prevalence of headache, breast tenderness, nausea, and dizziness may be somewhat elevated among POP users. The data regarding psychological complaints are sparse, but they do not suggest an association with POP use for such problems as depression,
nervousness, or changes in libido. Androgenic side effects such as acne, hirsutism, and weight
gain occur rarely. Because POPs contain no estrogen and a lower dose of progestin than
combined OCs, they may be particularly advantageous for women who have experienced side
effects with COCs. (Types of evidence: I A, D; II A, B, C, D.)
XI. BREASTFEEDING

Women who have recently given birth have special needs with regard to contraception. It is particularly important that they delay another pregnancy because of the many adverse consequences of closely spaced births, and yet the array of contraceptive choices available to them may be limited, in part because of concerns about postpartum physiology and breastfeeding. Whether progestin-only pills can be safely used by breastfeeding women and, if so, when their use should begin are thus important policy questions.

A. Breastfeeding and Postpartum Risk of Pregnancy in the United States

Just over half of infants in the United States are breastfed, with the 1988 National Survey of Family Growth finding an incidence of 56.3% in 1987 (Ryan et al., AJPH, 1991) and the most recent data reported by the Ross Laboratories Mothers' Survey showing an incidence of 52.5% in 1989 (Ryan et al., Pediatrics, 1991). By the age of 6 months, less than 20% of infants are still being breastfed (18.1% in 1989) (Ryan et al., Pediatrics, 1991). Although breastfeeding rates increased dramatically during the 1970s, they peaked in the early 1980s and have declined somewhat since then (Ryan et al., 1991, AJPH; Ryan et al., Pediatrics, 1991).

Most breastfeeding mothers are sexually active, with two-thirds resuming sexual activity within one month after delivery and 97.5% having intercourse in months 4-6 (Ford & Labbok, 1987). Although most of these women were using contraception, about 15% of breastfeeding mothers were sexually active but not using a contraceptive method. These data are from the 1982 National Survey of Family Growth; there is no reason to expect that patterns of sexual behavior and overall
contraceptive prevalence have changed in the intervening decade, although the distribution of contraceptive methods has presumably changed for breastfeeding mothers just as for the population as a whole. In 1982 about 10 percent of breastfeeding women were using oral contraceptives; what fraction of these were POP users is unknown. Another related question of interest (for which there are no data) is how many women were advised not to use OCs while breastfeeding and therefore decided to not breastfeed or to curtail breastfeeding in order to use OCs (Hatcher et al., 1994).

Mothers who are not breastfeeding generally resume menstruation and ovulation within the first 3 months after delivery, but resumption for breastfeeding mothers varies depending on infant feeding practices. A study of 22 non-breastfeeding and 60 breastfeeding mothers in Baltimore found that all of the non-breastfeeding mothers menstruated during the first 12 weeks postpartum, compared to only 20% of those who were breastfeeding (Campbell & Gray, 1993). Two-thirds of first menses in both groups were preceded by presumptive ovulation (as assessed by urinary pregnanediol-3 \( \alpha \)-glucuronide and luteinizing hormone); the percentage of first cycles that were ovulatory increased steadily over time among breastfeeders, from 45% during the first 12 weeks to 100% after 12 months. The number of breastfeedings per day and the mean duration of suckling episodes were highly predictive of ovulation. Although the number of supplementary feedings was important in bivariate analysis, this variable was no longer statistically significant when the number of breastfeedings was considered simultaneously. (Increasing number of bottlefeeds was associated with reduced number of breastfeeds, but this pattern was much less apparent for number of feedings of solids or feedings by cup.) This study, as well as studies in Australia (Lewis et al., 1991) and Scotland (Howie et al., 1981), indicate that breastfeeding can have an important fertility-inhibiting effect for women in developed countries -- but that the breastfeeding patterns necessary for such an effect are not typical of U.S. breastfeeding patterns. For example, the breastfeeding mothers enrolled in the Baltimore study all intended to
breastfeed for at least six months, whereas the national data reported above indicate that only one-third of infants who are breastfed initially are still breastfed at six months.

B. Effect of POPs on Breastfeeding

Virtually all studies of progestin-only contraceptives (regardless of route of administration) have found no effect on breastfeeding performance, as reviewed by McCann et al. (1984). In contrast, most studies of combined OCs, including those with lower dosages, have demonstrated a small negative impact on breast milk production (Croxatto et al., 1983; Diaz et al., 1983; McCann et al., 1984; WHO, SFP, 1988).

Studies of breastfeeding performance among mothers using either norgestrel/levonorgestrel or norethindrone POPs are shown in Table 8. There is no evidence of an adverse effect on breast milk production, regardless of how breastfeeding is assessed. This is true even for studies in which POP use began within the first week postpartum. (Some of these same studies also included combined OCs, which were shown to have a small adverse effect.) Limited data suggest that progestins could possibly enhance lactation by stimulating greater prolactin release (Chaudhury et al., 1977; Fraser, 1991).

Table 9 displays the studies of transmission of progestins to breast milk. Although both norgestrel and norethindrone pass through to breast milk, the actual amounts transferred are extremely small. The concentrations of these two progestins in breast milk is only about 10% of that in maternal serum, because of their high affinity for SHBG in the plasma (Johansson & Odlind, 1987); much higher rates of transfer are found for other progestins with low protein binding capacity, such as
DMPA (Johansson & Odlind, 1987). NET and LNG are transferred from breast milk to infant plasma at a higher rate than from maternal plasma to breast milk, with the levels in infant plasma being about 40 percent of the levels in the milk of POP users (Table 9). The net result is that the levels in infant plasma are about 1-6% of the levels in maternal plasma. There is considerable variation in absolute progestin concentrations, depending on when the sample is obtained in relation to when the progestin is administered, other aspects of study methodology, and whether the progestin was administered orally or by other routes and whether estrogen was given as well; there is also considerable variation among individuals within each study. Despite these differences, the similarities in the concentration ratios among studies shown in Table 9 is remarkable. It should also be noted in Table 9 that when LNG or NET are given together with estrogen, as a COC, the progestin concentrations in milk and in infant plasma are much higher than for the POP, reflecting the higher dose of progestin in the COC. The absolute amount of progestin is also higher for norethindrone than for levonorgestrel (in both POPs and COCs), because of the higher dosage levels administered, although the steroidal activity of the two progestins is presumably similar in breast milk, just as it is in maternal plasma. (See Section III.)

The absolute amount of progestin ingested by the infant is determined in part by the volume of breast milk consumed. In the studies reported in Table 9, the infants were generally less than 6 months old and fully breastfeeding. One study assessed the amount of milk consumed by test-weighing the infants before and after each feeding, and combined that information with data on progestin levels in the milk; the resulting calculation indicated that the infant consumed 0.02% of the maternal dose. The daily dose to the infant has also been estimated, based on an average daily intake of 600 ml of milk, to be about 1% of the maternal dose (Nilsson et al., AJOG, 1977; Fraser, 1991);
because the infant's weight is about 10% of the mother's weight, the dose to the infant per kilogram of bodyweight is about 1% of the maternal dose on a bodyweight basis (Johansson & Odlind, 1987).

If a mother wishes to further reduce the infant's exposure to steroids, she can select the time of her pill-taking in order to do so. Because the steroid levels in both maternal plasma and milk are highest 2-3 hours after a feeding (Nilsson et al., Contrace, 1977; Saxena et al., 1977; Toddywalla et al., 1980), the POP could be taken just after a feeding and/or when the time to the next feeding would be longest (such as the last evening feeding or when the mother leaves her infant to go to work).

Research on NORPLANT® use beginning 4-6 weeks after delivery has also found no negative effects in infant growth or health (Affandi et al., 1986; Diaz et al., 1985; Shaaban et al., 1985); there are no data on NORPLANT® insertion early in the postpartum period (Population Council, 1990). Three studies have assessed the potential for steroid transfer to the infant. One of these studies, carried out in Chile, found an average of about 100 pg/ml of LNG in breast milk; a fully breastfed infant was estimated to receive 90 ng/day, or 15-18 ng/kg/day (Diaz et al., 1985). Another study, conducted in Egypt, reported mean LNG concentrations in infant serum of 0.14 nmol/l (0.04 ng/ml), or about 8% of that in maternal serum (Shaaban et al., 1986). The results of the third such study by Shikary et al. (1987) are included in Table 9, again indicating very low rates of transfer. The researchers who conducted this latter study noted that the absolute amount of steroid transferred by POP users would actually be much less than that for NORPLANT® users; not only are the reported levels somewhat less, but these levels are the peak levels for POP users (so that for most of the day the levels are lower), whereas they are the steady-state levels for NORPLANT® users. The NORPLANT® labeling states that steroids are not the contraceptives of first choice for breastfeeding
women and that LNG has been found in the breast milk of implant users, but that no significant
effects on the growth or health of infants has been reported.

Although there are theoretical concerns about long-term effects on sexual development (Harlap,
1987), no data thus far support these concerns (Fraser, 1991). There have been isolated reports of
gynecomastia in male infants of mothers taking combined OCs, but these are anecdotal and there are
no such reports for POPs (Shikary et al., 1986). Because it is possible that androgenic progestins
could affect the testosterone surge seen in male neonates, Shikary and colleagues (1986) compared
male breastfeeding infants of mothers who were using POPs (LNG 30 mcg), NORPLANT®, and no
hormonal method; they found no significant differences in urinary FSH, LH, or testosterone levels in
the early postpartum period. A similar study produced no significant differences in serum LH and
testosterone levels in male infants among mothers taking LNG 30 mg compared to no hormonal
contraceptive (Toddywalla et al., 1984).

No studies have been published on potential long-term effects of POP exposure on infants, but
several such studies of other hormonal contraceptives have found no adverse effects. Offspring of
mothers who used the injectable progestin DMPA have been followed-up in Thailand for up to 17
years (Pardthaisong et al., 1992; Koetsawang et al., 1984) and in Chile for 4 1/2 years (Jimenez et al.,
1984). Similarly, Swedish children whose mothers used combined OCs were observed for up to 8
years (Nilsson et al., 1986). None of these studies demonstrated effects on children's health, growth,
or development.

Long-term studies of infants exposed to POPs through breast milk are clearly needed to verify the
absence of detrimental effects, but the very small amounts of steroid transferred, the absence of short-
term effects with POPs, and the absence of long-term effects from other hormonal contraceptives are reassuring. Furthermore, it must be recognized that all breastfed infants are exposed to endogenous maternal steroids and that infants fed on cows’ milk formula are also exposed to reproductive steroids (Fraser, 1991). Concerns about long-term effects remain speculative and are based primarily on animal data (Harlap, 1987).

It can thus be concluded that use of POPs by breastfeeding mothers appears to have no adverse effects on the infant. In contrast, another pregnancy usually results in curtailment of breastfeeding and other negative consequences for both the infant and the mother, because this new pregnancy closely follows the birth of the breastfeeding infant.

Another aspect of the relationship between POP use and breastfeeding that has recently been raised is the potentially beneficial effect of progesterone on lactational infertility. Diaz and colleagues (1991) compared breastfeeding women using 15 mg progesterone-releasing vaginal rings with those wearing copper-releasing IUDs. Women in the hormonal group had a longer period of amenorrhea, lower estradiol levels, earlier arrest of follicular growth, and greater prolactin release in response to suckling compared to the control group. The endocrine profile of the progesterone-treated women was similar to that usually associated with prolonged lactational infertility. These findings suggest that progesterone administration enhances the influence of suckling on the hypothalamic-pituitary-ovarian axis, thus sustaining lactational infertility. A small study of DMPA users also indicated an enhanced prolactin response to suckling (Chaudhury et al., 1977). If POPs have similar effects, then this would be another indication that POPs are particularly appropriate for breastfeeding women.
The American College of Obstetrics and Gynecology (ACOG) and INTRAH both give breastfeeding as one of the primary indications for POP use (ACOG, 1987; INTRAH, 1993). Both IPPF and WHO state that nonhormonal methods should be considered first by breastfeeding women, but that if none of these methods is acceptable then progestin-only methods (including POPs, the NORPLANT® or injectables such as DMPA) can be used (Huezo & Briggs, 1992; WHO, book, 1993).

CONCLUSION: Numerous studies have found no effect of POPs on breastfeeding, whereas studies of combined OCs show a small negative effect. Also, when breastfeeding mothers use POPs no estrogen and much smaller amounts of progestin are transferred to the infant, and no adverse effects of this steroid transfer have been documented. Because very small amounts of progestin are passed into the breastmilk and thus to the infant, POPs are not considered the best contraceptive method for breastfeeding women, but non-hormonal methods may not be acceptable, medically indicated, or available to all breastfeeding women. Thus, for breastfeeding women who want to use oral contraceptives, progestin-only pills are recommended. (Types of evidence: II A, B, C, D.)

C. Timing of Postpartum POP Initiation

The challenge in recommending the appropriate time postpartum for initiation of contraceptive use is to provide additional contraceptive protection before the efficacy of lactational amenorrhea declines to unacceptably low levels, but without giving contraception that is unnecessarily redundant with lactational anovulation (Chi et al., 1992; McCann et al., 1984). Clearly, the timing of contraceptive use initiation during the postpartum period should be based in part on the estimated time of the return of ovulation, but this varies among women and depends on a number of factors,
including breastfeeding practices and menstrual status. In 1988, the Bellagio Consensus Conference on Lactational Infertility (Kennedy et al., 1989) stated:

The maximum birth spacing effect of breastfeeding is achieved when a mother "fully" or nearly fully breastfeeds and remains amenorrheic. When these two conditions are fulfilled, breastfeeding provides more than 98% protection from pregnancy in the first six months.

One approach is to recommend contraceptive initiation whenever menses resume. For methods that require medical services at the time of initiation, such as IUD or NORPLANT® insertion or DMPA injection, this recommendation could be problematic in terms of service provision, but for methods such as POPs the mother can be given a supply of pills and instructed to begin them immediately upon menses resumption. The only drawback to this approach is that the first ovulation can precede the first menstruation, but this is less likely in the early months after delivery (Campbell & Gray, 1993; Kennedy et al., 1989; Kennedy & Visness, 1992). Furthermore, ovulation in breastfeeding women is typically followed by a short or insufficient luteal phase; this condition of ovulation without sufficient hormonal support is also more likely to occur in the earlier postpartum months and most likely to occur prior to the first postpartum menses (Campbell & Gray, 1993; Kennedy & Visness, 1992).

An alternative, or complementary, approach is to recommend contraceptive initiation at a specific time postpartum, even if the woman is still amenorrheic. The Bellagio Consensus Conference specifies 6 months as the initiation time if the mother is still amenorrheic (Kennedy et al., 1989). A recent review of ovulation and pregnancy rates among breastfeeding women concludes that breastfeeding women who are amenorrheic at 12 months postpartum continue to have a high level of contraceptive protection (Kennedy & Visness, 1992). However, Speroff and Darney (1992) argue that, because breastfeeding in the United States is typically of shorter duration and with less frequent suckling than in developing countries, contraception should be initiated earlier than 6 months.
Specifically, they recommend that women who are fully breastfeeding should begin contraceptive use at 3 months postpartum and those who are partially breastfeeding (as well as those who are not breastfeeding) should begin at 3 weeks postpartum. These recommendations are repeated in the most recent revision of *Contraceptive Technology* (Hatcher et al., 1994).

The primary reason for delaying POP use as long as possible is to prevent unnecessary medication. In addition, because contraceptive discontinuation rates are high in some populations, beginning contraception earlier than needed (i.e., before ovulation has resumed) could result in women discontinuing just when they would otherwise have begun to ovulate and thus need contraception.

Women who wish to postpone POP initiation and instead rely on the lactational amenorrhea method of contraception should be advised to feed their infants frequently and on demand (including night-time feeds), to avoid any bottle feeds, and to provide only minimal supplements by cup or spoon (Kennedy et al., 1989; Perez et al., 1992; Hatcher et al., 1994). POPs should then be started at 6 months or earlier if menses resume, when breastfeeding frequency declines, or when bottle feeding begins.

While the above discussion focuses on how long POP initiation can be delayed without sacrificing contraceptive efficacy, it is also necessary to consider how early POP use can begin without adversely affecting the infant or the mother. The data presented in Table 8 indicate that breastfeeding performance is not affected by POP use even if begun in the first week postpartum, and Table 9 shows that only very small amounts of progestins are transferred to breast milk. Many authorities (Fraser, 1991; Guillebaud, BJFP, 1991; Speroff & Darney, 1992) believe that the potential risk to the newborn from these very low doses of progestins is exceedingly low. It should also be noted that the transfer
of steroids is likely to be lower immediately postpartum than later because of two special circumstances: (1) the higher SHBG levels at that time may mean that more hormone would be bound and less passed into the milk (Nilsson et al., Contrac, 1977); and (2) the lower fat content of colostrum compared with mature milk, together with the fact that contraceptive steroids are fat-soluble and found at higher concentrations in high-fat milk (Nilsson et al., AJOG, 1977), suggest that less steroid would be present in colostrum than in mature milk. Thus, there may actually be no reason for greater concern about the effects on the infant of early POP initiation. Regarding physiological effects on the mother, concern about postpartum thrombosis has led to the recommendation that OCs not be used in the first 2 weeks after delivery (even for non-breastfeeding women), but this is a potential concern only for combined OCs, not POPs (Fraser, 1991; Guillebaud, BJFP, 1991; Hatcher et al., 1994).

The NORPLANT® labeling notes that no data are available on implant use by breastfeeding mothers earlier than 6 weeks postpartum.

The only other issue that has been raised with regard to the initiation of POP use is the finding in one study that there is a greater likelihood of spotting and bleeding problems if POPs are started at 1 week postpartum compared to 6 weeks (Hawkins & Elder, 1979).

INTRAH, IPPF and WHO all recommend 6 weeks postpartum as the earliest initiation time (Huezo & Briggs, 1992; INTRAH, 1993; WHO, book, 1993). Recently, clinicians in both the United States (Speroff & Darney, 1992) and the United Kingdom (Fotherby, book, 1989; Guillebaud, 1991) have instead recommended initiation at 3 or 4 weeks; some (Speroff & Darney, 1992) see no harm in starting immediately postpartum. The American Academy of Pediatrics and the American College of Obstetrics and Gynecology (AAP and ACOG, 1992) have jointly stated that "oral contraceptives may
be used by breastfeeding women once lactation has been established." The recommendation to delay pill initiation until 6 weeks postpartum may result in part from the traditional proscription of sexual activity until after the postpartum follow-up visit, which is usually scheduled at 6 weeks. However, many women resume sexual relations prior to 6 weeks (Ford & Labbok, 1987), and recently it has been suggested that the postpartum visit would be optimally moved to 3 weeks (Hatcher et al., 1994; Speroff & Darney, 1992).

Until recently, it was assumed that women would want to switch from POPs to COCs when they stopped breastfeeding in order to maximize contraceptive efficacy, and some clinicians continue to make this recommendation. However, it is now becoming more common to acknowledge that the mother may prefer to continue with POPs (Chi et al., 1992; Guillebaud, book, 1993; Huezo & Briggs, 1992). There are several reasons why continued POP use may be preferred: the mother is accustomed to the side effects of POPs; the breastfeeding woman may be less concerned about irregular bleeding, which could be attributable in part to her postpartum status; the contraceptive efficacy of POPs is quite high if the pills are taken on schedule; and the woman may want to continue to minimize the amount of steroid ingested (with no estrogen and less progestin than in COCs).

Switching to COCs at some earlier milestone, such as when supplementation begins or when the infant has doubled in weight, has also been suggested. This practice should be discouraged because of the demonstrated inhibitory effect of COCs on lactation (Diaz et al., 1983; McCann et al., 1984; WHO, SFP, 1988), which would not be desirable even if breast milk is not the infant’s sole source of nutrition. It would also result in unnecessary exposure of the infant to estrogen and higher levels of progestin.
CONCLUSION: In the United States, mothers who are breastfeeding without giving supplementary foods should begin taking the POP 3 months postpartum -- unless the first menses occurs earlier, in which case POP use should begin with the first menses. Breastfeeding women who are also giving supplements (as well as non-breastfeeding women) should begin taking POPs 3 weeks after delivery. For populations in which breastfeeding is typically more intensive and of longer duration than in the United States, POP use can be delayed until 6 months for breastfeeding women who remain amenorrheic. Regardless of when initiation is recommended, mothers can be given the pills (or a prescription) earlier, with instructions about when to start. When breastfeeding ceases, the woman should be offered the options of either continuing with the POP or switching to a COC. (Types of evidence: II A, C.)
XII. TAKING POPs EFFECTIVELY

The most important aspects of effective POP use are starting, switching and stopping the method safely, and knowing how to handle late or missed pills, including use of additional back-up contraceptive methods, such as condoms, vaginal foam or sponge. (See Appendices D & E for current guidelines.) Based on the data presented previously in this paper, this Section reviews the current guidelines and makes recommendations for effective POP use. (See Appendix F for a draft of recommended instructions for POP use.)

A. Starting, Switching and Stopping

**Starting:** As with the combined pill, if progestin-only pills are started on the first day of the menstrual cycle, most guidelines do not require additional back-up contraception (Goldzieher, book, 1989; Guillebaud, book, 1993; INTRAH, 1993; Speroff & Darney, 1992). IPPF recommends more flexibility for the start day, suggesting that POPs be started any time within the first 5 days of menses without requiring a back-up method, since ovulation does not normally occur until about day 14 (Huezo & Briggs, 1992). The INTRAH Guidelines (1993), however, recommend using back-up contraception for 2 weeks if POPs are started even one day after menses begins, while the other guidelines recommend 7 days of back-up when POPs are started late. (See Appendix D.)

As discussed in Section II (Mode of Action), and later in this chapter, there is intense debate as to whether POPs require back-up contraception for 48 hours (Fotherby, book, 1989; Hatcher et al., 1994; Mills, 1987) or 7 days (Fotherby, book, 1989; Huezo & Briggs, 1992; Speroff & Darney, 1992; UKFPA, 1993). There is no specific, solid evidence of the need for 7 days of back-up whereas there
is evidence that the blood levels of the progestin reach peak levels within 2 hours of administration. The progestin's effect on cervical mucus also occurs within 2-4 hours, making it impervious to sperm penetration. (See Section II.)

For postpartum breastfeeding women, some experts recommend the earliest starting time for POPs as 4 weeks postpartum (Guillebaud, book, 1993; Fotherby, book, 1989), and others 6 weeks (INTRAH, 1993; Huezo & Briggs, 1992). Speroff and Darney (1992) see no reason for not starting POP use immediately after delivery. For non-lactating postpartum women, advice varies about how early they can or should start, but all sources say POPs can be started by the fourth week postpartum (Fotherby, book, 1989; Goldzieher, 1989; Guillebaud, book, 1993; Huezo & Briggs, 1992; INTRAH, 1993; Speroff & Darney, 1992). Based on endogenous hormonal levels in the postpartum period, postpartum initiation of POP use should be at 3 weeks for women who are not breastfeeding or who are both breastfeeding and giving supplementary foods. Mothers who are breastfeeding and not supplementing can wait until 3 months postpartum to begin POPs, unless menses begin before that time. (See Section XI.)

After an abortion, POPs should be initiated immediately. Unlike COCs, there is no demonstrated thrombogenic effect of progestin-only contraceptives, as reviewed in Sections V and VI (Fotherby, BJFP, 1989); therefore, POPs can safely be used immediately post-abortion (INTRAH, 1993). Ovulation is expected to return within two weeks after a first trimester abortion and 4 weeks after a second trimester abortion, making prompt contraceptive protection very important. In a Finnish study of 67 women, plasma progesterone samples were used to determine that the ovary resumed follicular development as early as one week after a first trimester abortion; 34% of participants had ovulated.
within 3 weeks; and 85% had ovulated within 6 weeks (Lahteenmaki et al., 1980). The authors concluded that immediate initiation of contraception is needed after an abortion.

Switching: Any time a user is changing brands of POPs, she can simply start the new brand as soon as she finishes her current pack of pills (or at any other time she chooses), thus providing uninterrupted protection. When switching from combined pills to POPs, the first POP should be taken the day after the last of the 21 days of the active combined pills are taken, discarding the placebo pills (Fotherby, book, 1989; Goldzieher, book, 1989; Guillebaud, book, 1991), to maintain the daily progestin levels without interruption. (See Appendix D.)

When switching from POPs to combined pills, the combined pill pack is best started on the first day of menses (Guillebaud, book, 1993) even if the POP pack has not been completed. This assures that there is no chance of ovulation during the transition period. If the POP user is amenorrheic, however, she should wait until pregnancy is ruled out before starting COCs (Fotherby, book, 1989).

Guidelines for the advisability of breastfeeding mothers switching to combined pills are also vague and inconsistent. Guillebaud (book, 1991) has suggested doing so when breastfeeding frequency has been reduced, unless the mother prefers to continue with the POP. IPPF Guidelines (Huezo & Briggs, 1992) suggest that a mother may change to COCs 6 months postpartum or when she is no longer breastfeeding, whichever comes first. Although switching to COCs when supplemental feeding is introduced has also been suggested, this practice should be discouraged because of the effect of COCs on breast milk production and because of the transmission to the infant of both estrogen and larger amounts of progestin with COCs. (See discussion in Section XI.)
Stopping: Use of the POP can be stopped at any time since it provides a continuous dose of a single hormone. This is unlike combined oral contraceptives, which should be taken until the end of the pack to maintain a regular cycle.

Some experts argue that when a user discontinues a hormonal method because she wishes to become pregnant, a non-hormonal method should be used temporarily, so that the natural cycle can be restored and the due date determined more accurately (Guillebaud, book, 1991; Hatcher et al., 1994). Others disagree (Mishell, letter, 1993; Rarick, letter, 1993; Angle, letter, 1993; and Killick, telephone conversation, 1993). Angle notes that such advice could give an unnecessary impression of danger if pregnancy occurs immediately after discontinuation; furthermore, modern technology allows estimating due dates simply and accurately. (See Appendix D.)

CONCLUSION: POPs, like COCs, should be started on the first day of menses if possible. If they are started later, a back-up method should be used for the first 48 hours. Postpartum POPs should be initiated at 3 weeks for partial and non-breastfeeders but can be delayed until 3 months postpartum for fully breastfeeding mothers, unless menses starts before that time. POP use can and should be initiated immediately after an abortion.

Switching to a new brand of POPs can be done at any time during the cycle or at the end of the last pack. Switching to POPs from COCs should occur at the end of the 21 active COC pills (discarding the placebos). Switching from POPs to COCs should take place on the first day of menses. Breastfeeders should be advised not to switch to COCs until they stop breastfeeding.

POPs can be stopped at any point in the cycle. (Types of evidence: II A, C; III A.)
B. Timing of Daily Pill-taking

Because the effect of POPs on cervical mucus is greatly diminished by 24 hours after administration (Section II), as are the steroid levels (Section III), POPs must be taken at the same time every day. Taking a combined oral contraceptive one day late only slightly increases the chance of pregnancy (Fraser & Jansen, 1983), yet taking a progestin-only pill just a few hours late can reduce protection against pregnancy. As long as the pills are taken at the same time every day without interruption, the specific time of day is not critical (Angle, letter, 1993; Fotherby, 1992; Guillebaud, book, 1993.) (See Appendix D.) However, taking the pill at bedtime could theoretically reduce contraceptive efficacy because the cervical mucus protection of POPs is greatest between 4 and 20 hours after ingestion. (See Section II.) Therefore, if the pill is taken at bedtime, by the next day at bedtime it has lost most of its effectiveness, yet bedtime is when couples are most likely to have sexual relations. Furthermore, if bedtime is the usual time for pill-taking, forgetting the pill would inevitably result in a span of many hours before the woman is likely to remember to take it.

The problem of taking POPs at bedtime was illustrated in a study of 307 POP users (Vessey et al., 1972), in which there were 11 failures in one year. All but one of those failures was considered a method failure, which may be due in part to the fact that, although women were told to take the pills whenever was most convenient for them, 95% chose the evening. As described above, evening is not the optimum time. The Vessey study suggests that the POP is best taken earlier in the day. In fact, some would call the POP the "teatime" pill (Angle, letter, 1993; INTRAH 1993), since taking it in the late afternoon or at the evening meal produces the full effect on the cervical mucus by bedtime. If dinnertime is a socially awkward time to take the pill, is difficult to remember or otherwise comply with, or if it is within three hours of bedtime, the pill can be taken in the morning or at lunch time.
Ultimately, it may be best to relate timing of POP-taking to the particular pattern of sexual behavior of the individual user (Fotherby, book, 1989).

CONCLUSION: Careful compliance to a regimen of one pill at the same time each day is essential to the effective use of progestin-only oral contraceptives. Selection of the time of day should be based on when it would be most convenient for the woman, although taking it at bedtime is probably the least preferable time in terms of effectiveness. (Types of evidence: II A, B, C, D; III A.)

C. Late/Missed POPs

Most guidelines for OC use (Appendix E) agree that, if a single POP is taken more than three hours late, a back-up contraceptive method should be used. However, there is debate as to whether that extra protection is needed for 48 hours or for 7 days. This is an important compliance issue because a few hours' delay in taking a single pill can be assumed to be the most common error in pill-taking. We have found no data specifying how many women take their combined or progestin-only pills late but on the same day, how many hours late, or how often pill-taking is delayed. As noted in the general medical compliance literature (Cramer et al., 1989) as well as the combined OC compliance literature (Oakley et al., 1991; Potter, 1991), irregular pill-taking is a very real problem.

More specifically, if a single pill is forgotten, all sources agree it should be taken as soon as it is remembered and then the next pill should be taken at the regular time (Fotherby, book, 1989; Goldzieher, book, 1989; Guillebaud, book, 1993; Hatcher et al., 1994; Huezo & Briggs, 1992; INTRAH, 1993; Speroff & Darney, 1992). It two or more pills are missed, instructions vary across
sources. Some suggest doubling up for the first two days, then continuing as usual (Hatcher et al., in press; INTRAH, 1993). Others simply recommend re-starting as soon as possible but not doubling up to make up the two missed pills (Fotherby, book, 1989; Goldzieher, book, 1989; Guillebaud, book, 1993; Huezo & Briggs, 1992; Speroff & Darney, 1992). Since there is not a clear contraceptive benefit to making up multiple missed pills, re-starting the pills as soon as possible would seem to be the simplest instruction, along with using a back-up contraceptive.

The more important component of managing missed pills is the use of a back-up method until continuity of pill-taking and pharmaceutical efficacy is restored. If a pill is 3 or more hours late, a back-up method of contraception should be used for the next 48 hours, according to Fotherby (book, 1989), Hatcher et al. (1994), Huezo and Briggs (1992), and Speroff and Darney (1992); however, Guillebaud (book, 1993) and INTRAH (1993) suggest using the back-up method for 7 days, and Goldzieher (book, 1989) recommends using a back-up method for the remainder of the cycle.

There are three parts to the discussion of when and for how long to use an additional back-up form of contraception: 1) the rationale for making a delay of 3 hours the cut-off point for recommending use of a back-up; 2) whether 48 hours or 7 days of back-up should be recommended for a single late pill; and 3) whether 48 hours or 7 days of back-up should be recommended for more than one missed pill.

Taking each of these points separately, the decision to set the number of hours after which back-up contraception is recommended at 3 has been based on clinical judgment rather than on systematic research data. By the end of 24 hours, the protection provided by the POP is low (as discussed in Section II). Because of the lower steroid levels, the cervical mucus is already thinning at 24 hours,
making the grace period for this mode of contraceptive action quite short. Too little is known about
the effects of interrupted dosing on the other mechanisms of action to be able to rely on their
providing continued protection at any given time. The 3-hour cut-off has been accepted as standard
practice, stretching slightly the convention of "on time" medication as within two hours of the
prescribed time. We have found neither data on nor argument for any change in the 3-hour definition
of "late".

Regarding the second point, there is heated debate as to whether once a POP is taken late or is
missed, the extra protection is needed for 48 hours or for 7 days. In the current labeling and
guidelines, the prescribed length of back-up use is specified anywhere from 7 to 28 days (see
Appendix E), regardless of whether a single pill was taken a few hours late or several pills have been
missed. It can be assumed that a 3-hour delay in pill-taking would be a fairly common error due to
daily variations in schedule. Requiring a full week or more of back-up for every pill that is 3 hours
late could lead to semi-permanent use of double methods by women who have occasional minor
fluctuations in their daily pill-taking schedules. Not using a back-up method of contraception is a
particularly serious compliance problem. In studies of combined pills, Brook and Smith (1991), Finlay
and Scott (1986), Kakouris and Kovacs (1992), Goldstuck et al. (1987), Oakley et al. (1991) and
Potter et al. (1988) all found inadequate use of back-up contraception with oral contraceptives.

Therefore, the decision as to whether back-up contraception should be required for 48 hours or 7
days when a single pill is late depends on one’s understanding of the mechanisms of action of the
POP. The use of a 48-hour back-up is based on the fact that the progestins reach their peak level in
the blood almost immediately (Odlind et al., 1979; Weiner et al., 1976), with a thickening of the
cervical mucus occurring within hours of pill-taking. (See Section II.) The use of 7 days of back-up
contraception is based on the concept of breakthrough ovulation, an issue with COCs, and the survival
time of sperm in the vagina. However, it is also based in large part on the desire to make instructions
consistent across oral contraceptive methods.

argue that pill-taking instructions should be the same for POPs as for the combined pills to aid
memory and for extra protection. Others, including Fotherby (letter, 1993) and Hatcher et al. (1994),
favor the 48-hour rule for POPs because of greater concern about making it as easy as possible to
comply, since the mucus barrier is re-established so quickly. This was also the position of the U.K.
Family Planning Association from 1987 until 1993. In fact, in 1987, when the UKFPA originally
replaced its old 14-day back-up rule with the 48-hour rule, it noted that since cervical mucus becomes
impenetrable within only 24 hours:

The [revised] guidelines... err on the side of caution by allowing the POP 48 hours to establish
an anti-fertility effect on the cervical mucus (Mills, 1987).

No increase in pregnancy rates was reported in the U.K. during the 6 years that the 48-hour rule
was in effect. When the UKFPA changed to the 7-day rule in 1993, they stated:

The FPA hopes the new guidelines [for 7 days of back-up contraception] will improve the
consistency and clarify advice given to women. The new recommendations do not add any
contraceptive efficacy to the FPA's previous two-day guideline. (Italics ours.)

Regarding the third point of what to do if more than one pill is missed, while some experts
accept a 48-hour contraceptive back-up for one missed pill, they worry about the increased chance of
breakthrough ovulation with 2 or more missed pills (Guillebaud, letter, 1993; Trussell, letter, 1993).
(See Appendix E.) Three factors argue against the need for longer back-up protection once pill-taking
resumes, regardless of the number of pills missed. First, ovulation occurs in about half of POP cycles
even when no pills are missed, so protection against ovulation is not the crucial line of defense.

Secondly, thickening of the cervical mucus occurs rapidly once pill-taking resumes. In addition, POP use affects the endometrium, the FSH and LH levels, and tubal motility as well as ovulation and the cervical mucus. This desynchronizes the cycle and further reduces the chance that a normal ovulation, fertilization and implantation can occur between the time the POP user begins to rectify her error and the full restoration of blood levels of the progestins. (See Section II.) Therefore, we would continue to recommend only 48 hours of back-up contraception even when 2 or more pills are missed.

Another possibility would be to recommend 48-hours of back-up for 1 missed pill and 7 days of back-up for two or more missed pills. This would be compatible with the current instructions for combined pills, which have different instructions for one vs. more missed pills. However, the available data on pharmacokinetics and mechanisms of action of the progestin-only pill do not suggest that the 7 days of double contraception are necessary.

When several pills have been omitted, the user should have a pregnancy test if 2 menstrual periods are missed or if her next menses seems unusually delayed. If she had sexual relations during the time she was without protection, she may want to use emergency post-coital contraception.

Women who are fully breastfeeding, i.e., providing no supplemental foods, rarely start ovulating before 6 months postpartum. (See Section XI.) For this reason, the breastfeeding itself can act as the back-up method of contraception until that time. On the other hand, breastfeeding women who are providing supplemental foods and/or have resumed menses increase their risk of ovulation and should protect themselves as carefully as non-breastfeeding women.
CONCLUSION: Instructions for using POPs should not have to be the same as for combined pills in order to enhance compliance; the two methods are not the same, the instructions for missed POPs are simple, and users can consult the labeling and/or their health care provider if they do miss a pill. For the user who is a few hours late taking a pill a couple of times each month, only occasionally misses a day, and rarely misses two or three pills in a row, 48 hours of additional contraception should provide sufficient protection. A pregnancy test should be performed if sexual relations occurred while she was unprotected or if two menstrual periods are missed. Emergency post-coital contraception within 72 hours of any unprotected intercourse is another option. Those who frequently take their pills late should consider changing the time of day they take the pill. Those who miss a pill more than once every cycle or two should consider using another contraceptive method.

Women who are fully breastfeeding and using POPs could probably be considered to be sufficiently protected by breastfeeding as their back-up method if they have not resumed menses and have an occasional, brief delay in POP use. They do not need to use a second back-up method if they miss pills. However, those who are partially breastfeeding or whose menses have returned should follow the instructions for regular POP users. (Types of evidence: II A, B, C; III A.)

(See Appendix F: DRAFT OF RECOMMENDED INSTRUCTIONS FOR POP USE.)
TABLE 1

Lowest Expected, Typical, and Lowest Reported Failure Rates During the First Year of Use of a Contraceptive Method and First-year Continuation Rates, United States (Trussell et al., 1990)

<table>
<thead>
<tr>
<th>Method</th>
<th>Percent of Women Experiencing an Accidental Pregnancy in the First Year of Use</th>
<th>Percent of Women Continuing Use at One Yeara</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest Expected*</td>
<td>Typicalb</td>
</tr>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>Chance*</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Spermicides*</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Periodic abstinence</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Calendar</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Ovulation method</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Symptothermal</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Post-ovulation</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Contraceptive foams</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>Parous women</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Nulliparous women</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Condom</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>IUD</td>
<td>2.0</td>
<td>3</td>
</tr>
<tr>
<td>Progestasert®</td>
<td>0.8</td>
<td>3</td>
</tr>
<tr>
<td>Copper T 380A</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Pill</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Combined</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Injectable progestogen</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>DMPA</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>NET</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Implants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NORPLANT® (6 capsules)</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>NORPLANT® (2 rods)</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Female sterilization</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Male sterilization</td>
<td>0.1</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly, the authors' best guess of the percentage expected to experience an accidental pregnancy during the first year if they do not stop use for any other reason). *Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. "In the literature on contraceptive failure, the lowest reported percentage who experienced an accidental pregnancy during the first year following initiation of use (not necessarily for the first time) if they did not stop use for any other reason. However, see note h. *Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year, under the alternative assumptions that no one becomes pregnant (column 4) and that the proportion becoming pregnant is given by column 1 (column 5). *The lowest expected and typical percent are based on data from populations where contraception is not practiced and from women who cease practicing contraception in order to become pregnant. These represent our best guess on the percent who would conceive among women now relying on reversible methods of contraception if they abandoned contraception altogether. The lowest reported percent is based on U.S. women who practice no contraception even though they do not wish to become pregnant. This group is selected for low fecundity or low coital frequency, and some fraction may use an unreported variant of periodic abstinence. *Too low, because rate is based on more than one year of exposure. See J. Trussell and K. Kost, "Contraceptive failure in the United States: A critical review of the literature," Studies in Family Planning 18 (1987):237-283. *Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases. *With spermicidal cream or jelly. *Without spermicides.
TABLE 2

Selected Studies of Pregnancies Among Users of Progestin-Only Oral Contraceptives, Including Failures Attributable to Non-Compliance

<table>
<thead>
<tr>
<th>Author, Date, Study Site</th>
<th>Hormone and Dose (in milligrams)</th>
<th>No. of Women, No. of Cycles</th>
<th>Ages</th>
<th>Failure Rate</th>
<th>Pregnancies Attributable to Non-Compliance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez-Manautou et al., 1967 (BMJ, p. 730) Mexico</td>
<td>CA 0.50</td>
<td>945 (8,091 cycles)</td>
<td>(Range = &lt;36)</td>
<td>TF = 2.1</td>
<td>13 of 14 (93%)</td>
<td>Non-compliers failed to take pills for several days.</td>
</tr>
<tr>
<td>Board, 1971 U.S.</td>
<td>NET 0.35</td>
<td>154 (1,888 cycles)</td>
<td>Not stated</td>
<td>TF = 1.3</td>
<td>1 of 2 (50%)</td>
<td>Single non-complier missed 7 days after 7 months of use.</td>
</tr>
<tr>
<td>Vessey et al., 1972 Yugoslavia</td>
<td>MA 0.70, NA 0.35, CA 0.50, NG 0.07</td>
<td>307 (cycles N.S.)</td>
<td>Mean = 29.1, 30.0, 30.4, 30.1 (Range = 18-44)</td>
<td>TF = Same as TFs</td>
<td>0 of 10 (0%)</td>
<td>None admitted to failing to take POPs. (All but 1 took POPs in evening.)</td>
</tr>
<tr>
<td>Nelson, 1973 U.S.</td>
<td>MA 0.50</td>
<td>342 (3653 cycles)</td>
<td>Not stated</td>
<td>TF = 2.7</td>
<td>2 of 10 (20%)</td>
<td>No explanation of errors.</td>
</tr>
<tr>
<td>Korba &amp; Paulson, 1974 U.S.</td>
<td>NG 0.07</td>
<td>2173 (21,854 cycles)</td>
<td>Not stated</td>
<td>TF = 2.37</td>
<td>27 of 53 (65%)</td>
<td>No explanation of errors.</td>
</tr>
<tr>
<td>Jubhri et al., 1974 Indonesia</td>
<td>QA 0.30</td>
<td>382 (3208 mo.)</td>
<td>Mean = 23.1</td>
<td>TF = 2.9</td>
<td>3 of 6 (50%)</td>
<td>No explanation of errors. Those with regular cycles became pregnant.</td>
</tr>
<tr>
<td>Hawkins &amp; Benster, 1977 U.K.</td>
<td>CA 0.50, MA 0.50, NET 0.35</td>
<td>556 (4500 mo.)</td>
<td>Mean = 26.1, 25.3, 24.7</td>
<td>TF = Same as TFs</td>
<td>20 of 35 (57%)</td>
<td>No explanation of errors. Some postpartum (does not provide number of breast feeders).</td>
</tr>
<tr>
<td>Postlethwaite, 1979 U.K.</td>
<td>ED 0.50</td>
<td>309 (10,046 cycles)</td>
<td>(Range = 17-48)</td>
<td>TF = 0.52</td>
<td>2 of 6 (33%)</td>
<td>1 missed 1 week, 1 missed 2 weeks. (Also 1 had diarrhea, 1 drug interaction).</td>
</tr>
<tr>
<td>Lawson, 1982 U.K., Jamaica, New Zealand</td>
<td>NET 0.35</td>
<td>913 (11,921 cycles)</td>
<td>Median = 27 (Range = 16-54)</td>
<td>TF = 2.21</td>
<td>8 of 22 (36%)</td>
<td>No explanation of errors, except &quot;missed pills&quot;. All user failures were in first 12 months. 4 method failures after 12 months. 9% of sample breastfeeding.</td>
</tr>
<tr>
<td>WHO, 1982 (Contrace p. 243) India, Yugoslavia</td>
<td>NET 0.35, LNG 0.03</td>
<td>258 (up to 24 cycles per person)</td>
<td>Mean = 25.6, 25.7 (Range = 18-38)</td>
<td>TF = Same as TFs</td>
<td>23 of 34 (68%)</td>
<td>No explanation of errors. 28 of 34 pregnancies were in Bombay (all but one of the user failures). All menstruating, even if lactating.</td>
</tr>
<tr>
<td>Author, Date, Study Site</td>
<td>Hormone and Dose (in milligrams)</td>
<td>No. of Women, No. of Cycles</td>
<td>Ages</td>
<td>Failure Rate</td>
<td>Pregnanacies Attributable to Non-Compliance</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------</td>
<td>------</td>
<td>-------------</td>
<td>---------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Shroff et al., 1987 U.K.</td>
<td>ED 0.50 (cycles N.S.)</td>
<td>425</td>
<td>Median = 30 (28% aged 35+) (Range = 16-35+)</td>
<td>TF = 1.1 (LT)</td>
<td>3 of 5 (60%) (2 of 4 first year failures)</td>
<td>Non-compliance defined as missing 1 or more pills without back-up.</td>
</tr>
<tr>
<td>McCann et al., 1989 Argentina</td>
<td>LNG 0.03 (cycles N.S.)</td>
<td>250</td>
<td>Range 30-35</td>
<td>TF = 3.9 (at 9 mo.)</td>
<td>N.S.</td>
<td>All postpartum, breastfeeding. 3 pregnancies. All pregnancies toward end of 9 month study period, when protection and compliance possibly waning.</td>
</tr>
<tr>
<td>Vessey et al., 1985, 1990 (BJFP, p 79) U.K.</td>
<td>ED 0.50, NET 0.35, LNG 0.07 Others (trial preps.)</td>
<td>(3,303 woman-yrs)</td>
<td>&lt; 25 = 38 (n) &gt; 40-50 (n) (Range = 25-39, 1985-25-44, 1990)</td>
<td>TF = 1.7 (PI)</td>
<td>8 of 30 (27%)</td>
<td>6 pregnant women missed no pills; 2 other missed no pills but were ill; 8 missed 1+ pills; 14 unknown.</td>
</tr>
<tr>
<td>Broome &amp; Fotherby, 1990 U.K.</td>
<td>ED 0.50, NET 0.35, LNG 0.03</td>
<td>358 (18,125 cycles)</td>
<td>&lt; 25-38 (n) &gt; 40-50 (n) (Range = &lt; 25-45+)</td>
<td>TF = 0.2 (PI)</td>
<td>0 of 3 (0%)</td>
<td>No explanation of errors. (Retrospective.) Those lactating excluded.</td>
</tr>
<tr>
<td>Bisset et al., 1990, 1992 U.K.</td>
<td>ED 0.50, NET 0.35, LNG 0.03</td>
<td>1042 (24,942 Mo)</td>
<td>&lt; 24 = 256 (n) 35 + =&gt; 333 (n)</td>
<td>TF = 1.01 (PI)</td>
<td>15 of 21 (62%)</td>
<td>4 late pills, 2 missed pills, 4 diarrhea, 2 drugs. (14 of 21 had previous unplanned pregnancies.) (Retrospective.)</td>
</tr>
<tr>
<td>Moggs et al., 1991 Argentina</td>
<td>NG 0.075</td>
<td>250 (cycles N.S.)</td>
<td>Range 18-35</td>
<td>TF = 0.5 (LT)</td>
<td>Single pregnancy due to user failure (missed 3 pills)</td>
<td>All postpartum, breastfeeding. Length of study 6 months.</td>
</tr>
<tr>
<td>Dunson et al., 1993 14 countries</td>
<td>NG 0.07</td>
<td>4088 (2450 woman-yrs)</td>
<td>Mean = 25.7, Median = 25 (Range = 18+)</td>
<td>TF = 1.2 (LT)</td>
<td>15 of 34 (29 in study period)</td>
<td>All postpartum, breastfeeding at initiation. User failure if missed ≥ 2 consecutive pills. Subjects were discontinued after 12 cycles or if missed ≤ 3 consecutive pills.</td>
</tr>
</tbody>
</table>

N.S. = Not specified. In chronological order. TF = Total Failure Rate (Use-effectiveness) MF = Method Failure Rate (Method effectiveness) PI = Pearl Index (per 100 woman-years) LT = Life Table (one year pregnancy rate per 100 women)
<table>
<thead>
<tr>
<th>Author, Date, Study Site</th>
<th>Formulation (mg)</th>
<th>N and No. of Cycles</th>
<th>Ectopic Pregnancy (EP) Rate</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisset et al. 1990 U.K.</td>
<td>ED 0.50, NET 0.35, LNG 0.03</td>
<td>1042 POP users (24,942 months)</td>
<td>2 EPs of 21 pregnancies (1 EP per 1000 woman-years)</td>
<td>Retrospective, no controls; Mean Exposure = 24 months</td>
</tr>
<tr>
<td>Bonnar 1974 U.K.</td>
<td>NET 0.35</td>
<td>135 POP users (1,024 months)</td>
<td>2 EPs of 4 pregnancies (20 EPs per 1000 woman-years)</td>
<td>Retrospective case study, no controls</td>
</tr>
<tr>
<td>de Muylder 1981 Zimbabwe</td>
<td>Multiple (not specified)</td>
<td>2931 POP users (No. of cycles N.S.)</td>
<td>10 POP users in 104 EPs (3 EPs per 1000 woman-years)</td>
<td>Retrospective; 0.5 EPs per 1000 woman-years for COCs (3 COC users) (STD biggest predictor of EP)</td>
</tr>
<tr>
<td>Hawkins &amp; Benson 1977 U.K.</td>
<td>CA 0.50, MA 0.50, NET 0.35</td>
<td>613 POP users (4,500 woman-months) (175 woman-years)</td>
<td>3 EPs of 35 pregnancies (8 EPs per 1000 woman-years)*</td>
<td>Prospective, no controls</td>
</tr>
<tr>
<td>Lawson 1982 U.K., Jamaica, New Zealand</td>
<td>NET 0.35</td>
<td>913 POP users (11,921 cycles)</td>
<td>3 EPs of 22 pregnancies (3 EPs per 1000 woman-years)</td>
<td>Retrospective, no controls; Patients with EPs were of multiple parity and were above average age</td>
</tr>
<tr>
<td>Linkko et al. 1977 Finland</td>
<td>LYN 0.50, LNG 0.03, NET 0.3</td>
<td>238 EPs (No. of cycles N.S.)</td>
<td>30 POP users in 238 EPs (12.6%) LYN 0.50 = 0.1 EPs per 1000 woman-years LNG 0.03 = 3 EPs per 1000 woman-years NET 0.30 = 4 EPs per 1000 woman-years</td>
<td>Retrospective, no controls; 2 Finnish hospitals (1973-76, 74-76); Rate calculated using sales data as denominator</td>
</tr>
<tr>
<td>Ulstein and Søvde 1980 Norway</td>
<td>&quot;Minipill&quot; (not specified)</td>
<td>206 EPs (No. of cycles N.S.)</td>
<td>11 POP users in 206 EPs (1.3 EPs per 1000 woman-years)</td>
<td>Retrospective (1973-77), no controls; 2.4 EPs for IUD users; Rate calculated using sales data as denominator</td>
</tr>
<tr>
<td>Vessey et al. 1985 U.K.</td>
<td>ED 0.50, NET 0.35, LNG 0.03</td>
<td>No. of POP users N.S. (3,303 woman-years)</td>
<td>1 EP of 30 pregnancies (0.0 EPs per 1000 woman-years)</td>
<td>Prospective, no controls</td>
</tr>
<tr>
<td>WHO (Sheth et al.) 1982 India, Yugoslavia</td>
<td>NET 0.35, LNG 0.03</td>
<td>302 POP users (Up to 24 cycles/woman) (120 observed at 12th cycle)</td>
<td>2 EPs of 22 pregnancies (0.9 EPs per 1000 woman-years)</td>
<td>No EPs among COC users. Prospective double-blind clinical trial.</td>
</tr>
</tbody>
</table>

N.S. = not specified

*EPs not separated by formulation in this paper
TABLE 4

Selected Studies of Lipid and Carbohydrate Metabolism Among Users of Progestin-Only Oral Contraceptives

<table>
<thead>
<tr>
<th>Author, Date, Study Site</th>
<th>Formulation of Progestin-Only Contraceptives (milligrams)</th>
<th>No. of Women</th>
<th>Study Description</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ball et al. 1991 England</td>
<td>Norethisterone 0.35 + Levonorgestrel 0.03</td>
<td>23</td>
<td>Half of the women were switched from combined OCs (primarily 30-35 mg estrogen, with LNG); half had not commonly used OCs. Sample was stratified on previous use and then randomly allocated. Women were excluded if hypertensive, smoked &gt;20 cigarettes/day, or were diabetic. Follow-up for 6 months (N=20 for NET and 15 for LNG).</td>
<td>Lipid metabolism: minimal changes from baseline and no differences between the two POPs (Cholesterol, HDL-C, HDL3, LDL-C, VLDL-C). Decrease in triglycerides, especially for switchers from COCs and especially for users of LNG. Small decrease in HDL2 for new users and increase for switchers to LNG, but no significant changes in HDL2/HDL3 ratio.</td>
<td>No significant differences between the two POP groups for any lab test at the end of follow-up.</td>
</tr>
<tr>
<td>Blau et al. 1993 Israel</td>
<td>Ethynodiol dicarbonate 0.5</td>
<td>14</td>
<td>Also included 13 women using various COCs. Follow-up for 3 months.</td>
<td>Lipid metabolism: no significant change in total cholesterol or triglycerides.</td>
<td>No significant change in blood glucose levels in glucose tolerance test.</td>
</tr>
<tr>
<td>Goldstein et al. 1990 (NEJM) England</td>
<td>Levonorgestrel 0.03/0.0375 + Norethindrone 0.35/ Ethynodiol dicarbonate 0.5</td>
<td>40</td>
<td>Also included 600 women using various monophasic COCs, 325 using various triphasic COCs, and 418 not using hormonal contraception. Cross-sectional study of white women age 18-45, within 20% of ideal body weight, with no known medical condition, not taking medications that affect metabolism, and who had not been pregnant in past 6 months. OC users had been taking OCs at least 3 months; non-users had not taken sex hormones for at least 3 months. Results were adjusted for several other variables.</td>
<td>Lipid metabolism: POPs containing LNG had no effect on lipid metabolism (total cholesterol, HDL, LDL, HDL2, LDL, triglycerides, and apolipoproteins A-I, A-II, and B); NET or ED alone significantly lowered HDL, cholesterol and apolipoprotein A-I and A-II levels.</td>
<td>No information on whether previous users had stopped OC use because of metabolic problems.</td>
</tr>
<tr>
<td>Kanu et al. 1990 Kenya</td>
<td>Levonorgestrel 0.03 + Ethinyl estradiol 0.03 + levonorgestrel 0.15</td>
<td>30</td>
<td>Oral glucose tolerance test performed before treatment and at 1, 3 and 6 months. Mean baseline weight similar for all groups; DMPA users older and higher parity; none had previously used OCs.</td>
<td>Carbohydrate metabolism: mean blood glucose levels higher at all three follow-up measurements than at baseline for both pill groups; no change for DMPA users. All changes for POP users were within normal limits.</td>
<td></td>
</tr>
<tr>
<td>Kapphahn-Makelin et al. 1992 Finland</td>
<td>Levonorgestrel 0.15 + Desogestrel 0.15</td>
<td>15</td>
<td>Healthy women, age 18-35, none had used hormones in past 2 months. Randomly allocated to LNG or DG. Given progestin alone for days 15-28 of first cycle. Given BE 30 plus progestin for next three cycles and then sequential for three cycles, always continuing with some progestin. Baseline testing for serum lipids and lipoproteins similar for LNG and DG groups. (Note: LNG done was five times usual dose for POP.) Significance testing corrected for multiple comparisons.</td>
<td>Lipid metabolism: For LNG alone, no significant differences from baseline in total, LDL, and VLDL cholesterol, but significant decrease for HDL cholesterol. Significant decrease in total, LDL, and HDL triglycerides; non-significant decrease in VLDL triglycerides. Significant decrease in total and LDL phospholipids; non-significant decrease in LDL and VLDL phospholipids. Significant decrease in HDL2 cholesterol and HDL2 phospholipids; nonsignificant increase in HDL3 cholesterol and nonsignificant decrease in HDL3 phospholipid levels. Post-heparin plasma HLP activity increased significantly. No significant change in LPL activity. SHBG levels declined. Plasma apo A-I did not change.</td>
<td>Changes were generally of less magnitude for DG alone than for LNG alone. Addition of EE had effect opposite that of progestin alone for some measurements (especially triglycerides and SHBG).</td>
</tr>
<tr>
<td>Author, Date, Study Site</td>
<td>Formulation of Progestin-Only Contraceptive (milligrams)</td>
<td>No. of Women</td>
<td>Study Description</td>
<td>Results</td>
<td>Comments</td>
</tr>
<tr>
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</tr>
<tr>
<td>Radberg et al. 1982 Sweden</td>
<td>Lynestrenol 0.5</td>
<td>23</td>
<td>Women with insulin-dependent diabetes mellitus, age 18-35. Randomly allocated to LYN alone or COC (LYN 2.5 + EE 0.05) for 6 months; then 2 months without OC; finally, crossed-over to other OC for 6 months. All women had normal serum lipids before OC use.</td>
<td>Lipid metabolism</td>
<td>For LYN alone, significant decrease in all serum lipids (cholesterol, triglycerides and phospholipids) and smaller decrease in HDL lipid parameters. Carbohydrate metabolism</td>
</tr>
<tr>
<td>Spellacy et al. 1976, 1981 -NO 1976 -ED 1975 -NET USA</td>
<td>Norgestimate 0.075 Norethindrone 0.35 Ethynodiol diacetate 0.25</td>
<td>71 31 36</td>
<td>Healthy women, at least 6 weeks postpartum. Normal glucose tolerance test at baseline. Laboratory studies performed before OC use begins and at 12 months; carbohydrate metabolism of 50 NO users also assessed at 18 months.</td>
<td>Lipid metabolism</td>
<td>No significant change in cholesterol for any group. Significant decline in fasting plasma triglycerides for NET and ED (which may be related to postpartum changes.) Carbohydrate metabolism</td>
</tr>
<tr>
<td>Wynn and Nitthyanthan 1982 England</td>
<td>Norethindrone 0.35 Levonorgestrel 0.035</td>
<td>26 16</td>
<td>Also included 418 women using various COCs and 293 non-users. Cross-sectional study. Two POP groups combined for analysis.</td>
<td>Lipid metabolism</td>
<td>No difference between POP users and controls in cholesterol, HDL, HDL3, or triglycerides. HDL2 and ratios of HDL2 to LDL significantly lower for POP users than controls.</td>
</tr>
</tbody>
</table>

Note: Most or all of the women in these studies were not breastfeeding.
<table>
<thead>
<tr>
<th>Author, Date, Study Site</th>
<th>Formulation of Progestin-Only Contraceptive (milligrams)</th>
<th>No. of Women</th>
<th>Study Description</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ball et al. 1991 England</td>
<td>Northlisterone 0.35, Levonorgestrel 0.03</td>
<td>23</td>
<td>Half of the women were switched from combined OCs (primarily 30-35 mg estrogen, with LNG); half had not recently used OCs. Sample was stratified on previous use and then randomly allocated. Women were excluded if hypertensive, smoked &gt;20 cigarettes/day, or were diabetic. Followed-up for 6 months (N=20 for NET and 15 for LNG). Data on vaginal bleeding collected on diary cards.</td>
<td>Mean number of bleeding episodes per month was 1.28 for LNG, 1.24 for NET. Slight decrease in menstrual cramps for both groups.</td>
<td>30% selected POPS because of side effects, contraindications, or women’s anxiety about COCs; 16% were switching from one POP to another; 13% were over 40 years old; 12% were smokers over 35 years old; 7% were breastfeeding; 15% were self-selection. About one-quarter of NO and LNG users were breastfeeding, but less than 10% of the other two POP groups (Bisset et al., 1990).</td>
</tr>
<tr>
<td>Bisset et al. 1992 Scotland</td>
<td>Northlisterone 0.35, Ethynodiol diacetate 0.5, Norgestrel 0.075, Levonorgestrel 0.03</td>
<td>369, 332, 155, 146</td>
<td>Data obtained from family planning clinic records for women who began use 1973-1986. Excluded women who were prescribed POPS but never returned for follow-up. Each segment of POP use treated as a separate case (728 women had 1042 segments of POP use).</td>
<td>15% discontinued because of menstrual disturbances (twice as common among younger than older women).</td>
<td>No logical differences among progestins; menstrual disturbances were more common with NO and least common with LNG.</td>
</tr>
<tr>
<td>Brecon &amp; Pethybridge 1990 England</td>
<td>Northlisterone 0.35, Ethynodiol diacetate 0.5, Levonorgestrel 0.03</td>
<td>189, 62, 27</td>
<td>Data obtained from family planning clinic records for women who began use 1977-1979. Breastfeeding women excluded. Age at first use: &lt;30 26.9%, 31-40 59.2%, 41-44 14.0%. Almost half used POPS for more than 4 years. Clinic records noted dates of menstrual bleeding and whether cycles were regular.</td>
<td>24.3% discontinued because of menstrual disturbances.</td>
<td>Age and smoking were most common reasons for choosing POPs; 29% had experienced side effects with COCs.</td>
</tr>
<tr>
<td>Hawkins &amp; Bennett 1977 England</td>
<td>Northlisterone 0.35, Chloestradiol acetate 0.5, Megestrol acetate 0.5</td>
<td>200, 182, 174</td>
<td>Prospective study, with 1-year follow-up. 70% of NET users and 87% of other POP users were &lt;6 months postpartum; nothing stated about breastfeeding. Medical and menstrual histories were similar for the 3 POP groups. Menstrual pattern data were recorded on menstrual diary cards.</td>
<td>Menstrual disturbance was reason for discontinuation as follows (1-year life table rates per 100 women):</td>
<td>Lower menstrual problem discontinuation rate for NET may be attributable to greater time since delivery (so menstrual patterns more stabilized).</td>
</tr>
</tbody>
</table>

**TABLE 5**

Selected Studies of Bleeding Patterns Among Users of Progestin-Only Oral Contraceptives
<table>
<thead>
<tr>
<th>Author, Date, Study Site</th>
<th>Formulation of Progestin-Only Contraceptive (milligrams)</th>
<th>No. of Women</th>
<th>Study Description</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korba et al. 1974 U.S.A.</td>
<td>Norgestrel 0.075</td>
<td>2,202</td>
<td>POP was administered continuously for 1-67 cycles, for a total of 29,006 cycles. Population studied included women of childbearing age at 7 sites in all geographical regions of US and reflected a cross-section of all major socio-economic groups.</td>
<td>13.7% of POP users discontinued because of bleeding problems (9.8% irregular bleeding, 3.1% amenorrhea, 0.8% spotting). The overall mean interval between bleeding episodes was 28.1 days, but this varied considerably among women and increased over time. 70.3% of bleeding intervals were between 21 and 45 days, 21-5 &lt;21 days, and 6.2% &gt;45 days. Mean length of bleeding episodes declined steadily. Incidence of intermenstrual bleeding also declined, from 16% in the first month to less than 10% after 3 months. Up to 3.4% of women reported amenorrhea each month. An average of 5.1% reported dysmenorrhea.</td>
<td>Pretreatment side effect prevalence is tabulated, but the time frame is not indicated; these pretreatment figures are much higher than during each month of treatment, for all side effects, suggesting that the time periods were not equal.</td>
</tr>
<tr>
<td>Lawson 1982 UK, Jamaica, New Zealand</td>
<td>Norethisterone 0.35</td>
<td>913</td>
<td>Multicenter study conducted from 1970 to 1981; 11,921 cycles. New patients patients changing from COCs, and postpartum women were enrolled; 9% were breastfeeding at study entry, and more than half of these women had not yet resumed menses. Median age 27 (range 16-54). Calendar cards used to record tablet taking, bleeding and symptoms.</td>
<td>The major reason for withdrawal from the study was irregular cycle control (3.1% of women), amenorrhea (2.5%), and prolonged or heavy periods (1.5%). The variation in cycle lengths was large, especially during the first cycle. The amount of menstrual flow tended to be less during the trial than the quantity reported before the trial. Breakthrough bleeding was particularly common in the first few cycles (24% in cycle 1, decreasing to 7.2% in cycle 12).</td>
<td></td>
</tr>
<tr>
<td>Paulsen et al. 1974 U.S.A.</td>
<td>Ethynodiol diacetate 0.25</td>
<td>43</td>
<td>Randomized double-blind clinical trial, comparing POP and COC (43 women taking ME 0.1 + ED 1.0) Primarily young nulliparous women without previous experience using COCs; mean age 20. Excluded if contraindications to OC use. Followed-up for one year. Women recorded data on menstrual calendar.</td>
<td>None of the ED users but 70% of the COC users had &quot;regular&quot; cycles (defined as 21-35 days between menstrual bleeding with no intermenstrual bleeding). ED users also had significantly more intermenstrual bleeding and significantly more cramping. One woman taking ED had amenorrhea for 7 months (until POP use stopped).</td>
<td></td>
</tr>
<tr>
<td>Vesey et al. 1972 Yugoslavia</td>
<td>Norgestrel 0.075</td>
<td>74</td>
<td>Randomized, double-blind clinical trial of 4 POPs; 71 COC (EE 0.1 + MA 2.0) users not randomized but followed-up in parallel. Participants age 18-44 (mean 29-30 for POP groups, 27 for COC users); of proven fertility; no hormone use in last 2 months; normal gynecologic exam; free from chronic liver disease, allergies, epilepsy; no history of thromboembolic disease. Observed at 1, 4, 7, 10, and 13 months. Women recorded pills taken and vaginal bleeding on daily record card.</td>
<td>Discontinuation because of menstrual disturbances was reported for 1.6% (NA) - 5.4% (NG) of POP users, compared to 0.7% of COC users. More menstrual disruption for POP users than COC users, with POP users having shorter mean cycle length, greater median range of cycle lengths, and longer duration of flow. One-third of cycles were 28 days. Among POPs, present disruption for NO and least for NA. Intermenstrual spotting reported in 3% of COC cycles and 5-6% of POP cycles. No consistent changes over time in cycle length or regularity.</td>
<td></td>
</tr>
<tr>
<td>Vesey et al. 1972 Yugoslavia</td>
<td>Norethisterone acetate 0.3</td>
<td>76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vesey et al. 1972 Yugoslavia</td>
<td>Megestrol acetate 0.7</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vesey et al. 1972 Yugoslavia</td>
<td>Chlormadinone acetate 0.5</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Authors, Date, Study Site
<table>
<thead>
<tr>
<th>Author, Date, Study Site</th>
<th>Formulation of Progestin-Only Contraceptive (milligrams)</th>
<th>No. of Women</th>
<th>Study Description</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessey et al. 1985 England</td>
<td>Norethisterone 0.35</td>
<td>1746</td>
<td>Data obtained from continuing follow-up of Oxford-Family Planning Association (OPA) contraceptive study, 17,032 while married women, aged 25-59 years, using oral contraceptives, a diaphragm or an IUD, were recruited at 17 family planning clinics in England and Scotland between 1968 and 1974. Follow-up information includes details of all changes in contraceptive practice with reason for changes.</td>
<td>54.3% of NET discontinuations and 62.8% of discontinuations of other POPs (excluding total preparations) were due to menstrual disturbances. (Percentages based on number of users were not reported.)</td>
<td>Bleeding patterns at the two study sites were generally similar, with women in Yugoslavia only somewhat more likely to have disturbances; yet women in Yugoslavia were 2.6 times more likely to discontinue POP use because of menstrual irregularities.</td>
</tr>
<tr>
<td>WHO 1982 (Contraceptives 243) India and Yugoslavia</td>
<td>Norethisterone 0.35</td>
<td>130</td>
<td>Randomized, double-blind, clinical trial of 2 POPs and 2 COCs (123 women taking ME 0.05 + NET 1.0 and 137 taking EE 0.03 + LNG 0.15. Women had no contraindications to OC use; had regular menstrual cycles; were at least 28 days postpartum and had resumed menses if breastfeeding, had been breastfeeding at least 165 days. Mean age 25.7. Observed every 3 cycles, for maximum of 24 cycles. Women recorded data daily on menstrual diary cards.</td>
<td>After 1 year, one-fourth of users of both POPs discontinued because of bleeding disturbances, increasing to one-third after almost 2 years. Rates were similar for the two POPs. POP rates similar to ME + NET, but higher than for EE + LNG. Analysis of menstrual diary cards also indicated that bleeding disturbances were generally less common with EE + LNG than for the other three groups. Based on the cards, amenorrhoea was present in the first three cycles of 8.2% of women taking NET and 3.1% for those taking LNG; infrequent bleeding 36.0% and 21.5%, respectively; prolonged bleeding 20.6% and 24.0%; frequent bleeding 51.8% and 54.9%; and irregular bleeding 15.3% and 11.0%. Percentages were lower for cycles 10-12.</td>
<td></td>
</tr>
</tbody>
</table>

### Studies in Breastfeeding Women

<table>
<thead>
<tr>
<th>Author, Date, Study Site</th>
<th>Formulation of Progestin-Only Contraceptive (milligrams)</th>
<th>No. of Women</th>
<th>Study Description</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apelo &amp; Veloso 1973 Philippines</td>
<td>Levonorgestrel 0.0375</td>
<td>99</td>
<td>Followed-up for 12 months. Age range 17-37 years, mean 26 years. Body weight range 75-149 lbs., mean 101.6. Parity at least 1.</td>
<td>3% discontinued because of menstrual disturbances. “Majority” of women were breastfeeding; all but 2 had resumed menses. Use of POPs began average of 8 months after delivery (range 1-55 months).</td>
<td></td>
</tr>
<tr>
<td>Dunson et al. 1993 22 sites in 14 countries</td>
<td>Norgestrel 0.075</td>
<td>4,088</td>
<td>Breastfeeding women were enrolled within 6 months postpartum (4% in first 2 months). Mean age 25.7. Followed for 11 months. No comparison group.</td>
<td>Discontinuation because of menstrual problems was reported for 4.9% of women. About one-third of women reported intermenstrual bleeding and about one-third complained of amenorrhoea.</td>
<td></td>
</tr>
<tr>
<td>Author, Date, Study Site</td>
<td>Formulation of Progestin-Only Contraceptive (milligrams)</td>
<td>No. of Women</td>
<td>Study Description</td>
<td>Results</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------------------------</td>
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</tr>
<tr>
<td>McCann et al., 1989, Argentina</td>
<td>Levonorgestrel 0.03</td>
<td>250</td>
<td>Breastfeeding women enrolled within 1 week postpartum. POP users began pill use immediately. Compared with 137 IUD users and 113 users of other nonhormonal methods. FU for 9 months.</td>
<td>Abnormal bleeding was reason for all 4 POP discontinuations (1.6% of POP users) and for 1 of 2 nonhormonal method discontinations.</td>
<td>Intermittent bleeding reported by POP users less than IUD users but more than other nonhormonal method users. One-third of POP users reported intermittent bleeding in first few months, declining to 20% in later months; two-thirds reported intermittent bleeding at least once in 9 months.</td>
</tr>
<tr>
<td>Moggia et al., 1991, Argentina</td>
<td>Norgestrel 0.075</td>
<td>241</td>
<td>Breastfeeding women enrolled within 1 week postpartum. POP users began pill use immediately; compared with 181 IUD users and 61 users of other non-hormonal methods. FU for 6 months.</td>
<td>Intermittent bleeding complaints similar for POP and IUD users (reported at 36% and 40%, respectively, of monthly visits). Significantly lower for users of other nonhormonal methods (3%).</td>
<td></td>
</tr>
<tr>
<td>West, 1983, Scotland</td>
<td>Norihabitron 0.35</td>
<td>84</td>
<td>227 new, fully breastfeeding, mothers were given detailed information about contraceptive methods prior to discharge. At six months postpartum they were sent questionnaires; 89% replied. 84 had used the POP, with use mainly begun in first 4 weeks after delivery.</td>
<td>4.8% discontinued because of irregular bleeding.</td>
<td>Patterns of bleeding experienced by the women while taking the progesterin-only contraceptive were related to the duration of breastfeeding. Of the 41 mothers who breast-fed for over 5 months 68% had complete amenorrhea while taking the POP, and only 12% of this group experienced abnormal bleeding. Irregular and prolonged breakthrough bleeding was significantly more common in mothers who stopped breastfeeding.</td>
</tr>
</tbody>
</table>

*Most or all of the women in these studies were not breastfeeding.*
## TABLE 6
Selected Studies of Non-Menstrual Side Effects as Reason for Discontinuation Among Users of Progestin-Only Oral Contraceptives

<table>
<thead>
<tr>
<th>Author, Date, Study Site</th>
<th>Formulation of Progestin-Only Contraceptives (milligrams)</th>
<th>No. of Women</th>
<th>Study Description</th>
<th>% of Users Discontinuing Because of Non-Menstrual Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies in Non-Breastfeeding Women</strong></td>
<td></td>
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</tr>
<tr>
<td>Bisset et al. 1992 Scotland</td>
<td>Norethisterone 0.35 Ethynodiol diacetate 0.5 Norgestrel 0.075 Levoorgestrel 0.03</td>
<td>369</td>
<td>332</td>
<td>195</td>
<td>146</td>
</tr>
<tr>
<td>Broome &amp; Fotherby 1990 England</td>
<td>Norethisterone 0.35 Ethynodiol diacetate 0.5 Levoorgestrel 0.03 More than one of above POPs</td>
<td>189</td>
<td>62</td>
<td>27</td>
<td>80</td>
</tr>
<tr>
<td>Hawkins &amp; Benster 1977 England</td>
<td>Norethisterone 0.35 Chlormadinone acetate 0.5 Megestrol acetate 0.5 (in oil)</td>
<td>200</td>
<td>182</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>Author, Date, Study Site</td>
<td>Formulation of Progestin-Only Contraceptives (milligrams)</td>
<td>No. of Women</td>
<td>Study Description</td>
<td>% of Users Discontinuing Because of Non-Menstrual Side Effects</td>
<td>Comments</td>
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<tr>
<td>Korba et al. 1974 U.S.</td>
<td>Norgestimate 0.075</td>
<td>2,202</td>
<td>POP was administered continuously for 1-67 cycles for a total of 20,006 cycles. Population studied included women of childbearing age at 7 sites in all geographical regions of U.S. and reflected a cross-section of all major socio-economic groups.</td>
<td>(Number of discontinuations = 464)</td>
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<td></td>
<td>Headaches 1.2, Weight gain 0.7, Generalized somatic complaints 0.5, Nervousness 0.5, Gastro-intestinal distress 0.5, Hair loss 0.4, Acne 0.4, Vaginitis 0.4, Skin rash 0.4, Total 7.4</td>
<td>≤5 women (&lt;0.2%) discontinued for: nausea and/or vomiting, pruritus, leg cramps, loss of libido, hirsutism, chloasma, dysmennorhea, weight loss, general malaise, dizziness, breast discomfort, increased or decreased appetite, back pain, chest pain, depression, migraine, blurring of vision, fatigue and galactorrhea.</td>
</tr>
<tr>
<td>Lawson 1982 U.K., Jamaica, New Zealand</td>
<td>Norethisterone 0.35</td>
<td>913</td>
<td>Multicenter study conducted 1970-1981; 11,021 cycles. New patients, patients changing from COCs, and post-partum women were enrolled; 9% were breastfeeding at study entry, and more than half of these women had not yet resumed menses. Median age 27 (16-54). Calendar cards used to record tablet taking, bleeding and symptoms.</td>
<td>Migraine or headache 3.0, Depression 1.5, Skin complaints 0.9, Other (not specified) 6.1, Total 11.5</td>
<td></td>
</tr>
<tr>
<td>Vessey et al. 1972 Yugoslavia</td>
<td>Norgestimate 0.075, Norethisterone acetate 0.3, Megestrol acetate 0.7, Chlormadinone acetate 0.5</td>
<td>74, 76, 80, 77</td>
<td>Randomized, double-blind clinical trial of 4 POPs; 71 COC (EE 0.1 + MA 2.0) users not randomized but followed-up in parallel. Participants age 18-44 (mean 29-30 or POP groups, 27 for COC users); of proven fertility; no hormone use in last 2 months; normal gynecologic exam; free from chronic liver disease, allergies, epilepsy; no history of thromboembolic disease. Observed at 1, 4, 7, 10, and 13 months. Women recorded pills taken and vaginal bleeding on daily record card.</td>
<td>All non-menstrual side effects:</td>
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<td></td>
<td>NG 1.2, NA 0.6, MA 1.5, CA 1.0, EE+MA 1.6</td>
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<tr>
<td>Author, Date, Site</td>
<td>Formulation of Progestin-Only Contraceptives (milligram)</td>
<td>No. of Women</td>
<td>Study Description</td>
<td>% of Users Discontinuing Because of Non-Menstrual Side Effects</td>
<td>Comments</td>
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<tr>
<td>Vessey et al. 1985 England</td>
<td>Noristerone 0.35 (Woman-years)</td>
<td>1746</td>
<td>Data obtained from continuing follow-up of Oxford-Family Planning Association (FPA) contraceptive study. 17,032 white married women, aged 25-39 years, using oral contraceptives, a diaphragm or an IUD, were recruited at 17 family planning clinics in England and Scotland between 1968 and 1974. Follow-up information includes details of all changes in contraceptive practices with reason for changes.</td>
<td>Weight gain 8.2</td>
<td>Other POPs include ED 0.5 mg and LNG 0.03 mg; trial preparations excluded from discontinuation data.</td>
</tr>
<tr>
<td></td>
<td>Norgestrel 0.075</td>
<td>555</td>
<td></td>
<td>Headache 7.4</td>
<td>Data presented are % of all discontinuations, not % of all women.</td>
</tr>
<tr>
<td></td>
<td>Ethynodiol diacetate 0.5</td>
<td>459</td>
<td></td>
<td>Gastro-intestinal disturbances 3.1</td>
<td>Among women who discontinued OCs because of side effects, headache was much less common for POP than for COC; psychological disturbances and hypertension were somewhat less common. Breast discomfort was somewhat more common among POP discontinuers.</td>
</tr>
<tr>
<td></td>
<td>Levonorgestrel 0.03</td>
<td>405</td>
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<td>Breast discomfort 5.1</td>
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<tr>
<td></td>
<td>Others (including trial preparations)</td>
<td>138</td>
<td></td>
<td>Psychological disturbance 3.8</td>
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<td></td>
<td></td>
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<td></td>
<td>Thromboembolism 1.1</td>
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<td>Hypertension 3.6</td>
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<td></td>
<td></td>
<td>Other reasons (not specified) 13.4</td>
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</tr>
<tr>
<td>WHO 1982 (Contracep, pp 243-52) India and Yugoslavia</td>
<td>Noristerone 0.35</td>
<td>130</td>
<td>Randomized, double-blind, clinical trial of 2 POPs and 2 COCs (123 women taking ME 0.05 + NET 1.0 and 137 taking EE 0.03 + LNG 0.15). Women had no contraindications to OC use; had regular menstrual cycles; were at least 28 days postpartum and had resumed menses; if breastfeeding, had been breastfeeding at least 165 days. Mean age 25.7. Observed every 3 cycles, for maximum of 24 cycles.</td>
<td>Gastro-intestinal*</td>
<td>Other medical reasons for discontinuation:</td>
</tr>
<tr>
<td></td>
<td>Levonorgestrel 0.03</td>
<td>128</td>
<td></td>
<td>Central Nervous System (including headache and dizziness).*</td>
<td>Hypertension (N=3)</td>
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<td>Infectious or amoebic hepatitis (N=6)</td>
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<td>Tuberculosis (N=3)</td>
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<td>Breast lumps (N=3)</td>
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<td>Other (not specified) (N=5)</td>
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<tr>
<td>Studies in Breastfeeding Women</td>
<td>Levonorgestrel 0.0375</td>
<td>99</td>
<td>Followed-up for 12 months. Age range 17-37 years, mean 26 years. Body weight range 75-149 lbs., mean 101.6. Parity at least 1.</td>
<td>Dizziness 1.0</td>
<td>(See comment in Table 5.)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Loss of appetite and insomnia 1.0</td>
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<td>Loss of weight 2.0</td>
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<td>Total 4.0</td>
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<tr>
<td>Apelo &amp; Veloso 1973 Philippines</td>
<td>Levonorgestrel 0.0375</td>
<td>99</td>
<td>Followed-up for 12 months. Age range 17-37 years, mean 26 years. Body weight range 75-149 lbs., mean 101.6. Parity at least 1.</td>
<td>Dizziness 1.0</td>
<td>(See comment in Table 5.)</td>
</tr>
<tr>
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<td>Loss of appetite and insomnia 1.0</td>
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<td>Loss of weight 2.0</td>
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<td>Total 4.0</td>
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<tr>
<td>Dunson et al. 1993 22 sites in 14 countries</td>
<td>Norgestrel 0.075</td>
<td>4,088</td>
<td>Breastfeeding women were enrolled within 6 months postpartum (74% in first 2 months). Mean age 25.7. Followed for 11 months. No comparison group.</td>
<td>Side effects of OCs (e.g., headaches, nausea): 2.9</td>
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<td>Other medical conditions: 2.6</td>
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<td>Total 5.5</td>
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<tr>
<td>Author, Date, Study Site</td>
<td>Formulation of Progestin-Only Contraceptives (milligrams)</td>
<td>No. of Women</td>
<td>Study Description</td>
<td>% of Users Discontinuing Because of Non-Menstrual Side Effects</td>
<td>Comments</td>
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<tr>
<td>West 1983, Scotland</td>
<td>Norethisterone 0.35</td>
<td>227</td>
<td>227 new, fully breastfeeding, mothers were given detailed information about contraceptive methods prior to discharge. At six months postpartum they were sent questionnaires. 89% replied. 84 had used the POP, with use mainly begun in first 4 weeks after delivery.</td>
<td>Advised by doctor 3.5  Headaches 1.2  Nausea 2.4  Total 7.1</td>
<td></td>
</tr>
</tbody>
</table>

'Most or all of the women in these studies were not breastfeeding.

'Discontinuation rate per 100 women-months.

'Life table discontinuation rate per 100 women. (For Dunson et al., this is 11-month rate).
### TABLE 7

**Selected Studies of Non-Menstrual Side Effects Among Users of Progestin-Only Oral Contraceptives**

<table>
<thead>
<tr>
<th>Author, Date, Study Site</th>
<th>Formulation of Progestin-Only Contraceptive (milligrams)</th>
<th>No. of Women</th>
<th>Study Description</th>
<th>% of Users Reporting Non-Menstrual Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>All Non-Menstrual Side-Effects</td>
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<td></td>
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<td></td>
<td>Headaches</td>
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<td></td>
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<td></td>
<td>Breast Tenderness</td>
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<td></td>
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<td>Nausea</td>
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<td></td>
<td>Dizziness</td>
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<td></td>
<td></td>
<td>Mood Changes, Nervousness, Depression</td>
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<td>Weight Gain</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Other</td>
<td></td>
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<tr>
<td><strong>Studies in Non-Breastfeeding Women</strong></td>
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<tr>
<td>Bisset et al. 1992 Scotland</td>
<td>Norethisterone 0.35</td>
<td>369 Data obtained from family planning clinic records for women who began use 1973-1986. Excluded women who were prescribed POPs but never returned to follow-up. Each segment of POP use treated as a separate case (728 women had 1042 segments of POP use).</td>
<td>2 2 -- -- --</td>
<td>0.7 Premenstrual tension and Premenstrual tension 4 Menopausal symptoms 3 Migraine 0.7 Thromboembolic disease 0.1 Breast pathology (foreign or malignant) 0.5 Ovarian cyst (N=1) Abdominal pain (N=6)</td>
<td>(See comment in Table 5.)</td>
</tr>
<tr>
<td></td>
<td>Ethynodiol diacetate 0.5</td>
<td>332</td>
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<tr>
<td></td>
<td>Norgestrel 0.075</td>
<td>195</td>
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<td></td>
<td>Norelengestrel 0.03</td>
<td>146</td>
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<tr>
<td><strong>Broome &amp; Forderby 1990 England</strong></td>
<td>Norethisterone 0.35</td>
<td>189 Data obtained from family planning clinic records for women who began use 1977-1979. Breastfeeding women excluded. Age at first use: ≤30 26.8%, 31-40 50.2%, 41+ 14.0%. Almost half used POPs for more than 4 years. Clinic records noted dates of menstrual bleeding and whether cycles were regular.</td>
<td>21.5 2.8 11.1 1.4 -- 1.1</td>
<td>2.2 Bleeding 2.8 Leg pain 1.1 Premenstrual tension 0.8 Tenderness 0.3 Premenopausal symptoms 0.3 Vaginal discharge 0.3 Pigmentation 0.3 Pain, discomfort, dizziness 2.2</td>
<td>(See comment in Table 5.)</td>
</tr>
<tr>
<td></td>
<td>Ethynodiol diacetate 0.5</td>
<td>62</td>
<td></td>
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<tr>
<td></td>
<td>Norelengestrel 0.03</td>
<td>27</td>
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<tr>
<td></td>
<td>More than one of above POPs</td>
<td>80</td>
<td></td>
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<tr>
<td><strong>Korke et al. 1974 U.S.</strong></td>
<td>Norgestrel 0.75</td>
<td>2,202 POP was administered continuously for 1-67 cycles and a total of 29,006 cycles. Population studied included women of all ages and all geographical regions of U.S. and reflected a cross-section of all major socioeconomic groups.</td>
<td>44.7 7.0 1.4 2.0 3.3 5.5 --</td>
<td>Abdominal cramps/bloating 3.1 Migraine 0.2 Premenstrual edema 0.7 Vaginal discharge 4.3 Acne 2.1 Leg cramps 1.0 Backache 2.2 Fatigue 2.7 Increased appetite 2.2 Breast enlargement 0.4 Breast acession 0.4</td>
<td>(See comment in Table 5.)</td>
</tr>
<tr>
<td>Author, Date, Study Site</td>
<td>Formulation of Progestin-Only Contraceptive (milligrams)</td>
<td>No. of Women</td>
<td>Study Description</td>
<td>% of Users Reporting Non-Menstrual Side Effects</td>
<td>Comments</td>
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<td></td>
<td>All Non-Menstrual Side-Effects</td>
<td>Headaches</td>
</tr>
<tr>
<td>Lawryn 1982 U.K., Jamaica, New Zealand</td>
<td>Norethisterone 0.35</td>
<td>913</td>
<td>Multicenter study conducted 1970-1981; 11,921 cycles. New patients, patients changing from COCs, and postpartum patients were enrolled; 96% were breastfeeding at study entry, and more than half of these women had not resumed menses. Median age 27 (16-54). Calendar cards used to record tablet taking, bleeding and symptoms.</td>
<td>Cycle 1</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>Norgestrel 0.075</td>
<td>74</td>
<td>Randomized, double-blind clinical trial of 4 POPs; 71 COC (EE 0.1 + MA 2.0) users not randomized but followed-up in parallel. Participants age 18-44 (mean 20-30 for POP groups, 27 for COC users) of proven fertility; no hormone use in last 2 months; normal gynecologic exam; free from chronic liver disease, allergies, epilepsy; no history of thromboembolic disease. Observed at 1, 4, 7, 10 and 13 months. Women recorded pills taken and vaginal bleeding on daily record card.</td>
<td>NA 28</td>
<td>5</td>
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<tr>
<td></td>
<td>Norethisterone acetate 0.3</td>
<td>76</td>
<td></td>
<td>NG 35</td>
<td>11</td>
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<tr>
<td></td>
<td>Megestoral acetate 0.7</td>
<td>80</td>
<td></td>
<td>MA 38</td>
<td>9</td>
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<tr>
<td></td>
<td>Chlormadinone acetate 0.5</td>
<td>77</td>
<td></td>
<td>CA 30</td>
<td>12</td>
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<td></td>
<td></td>
<td>E+MA 27</td>
<td>3</td>
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<tr>
<td>Studies in Breastfeeding Women</td>
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<td></td>
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</tr>
<tr>
<td>Apelo &amp; Veloso 1973 Philippines</td>
<td>Levonorgestrel 0.0375</td>
<td>99</td>
<td>Followed-up for 12 months. Age range 17-37 years, mean 26 years. Body weight range 75-149 lbs., mean 101.6. Parity at least 1.</td>
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<td>35</td>
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<tr>
<td>Author, Date, Study Site</td>
<td>Formulation of Progestin-Only Contraceptive (milligrams)</td>
<td>No. of Women</td>
<td>Study Description</td>
<td>% of Users Reporting Non-Menstrual Side Effects</td>
<td>Comments</td>
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<tr>
<td>Dunson et al., 1993</td>
<td>Norgestrel 0.075</td>
<td>4,088</td>
<td>Breastfeeding women were enrolled within 6 months postpartum (74% in first 2 months). Mean age 25.7. Followed for 11 months. No comparison group.</td>
<td>-</td>
<td>39.0 10.1 14.6 19.1 -</td>
</tr>
<tr>
<td>West 1983 Scotland</td>
<td>Norethisterone 0.35</td>
<td>84</td>
<td>227 new, fully breastfeeding, mothers were given detailed information about contraceptive methods prior to discharge. At six months postpartum they were sent questionnaires; 89% replied. 84 had used the POP, with use mainly beginning in first 4 weeks after delivery.</td>
<td>-</td>
<td>1.0 2.4 - - -</td>
</tr>
</tbody>
</table>

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* = Not reported.

*Most or all of the women in these studies were not breastfeeding.
TABLE 8
Selected Studies of Breastfeeding Performance Among Users of Progestin-Only Oral Contraceptives

<table>
<thead>
<tr>
<th>Author Date, Study Site</th>
<th>Formulation of Progestin-Only Contraceptive (milligrams)</th>
<th>No. of Women</th>
<th>Initiation (Time Post-Partum)</th>
<th>Length of Observation</th>
<th>Criteria Used to Assess Breastfeeding</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begun Within One Week Postpartum</td>
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<tr>
<td>Delgado Betancourt et al. 1984 Mexico</td>
<td>Lynestrenol 0.5</td>
<td>75</td>
<td>≤ 1 week</td>
<td>6 months</td>
<td>Infant weight, length, and head circumference</td>
<td>NSS</td>
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<td></td>
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<td></td>
<td></td>
<td>Maternal assessment of milk production</td>
<td>NSS</td>
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<td></td>
<td>Supplementary feeding</td>
<td>Number of feeds similar for the three groups</td>
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<tr>
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<td>Study discontinuation due to perceived inadequacy of lactation</td>
<td>NSS</td>
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<td></td>
<td>76 copper IUD users and 80 users of other nonhormonal methods. (POP and nonhormonal groups similar on baseline characteristics.)</td>
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<td>All parity 2+ with previous breastfeeding experience.</td>
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<tr>
<td>McCain et al. 1989 Argentina</td>
<td>Levonorgestrel 0.03</td>
<td>250</td>
<td>≤ 1 week</td>
<td>9 months</td>
<td>Infant weight, length, and head circumference</td>
<td>NSS</td>
<td>Within the nonhormonal group, infant growth was similar for users of IUD and other methods. Potential confounding by other variables was considered in weight gain analysis.</td>
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<td>Maternal assessment of milk production</td>
<td>NSS</td>
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<td>Weight gain of unsupplemented infants</td>
<td>NSS</td>
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<td>Maternal assessment of milk production</td>
<td>NSS</td>
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<td>Supplementary feeding</td>
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<td></td>
<td>Discontinuation of breastfeeding</td>
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<tr>
<td>Author</td>
<td>Study Site</td>
<td>Formulation of Progestin-Only Contraceptive (milligrams)</td>
<td>No. of Women</td>
<td>Initiation (Time Postpartum)</td>
<td>Length of Observation</td>
<td>Comparison</td>
<td>Criteria Used to Assess Breastfeeding</td>
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</tr>
<tr>
<td>Moggia et al.</td>
<td>Argentina</td>
<td>Norgestrel 0.075</td>
<td>241</td>
<td>≤ 1 week</td>
<td>6 months</td>
<td>181 IUD-users and 61 users of other non-hormonal methods. (POP and nonhormonal groups similar on baseline characters except that POP infants weighed more.) All parity 2-6, with previous breastfeeding experience.</td>
<td>Infants weight, length, and head circumference</td>
</tr>
<tr>
<td>Abdel-Kader et al.</td>
<td>Egypt</td>
<td>Lynestrenol 0.5</td>
<td>10</td>
<td>6-10 weeks</td>
<td>16 weeks</td>
<td>10 using IUD plus placebo; 30 using combined OCs.</td>
<td>Comparison with pretreatment milk.</td>
</tr>
<tr>
<td>Gupta et al.</td>
<td>India</td>
<td>Norgestrel 0.05</td>
<td>30</td>
<td>6 weeks</td>
<td>4.5 months</td>
<td>Nonhormonal group: 28 using female sterilization and 14 using other methods; 64 using combined OCs (Norgestrel 500 + EE 50 or Norethisterone acetate 1000 + EE 50; pills allocated according to women's endocrine profiles.)</td>
<td>Milk volume by test weighing and breast pump.</td>
</tr>
<tr>
<td>Kamal et al.</td>
<td>Egypt</td>
<td>Lynestrenol 0.5</td>
<td>NR (Total number in study 120)</td>
<td>6-10 weeks</td>
<td>5 months</td>
<td>Women using IUD plus placebo or 3 combined OCs; double-blind. Also, previous breastfeeding experience.</td>
<td>Milk volume by test weighing and breast pump; feed-to-weight adequacy; infant growth curves; age at supplementation and weaning; women's impressions of breast size and fullness and of adequacy of milk supply.</td>
</tr>
<tr>
<td>Author Date, Study Site</td>
<td>Formulation of Progestin-Only Contraceptive (milligrams)</td>
<td>No. of Women</td>
<td>Initiation (Time Post-Partum)</td>
<td>Length of Observation</td>
<td>Comparison</td>
<td>Criteria Used to Assess Breastfeeding</td>
<td>Results</td>
</tr>
<tr>
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</tr>
<tr>
<td>WHO 1988 Hungary &amp; Thailand</td>
<td>Norgestrel 0.075</td>
<td>85</td>
<td>6 weeks</td>
<td>24 weeks</td>
<td>111 nonhormonal method users; 59 using DMPA; 86 using combined OCs (EE 0.03 + LNG 0.15). Random allocation of OC users to POP or COC.</td>
<td>Milk volume by breast pump. Milk composition (fat, nitrogen, lactose). Caloric concentrations, total calories and osmolality. Infant weight, length, triceps fat-fold thickness, ponderal index, arm circumference, head circumference. Study discontinuation because of maternal perception of inadequate breast milk or because of slow infant weight gain.</td>
<td>NSS for comparison with nonhormonal and DMPA groups. Greater volume in POP than COC users. No consistent differences. NSS for caloric concentration. COC users had 35 fewer total calories than other groups because of less volume. NSS for osmolality.</td>
</tr>
<tr>
<td>Begun at Various Times Postpartum</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>West 1983</td>
<td>Norathisterone 0.35</td>
<td>79</td>
<td>Up to 6 weeks</td>
<td>5 months</td>
<td>89 using nonhormonal contraception or no method.</td>
<td>Age at supplementation; duration of breast-feeding.</td>
<td>Duration and age at supplementation similar in both groups.</td>
</tr>
</tbody>
</table>

Source: Table adapted from McCann, et al., 1984.

NSS = Difference between groups was not statistically significant
SS = Difference between groups was statistically significant
NR = Not reported
### TABLE 9

Selected Studies of the Transmission of Progestins in Breast Milk

<table>
<thead>
<tr>
<th>Author, Date, Study Site</th>
<th>Hormone &amp; Dose (in milligrams)*</th>
<th>No. of Women</th>
<th>Initiation (Time Post-partum)</th>
<th>Length of Observation</th>
<th>Ratio of Concentrations in Maternal Plasma and in Milk</th>
<th>Ratio of Concentration in Milk* (ng/ml)</th>
<th>Ratio of Concentration in Milk and Infant Plasma</th>
<th>Peak Concentration in Infant Plasma* (ng/ml)</th>
<th>Ratio of Concentration in Maternal Plasma and Infant Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertrabet et al. 1987 India</td>
<td>Levonorgestrel 0.03</td>
<td>10</td>
<td>6-20 weeks</td>
<td>1 day</td>
<td>100:6</td>
<td>0.05</td>
<td>100:38</td>
<td>0.06</td>
<td>100:2</td>
</tr>
<tr>
<td></td>
<td>Levonorgestrel 0.25 (+ EE 0.05)</td>
<td>15</td>
<td>100:9</td>
<td>0.64</td>
<td>100:12</td>
<td>0.25</td>
<td>100:1</td>
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<td></td>
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<tr>
<td></td>
<td>Norethisterone 3.0 (+ EE 0.05)</td>
<td>15</td>
<td>100:10</td>
<td>2.50</td>
<td>100:8</td>
<td>0.65</td>
<td>100:1</td>
<td></td>
<td></td>
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<tr>
<td>Cooke et al. 1985 England</td>
<td>Ethynodiol diacetate 0.5</td>
<td>12</td>
<td>4-8 weeks</td>
<td>2 days</td>
<td>100:15</td>
<td>0.27*</td>
<td>100:37</td>
<td>0.10*</td>
<td>100:6</td>
</tr>
<tr>
<td>Nilsson et al. 1977 (AJOG) Sweden</td>
<td>Levonorgestrel 0.03</td>
<td>5</td>
<td>8 weeks</td>
<td>&quot;As long as lactation lasted&quot;</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND (N=1)</td>
<td>ND</td>
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<tr>
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<td>Levonorgestrel 0.15 (+ EE 0.03)</td>
<td>5</td>
<td>100:15</td>
<td>0.44</td>
<td>--</td>
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<tr>
<td></td>
<td>Levonorgestrel 0.25 (+ EE 0.05)</td>
<td>5</td>
<td>100:15</td>
<td>0.75</td>
<td>100:15</td>
<td>0.1</td>
<td>100:2</td>
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<tr>
<td>Saxena et al. 1977 UK</td>
<td>Norethisterone 0.35</td>
<td>5</td>
<td>≤ 1 month</td>
<td>1 day</td>
<td>100:18</td>
<td>0.67</td>
<td>--</td>
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<td></td>
<td>DMPPA 150 (injection)</td>
<td>7</td>
<td>1 week</td>
<td>≤ 3 months</td>
<td>100:85</td>
<td>2.16</td>
<td>--</td>
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<tr>
<td></td>
<td>Levonorgestrel 0.15 (+ EE 0.03)</td>
<td>2</td>
<td>100:6</td>
<td>--</td>
<td>--</td>
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<tr>
<td>Shikary et al. 1987 India</td>
<td>Levonorgestrel 0.03</td>
<td>10</td>
<td>4-6 weeks</td>
<td>28 days</td>
<td>100:5</td>
<td>0.05</td>
<td>100:40</td>
<td>0.02</td>
<td>100:2</td>
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<tr>
<td></td>
<td>Levonorgestrel 70 (implant)</td>
<td>14</td>
<td>100:7</td>
<td>0.07</td>
<td>100:69</td>
<td>0.05</td>
<td>100:5</td>
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<tr>
<td></td>
<td>Levonorgestrel IUD 43</td>
<td>14</td>
<td>100:10</td>
<td>0.05</td>
<td>100:65</td>
<td>0.03</td>
<td>100:6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, Date, Study Site</td>
<td>Hormone &amp; Dose (in milligrams)*</td>
<td>No. of Women</td>
<td>Initiation (Time Post-partum)</td>
<td>Length of Observation</td>
<td>Ratio of Concentrations in Maternal Plasma and in Milk</td>
<td>Peak Concentration in Milk* (ng/ml)</td>
<td>Ratio of Concentration in Milk and Infant Plasma</td>
<td>Peak Concentration in Infant Plasma (ng/ml)</td>
<td>Ratio of Concentration in Maternal Plasma and Infant Plasma</td>
</tr>
<tr>
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<td>-------------------------------------------------</td>
<td>------------------------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Thomas et al. 1977 Thailand</td>
<td>Levonorgestrel 0.03</td>
<td>3</td>
<td>2 weeks</td>
<td>4-6 weeks</td>
<td>NR</td>
<td>0.074</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Toddywalla et al. 1980 India</td>
<td>Norethisterone 0.35</td>
<td>4</td>
<td>&gt; 3 months</td>
<td>1 day</td>
<td>100:10</td>
<td>0.4</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Levonorgestrel 0.05</td>
<td>4</td>
<td>&gt; 3 months</td>
<td>1 day</td>
<td>100:10</td>
<td>0.1</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Norethisterone acetate + EE 0.03</td>
<td>4</td>
<td>&gt; 6 months</td>
<td>1 day</td>
<td>100:10</td>
<td>1.0</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td></td>
<td>Levonorgestrel 0.15 + EE 0.03</td>
<td>4</td>
<td>&gt; 6 months</td>
<td>1 day</td>
<td>100:10</td>
<td>0.4</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Norethisterone 25 (implant)</td>
<td>4</td>
<td>6-12 weeks</td>
<td>up to 6 months postpartum</td>
<td>100:10</td>
<td>0.2</td>
<td>--</td>
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<tr>
<td></td>
<td>Levonorgestrel 25 (implant)</td>
<td>4</td>
<td>6-12 weeks</td>
<td>up to 6 months postpartum</td>
<td>100:10</td>
<td>0.1</td>
<td>--</td>
<td>--</td>
<td>--</td>
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</tbody>
</table>

Source: Table adapted from McCann, et al., 1984.

ND = not detectable
-- = not reported
*Administered orally unless otherwise specified.
*Peak concentration in milk for OC users at 2-4 hours after pill ingestion; for implant and injectable users at 1-2 days after administration.
*Peak concentration in infant plasma for OC users at 4-8 hours after pill ingestion.
*Median norethisterone concentrations.
Fig. 1 Mean plasma levels during first 24 hours after oral intake. A, norethindrone 0.35 mg (n=16) (Prasad et al., 1979); B, levonorgestrel 0.03 mg (n=5) (Weiner et al., 1976).
## APPENDIX A

<table>
<thead>
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<td>✓</td>
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<td>✓</td>
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<td>Inability to take correctly when absolute protection needed</td>
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<td>✓</td>
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</table>

1/ During the past three months
2/ Also benign or malignant liver tumors
3/ CV including myocardial infarction; cerebral vascular accident; coronary artery disease; angina
4/ Speroff & Darney also include the following relative contraindications for NORPLANT®: heavy smoking (women over 35); diabetes mellitus; hypercholesterolemia; severe acne; hypertension; gallbladder disease; severe vascular or migraine headaches; severe depression
5/ With high hCG levels
6/ Also includes severe anemia and bleeding disorders or undergoing anti-coagulant therapy
7/ If cysts have been painful

Note: ACOG has no guidelines for POP use; WHO and PPFA are in process of revising theirs.
APPENDIX B

Indications to Use Progestin-Only Oral Contraceptives (☑️) and NORPLANT* ([☐️]) as Explicitly Stated in Selected Contraceptive Use Guidelines

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<td>COC estrogen side effects</td>
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<td>☑️☐️</td>
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<td>(Mild) hypertension</td>
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<td>Obesity</td>
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<td>Hx of thromboembolism/CV disease</td>
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<tr>
<td>To test suitability for NORPLANT*</td>
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</table>

1️⃣ Especially if smokers
 avons chronic systemic diseases where oestrogen should be avoided
3️⃣ If ≥70 kg may need 2 POPs/day
4️⃣ Implant probably has the same effect on lactating women as POPs
5️⃣ Opinions vary as to how soon postpartum to insert NORPLANT*
6️⃣ From six weeks postpartum
7️⃣ When there is past history on pills of - or extreme patient concern about - acne, weight gain, severe headaches, depression, allergy to levonorgestrel

Note: ACOG has no guidelines for POP use; WHO and PPFA are in process of revising theirs.

Goldzieher, Hormonal Contraception, 1989
Guillebaud, Questions Answered, 1993
Hatcher et al., Contraceptive Technology, 1994
Huezo & Briggs, IPPF Guidelines, 1992
INTRAH, Guidelines, 1993
# APPENDIX C

Common Side Effects of Progestin-Only Oral Contraceptives (√) and NORPLANT® (√)
as Explicitly Stated in Selected Contraceptive Use Guidelines

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Menstrual cycle changes¹</td>
<td>✓ (√)⁴</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
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</tr>
<tr>
<td>Breast tenderness</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
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</tr>
<tr>
<td>Headaches</td>
<td>✓ (√)²</td>
<td>✓ (√)²</td>
<td>✓ (√)²</td>
<td>✓ (√)²</td>
<td>✓ (√)²</td>
<td>✓ (√)²</td>
<td>✓ (√)²</td>
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<tr>
<td>Weight gain</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
</tr>
<tr>
<td>Mood changes, nervousness, depression</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
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<tr>
<td>Acne</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
<td>✓ (√)</td>
</tr>
</tbody>
</table>

¹ Amenorrhea, changes in length of cycle, spotting, breakthrough bleeding, etc.
² Less headaches than with combined pill
³ If pregnancy occurs, more likely to be ectopic than with combined OC
⁴ Subjective side effects cannot be adequately evaluated because of the absence of appropriate controls.

Goldzieher, Hormonal Contraception, 1989
Guillebaud, Questions Answered, 1993
Hatcher et al., Contraceptive Technology, 1994
Huezo & Briggs, IPPF Guidelines, 1992
INTRAH, Guidelines, 1993

Note: ACOG has no guidelines for POP use; WHO and PPFA are in process of revising theirs.
## APPENDIX D

### Selected Sources: Instructions for Taking Progestin-Only Oral Contraceptives

<table>
<thead>
<tr>
<th>Instruction Source</th>
<th>When to Start First Packet of POPs/ Daily POP Use</th>
<th>Backup Method Use for 1st Packet of POPs</th>
<th>Switching from COCs to POPs</th>
<th>Switching from POPs to COCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldzieher, J. Starting, Stopping and Switching OCs (Ch.7). Progestin-Only Pills: The “Minipill” (Ch.8). In Hormonal Contraception: Pills, Injections, &amp; Implants (pp. 66-75, 76-80), 1989.</td>
<td>Daily, starting on cycle day one. Take at same time every day, preferable morning. Consistency is important.</td>
<td>If hormonal contraception started properly, no additional backup contraceptive methods necessary during first cycle</td>
<td>Safest to begin them immediately after a conventional OC package has been finished, without a break</td>
<td>Not specified</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Guillebaud, J. Oestrogen-free hormonal contraception: Progestogen-only Pill (POP). In Contraception: Your Questions Answered. 1993 edition.</td>
<td>Take first tablet on the first day of your next period, and start each subsequent packet immediately following the last tablet of the previous one. Women should be encouraged to take their tablets at precisely the same time each day (plus or minus one hour). The best regular pill-taking time is in the early evening, if the woman usually has intercourse when she goes to bed. <strong>Postpartum:</strong> This pill does not increase the risk of blood clots. It can be started as early as the seventh day. Extra bleeding or spotting can be caused by an early start even in breast-feeders. Like the COC, it is usually better to start in the fourth week after birth.</td>
<td>No extra precautions are now advised with a first day start.</td>
<td>Instant switch (at end of packet), no need for extra contraceptive precautions.</td>
<td>First day of period if having bleeds, or ANY DAY that suits her; if she has POP-induced amenorrhea, pregnancy should be excluded.</td>
</tr>
<tr>
<td>Instruction Source</td>
<td>When to Start First Packet of POPs/ Daily POP Use</td>
<td>Backup Method Use for 1st Packet of POPs</td>
<td>Switching from COCs to POPs</td>
<td>Switching from POPs to COCs</td>
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<tr>
<td>Hatcher, R. et al. Norplant, Depo-Provera and Progestin-only pills (Mini-pills). In Contraceptive Technology 1994 (pp.2-43), (in press).</td>
<td>Swallow 1 pill each day until you finish your pill pack. Then start your new pack the next day. Never miss a day. The evening meal may be the best time to take progestin-only pills. Start day not specified. Postpartum: Immediately or at 6 week check-up (whether breastfeeding or not).</td>
<td>Use a back-up method while waiting to start POP's and during your first 7-28 days on 'minipills'.</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Huezo, C.M. &amp; Briggs, C., International Planned Parenthood Federation. Instructions to the Client. In Medical and Service Delivery Guidelines for Family Planning (pp.45-46), 1992.</td>
<td>Take the first pill within the first five days of the menstrual period, preferably the first day. One pill should be taken every day at the same time until the packet is finished; the next packet should be started the following day. Post-partum: If breast feeding, she can start the POP from the 6th post-partum week, but not earlier. If a client with lactational amenorrhoea requests the POP after two months post-partum the POP can be taken if it can be established that she is not pregnant. If not breast feeding, she should start the POP immediately or at any time within the first four weeks post-partum. If the woman wishes to start after the first four weeks post-partum and she has not yet seen the first post-partum menses, the possibility of pregnancy should be ruled out before starting the POP.</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Instruction Source</td>
<td>When to Start First Packet of POPs/ Daily POP Use</td>
<td>Backup Method Use for 1st Packet of POPs</td>
<td>Switching from COCs to POPs</td>
<td>Switching from POPs to COCs</td>
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</tr>
<tr>
<td>(INTRAH) School of Medicine, Univ. of NC-Chapel Hill. Progestin-only pills (POPS). In Guidelines for Clinical Procedures in Family Planning: A reference for trainers. (pp. 69-84), 1992.</td>
<td>Start taking the pills on the first of your period (this is the first day of bleeding). Take one pill at the same time each day even if you do not have sexual relations. <strong>Postpartum:</strong> If you are breastfeeding, and it has been at least 6 weeks since you had your baby, and your periods have not resumed, start your pills today and abstain or use condoms and/or spermicides for the next week.</td>
<td>If pills are begun on day 2 to day 5 of the cycle, use a NON-hormonal method (such as condoms) during the first 2 weeks.</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Speroff, L. &amp; Dansey, P. Special Uses of Oral Contraception: The Progestin-Only Minipill, Emergency Contraception (Ch.3). A Clinical Guide to Contraception (109-116; 117-156, 1992).</td>
<td>The minipill should be started on the first day of menses. The pill should be keyed to a daily event to ensure regular administration at the same time of the day. <strong>Postpartum:</strong> Can be started immediately after delivery.</td>
<td>A backup method must be used for the first 7 days.</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Family Health International (FHI) McCann, M. &amp; Potter, L. The Progestin-Only Pill: A Comprehensive Review, 1994.</td>
<td>Take your first minipill of first pack in first 24 hours of your menstrual period. Take one minipill at same time every day, preferably in late afternoon or at dinnertime, until pack is empty. Do not skip pills. <strong>Postpartum:</strong> If you have just had a baby and are not fully breastfeeding, you should start POPs 3 weeks after delivery. If you are fully breastfeeding, without giving any other foods, you can wait until 3 months after delivery unless you start menstrual bleeding sooner.</td>
<td>No backup contraception is needed since you are starting minipill at the beginning of your period. If breastfeeding, without giving any other food, you need no additional backup method. If you are giving other foods too, use a backup method for the first 48 hours.</td>
<td>If your are switching from another type of pill, take first minipill the day after you finish the last active pill of your other pill pack. (Do not take any of the reminder pills.)</td>
<td>If you switch to combined pills, start the new pills on the first day of your period, even if you have not finished your current pack.</td>
</tr>
</tbody>
</table>
## APPENDIX E

### Selected Sources: Instructions for Managing Missed Progestin-Only Oral Contraceptives

<table>
<thead>
<tr>
<th>Instruction Source</th>
<th>Making Up Missed or Late POPs (Advice by # of Pills Missed or # Hours Late)</th>
<th>When to Use Backup Methods (Types and Duration)</th>
<th>Other Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldzieher, J. Starting, Stopping and Switching OCs (Ch.7). Progestin-Only Pills: The &quot;Minipill&quot; (Ch.8). In Hormonal Contraception: Pills Injections, &amp; Implants (pp. 66-75, 76-80), 1989.</td>
<td>If a pill is forgotten: It should be taken as soon as it is remembered.</td>
<td>If you are more than 3 hours overdue: Additional contraception should be used for that cycle.</td>
<td></td>
</tr>
<tr>
<td>Guillebaud, J. Oestrogen-free hormonal contraception: Progestogen-only Pill (POP). Contraception: Your Questions Answered. 1993 edition.</td>
<td>If you are more than 3 hours late: Take the one you have missed.</td>
<td>If you are more than 3 hours late: Seven (7) days is now recommended as appropriate duration for extra precautions (to be consistent with combined OCs).</td>
<td>Vomiting: Following the new specifications, use extra precautions for 7 days following the illness.</td>
</tr>
<tr>
<td>Hatcher, R. et al. Norplant, Depo-Provera and Progestin-only pills (Mini-pills). In Contraceptive Technology 1994 (pp.2-43), (in press).</td>
<td>If you miss 1 minipill: Take the missed pill as soon as you remember. Also take today's minipill at the regular time even if that means taking 2 pills in 1 day. If you miss 2 or more minipills in a row: Restart your minipills right away and double up for 2 days.</td>
<td>If you are more than 3 hours late: Use your back-up method for the next 48 hours (2 days). If you miss 2 or more minipills in a row: Immediately start using your back-up method.</td>
<td>Vomiting, severe diarrhea or both: Use your back-up method of birth control along with your minipills until 48 hours (2 days) after your illness is over.</td>
</tr>
<tr>
<td>Huezo, C.M. &amp; Briggs, C. International Planned Parenthood Federation. Instructions to the Client. In IPPF's Medical and Service Delivery Guidelines for Family Planning (pp.45-46), 1992.</td>
<td>If you miss a pill: Restart taking the pills as soon as possible.</td>
<td>If you are more than three hours late: Abstain from sexual intercourse or use another method of birth control for the next 48 hours after restarting the pills. May consider postcoital contraception if she has had intercourse during &quot;unprotected&quot; period.</td>
<td>If vomiting and/or diarrhoea should occur: The use of additional contraceptive protection for at least seven days may be required.</td>
</tr>
<tr>
<td>Instruction Source</td>
<td>Making Up Missed or Late POPs (Advice by # of Pills Missed or # Hours Late)</td>
<td>When to Use Backup Methods (Types and Duration)</td>
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</tr>
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</tr>
<tr>
<td>(INTRAH) School of Medicine, Univ. of NC-Chapel Hill. Progestin-only pills (POPS). In Guidelines for Clinical Procedures in Family Planning: A reference for trainers, (pp. 69-84), 1992.</td>
<td>If you miss 1 POP: Take it as soon as you remember and take next POP at the regular time.</td>
<td>If you are more than 3 hours late: Abstain or use condoms and/or spermicides for the next week.</td>
<td>If gastro-intestinal illness impairs absorption, resume minipill as soon as possible and use backup method for 2 days.</td>
</tr>
<tr>
<td></td>
<td>If you miss 2 or more POPs in a row: Take 2 pills as soon as you remember, and 2 the next day.</td>
<td>If you miss 2 or more POPs in a row: Abstain or use condom and/or spermicides for next week in addition to pills. If you don't have period within a month, come to clinic to be checked for pregnancy.</td>
<td>If you vomit soon after taking the minipill, use a back-up method if you have sex in the next 48 hours.</td>
</tr>
<tr>
<td>Speroff L. &amp; Darney, P. Special Uses of Oral Contraception: The Progestin-Only Minipill, Emergency Contraception (Ch.3). A Clinical Guide to Contraception (109-116; 117·156, 1992.</td>
<td>If pills are forgotten: Resume minipill as soon as possible and use backup method for 2 days.</td>
<td>If more than three hours late: A backup method should be used for 48 hours.</td>
<td>If you are still not sure what to do about the pills you have missed: 1. Use a backup method anytime you have sex AND 2. Keep taking one pill at same time each day until you can talk with your doctor or clinic.</td>
</tr>
<tr>
<td>Family Health International (PHI) McCann, M. &amp; Potter, L. The Progestin-Only Pill: A Comprehensive Review, 1994.</td>
<td>If you are more than 3 hours late: Take the next pill as soon as you remember, then continue on your normal schedule.</td>
<td>If you are more than 3 hours late: Use a backup birth control method, such as condoms, foam or sponge, anytime you have sex until 48 hours after you start taking the pill again.</td>
<td>If you missed one or more pills: Follow the same instructions. If you had sex during that time, you may want to ask your doctor or clinic about emergency contraception (but must be within 72 hours of intercourse).</td>
</tr>
<tr>
<td></td>
<td>If you missed one or more pills: Follow the same instructions.</td>
<td>If you missed one or more pills: Follow the same instructions. If you had sex during that time, you may want to ask your doctor or clinic about emergency contraception (but must be within 72 hours of intercourse).</td>
<td>If fully breastfeeding, you do not need a second backup method. If partially breastfeeding, you should follow the instructions for regular POP users.</td>
</tr>
</tbody>
</table>
APPENDIX F

PROPOSED DRAFT

HOW TO TAKE THE PROGESTIN-ONLY ORAL CONTRACEPTIVE "MINIPILLS"

IMPORTANT POINTS TO REMEMBER

THE MINIPILL HAS ONLY ONE HORMONE, A PROGESTIN. IT DOES NOT HAVE ESTROGEN. THEREFORE, IT WORKS IN A DIFFERENT WAY FROM THE COMBINED PILLS AND HAS DIFFERENT RULES FOR CORRECT USE.

1. BE SURE TO READ THESE DIRECTIONS:
   -- Before you start taking your minipills.
   -- Any time you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE MINIPILL IS TO TAKE IT AT THE SAME TIME EVERY DAY.
   -- If you are even 3 hours late taking your minipill YOU COULD GET PREGNANT.
   -- The longer it is after your regular time to take the minipill and the more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN HAVE SOME SPOTTING OR LIGHT BLEEDING WITH THE MINIPILL. THE TIME BETWEEN PERIODS MAY ALSO GET A LITTLE LONGER OR SHORTER. This is normal. However, if you are concerned, check with your doctor or clinic.
   -- Skipping or forgetting minipills also can cause spotting or light bleeding.

4. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE MINIPILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

5. IF YOU TAKE CERTAIN MEDICINES, your minipills may not work as well as they should.
   -- If you take medicine for seizures (except sodium valporate) or if you take medicine for tuberculosis (rifampin or rifampicin), use a back-up method of birth control (such as condoms, foam, or sponge) until you can check with your doctor or clinic. Most medicines, including antibiotics, are not a problem.
   -- Most medicines, including antibiotics, are not a problem when you use the minipill. But ask your doctor or clinic if you have a question about any medicine you take.

6. IF YOU VOMIT SOON AFTER TAKING YOUR MINIPILL, use a back-up method if you have sex in the next 48 hours.

7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.
BEFORE YOU START TAKING YOUR MINIPILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR MINIPILL:

   It is important to **take it at the same time every day**.

   The minipill works best between 3 to 20 hours after taking it. Therefore,
   - If bedtime is when you are most likely to have sex, bedtime is **not** a good time to take the minipill.
   - Late afternoon or dinner time is the best time to take your minipill to be sure it is working at bedtime.
   - Morning is also a good time to take the minipill, and it may be easier to remember to take it as a part of your regular morning routine.

2. BE SURE YOU HAVE READY AT ALL TIMES:

   - **ANOTHER KIND OF BIRTH CONTROL** (such as condoms, foam or contraceptive sponge) to use if you are more than 3 hours late or if you miss any minipills.
   - **AN EXTRA, FULL PACK OF MINIPILLS** so you do not start your next pack late.

WHEN TO START THE FIRST PACK OF MINIPILLS

IF YOU ARE A NEW PILL USER:

1. Take your first minipill of the first pack in the **first 24 hours of your menstrual period**.

2. You will not need to use a back-up method of birth control, since you are starting the minipill at the beginning of your period.

IF YOU ARE BREASTFEEDING:

1. **--** If you are **fully** breastfeeding, that is, providing no formula or other foods, you can wait until 3 months after delivery to start taking minipills, although you can safely start earlier. If your menstrual periods return or you start giving your baby formula or other foods before 3 months, start taking minipills right away.

2. **--** If you are breastfeeding but also giving your baby formula or other foods, you should start taking minipills **3 weeks** after your baby is born, although you can safely start earlier.

IF YOU HAVE JUST HAD A BABY BUT ARE NOT BREASTFEEDING:

You should start taking minipills **3 weeks** after your baby is born, although you can safely start earlier.

IF YOU HAVE HAD A MISCARRIAGE OR ABORTION:

You can start the minipill the next day.

IF YOU ARE SWITCHING FROM ANOTHER TYPE OF PILL:

If you are switching from the combined pill, take the first minipill the day after you finish the last active hormone pill of your other pill pack. **Do not take any of the reminder pills** (the last 7 in the combined pill pack).

Your bleeding patterns may be a little less regular when taking the minipill.
ONCE YOU START USING MINIPILLS

1. TAKE ONE MINIPILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY:
   -- Remember that all 28 minipills are active pills; there are no placebo ("reminder" or "sugar") pills.
   -- Do not skip pills, even if you have bleeding between monthly periods or even if you don't have your monthly period.
   -- Do not skip any minipills, even if you do not have sex very often.
   -- Take the minipill at the same time each day, preferably in the late afternoon or at dinnertime.

2. WHEN YOU FINISH A PACK OR CHANGE YOUR BRAND OF PILLS:
   -- Start the next pack on the day after your last minipill. Do not wait a single day between packs.

3. IF YOU MISS MORE THAN ONE MENSTRUAL PERIOD:
   -- Check with your doctor or clinic about getting a pregnancy test.
   -- Do not stop taking your minipills unless you know you are pregnant.

WHAT TO DO IF YOU MISS MINIPILLS

IF YOU ARE LESS THAN 3 HOURS LATE TAKING A MINIPILL:
1. Take the next pill as soon as you remember, then continue on your normal schedule.
2. You do not need to use a back-up birth control method.

IF YOU ARE MORE THAN 3 HOURS LATE TAKING A MINIPILL:
1. Take the next pill as soon as you remember, then continue on your normal schedule.
2. Use a back-up birth control method (such as condom, foam or contraceptive sponge) anytime you have sex until 48 hours after you start taking the pill again.

IF YOU MISS ONE OR MORE MINIPILLS:
1. The more pills you miss the more likely you are to get pregnant.
2. Take the next pill as soon as you remember, then continue on your normal schedule.
3. Use a back-up birth control method (such as condom, foam or contraceptive sponge) anytime you have sex until 48 hours after you start taking the pill again.
4. If you had sex during that time, you may want to ask your doctor or clinic about using emergency contraception (the "morning after" pill). You must take this within 72 hours of having sex.
IF YOU ARE BREASTFEEDING:

1. If your baby is less than 6 months old and the baby is not getting anything to eat or drink except breastmilk and you have not yet started having menstrual periods since delivery, then breastfeeding itself is your back-up birth control method.

2. If your baby is more than 6 months old or if the baby is getting formula or other foods in addition to breastmilk or if you have started having menstrual periods since delivery, then breastfeeding is not an effective back-up method. Therefore, you should follow the instructions above about using a back-up method, such as a condom, if you miss any minipills.

IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE MINIPILLS YOU HAVE MISSED:

1. Keep taking one minipill at the same time each day AND
2. Use a back-up birth control method anytime you have sex UNTIL
3. You can talk with your doctor or clinic.

IF YOU MISS MORE THAN ONE MENSTRUAL PERIOD:

1. Check with your doctor or clinic about getting a pregnancy test. Do not stop taking your minipills unless you know you are pregnant.
2. If you do find you are pregnant, it is important to know that the minipill does not affect your baby in the early months of pregnancy.

IF YOU WANT TO STOP OR SWITCH PILLS

1. If you want to stop taking the minipills, you can do so at any time during your cycle.
2. If you want to switch to another brand of minipills: Just start the new brand after you finish the last minipill in your current pack.
3. If you want to switch to combined pills: Start the new pills on the first day of your period, even if you have not finished your current pack.
4. If you are breastfeeding, you can switch to another method of family planning at any time BUT do not switch to combined pills until you stop breastfeeding.
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497. WHO Collaborative Study of Neoplasia and Steroid
Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and

498. WHO Collaborative Study of Neoplasia and Steroid
Contraceptives. Endometrial cancer and combined oral

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Contraceptives. Epithelial ovarian cancer and combined oral

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Contraceptives. Invasive cervical cancer and combined oral

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contraception: A multicentre clinical trial: 3. The
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groups of oral combined contraceptive users and a control

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Regulation. A multicentre comparative study of serum lipids
and apolipoproteins in long-term users of DMPA and a control

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blind study of two combined and two progestogen-only oral


