Jadelle® Levonorgestrel Rod Implants: A Summary of Scientific Data and Lessons Learned from Programmatic Experience

Irving Sivin, Harold Nash, and Sandra Waldman

POPULATION COUNCIL NEW YORK

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50 YEARS 1952–2002
Population Council

The Population Council is an international, nonprofit, nongovernmental institution that seeks to improve the well-being and reproductive health of current and future generations around the world and to help achieve a humane, equitable, and sustainable balance between people and resources. The Council conducts biomedical, social science, and public health research and helps build research capacities in developing countries. Established in 1952, the Council is governed by an international board of trustees. Its New York headquarters supports a global network of regional and country offices.

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ACKNOWLEDGMENTS

Many people and organizations contributed to the more than three decades of research, development, and introduction of levonorgestrel (LNG) contraceptive implants—both the Jadelle® rods and the earlier Norplant® capsules. Colleagues in the Population Council's Center for Biomedical Research (CBR) and the International Committee for Contraception Research (ICCR) developed the implant concept and tested the two methods in clinical trials. Public health experts in the Council's International Programs Division field-tested Norplant in preintroduction and acceptability studies.

Norplant capsule and Jadelle rod development and introduction involved collaboration among a number of international technical assistance agencies, research institutions in developed and developing countries, and pharmaceutical companies—Leiras Oy in Finland and Wyeth-Ayerst Laboratories in the United States. Other principal collaborators in the initial Norplant capsule introduction efforts included EngenderHealth (formerly AVSC International), Family Health International (FHI), the Program for Appropriate Technology in Health (PATH), and the World Health Organization (WHO). Investigators from international training centers as well as clinics in many countries contributed to the wealth of scientific data that document the Norplant method. Their work was described in a 1990 monograph, *Norplant® Levonorgestrel Implants: A Summary of Scientific Data*, and is included in the extensive bibliography at the end of this monograph. Organizations involved in Jadelle rod training activities include EngenderHealth, Pathfinder, JHPIEGO, and the Population Council.

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ABOUT THIS MONOGRAPH

This scientific monograph provides a comprehensive summary of the clinical characteristics of Jadelle levonorgestrel (LNG) rod implants, as observed during clinical trials conducted by the Population Council. The monograph also reviews lessons learned about how to provide Jadelle, based partly on conclusions gleaned from the extensive experience with Norplant, the earlier implant system, and suggests practical ways in which to introduce Jadelle into family planning programs. The extensive question-and-answer section presents some of the scientific information in an easy-to-understand format that serves as a counseling tool. The section includes language from the Jadelle product labeling and also reflects the postmarketing, as well as clinical, experience with Norplant. In addition, the monograph summarizes new results from a five-year postmarketing study of Norplant in eight developing countries—information with direct relevance to Jadelle. Finally, a bibliography documents the extensive published research about contraceptive implants over more than four decades.

The monograph is written for health care professionals and policymakers interested in learning more about Jadelle as a possible addition to the contraceptives available in national family planning programs and in private practice.

DEVELOPMENT AND INTRODUCTION OF CONTRACEPTIVE IMPLANTS

The Population Council has devoted more than 30 years to the invention, development, and introduction of contraceptive implants—Norplant* capsules and Jadelle* rods. Through this extended undertaking, the Council not only developed a new form of reversible, long-acting contraception but also pioneered a careful process of new method introduction, with attention to research, training, counseling, and consumer information.

Several hundred steps went into implant invention and development. Basic research determined the feasibility of the concept: which steroids were best suited for an implant system, how many capsules or rods would be needed, the dimensions and thickness of the implant walls and the inner core of the rods, and the optimum release rate and blood level for safe and effective contraception. Wyeth-Ayerst Laboratories had earlier conducted animal and toxicology studies on its synthetic progestin, levonorgestrel, and Dow Corning had conducted animal studies and human trials with its silicone rubber elastomer. The Council also gained access in later stages of development to National Institutes of Health toxicology studies involving continuous levonorgestrel release by implants in animal systems. Although the Council did not have to duplicate previously conducted studies, challenging tasks remained: to conceive of subdermal implants as a mode of delivering contraceptive steroids; to design implants with doses presumed to prevent pregnancy; and to conduct and analyze studies demonstrating safety, effectiveness, and acceptability.

A team of scientists at the Population Council's Center for Biomedical Research (CBR) accomplished the day-to-day development of both Norplant and Jadelle, working closely with the network of clinical investigators of the Council's International Committee for Contraception Research (ICCR). The project was under the leadership, first, of Sheldon J. Segal, who was director of biomedical research from 1963 to 1978, and later of C. Wayne Bardin, who succeeded Segal and served as director through 1995. The current director is Elof Johansson, who was a member of the ICCR when implant research was initiated.

*Norplant® is the registered trademark of the Population Council for levonorgestrel subdermal implants. Jadelle® is the registered trademark of Leiras Pharmaceuticals (Turku, Finland) for levonorgestrel rods.

Research and development

The research and development program that produced contraceptive implants—the implants had no brand names until they became products much later—began in 1966 in the Population Council's biomedical research laboratories when scientists initiated laboratory investigations on the release of steroid hormones from silicone rubber capsules. Their results showed that the continuous release of hormones could be sustained for long periods, and that hormonal effects in animals could be maintained for over a year. These results formed the basis of the implant concept: that an appropriate contraceptive steroid, placed under the skin in silicone tubing, could provide effective contraception for many years, and that a single act of contraceptive acceptance could replace more than a thousand days of pill taking (Segal 1983; International Development Research Centre 1990).

By late 1974, studies had been started in humans of a six-capsule contraceptive drug delivery system. Several synthetic hormones were compared and evaluated. The next year a randomized clinical trial testing implants containing three different hormones was initiated in six countries (Brazil, Chile, Denmark, Dominican Republic, Finland, and Jamaica). A six-capsule implant system containing levonorgestrel emerged as the best of the three, on the basis of effectiveness, clinical acceptability, and safety. The drug's safety was supported by extensive animal studies and by large-scale human studies conducted by Wyeth-Ayerst Laboratories, which marketed oral contraceptives containing levonorgestrel.

Two delivery systems and two variations of capsules and rods

Although the levonorgestrel capsules were in clinical trials by 1975 and appeared to be safe, effective,

and acceptable, scientists believed that development of a method with fewer than six implants would make insertion and removal easier and would therefore be beneficial. While still studying Norplant implants, CBR scientists found that a silicone cover on a solid rod composed half of levonorgestrel, half of silicone elastomer, increased the rod's physical strength and gave a more constant pattern of steroid release. By 1977, a small trial of rods containing levonorgestrel was underway. Over the next few years, clinical pharmacology studies and clinical trials were started and mechanized production methods for the rods were worked out.

By 1982, CBR scientists working in conjunction with Leiras for industrial-scale production had designed and produced a new rod system. Using two 4 cm rod implants, this system was designed to release the same dose of levonorgestrel as did the original six-capsule system for sustained time periods.

A technical evaluation of Norplant by the World Health Organization in 1984 concluded that the implants are an "effective and reversible long-term method of fertility regulation." The contraceptive, the report said, was "particularly advantageous to women who wish an extended period of contraceptive protection" (WHO 1985).

In 1987, as the Council prepared a New Drug Application (NDA) for the rod system, then called Norplant-2, production ceased of a component (Medical Grade Elastomer 382) critical to the manufacture of the rods. The Council began immediately to reformulate the rod system, using similar elastomers that are safe for human use. Thus, work on a reformulated Norplant-2 continued even as Norplant capsules neared approval by the U.S. Food and Drug Administration (FDA).

The Norplant capsule system also had undergone changes. There were two formulations of the capsules, one with softer, less dense tubing than the other. The New Drug Application, submitted in 1988, contained data about experience with both kinds of tubing; earlier testing had been conducted with the denser tubing, while later testing was conducted with the softer tubing that was to become the world standard. Clinical studies had shown both kinds of tubing to be safe and effective with diverse groups of women. The FDA approved soft-tubing Norplant in December 1990 for use up to five years. In 2000, the Population Council published data showing that Norplant was safe and effective for up to seven years (Sivin, Mishell, Diaz et al. 2000). The data were submitted to the FDA in December 2000.

An estimated 10.5 million sets of implants have been distributed worldwide since Norplant went on the market in 1984. Norplant has achieved regulatory approval in more than 60 countries.

Studies comparing Norplant and the new, reformulated levonorgestrel rods were initiated in 1990. The trial, which involved 2,800 women in seven countries, was supported by Wyeth-Ayerst Laboratories (the U.S. distributor of the Norplant system), USAID, the Mellon Foundation, and UNFPA. A submission for FDA approval of the rods as a method for three years' use was filed in June 1995. Although FDA approval for marketing was gained in 1996, the clinical trial continued to gather data on effectiveness and safety for up to five years' use. In July 2001, the FDA gave tentative approval for extension of the period of use to five years. In Finland, regulatory authorities approved the rods—now called Jadelle—for three years in 1997 and, in 2000, extended the period of use to five years. In 2001, Jadelle was approved as a five-year method in France, Iceland, Luxembourg, the Netherlands, Norway, Spain, and Sweden. Jadelle is approved as a three-year method in Indonesia and Thailand.

Introduction activities

By 1980, with laboratory research and development of Norplant capsules essentially completed, the Council began to address some of the issues critical to the introduction of the method, to ensure that the new contraceptive would be offered in a balanced and culturally sensitive way (Spicehandler 1988). The end of Norplant development and the beginning of introduction overlapped by several years: the early 1980s included trials to gain additional data for regulatory filings in some countries and the special preintroduction studies that are a hallmark of the Council's introduction of the method. From a medical standpoint, the implant system is a very simple method: long-acting, effective, convenient, and reversible. But, from a service delivery perspective, implants are complicated

because much depends on the preparations a family planning program makes before the first set of capsules or rods is inserted into the first woman's arm. That is where the contraceptive introduction program played an important role.

Introduction activities included support for three international training centers: in-country training of health care providers; development of prototype informational materials; and user-related research. Following incorporation of implants into national family planning programs, the Council worked with health ministries and other organizations to assess how services have been provided and how they could be improved.

Norplant preintroduction studies

Working with other agencies, the Council initiated a series of preintroduction trials—altogether more than 30—to evaluate the effectiveness, safety, and acceptability of the method under local conditions. Preintroduction studies were an innovation of Norplant implant introduction. They helped national programs and health care providers evaluate the method in specific settings and provided a mechanism to transfer the training skills for proper use of the method. Where local experience was required for regulatory approval, the studies provided data to further inform governmental authorities about the method. They provided a basis for assessment of user and programmatic needs in different cultural and socioeconomic situations. They also served as a way to develop and test local management practices for responsible incorporation of the method into family planning programs and to disseminate informational materials.

Introduction of Jadelle

Because of the extensive experience with implants in many countries, Jadelle does not need to undergo the same kind of preintroduction studies as Norplant did. Information is needed, however, on how family planning programs that already provide Norplant can make the transition to offering Jadelle. The Council in collaboration with local partners initiated transition studies in the Dominican Republic and Guatemala. The Dominican Republic has had a successful implant program for years, while Guatemala has offered Norplant only for the past year. These transition studies were designed to discover the best ways family planning programs can provide Jadelle. The studies will evaluate the system readiness, training requirements, clinical performance, and acceptance of Jadelle implants when offered as an additional contraceptive option, or as an option i n place of Norplant. In this way, family planning providers, program managers, and planners can begin to develop knowledge of how to ensure a smooth transition to newer technologies. The studies will provide key information about which interventions are necessary to prepare the service delivery system to provide Jadelle with the highest quality services.

The transition studies will not only provide information to register Jadelle in these two countries, they will also determine whether the service delivery systems are ready to offer implants with high-quality care and establish what activities should be added or altered to optimize the introduction of Jadelle. Finally, the studies will examine the impact of the addition of a new, reversible implantable hormonal method on the total acceptance of reversible methods, as well as the influence of the introduction of Jadelle on the quality of contraceptive services.

Lessons learned from the introduction of Norplant capsules into different health delivery systems have accentuated the need for training of providers in insertion and removal techniques and counseling; provision of full information through counseling and informational materials for clients on implants and other available contraceptive methods; supervision of providers; development and implementation of a client-tracking system; and ongoing program evaluation. For more information, see the section in this monograph titled "Recommendations for introducing Jadelle into developing-country family planning programs: Lessons learned from the Norplant experience."

In countries with no prior experience with Norplant implants, the Council and other groups will help evaluate the needs of women for a long-acting contraceptive method and the ability of the health delivery systems to provide implant services with the highest quality possible. The countries that participated in Norplant and Jadelle trials and other studies are listed on page 4.

Countries with Norplant and Jadelle experience, 1980–2001

Norplant clinical trials: 13 countries

Brazil, Chile, Denmark, Dominican Republic, Finland, Jamaica, Sweden, United States (PC/ICCR);* Colombia, Ecuador, Egypt, Indonesia, Thailand (PC)

Jadelle clinical trials: 7 countries

Chile, Dominican Republic, Egypt, Finland, Singapore, Thailand, United States (PC/ICCR)

Norplant preintroduction studies: 30 countries, 1984 through 1990

Bangladesh, Brazil, Chile, China, Dominican Republic, Haiti, Kenya, Nepal, Nigeria, Philippines, Singapore, Sri Lanka, Zambia (1984–85); Colombia, El Salvador, Ghana, Malaysia, Mexico, Pakistan, Peru, Senegal, South Korea, Tunisia, Venezuela, Zambia (1986–88); Bahamas, Rwanda, Zaire (1989); Bolivia, Madagascar (1990)

Jadelle transition studies: 2 countries (starting 2001)

Dominican Republic, Guatemala

Norplant private-sector training: 8 countries

Belgium, Bulgaria, France, Israel, Soviet Union, Taiwan, West Germany (Leiras, 1988); United States (Wyeth-Ayerst, 1990)

Norplant postmarketing surveillance: 8 countries (UNDP/UNFPA/WHO/HRP,* Population Council, FHI*)

Bangladesh, Chile, China, Colombia, Egypt, Indonesia, Sri Lanka, Thailand

Norplant training curriculum testing: 3 countries

Kenya, Nigeria, Rwanda

Norplant international training centers: 3 countries

Dominican Republic, Egypt, Indonesia

Norplant regional training center: 1 country

Kenya

Norplant acceptability studies: 20 countries (Population Council, PATH,* FHI)

Bangladesh, Brazil, China, Colombia, Dominican Republic, Ecuador, Egypt, Haiti, Indonesia, Kenya, Mexico, Nepal, Nigeria, Peru, Philippines, Rwanda, Sri Lanka, Thailand, United States, Zambia

Norplant regulatory approvals: 62 countries since 1983

Bahrain, Bangladesh, Botswana, Burkina Faso, Canada, Chile, China, Colombia, Costa Rica, Cyprus, Czech Republic, Dominican Republic, Ecuador, Egypt, Ethiopia, Finland, France, West Germany, Ghana, Greece, Haiti, Indonesia, Iran, Israel, Jamaica, Jordan, Kenya, Kuwait, Luxembourg, Madagascar, Malawi, Malaysia, Mali, Mauritius, Mexico, Nepal, Netherlands, Nigeria, Pakistan, Palau, Peru, Philippines, Russia, Rwanda, Senegal, Singapore, Slovak Republic, South Africa, Sri Lanka, Sweden, Switzerland, Syrian Arab Republic, Taiwan, Tanzania, Thailand, Uganda, United Kingdom, United States, Venezuela, Vietnam, Zambia, Zimbabwe

Jadelle regulatory approvals: 11 countries

United States (1996); Finland (1997); Indonesia, Thailand (2000); France, Iceland, Luxembourg, Netherlands, Norway, Spain, Sweden (2001)

*Collaborating organizations:
PC: Population Council and the ICCR: International Committee for Contraception Research
FHI: Family Health International
PATH: Program for Applied Technology in Health
UNDP/UNFPA/WHO/HRP: World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction

Chronology of important events in the development of Norplant and Jadelle, 1966–2001

(Events related to Jadelle are indicated in italicized type)

1966 Research and development program begins in the laboratories of the Population Council.

1968 First clinical experience with a progestin released from silicone rubber capsules is reported in Santiago, Chile.

1974 Six-capsule silicone rubber drug delivery system is developed. First clinical studies begin in Chile. *Work proceeds on levonorgestrel (LNG) rod implants.*

1975 Multinational Phase 3 trial of capsule method is initiated in Brazil, Chile, Denmark, Dominican Republic, Finland, and Jamaica. Trial is monitored by the Population Council's International Committee for Contraception Research (ICCR).

1977 *Limited trial of LNG rod begins.*

1980–1982 Trials of Norplant capsules begin in Colombia Ecuador, Egypt, India, Indonesia, and Thailand. Phase 2 and 3 and clinical pharmacology studies begin in the United States. *Multinational clinical trial comparing Norplant and LNG rods (original version) begins in Chile, Dominican Republic, Finland, Sweden, and United States.*

1983 Leiras Oy, of Finland, is licensed to manufacture and distribute Norplant capsules. Finland becomes the first country to give regulatory approval to the method.

1984 The World Health Organization (WHO) evaluates the Norplant method in response to a request for a technical evaluation by the United Nations Population Fund (UNFPA). WHO concludes that Norplant implants are an "effective and reversible long-term method of fertility regulation... particularly advantageous to women who wish an extended period of contraceptive protection."

1984–1985 Preintroduction trials begin in Bangladesh, China, Ghana, Haiti, Kenya, Nepal, Nigeria, Philippines, Sri Lanka, and Zambia. Ecuador, Indonesia, and Sweden approve Norplant. The International Planned Parenthood Federation includes Norplant on the commodities list made available to its affiliates.

1986–1987 Norplant is approved by Colombia, Dominican Republic, Peru, Sri Lanka, Thailand, and Venezuela.

1988 Norplant is approved by Chile. The Population Council files for U.S. FDA approval of Norplant. Five-year postmarketing surveillance of Norplant capsules is started in eight developing countries.

1989–1990 Norplant is approved in Bangladesh, China, Czech Republic, Haiti, Kenya, Malaysia, Nepal, Singapore, and Tunisia. Norplant is approved in the United States in December 1990.

1990 *Jadelle clinical trials begin in Chile, Dominican Republic, Egypt, Finland, Singapore, Thailand, and United States.*

1991–1992 Norplant is approved in Jamaica, Mali, Mauritius, Mexico, Pakistan, Palau, Russia, Rwanda, and Taiwan.

1993–1994 Norplant is approved in Bahrain, Canada, Costa Rica, Egypt, France, Ghana, Iran, Luxembourg, Madagascar, Malawi, Philippines, Romania, Senegal, South Africa, Tanzania, and United Kingdom.

1995 *Application for approval of Jadelle is made to the U.S. Food and Drug Administration.*

continued

Chronology *(continued)*

1995–1996 Norplant capsules are approved in Burkina Faso, Cyprus, Denmark, Greece, Germany, Israel, Kuwait, Netherlands, Switzerland, Zambia, and Zimbabwe. *Jadelle is approved in the United States as a three-year method.*

1997 *Jadelle is approved in Finland as a three-year method.*

2000 *Jadelle use is extended to five years' use in Finland and for three years' use in Indonesia and Thailand. The U.S. FDA is asked to extend Jadelle use to five years. Leiras introduces its pre-loaded, disposable inserter for Jadelle.* The Council submits seven-year data for Norplant to the FDA.

2001 *Jadelle is approved for five years' use in France, Iceland, Luxembourg, Netherlands, Norway, Spain, and Sweden. In July, the FDA sends an approvable letter extending Jadelle use to five years in the United States. Jadelle transition studies begin in the Dominican Republic and Guatemala.*

HIGHLIGHTS OF CLINICAL PERFORMANCE OF JADELLE IMPLANTS

Summary of characteristics

Indications: long-term reversible method of contraception indicated for prevention of pregnancy

Active ingredient: levonorgestrel

Annual pregnancy rate per 100 users in clinical trials: 0.1 for each of years 1 through 3, 0 for year 4, 0.8 for year 5

Cumulative pregnancy rate in clinical trials: 3 years: 0.3; 5 years: 1.1

Duration of use: 5 years (Finland and other European countries); 3 years (United States, but the FDA in July 2001 indicated extending duration of use to 5 years is approvable subject to agreement on labeling and quality assurance concerns)

Release rate: 100 µg/day at 1 month, declining to about 40 µg/day at 12 months, and stabilizing at about 30 µg/day at 24 months and thereafter

Return to fertility: In the year following removal, pregnancy rates are comparable to those for women of similar age using no contraception

Continuation rates in clinical trials: 1 year: 88.3 per 100; 3 years: 60.6 per 100; 5 years: 41.5 per 100; average use 3.35 years through the end of 5 years

Mechanisms of action: inhibition of ovulation, thickening of cervical mucus

Most frequently reported side effects: In addition to bleeding irregularities, 10 percent or more of women in clinical trials reported these adverse reactions: headache, dizziness, weight gain, infection/pain at implant site, leukorrhea, mastalgia, nausea, pelvic pain, urinary tract symptoms/infection, and vaginitis. Other frequently reported side effects related to Jadelle use were nervousness; acne, hair loss, and other skin and hair disorders; and ovarian cyst or follicle enlargement (see Table 5 for additional adverse events).

Clinical pharmacology: no clinically significant unfavorable changes in liver, kidney, adrenal, or thyroid function. Lipoproteins: decreases in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides but no clinically significant change in ratio of HDL to total cholesterol

Contraindications: known or suspected pregnancy; active thrombophlebitis or thromboembolic disorders; undiagnosed abnormal genital bleeding; acute liver disease, benign or malignant liver tumors; known or suspected breast cancer; history of idiopathic intracranial hypertension; hypersensitivity to levonorgestrel or any of the components of Jadelle

Provision: rods are inserted under the skin in the woman's upper arm through a small incision and are removed through the same incision

STD protection: no known protection against HIV/AIDS or other sexually transmitted diseases

Components

Jadelle is a set of two flexible cylindrical implants consisting of a dimethylsiloxane/methylvinylsiloxane copolymer core enclosed in thin-walled silicone tubing. Each rod contains 75 mg of the progestin levonorgestrel. The core of each rod is a mixture, half of levonorgestrel, half of the elastomer. The rods are sealed with polydimethylsiloxane adhesive and sterilized. Each rod is approximately 2.5 mm in diameter and 43 mm in length.

By comparison, the Norplant system consists of six flexible silicone capsules containing levonorgestrel in dry, crystalline form packed within the rubber tubing and sealed at each end by polydimethylsiloxane medical adhesive and sterilized. Each capsule contains 36 mg of levonorgestrel and is 2.4 mm in diameter and 34 mm long (see Figure 1).

Jadelle is a progestin-only product and does not contain estrogen. The sole active ingredient in the rods is levonorgestrel (-)-13-ethyl-17-hydroxy-18, 19-dinor-17α-pregn-4-en-20-yn-3-one. It has a molecular weight of 312.45 and the structural formula shown in Figure 2.

Medical grade silicone rubber materials, including the type used in Jadelle, have been employed in various implantable devices for humans since 1950.

These implants have included prosthetic devices, heart valves, and drainage tubes. Silicone rubber was chosen for use in Norplant capsules and Jadelle rods because it is soft and flexible. Levonorgestrel diffuses through it at a rate that delivers an appropriate contraceptive dose over a period of years; there is long experience with its use in contact with tissues.

Preclinical evaluation

Pharmacology

Levonorgestrel is a totally synthetic and biologically active progestin that exhibits no significant estrogenic activity and is highly progestational. It is the progestational ingredient in many oral contraceptives. The absolute configuration conforms to that of D-natural steroids. Levonorgestrel delivered subdermally is not subject to a "first-pass" effect through the liver and is virtually 100 percent bioavailable (Back, Bates, Breckenridge et al. 1989; Humpel, Wendt, Pommerenke et al. 1978).

Release rates of levonorgestrel

Release of levonorgestrel sufficient to prevent conception is reached within 24 hours after placement of the rods and is maintained at an effective rate for five years. First-month pregnancies may occur if the implants are placed sufficiently late in the follicular stage so that ovulation is not blocked.

Diffusion of levonorgestrel from the rods provides a continuous low dose of the progestin. Resulting blood concentrations are substantially below those generally observed among users of combination oral contraceptives containing the progestins norgestrel or levonorgestrel.

The calculated mean *in vivo* release rate of levonorgestrel provided by Jadelle is about 100 µg/day at one month, declining to about 40 µg/day at 12 months and to about 30 µg/day at 24 months, stabilizing thereafter at about 30 µg/day (Leiras 2000).

Blood levels

Levonorgestrel is delivered directly into interstitial fluids from the subcutaneous implants. However, the bioavailability of levonorgestrel after insertion of Jadelle rods compared with intravenous administration is not known. After placement of Jadelle rods, levonorgestrel concentrations reach a maximum, or near maximum, level within two to three days after

Figure 1. Composition of Jadelle and Norplant

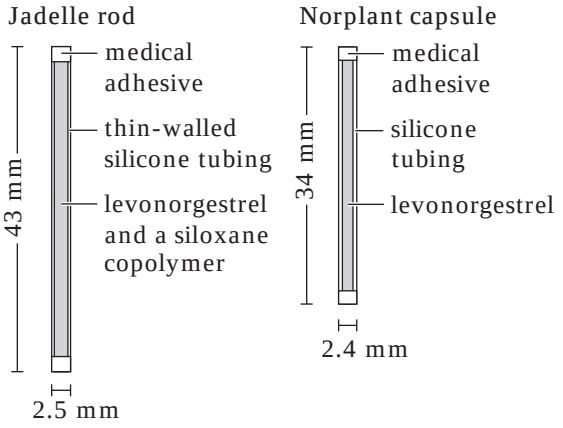
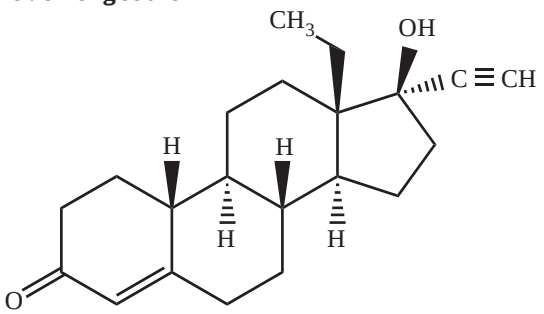


Figure 2. Structural formula of levonorgestrel



placement, with mean values of 772 ± 414 pg/mL at two days (Sivin, Lähteenmäki, Ranta et al. 1997). They decline rapidly over the first month both because of a decrease in the rate of release and because of decreased circulating levels of sex hormone binding globulin (SHBG), a protein that binds levonorgestrel. Mean levonorgestrel concentrations slowly decline to 435 ±172 pg/mL at one month (see Table 1), 357±155pg/mL at six months, and 280±123 pg/mL at three years. Concentrations at four and five years are similar to those at three years (Sivin, Wan, Ranta et al. 2001).

Serum levonorgestrel concentrations show considerable variation among women, depending on individual metabolic clearance rates, body weight, and other factors. Serum concentrations alone are not predictive of the risk of pregnancy in an individual woman. Levonorgestrel concentrations in Jadelle users are substantially below those generally observed in users of oral contraceptives containing norgestrel or levonorgestrel.

Table 1. Serum concentration of levonorgestrel with Jadelle rods

Time after placement (months)	Mean ± SD (pg/mL)	n
1	435 ± 172	181
3	393 ± 191	165
6	357 ± 155	160
12	340 ± 159	148
24	312 ± 153	126
36	280 ± 123	89
48	271 ± 126	67
60	279 ± 123	65

Levonorgestrel serum concentrations are inversely related to body weight. For example, serum levonorgestrel concentrations in women weighing more than 70 kg were approximately half those in women weighing less than 50 kg (Affandi, Suherman, Djajalelana et al. 1987; Fotherby 1995). It has been suggested that some individual variations—possibly fibrous encapsulation, local capillarity, or local body fat—may reduce levonorgestrel release from the implants. Women vary in their rates of levonorgestrel metabolism and in their levels of SHBG that bind to levonorgestrel (Weiner and Johansson 1976).

Distribution

Levonorgestrel in serum is primarily protein bound. Approximately half is bound to albumin and a little less is bound to sex hormone binding globulin. SHBG concentrations are depressed by levonorgestrel within a few days of administration, with resultant decreases in circulating levonorgestrel concentrations.

Metabolism

Levonorgestrel metabolic pathways have been only partially delineated. 16ß-hydroxylation is an identified pathway of metabolism. Concentrations of metabolites in circulation soon exceed those of levonorgestrel, mostly as conjugated sulfates. Metabolic clearance rates may differ among individuals by several fold; this fact is believed to account in part for the wide variation observed in levonorgestrel serum concentrations among implant users.

Excretion

After removal of the implants, levonorgestrel concentrations decrease below 100 pg/mL by 96 hours and below sensitivity of the assay by five days to two weeks. The elimination half-life of levonorgestrel is approximately 13 to 18 hours (Sisenwine, Kimmel, Liu et al. 1975). Levonorgestrel and its metabolites are primarily excreted in the urine (40 percent to 68 percent) and a lesser amount in the feces (16 percent to 48 percent).

Mechanisms of action

The mechanisms of action of Norplant capsules and Jadelle are the same, since the two dosage forms provide comparable levonorgestrel blood levels after the first week of use. At least two mechanisms are active in preventing pregnancy: ovulation inhibition and thickening of the cervical mucus, thus preventing passage of sperm into the uterus. Other mechanisms may add to these contraceptive effects.

Studies were conducted to evaluate the effects of Norplant use on cervical mucus. As has been reported for users of progestin-only minipills, the cervical mucus collected from implant users was found to be thick and impermeable even if the users were regularly menstruating, thereby hampering sperm mobility. This is believed to explain how Jadelle protects against pregnancy even when a woman is ovulating. *In vitro* examination showed sperm penetration to be markedly poorer in mucus collected from implant users than in mucus from the matched control subjects not using hormonal contraceptives.

In another implant user study in which postcoital tests were performed, results indicated that few sperm reached the cervical canal, and those that did were of reduced motility. Microscopic observations of the morphology of implant users' cervical mucus were also consistent with the prevention of conception (Brache, Faundes, Johansson et al. 1985; Croxatto, Diaz, Salvatierra et al. 1987). An analysis of changes in cervical mucus following Norplant insertion showed a rapid decline in mucus receptivity to sperm (Dunson, Blumenthal, Alvarez et al. 1998).

In studies to determine the extent of ovulation suppression occurring with levonorgestrel implant use, blood samples were drawn from users twice a week for five or six consecutive weeks. Samples

were classified as compatible with ovulation if a progesterone level above 9.5 nanamoles (nM) per liter was demonstrated in at least one sample and was immediately followed or preceded by one or more samples with values above 6.4 nM per liter.

Levonorgestrel, at the average dose of 30 µg per day as delivered subdermally, was shown to suppress ovulation in about 50 percent of the cycles studied (Croxatto, Diaz, Salvatierra et al. 1987; Brache, Alvarez-Sanchez, Faundes et al. 1990). Even when progesterone levels rise above those that are conventionally taken as signaling ovulation, mean levels are below those found in normally ovulating women who were not using hormonal contraceptives (Brache, Faundes, Johansson et al. 1985; Brache, Alvarez-Sanchez, Faundes et al. 1990; Brache, Alvarez-Sanchez, Faundes et al. 1992). This deviation from normal hormone patterns may contribute to contraceptive effect (Faundes, Brache, Tejeda et al. 1991; Brache, Faundes, Johansson et al. 1985; Olsson and Odlind 1988).

Another study (Segal, Alvarez-Sanchez, Brache et al. 1991) assessed human chorionic gonadotropin (HCG) levels in women using Norplant and women not using a contraceptive and attempting to conceive. (HCG appears in blood soon after implantation.) Among women in the control group, nine had evidence of HCG production and six advanced to clinical pregnancies. In 13 cycles judged by progesterone levels to be ovulatory in the Norplant group, HCG was not detected.

Toxicology

Toxicology studies in animals have been conducted using both subdermal implants and oral administration of levonorgestrel (Nash 1990). The studies using subdermal implants supplied doses 14 and 56 times the human dose on a body weight basis to monkeys and 80 times the human dose on a body weight basis to rats. Effects on organs in both the oral and the implant animal safety studies were largely those expected of progestational agents.

The animal studies using the oral route of administration have served as a basis for U.S. Food and Drug Administration approval as safe of oral contraceptives containing (a) dl-norgestrel or levonorgestrel in combination with ethynylestradiol and (b) dl-norgestrel alone. The Toxicology Review Panel of the World Health Organization also assessed toxicology findings (World Health Organization 1985).

Clinical overview

Extent of clinical experience

Much of the information regarding the characteristics of levonorgestrel implants, including mechanisms of action and side effects, is similar for Jadelle rods and Norplant capsules. Release rates and blood levels are comparable, as is effectiveness over three and five years. Jadelle is easier to insert and remove because it uses two instead of six implants and thus lessens placement and removal time and tissue trauma.

The current Jadelle rod underwent clinical trials beginning in 1990. The Population Council conducted studies comparing Jadelle with the earlier rod version and with Norplant capsules made with soft tubing. Data about Jadelle were obtained from 1,393 women in the following Council studies:

- randomized blood level studies: A total of 199 women used Jadelle, half at four sites in the United States and half in Chile, the Dominican Republic, Singapore, and Thailand. For the first three years, blood serum concentrations for women using Jadelle were compared with blood levels for women at the same sites using the earlier rod.
- randomized Phase 3 clinical trial: This trial compared efficacy and long-term effectiveness of the Jadelle rods with the soft tubing Norplant capsules. Six hundred women used Jadelle and 594 used soft-tubing Norplant in clinics in Chile, Egypt, Finland, Singapore, Thailand, and the United States. This randomized study provides data on safety and efficacy for five years (Sivin, Lähteenmäki, Ranta et al. 1997).
- comparative Phase 3 study: This study at five clinics (four in the U.S. and one in the Dominican Republic) provided safety and efficacy data for five years for Jadelle rods and soft-tubing Norplant capsules. Six hundred women used each method.

Contraceptive effectiveness

The overall assessment of Jadelle effectiveness is based on the comparative clinical trials described

above. Eight women became pregnant during the first five years in multicenter clinical trials with 1,393 women. One of the eight pregnancies was ectopic. The annual pregnancy rate per 100 users was 0.1 at one, two, and three years, 0.0 at four years, and 0.8 at five years. The Pearl Index pregnancy rate was less than 0.2 pregnancies per hundred woman-years (Sivin, Viegas, Campodonico et al. 1997; Sivin, Campodonico, Kiriwat et al. 1998; Population Council data submitted to the FDA, 2001).

Typically, pregnancy rates with contraceptive methods are reported only for the first year of use. The efficacy of many of these methods depends in part on the reliability of use. This is not the case for Jadelle or Norplant, which are among the most effective contraceptives (see Table 2). No contraceptive method is 100 percent effective.

Relationship of weight to effectiveness

A woman's weight correlates with blood concentrations of levonorgestrel: concentrations decrease with increased weight. Studies with Jadelle showed effective protection through five years (Sivin, Alvarez, Mishell et al. 1998; Sivin, Campodonico, Kiriwat et al. 1998). Through four years, annual pregnancy rates for all women were less than 0.1 per 100 women per year, with no significant difference by weight group. In the fifth year, the annual pregnancy rate was 0.8 per 100 for all women. There was no significant difference in the fifth-year pregnancy rate

Table 2. Comparison of contraceptive failure rates during the first year of use

Method	Perfect use	Typical use
Jadelle rod implants	0.05	0.1
Norplant system (6 capsules)	0.05	0.1
Male sterilization	0.10	0.15
Female sterilization	0.5	0.5
Depo-Provera (injectable progestogen)	0.3	0.3
Oral contraceptives		5.0
Combined	0.1	NA
Progestin only	0.5	NA
IUD		
Progesterone	1.5	2.0
Copper T 380A	0.6	0.8
Condom		
(male) without spermicide	3	21
(female) without spermicide	5	14
Cervical cap		
Nulliparous women	9	20
Parous women	26	40
Sponge		
Nulliparous women	9	20
Parous women	20	40
Diaphragm with spermicidal cream or jelly	6	18
Spermicides alone (foam, creams, jellies, and vaginal suppositories)	6	21
Periodic abstinence (all methods)	1–9*	20
Withdrawal	4	19
No contraception (planned pregnancy)	85	85

NA: Not available

*Depending on method (calendar, ovulation, symptothermal, post-ovulation)

Adapted from Hatcher, R.A. et al., *Contraceptive Technology*, 17th Revised Edition. New York: Ardent Media, Inc., 1998.

between women who weighed less than 60 kg and women who weighed more than 60 kg. Nor was there a statistically significant difference in the cumulative five-year pregnancy rates of women in these two comprehensive weight groups.

Outcome of pregnancies

Ectopic pregnancies: The absolute risk of ectopic pregnancy is low because the contraceptive method is highly effective. Ectopic pregnancies occur with Jadelle at a rate of less than 0.5 per 1,000 woman-years; this rate is almost identical with the ectopic rate for Norplant. This rate is significantly below the rate for U.S. women of reproductive age who do not use contraception (2.7 to 3.0 per 1,000 woman-years) (Sivin 1985). It is also significantly below the ectopic pregnancy rate for women in developing countries who do not use contraception (2.7 per 1,000 woman-years), reported in postmarketing surveillance studies (Meirik, Farley, Sivin et al. 2001b).

However, any pregnancy that does occur with Jadelle use is more likely to be ectopic than a pregnancy occurring in a woman using no contraception. Physicians should be alert to the possibility of an ectopic pregnancy among women using Jadelle who become pregnant or complain of lower abdominal pain. Clinical and controlled postmarketing studies have shown no increase in the rate of ectopic pregnancies per year among women using Norplant as compared with women using IUDs, condoms, and pills (Meirik, Farley, and Sivin 2001a; Meirik, Farley, Sivin et al. 2001b).

Birth defects: There were no reports of congenital anomalies for the pregnancies that occurred during use of Jadelle in clinical trials. However, in postmarketing use of Norplant, there have been reports of congenital anomalies in the offspring of women who were using the contraceptive inadvertently during early pregnancy. A cause and effect relationship has not been established. There is no evidence suggesting that the risks associated with levonorgestrel-containing implants are different from those associated with oral contraceptives.

In the WHO–Population Council–FHI five-year postmarketing surveillance of Norplant implants, reported birth anomalies were of the same kind and frequency as those reported for a larger group of women from the same study who conceived after using IUDs or other nonhormonal methods (Meirik, Farley, and Sivin 2001a; Meirik, Farley, Sivin, et al. 2001b).

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives before pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy.

Continuation and termination rates

In the Jadelle clinical trials, the first-year continuation rate was 88.3 per 100 women, the three-year cumulative rate was 60.6 per 100, and the five-year cumulative rate was 41.5 per 100 (see Table 3). In the first year, 4.5 per 100 women cited irregular bleeding as the principal reason for discontinuing the method. The cumulative rate for discontinuation because of irregular bleeding was 14.1 per 100

Table 3. Cumulative discontinuation and continuation rates for Jadelle (±SE)

	Year		
Reasons for discontinuing	1	3	5
Pregnancy	0.1±0.1	0.3±0.2	1.1±0.4
Menstrual	4.5±0.6	14.1±1.0	19.3±1.2
Medical	4.7±0.6	14.7±1.0	23.1±1.3
Used other method	0.2±0.1	0.9±0.3	3.7±0.7
Planned pregnancy	1.1±0.3	9.7±0.9	18.6±0.3
Personal (other)	1.6±0.3	7.2±0.8	12.5±0.1
Continuation	88.3±0.9	60.6±1.3	41.5±1.3

through the third year and 19.3 per 100 through the fifth year. Other medical conditions were cited as reasons for stopping method use by 4.7 per 100 users in the first year, 14.7 per 100 cumulatively by the third year, and 23.1 per 100 cumulatively by the fifth year. Three conditions—headache, weight gain, and acne—jointly accounted for more than 50 percent of the medical removals. About 10 percent of the women stopped use before the end of the third year and about 19 percent by the end of the fifth year because they desired to become pregnant (Sivin, Campodonico, Kiriwat et al. 1998).

Possible adverse events

Clinical trial investigators record all medical conditions and complaints reported by the participants during method use, whether or not these conditions are thought to be directly related to the method. Possible side effects and adverse events listed here were reported during Jadelle clinical trials.

Bleeding irregularities: Because Jadelle contains no estrogen, disruption of the menstrual cycle is the method's predominant side effect. Most women can expect some variation in menstrual bleeding patterns. Women using Jadelle can expect the same irregularities as do Norplant users: irregular menstrual bleeding, prolonged episodes of bleeding or spotting (more days than a woman would usually experience), heavy bleeding, bleeding or spotting between periods, no bleeding at all for several months, or a combination of these patterns (Balogh, Klavon, Basnayake et al. 1989; Biswas, Leong, Ratnam et al. 1996; Diaz, Pavez, Herreros et al. 1986; Fakeye and Balogh 1989; Faundes, Demejias, Leon et al. 1979; Faundes, Tejada, Brache et al. 1987; Sivin 1988; Sivin, Viegas, Campodonico et al. 1997) (see Table 4). No one can predict what kind of menstrual change a woman will have with Jadelle. But, for most women, these menstrual irregularities will diminish gradually with continuing use (Biswas, Leong, Ratnam et al. 1996). Altered bleeding patterns associated with Jadelle use could possibly mask symptoms of cervical or endometrial cancer, although this was not observed in any of the studies of Jadelle or Norplant.

Because some levonorgestrel implant users have periods of amenorrhea, missed menstrual periods cannot serve as the only means of identifying early pregnancy. Pregnancy tests should be performed whenever a pregnancy is suspected. Six weeks or more of amenorrhea after a pattern of regular menses may signal pregnancy. If pregnancy occurs, the rods must be removed.

Table 4. Menstrual conditions reported in clinical trials of Jadelle

Menstrual condition	Year 1 (%)	Years 1–5 (%)
Menorrhagia (increased duration)	13.4	25.9
Amenorrhea	9.8	13.9
Menometrorrhagia	9.6	20.5
Oligomenorrhea	9.5	12.8
Long spotting duration or length unclear	8.9	15.1
Dysmenorrhea	3.5[a]	8.0[a]
Polymenorrhea	2.7	5.0
Premenstrual syndrome	1.8[a]	5.8[a]
Menorrhagia (increased amount)	1.6	4.5
Other	1.5	2.9

[a] Excludes women with conditions reported at admission, before initiation of Jadelle

Although women in clinical trials reported bleeding irregularities, proportionately more women had increases rather than decreases in blood hemoglobin concentrations, a difference that was highly statistically significant (Sivin 1988). This finding generally indicates that, despite increased bleeding days, menstrual blood loss was reduced for Jadelle users. Similar results were reported with Norplant capsules (Faundes, Tejada, Brache et al. 1987; Gu, Du, Yuan et al. 1988; Shaaban, Salah, Zarzour et al. 1983). Rarely, blood loss resulted in hemoglobin values indicative of anemia.

Other adverse events: Aside from menstrual irregularities, adverse reactions reported by more than 10 percent of women in the Jadelle clinical trials were pain, discoloration or other skin reactions at the implant site, dizziness, headache, leukorrhea, mastalgia, nausea, pelvic pain, urinary tract symptoms/infection, vaginitis, and weight increase. All but pain and discoloration or other skin reactions at the implant site

are adverse reactions common to other hormonal contraceptives. Table 5 shows adverse reactions reported during Jadelle clinical trials.

Ovarian cysts

Ovarian cysts or delayed follicular atresia sometimes occurred in Jadelle users. If follicular development occurs, atresia of the follicle may be delayed and the follicle may continue to grow beyond the size it would attain in a normal cycle. The cysts are generally asymptomatic but may be palpable by clinicians; in the majority of women, the enlarged follicles (cysts) will usually disappear spontaneously after a few weeks and do not require surgery. Rarely, they may twist or rupture, sometimes causing abdominal pain and surgical intervention may be required. In

Table 5. Adverse reactions during five years of Jadelle use in clinical trials

Adverse reactions reported by 10% or more of women:

Application site reaction, pain, etc.	Nausea
Dizziness	Pelvic pain
Headache	Urinary tract symptoms, infection
Leukorrhea	Vaginitis[a]
Mastalgia	Weight increase

[a]includes also genital pruritus, infections, and vaginal problems not elsewhere classified

Adverse reactions reported by 1.0 to 9.9% of women:

Abdominal pain	Folliculitis
Abnormal vision	Hypertension
Acne	Hypertrichosis
Alopecia	Hypoesthesia
Anorexia	Injury
Anxiety	Insomnia
Appetite increase	Libido decreased
Asthenia	Migraine
Asthma	Nervousness
Back pain	Nonpuerperal lactation
Benign breast neoplasm	Ovarian cyst, follicle enlargement
Breast fibroadenosis	Pain
Bronchitis	Palpitation
Cervical cytology, grade 3 or 4	Perineal pain
Cervical lesion	Pruritus
Cervicitis	Purpura
Chest pain	Rash
Constipation, flatulence, or dyspepsia	Somnolence
Contact dermatitis	Syncope
Depression	Upper respiratory infection[b]
Dermatitis	Uterine enlargement
Dyspareunia	Varicose veins
Dyspnea	Vomiting
Emotional lability	Vulvar disorder[c]
Fatigue	Weight decrease
Flu-like symptoms	

[b] includes rhinitis, pharyngitis, and sinusitis, as well as undefined upper respiratory infection
[c] includes genital ulceration, herpes simplex, and papilloma virus and other vulvar disorders

the Population Council's clinical trials, surgery for delayed follicular atresia was performed in four of 1,400 women over seven years.

Weight gain

In clinical trials of Jadelle use, the average weight change over five years of use was a gain of about 9 pounds. Approximately 20 percent of women gained at least 10 pounds in the first year, and 50 percent gained at least 10 pounds by the end of the fifth year of use.

Insertion and removal

Jadelle rods can be inserted just below the skin of the woman's inner upper arm through a small incision made either with a scalpel or a disposable pre-loaded inserter. The two rods are placed in the shape of a V opening toward the shoulder. Strict asepsis must be observed to avoid infection. Training of health care providers is essential for proper placement and removal. The better the placement, the easier removal will be.

Removal times were recorded for 260 Jadelle and 260 Norplant users. From incision to closure, mean removal time for Jadelle was 4.8 minutes, while removals in the Norplant group took 9.6 minutes. Among the rod removals, 2 percent required more than 15 minutes, while 14 percent of Norplant removals needed that time and 6.5 percent took longer than 20 minutes. Mean rod removal times ranged from 4.6 to 5 minutes, compared with 7.8 to 10.9 minutes for Norplant removal (Sivin, Campodonico, Kiriwat et al. 1998).

Insertion complications: An incision is required to insert Jadelle implants. Complications related to insertion, such as pain, edema, and bruising, may occur. Bruising is commonly seen following implant placement. Arm pain, numbness, and tingling may occur following insertion and removal. Reports of infection (including cellulitis and abscess formation), blistering, ulcerations, sloughing, excessive scarring, phlebitis, and hyperpigmentation have been reported at the insertion site for Norplant and may occur with Jadelle. Reports of nerve injury, most commonly associated with deep placement and removal, also were reported with Norplant.

During Jadelle clinical trials, infection at the insertion site occurred in 0.4 percent of women over five years. Expulsion of one or both rods, which was uncommon during the trials, is more likely to occur when placement of the rods is extremely shallow, too close to the incision, or when the area is infected. There have been reports of implant movement, most of which involved minor changes in position of the implants, but some have involved significant displacement of up to several inches.

Removal complications: Removal is achieved through an incision close to the rods. Removal may take longer, be more difficult, and/or cause more pain than insertion and may be associated with difficulty in locating implants. Additional incisions and/or office visits may be required. The two-rod system is expected to reduce the incidence of removal difficulties in comparison with Norplant.

In a five-year study of the performance of levonorgestrel rods and implants, 52 (9.9 percent) of 524 removals were considered to have complications. Removals produced some complication in 6.9 percent of rod users and 14.8 percent of Norplant users. Half of the Norplant complications were reported at a single clinic (Sivin, Campodonico, Kiriwat et al. 1998). Many of these difficulties were related to improper placement. In all of the Population Council's clinical trials of Jadelle, removal problems affected 1.5 percent of users (deep placement, multiple or long incisions, bruising, displacement, or pain), while an additional 6.0 percent involved problems for providers (broken implants and fibrous pericapsular tissue).

Reversibility/return to fertility

Rates and outcomes of planned pregnancy were studied among users of four long-acting contraceptives: an earlier version of the rods, Norplant capsules, and two intrauterine devices (Sivin, Stern, Diaz et al. 1992). This study found that 83 per 100 Norplant users and 84 per 100 rod users became pregnant by the end of the first year after stopping contraception, while 87 per 100 Norplant users and 92 per 100 rod users became pregnant by the end of two years. Another study of 214 Jadelle users showed that 42 percent became pregnant at three months, 86 percent at one year, and 92 percent by two years (Sivin, personal communication, 2001).

Additional evidence that prolonged use of Norplant capsules does not impair subsequent fecun-

dity was provided in a study in Indonesia, where post-removal conception rates for former Norplant users are reported to be virtually identical with those of former IUD and injectable contraceptive users (Affandi, Santoso, Djajadilaga et al. 1987a).

Effect on lactation

Steroids are not considered the contraceptives of first choice for breastfeeding women (Winikoff, Semeraro, and Zimmerman 1988). Levonorgestrel is transferred from maternal circulation to the newborn infant's circulation via breastmilk (Shaaban, Odlind, Salem et al. 1986; Shikary, Betrabet, Patel et al. 1987). However, studies have revealed no clinically important effects on the growth or health of infants whose mothers use levonorgestrel implants beginning six weeks after childbirth (Diaz 1998; Diaz, Herreros, Juez et al. 1984, 1985). A comprehensive study of infant development and progestogen-only contraceptives in five countries found no adverse effect on development of infants whose mothers used progestogen-only methods compared with infants whose mothers used nonhormonal methods during breastfeeding (World Health Organization 1994).

Drug interactions

Jadelle is not recommended for women with epilepsy who use phenytoin, carbamazepine, or oxcarbazepine, because Jadelle is likely to be less effective for these women. These drugs may increase the metabolism of levonorgestrel through induction of microsomal liver enzymes. Although the large clinical trials of Norplant and Jadelle excluded women with epilepsy, published studies show decreased levonorgestrel concentrations in women using phenytoin, carbamezepine, or oxcarbazepine along with levonorgestrel-containing contraceptives (Haukkamaa 1986; Odlind and Olsson 1986). In clinical trials of Norplant, rifampin was judged to have diminished the effectiveness of the contraceptive as it does with other progestin-only products (United States Pharmacopeia 1999).

Metabolic effects

Judgments on metabolic effects derive from extensive studies of pharmacologic indicators among users of levonorgestrel implants, including Jadelle, an earlier rod version, and Norplant capsules.

Indicators of change in liver and kidney function and in metabolism in women using Norplant have been monitored in several studies (Affandi, Suherman, Djajalelana et al. 1987; Bayad, Ibrahim, Fayad et al. 1983; Brache, Alvarez-Sanchez, Faundes et al. 1990; Croxatto, Diaz, and Pavez 1978; Croxatto, Diaz, Robertson et al. 1983; Dash, Das, Nanda et al. 1988; Diaz, Pavez, Brandeis et al. 1989; Diaz, Pavez, Robertson et al. 1979; Holma and Robertson 1985; Johansson and Odlind 1983; Nash 1990; Olsson, Wide, and Odlind 1986; Osman, Abdalla, Toppozada et al. 1983; Shaaban, Elwan, El-Sharkawy et al. 1984; Singh, Viegas, Koh et al. 1989a, 1989b, 1989c; Weiner and Johansson 1976). They are summarized below.

Liver function

Assessment is based on total bilirubin, direct bilirubin, total protein, albumin, alkaline phosphatase, lactic dehydrogenase, SGOT, SGPT, and GGT. The only consistent change has been a small increase in total bilirubin, with all means remaining within the normal range. The change has been non-progressive over extended periods of implant use.

Kidney function

Assessment is based on levels of uric acid, urea nitrogen, sodium potassium, calcium, and inorganic phosphorous. There were no indications of compromised kidney function.

Adrenal function

Either no change or a slight decrease in peripheral cortisol levels was reported, but within normal range. Response to ACTH stimulation was normal.

Thyroid function

Some evidence was reported of minor decrease in thyroxin and triiodothyronine levels, not accompanied by changes in free thyroxin.

Lipid metabolism

Serum lipoprotein levels were altered in three clinical studies involving 544 women using Jadelle. The rod users had mean decreases from baseline in total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol

of approximately 12 percent, 14 percent, and 10 percent respectively. Triglyceride levels decreased about 25 percent from pretreatment values. Although these decreases were statistically significant, a great majority of individual values remained within the normal ranges. Changes in the lipoprotein levels associated with levonorgestrel implants are considered to have little, if any, deleterious effect on the risk of cardiovascular disease.

A two-year longitudinal study undertaken by the WHO compared 177 Norplant users with a similar number of copper IUD users. The study found changes of similar magnitude to those cited above. Lipid changes were greatest three months after implant insertion, with a slow reversal of these trends during the next 19 months. The report concludes that lipid changes induced by Norplant will probably not affect the risk of atherosclerotic disease in women who use this contraceptive method (WHO 1999).

Women who are being treated for hyperlipidemias should be followed closely if they elect to use Jadelle. Some progestins may elevate LDL levels and may render the control of hyperlipidemias more difficult.

Carbohydrate metabolism

Decreased insulin sensitivity following glucose loading has been found in some users of combination and progestin-only oral contraceptives. The effect of levonorgestrel-containing implants on carbohydrate metabolism appears to be minimal. In studies in which pretreatment fasting serum glucose concentrations were compared with concentrations following up to 20 months of Jadelle use, no clinically significant mean differences were evident. Changes in carbohydrate tolerance and insulin sensitivity following oral glucose loads have been reported in some studies among users of Norplant capsules and Jadelle rods (Singh, Viegas, Loke et al. 1992; Bala, Dhall, and Majumdar 1991; Konje, Otolorin, and Ladipo 1991; Konje, Odukoya, Otolorin et al. 1992; Konje, Otolorin, and Ladipo 1992). These changes include modest elevations of serum insulin concentrations as well as increments in serum glucose levels. These changes were not associated with development of clinical or laboratory evidence of diabetes mellitus. While the clinical significance of these findings is unknown, diabetic patients should be carefully observed while using Jadelle. During the Norplant postmarketing surveillance study, diabetes mellitus developed in Norplant users at the rate of 0.2 per 1,000 woman-years, a rate not significantly above that of women who were using IUDs or sterilization (Meirik, Farley, and Sivin 2001a; Meirik, Farley, Sivin et al. 2001c).

Hematology

In general, there have been no noteworthy findings in blood cell counts among Jadelle users. An exception is platelet counts, which were found to increase in studies in Singapore (Singh, Viegas, Loke et al. 1993b), as did indicators of platelet aggregation tendency. However, in studies in three other clinics, platelet counts decreased during implant use (Gu, Du, Zhang et al. 1993). Studies of coagulation factors, coagulation inhibitors, and fibrinolytic indicators in Singapore (Singh, Viegas, Loke et al. 1992) evidenced small decreases in prothrombin time and activated partial thromboplastin time, decreases in several coagulation promotion factors (II, V, VII), and no change in fibrinolytic activity or coagulation inhibitors.

Hemoglobin

Despite changes in menstrual bleeding patterns, mean hemoglobin levels among Jadelle users remained unchanged or increased. Experience among Norplant users has shown that in rare cases, menstrual bleeding is sufficiently voluminous to decrease hemoglobin concentration markedly.

Endocrine changes

Estradiol serum levels during Norplant use have shown irregular patterns, with base values of 30–70 picograms per milliliter and occasional peaks reaching between 200 and 400 picograms per milliliter or, infrequently, peaks of approximately 600 picograms per milliliter. Average estradiol levels can vary greatly, ranging from a low of about 50 picograms per milliliter during menses and the first week or so of the follicular phase to a high of about 200 picograms per milliliter after the LH peak. Peaks can be much higher than these norms or averages.

Statistically significant decreases in circulating total testosterone and androstenedione have been

found among levonorgestrel implant users. They were accompanied by large decreases in sex hormone binding globulin (SHBG). Since testosterone is highly bound to SHBG, the decreased SHBG concentrations predict slightly lower testosterone concentrations. Unbound testosterone concentrations were essentially unchanged. These studies give no evidence that the effect of Jadelle use on androgens is likely to be of clinical significance.

Several pathologists have evaluated the effect of the altered hormone patterns on the endometrium. Some 150 endometrial biopsies from women who used Norplant for 2 to 116 months were examined histologically. The picture is one of mixed proliferative and secretory activity, with a fairly large number of biopsies showing considerable suppression. According to pathologists, histological studies have identified no cause for clinical concern. Of some 150 biopsies for which histological interpretation is available, only two showed hyperplastic characteristics and another two some degree of decidualization. Several investigators who examined the effect of duration of implant use on endometrial patterns have found no convincing evidence of progressive changes in pattern with length of use.

Summing up

In 1998, the Institute of Medicine published a report based on a workshop, *Contraceptive Research, Introduction, and Use: Lessons from Norplant* (Institute of Medicine 1998). The report concluded that "both Norplant and the two-rod levonorgestrel implant system are highly efficacious with failure rates under 1 percent per year, thus providing reversible contraceptive protection essentially equal to that of permanent methods, that is, tubal ligation and vasectomy."

With respect to safety, the report said that "As with all hormonal methods, the contraceptive implant is unsuitable for some women and those contraindications are detailed in its labeling. The Postmarketing Surveillance and Population Council studies found serious adverse events to be extremely rare among implant users over five years of study and concluded that, in the settings where those studies were carried out, the method proved to be safe and well-tolerated."

"In sum," the report continued, "no good scientific reasons emerged in the workshop for not making Norplant available to all women for whom its use is not counterindicated in labeling."

RECOMMENDATIONS FOR INTRODUCING JADELLE INTO DEVELOPING-COUNTRY FAMILY PLANNING PROGRAMS: LESSONS LEARNED FROM THE NORPLANT EXPERIENCE

Family planning professionals and policymakers can learn from the Norplant experience—in their own countries or in others—whether, or how best, to introduce or incorporate Jadelle implants into existing family planning programs. In addition, the Population Council in collaboration with local partners in the Dominican Republic and Guatemala initiated transition studies on how programs that currently provide Norplant can successfully offer Jadelle, either as an additional or replacement implant option. (For details on these transition studies, see the first section of this monograph.)

The recommendations listed below, while specific to implants, raise some general points that could be applied as well to high-quality provision of other long-acting, provider-dependent contraceptives. These recommendations are not absolutes—some programs may have difficulty achieving all of them—but they are guiding principles that Population Council health professionals who are experienced in provision of Norplant believe are worth considering. A discussion of some of these issues also can be found in *Contraceptive Research, Introduction, and Use: Lessons from Norplant* (Institute of Medicine 1998).

Establishing standardized practices to achieve an acceptable level of quality of care, including technical competence and counseling, should be part of the planning for the introduction of implants. Understanding the different types of service delivery systems—commercial, public, private, nongovernmental organization (NGO)—in which the method may be offered is essential. In settings where a large population is at risk for sexually transmitted diseases, attention should be paid to the appropriateness of such a method given that implants will not protect against STDs.

When considering Jadelle, family planning program managers should be aware that implants will fill a small niche in their cafeteria of choices and that no one contraceptive method should be touted as a panacea for solving demographic and social problems.

We offer these recommendations, based on the experience of public health experts from the Population Council and country and international organizations:

1. Program assessment should precede Jadelle introduction

Before a country incorporates Jadelle into its national family planning program, it should undertake an assessment of the capacity of its services to deliver the method in a safe manner. If the program has past or current experience with Norplant implants, a review of that experience should point out strengths or weaknesses of implant provision. Addition of Jadelle may provide an opportunity to improve implant delivery and the quality of services and to attract new users.

Jadelle rods, like Norplant capsules, have a number of characteristics that may make them appropriate in some settings. Implant technology should not automatically be introduced in every setting: some family planning programs can manage the method well, while others do not have the requisite infrastructure. The provision of this method requires that there be:

- attention to counseling and information provided to clients;
- access to and availability of trained providers at the time of insertion and when removal is requested and/or needed;
- assurance of provider competence;
- adherence to aseptic procedures at all times;
- a well-functioning logistics system to maintain the delivery of commodities and all related equipment;
- a relatively sophisticated management information system (MIS) to locate clients at the end of the period for which the method is approved;
- supervision and evaluation systems to monitor quality of care;
- sustained commitment by national programs or donors to provide Jadelle;

- private location for insertions and removals and confidential counseling.

2. Addition of Jadelle should expand contraceptive choice

Jadelle should be offered within the context of a range of methods in order to increase options available for women. Jadelle should be positioned as a long-acting alternative to short-term contraceptives, such as birth control pills, or as a substitute for sterilization, the IUD, or injectables. Within many settings, implants can have an important place in a program's method mix. However, if Jadelle is not widely available or if its provision cannot be sustained over time (because of cost or training requirements or for any other reason), then its addition will not automatically expand choice. The WHO has developed a strategic approach that includes an assessment of the need for a new contraceptive in an existing national family planning program (WHO 1996).

3. Community participation should be part of an introduction strategy

Key stakeholders—ministry of health officials, NGO program managers, service providers, women's health advocates, and potential users—should be included, to the extent possible, in the design and implementation of an introduction strategy. Failure to involve the community in introduction efforts can have a negative effect on the performance and acceptability of the method and the family planning program more generally, particularly if misinformation and rumors are not corrected. Interested stakeholders should be provided with understandable information about issues related to proper use, including the method's safety, efficacy, potential side effects, return to fertility, and the lack of protection against disease. A full discussion with community groups should precede the introduction of Jadelle.

4. Jadelle rods should be acceptable to clients who choose to use them

Numerous studies of both rods and capsules have documented their safety and efficacy. However, safety and efficacy do not necessarily translate into social or cultural acceptability. For example, the irregular bleeding that results from a progestin-only method may cause problems for women. In some societies, women may want their husbands to be informed about the method; in other settings, women might not want to involve their spouses. Clients also should know that Jadelle, like other hormonal contraceptives, offers no protection against HIV/AIDS and other STDs.

5. The method should be sustainable once it is introduced

Because Jadelle initially has greater up-front costs than other methods, the introduction strategy should ensure an adequate supply of implants over time, through donor purchases, country contributions, and, where possible, the private sector. However, long-range predictions of what constitutes an adequate supply may not be attainable at the outset of program planning; the system needs to have room for feedback.

6. Jadelle providers must be trained in insertion and removal techniques

Physicians, nurse-midwives, and paramedics can provide Jadelle, as long as they have been well trained in insertions and removals and have appropriate equipment and supplies. In addition, since providers often are called upon to remove implants long after initial training, retraining in removal techniques is often essential. In large part, the ease in removing Jadelle relates to how well the rods were inserted. Removing (and inserting) Jadelle is expected to be easier than in the case of Norplant, because there are only two rods compared with six capsules. In a large study, mean removal time for the rods was reported as 4.8 minutes, while mean removal time for Norplant capsules was 9.6 minutes. Programs should ensure that sufficient numbers of providers are trained in insertion and removal techniques to handle the expected case load, particularly when there will be large numbers of women seeking removal at the end of Jadelle's approved use life.

7. Clinic staff should be trained in counseling techniques and concepts

Sensitive and comprehensive counseling about all available contraceptives—not only Jadelle—will enable a woman to decide which method is best for her. Counseling should include information about all methods available at the service delivery point, along

with information concerning the degree to which they offer protection against sexually transmitted diseases. Counseling should be integrated into ongoing training and supervisory tasks. Physicians and other clinic staff have benefited from being included in counseling workshops. Counseling about menstrual bleeding irregularities related to implants and other progestin-only contraceptive methods is the best way to minimize discontinuation for this reason.

8. Accurate information should be prepared for clients, providers, and the community

Informational material for clients and service providers must be developed and produced in appropriate languages, particularly if implants have not been available previously. Women and clinicians need to know how implants compare with other contraceptives; that they do not protect against STDs; about side effects and possible complications; about the insertion and removal procedures; and about access to timely removal. If Jadelle will be provided in addition to or instead of Norplant implants, the most salient technical differences and similarities between the two implant systems must be communicated to program managers and providers.

9. Supervision and ongoing program evaluation are essential

A strategic introduction plan should ensure the appropriate supervision of providers. In addition, programs need a client tracking system or other methods, such as publications or correspondence, to ensure that women return for Jadelle removal at the end of the use life. Programs should undergo continuous evaluation to make sure the method is being provided well, that the supply line is adequate, and that counseling and informational materials are sensitive and accurate.

10. Women must have access to removal on demand or when the approved duration of use is reached

Because Jadelle is a provider-dependent method, women cannot initiate or discontinue use of the contraceptive by themselves. Women who choose Jadelle must be assured that they can obtain removals on request, without restrictions, by providers who have undergone training or retraining. The fees women pay at the time of insertion should also cover the later cost of removal. Programs must have a plan for client record keeping and follow-up to anticipate future demand for removal, and they must attempt to locate clients who do not return on their own. Information materials and counseling must emphasize the reasons for removal at five years and stipulate that a woman has the right to removal at any time. This information should be repeated during follow-up visits to ensure that the woman is aware that she must return for removal at the end of Jadelle's approved use life.

11. Early removal should not automatically be viewed as failure of the method

A woman can choose to use Jadelle for the full use life, but she should be free to have it removed at any time without having to justify her request. Her choice to have the rods removed early does not necessarily mean the method has failed her. She may want to become pregnant; her lifestyle may have changed; or she may want to discontinue because she is unhappy with the method. Good counseling prior to selection of Jadelle will minimize later rejection of the implant system.

12. The program's efforts should focus on meeting the woman's needs

The introduction of a new method provides an opportunity to help individual clients achieve their reproductive intentions in a healthful manner. The manner in which services are offered, along with the intrinsic properties of the method, will shape users' perceptions and experiences with Jadelle. Client feedback about experiences with the method is an invaluable tool for providers and program managers.

13. All contraceptives should be provided ethically

Users of family planning services should be assured that their conversations and records will be kept strictly confidential and that they will be given the opportunity for informed choice and informed consent. A private location should be provided for counseling about Jadelle.

ANSWERS TO FREQUENTLY ASKED QUESTIONS ABOUT JADELLE

This discussion can be used by health care providers as a counseling tool. While it can also offer useful information to potential Jadelle users, it should not take the place of counseling by health care providers.

General information

1. What is Jadelle?

Jadelle is an implant system that provides effective, long-acting, reversible contraception for women. Two thin, flexible rods made of silicone tubing and filled with levonorgestrel, a synthetic progestin, are inserted just under the skin of a woman's upper, inner arm in a minor surgical procedure. Protection from pregnancy is provided within 24 hours, when insertion is performed during the first week of a woman's menstrual cycle. The woman rapidly returns to her normal fertility when the implants are removed. Because Jadelle contains no estrogen, the most common side effects are changes in menstrual bleeding patterns. Most other common side effects are similar to those experienced by women who use other hormonal contraceptives.

2. What is Jadelle made of?

The outer part of the Jadelle rod is silicone rubber tubing, similar to the material used in catheters and heart valves since the 1950s. It also is the same kind of material used in Norplant capsules, another contraceptive implant system. The rods release levonorgestrel, a synthetic progestin that has been used in combined oral contraceptives and in progestin-only pills for more than 30 years. What is "new" about the rods is their delivery system, which can provide contraceptive protection for up to five years.

3. How do Jadelle rods differ from Norplant capsules?

The Jadelle system consists of two rods, while the Norplant system has six capsules. Because there are fewer implants, Jadelle is easier to insert and remove than Norplant. Rods differ from capsules. Each Jadelle rod is 43 millimeters long and 2.5 millimeters in diameter, slightly longer (one centimeter) and slightly thicker (0.1 millimeter) than each Norplant capsule. Each rod contains 75 mg of levonorgestrel for a total of 150 mg, while the six Norplant capsules each contain 36 mg, for a total of 216 mg. Both the capsules and rods have outside sheaths composed of silicone rubber, but they are made differently. In the Norplant capsule, levonorgestrel crystals are packed within the rubber sheath, which is then sealed at each end. In the Jadelle rod, a core of mixed levonorgestrel and elastomer (a polymer having the elastic properties of natural rubber) is enclosed within the rubber sheath, which is then sealed at each end with medical adhesive.

4. How effective is Jadelle in preventing pregnancy?

Jadelle is one of the most effective reversible contraceptives available. The cumulative pregnancy rate in clinical trials was 0.3 for three years and 1.1 percent for five years. Jadelle has a lower failure rate than the pill and most IUDs. Its efficacy is comparable to that of surgical sterilization.

5. For how long is Jadelle effective?

The U.S. Food and Drug Administration (FDA) initially approved Jadelle for three years' use. In July 2001 the FDA sent an approvable letter for extension of use to five years. The method is approved for five years in Finland and other European countries, and for three years in Indonesia and Thailand. Data for both three and five years are included in this section.

6. How does Jadelle work?

Pregnancy is prevented in Jadelle users by a combination of mechanisms. The most important are the inhibition of ovulation and the thickening of the cervical mucus, making it impermeable to sperm. Other mechanisms may add to these contraceptive effects.

7. When was Jadelle approved?

Jadelle was approved for marketing as a three-year method in the United States in 1996 and in Finland in 1997. In 2000, Finland approved the extension of use of the method to five years. In 2001, the FDA sent an approvable letter for extension of use to five years.

8. Who can use Jadelle?

Almost any fertile woman without contraindications (see below) who wants to avoid pregnancy may use

Jadelle. The method is suitable for women who are seeking continuous, yet reversible contraception; who want to space their children; who cannot use methods that contain estrogen; who do not want to be sterilized; and/or who desire a method that is convenient and not related to sexual intercourse.

9. Who should not use Jadelle?

Jadelle should not be used by women who are pregnant or who have any of these contraindications: active thrombophlebitis or thromboembolic disorders, such as blood clots in the legs, lungs, or eyes; undiagnosed abnormal genital bleeding; acute liver disease; noncancerous or cancerous liver tumors; known or suspected breast cancer; a history of idiopathic intracranial hypertension; or hypersensitivity to levonorgestrel or any of the other components of the rods (e.g., silicone elastomer). Women who have had previous blood clots or other thromboembolic disorders should consult with their health care providers about whether to use the method.

10. Is Jadelle effective for women of differing weights?

Yes. Even among heavier women, annual pregnancy rates for Jadelle users over three years and five years are well below those of oral contraceptives. A comparative five-year study of Jadelle and Norplant users showed no significant effect of weight on pregnancy risk.

11. What do women like most about Jadelle?

Discussions with women using Jadelle in various countries show they like the method's reliability, convenience, effectiveness, and reversibility. Other advantages mentioned are the method's long-term duration and the fact that the rods are placed in the arm.

12. What do women dislike about Jadelle?

The side effect that women like least is menstrual irregularity, which can mean heavy or prolonged bleeding, spotting, or no bleeding at all. This kind of irregular bleeding occurs because the method contains no estrogen. While such irregular bleeding is usually no cause for alarm, it can be troublesome for some women. In addition, women complain about side effects common to other hormonal methods, such as weight gain, headaches, acne, and mood changes. Some rod users are anxious about possible pain and complications from the insertion and removal procedures. Since the Jadelle system is not user-controlled, it is important that women be able to request removal and receive it promptly from competent providers.

13. How many Jadelle users continue past the first year?

In the clinical studies on which approval was based, cumulative continuation rates were 88.3 percent after the first year, 60.6 percent after three years, and 41.5 percent at five years. These figures may vary. Younger women have lower continuation rates; older women, whose families are completed, have higher continuation rates.

14. Why do women discontinue using this method?

Women discontinue using Jadelle because of side effects, because they want to become pregnant, or for other personal reasons. Studies conducted by the Population Council indicate that, over a three-year period, 14.1 per 100 women stopped using Jadelle because of menstrual irregularities and 14.7 per 100 women discontinued for other medical reasons; 9.7 per 100 women did not continue for the full three years because they were planning a pregnancy. Medical occurrences most frequently cited as reasons for removal were headaches, depression, weight gain, or hair loss.

15. Why is counseling important?

Studies have shown that women who receive good counseling are more satisfied with the method they adopt and are more likely to continue using it. Contraceptive users who believe they have been fully and accurately informed about their choices will feel more confident about their methods and their providers. Inadequate counseling about Jadelle may result in early removals and loss of contraceptive protection.

16. What topics should be covered in counseling?

The Jadelle user should know the most important facts before the rods are inserted: how the method works, any discomfort she might feel following the insertion procedure, what side effects she might encounter, the likelihood of failure, how to recognize warning signs of possible complications, and when to have the rods removed. She should also learn how the method compares with other available contraceptives. Jadelle users should know that most

insertions and removals are easily accomplished when performed by trained health care providers and are not painful for most women.

17. Does the age of the user matter?

Although women from ages 18 to 40 years participated in the clinical trials, women younger and older than those ages also can use Jadelle. If there are no contraindications, the rods may be used by women throughout their reproductive years. Several studies of Norplant use by teenagers in the United States have shown the method to be effective and well accepted. Although there are no studies specific to older women, women can use Jadelle as they approach menopause.

Insertion and removal

18. Should a woman undergo a physical exam before receiving Jadelle?

It is recommended but not essential that a woman considering Jadelle undergo a medical examination. This may include giving a medical history and having a pelvic exam to ensure that she has no diseases or conditions that would make it unsafe for her to use this method.

19. Can Jadelle be inserted at any time?

To make sure the woman is not pregnant, Jadelle rods should be inserted within seven days after the onset of menstrual bleeding or immediately following an abortion. If Jadelle implants are inserted at any other time in the menstrual cycle, the possibility of a preexisting pregnancy must be ruled out and a nonhormonal contraceptive method (such as condoms, spermicides, or diaphragms) must be used for at least seven days following insertion to avoid pregnancy. If ovulation and conception have already occurred before Jadelle is inserted, pregnancy could occur during the month following insertion.

20. How are the rods inserted?

The rods are inserted under the skin of the inner side of the upper arm in a minor surgical procedure. In some countries, a pre-loaded disposable inserter (developed by Leiras) is available. Elsewhere, the rods are loaded in a reusable hollow needle called a trocar. In either technique, a local anesthetic is injected and the clinician makes a small incision—about 3 mm long—using either the disposable inserter or the trocar. The rods are placed subdermally in the shape of a V opening toward the shoulder. The procedure should take only a few minutes. Often the only pain is associated with the injection of the anesthetic. Usually the incision does not require stitches and is covered with a small adhesive bandage and protective gauze bandage.

21. Who performs the insertions?

The rods should be inserted by health care providers who have received training in the procedure. Generally, any trained physician, nurse, nurse-midwife, or other health care provider can perform the insertion.

22. What kind of complications are possible?

The needle providing the anesthetic may sting briefly. Rarely, women may have reactions to the anesthetic used. When the anesthetic wears off, there may be tenderness as well as discoloration, bruising, and/or swelling in the area of the insertion for a few days after placement. There have also been reports of arm pain, numbness, and tingling following placement. During Jadelle clinical trials, infection at the insertion site occurred in 0.4 percent of women over five years. Attention to aseptic technique and proper insertion and removal of Jadelle rods reduce the possibility of infection. In some women, hyperpigmentation occurs over the implantation site, but this effect is usually reversed following removal. During postmarketing use of Norplant, other cutaneous reactions reported include blistering, ulcerations, and sloughing. There have been reports of nerve injury with Norplant, most commonly associated with deep placement and removal. Expulsion of Norplant implants has been reported, more frequently when implant placement was shallow or too close to the incision or when infection was present.

23. How should the insertion site be cared for?

The insertion site should not be bumped for a few days and the area should be kept dry. Also, the woman should avoid heavy lifting for two to three days after the insertion. The protective gauze bandage should be left in place for three days and the small adhesive bandage should be left on for a day or

two longer. Some women have reactions to the adhesive of the bandage.

24. Are Jadelle rods visible?

Since the incision is small, most women do not have a noticeable scar. The rods are usually comfortable and barely visible. When they are visible, the outline of the rods can be seen under the skin and they resemble colorless veins.

25. Will the rods move around?

The rods' location may shift. There have been rare postmarketing reports of movement of Norplant capsules. Most of the movement involved minor changes in the positioning of the implants, but some have involved significant displacement of up to several inches. Some of these reported displacements have been associated with pain and subsequent difficult removal of Norplant.

26. Can a woman work after the insertion?

Yes. She can resume her normal work and domestic activities, as long as she does not bump the site, avoids heavy lifting, and keeps the incision site dry for at least three days. The woman does not have to be concerned if pressure is put on the area during normal activities. After the incision has healed, the skin over the rods can be touched at any time.

27. How soon after insertion can a couple have sexual relations?

This depends on when in her menstrual cycle a woman has the rods inserted. If Jadelle rods are inserted during a woman's menses (to ensure she is not pregnant at the time of insertion), the couple may have sexual relations without a back-up contraceptive method 24 hours after the insertion. If the rods are inserted at any other time during the cycle, the possibility of a preexisiting pregnancy must be ruled out and a nonhormonal contraceptive method should be used for at least seven days following the procedure to avoid pregnancy. If a woman does get pregnant, the rods must be removed.

28. When should the woman return to the clinic for a checkup?

The follow-up schedule depends on the practice of the particular clinic or physician's office in which a woman receives the rods. She may be asked to return for periodic health checkups or to report on her experience with the rods. She should be encouraged to return to the same provider or clinic if she has any health problems that worry her; if she wishes to become pregnant; or if she is moving and needs the address of a clinic that provides Jadelle in her new area. Annual checkups offer an occasion to remind women when to have their rods removed, but are not required.

29. How is Jadelle's protection reversed?

One of the most important characteristics of Jadelle is its reversibility. The contraceptive action stops within two to three days after removal of the rods. The rods are removed during a clinical procedure under a local anesthetic, similar to the insertion process. An alternative form of contraception should be used as soon as the rods are removed, unless the woman desires pregnancy.

30. When should Jadelle be removed?

The rods should be removed at the end of the approved duration of use—either five or three years. However, the woman should be able to request and obtain removal of the rods at any time, for any reason.

31. What happens if the rods are not removed after the approved period of use?

Data have shown that women are protected for up to five years. If the rods are not removed at five years, the risks of pregnancy and of ectopic pregnancy increase.

32. Who should remove the rods?

Health care providers experienced in removals should perform the procedure. The rods can be removed at the same clinic or office where they were inserted or at another health facility that offers the method. Before insertion, a woman should confirm that she will have access to a competent provider at removal time.

33. Is removal painful?

Just as when the capsules are inserted, the health professional will apply a local anesthetic to prevent pain, but the anesthetic injection itself may hurt briefly. If the rods have been inserted properly, removal should be rapid and uncomplicated. When the anesthetic wears off, there may be some tenderness, discol-

oration, bruising, and swelling in the area for a few days. It is neither necessary nor recommended that general anesthesia be used for this procedure.

34. Are removals more difficult than insertions?

Yes. Although most removals are not difficult, the procedure usually takes longer than insertion. Some rods may be harder than others to locate and remove if they were inserted too deeply or if temporary swelling of the arm occurs during removal. A small incision about 4 mm long will be made, through which both rods are removed. If the clinician is unable to remove both rods during one procedure, the woman should return after her arm heals. Women should be informed of the possibility of needing a subsequent visit for removal and should not be alarmed if this is necessary. Clinicians should feel the insertion site to be sure they can locate both rods before attempting to remove them. If they cannot be felt, the rods can be located through x-ray, ultrasound, or compression mammography, all of which are painless procedures. Removal complications or difficulties were reported in 7.5 percent of more than 1,100 women who had Jadelle removed. Complications (some related to deep placement) included multiple or long incisions, bruising, displacement, pain, prolonged removal, incomplete removal requiring an additional visit or visits, broken implants, and fibrous pericapsular tissue.

35. How should a woman care for the site after removal?

As with insertion, it is important to avoid bumping the removal site for a few days. The area should be kept clean, dry, and bandaged until healed (3 to 5 days) so that the site does not become infected.

36. How soon after removal can a woman become pregnant?

The reversibility of protection afforded by Jadelle is one of the advantages of the method. Once the rods are removed, the contraceptive effect wears off within a few days.

37. Can another set of rods be inserted when the old set is removed?

Yes. If a woman wants to continue using Jadelle, a new set can be inserted when the old set is removed. Or a woman can use Norplant and then switch to Jadelle. The second set can be placed through the incision from which the earlier set was removed or in the other arm. If a woman does not want to continue with the rods and does not want to become pregnant, she should be offered another contraceptive method before she leaves the clinic.

Side effects and health considerations

38. What are the most common side effects reported with Jadelle use?

The most common side effect of Jadelle use is irregular menstrual bleeding—most women can expect some variation in menstrual bleeding patterns. Irregularities vary from woman to woman and may include prolonged menstrual bleeding (more days than a woman would normally experience), heavy bleeding, prolonged spotting or spotting between periods, no bleeding at all, or a combination of these patterns.

Other adverse reactions reported by 10 percent or more of women during five years of Jadelle use in clinical trials were application site reaction, discoloration, or pain; dizziness; headache; leukorrhea (whitish discharge from the vagina and uterine cavity); mastalgia (breast pain); nausea; pelvic pain; urinary tract symptoms; vaginitis (including genital pruritus and infections); and weight gain.

Women using Jadelle have also experienced acne, appetite changes, contact dermatitis, hair loss, lesions or inflammation of the cervix, libido decrease, and nervousness.

Preexisting conditions of acne or excessive growth of body or facial hair could worsen. Occasionally, an infection may occur at the implant site (treatable with an antibiotic), or there may be a brief incidence of pain or itching at the insertion site.

Many of these adverse events associated with use of Jadelle are commonly experienced by users of other hormonal methods.

39. Do most Jadelle users experience side effects?

Yes, although it will frequently not be clear whether an adverse event was caused by the implants. All contraceptive methods have side effects and Jadelle is no exception. Bleeding irregularities (including spotting, longer or heavier periods than previously, or no bleeding) are reported by about 65 percent of

rod users. A five-year clinical trial in seven countries showed that the two most frequent medical reasons, other than bleeding irregularities, leading to removal were headache and weight gain. About 19 per 100 women discontinued use of Jadelle because of bleeding problems.

40. Are bleeding irregularities associated with Jadelle serious?

A change in the menstrual bleeding pattern—the most frequently reported side effect—is to be expected with hormonal methods that do not contain estrogen. Most bleeding irregularities associated with Jadelle are not serious, although they may be troublesome for some users. If a woman experiences heavy bleeding, she should see her physician or health care provider to make sure the bleeding is not masking another condition. Because some rod users experience amenorrhea, missed menstrual periods cannot serve as the only means of identifying early pregnancy.

41. What kind of bleeding pattern can be expected?

It is not possible to predict the kind of bleeding pattern a woman will have while using Jadelle. Many women can expect an altered menstrual bleeding pattern to become more regular after six to nine months. Both increased and reduced bleeding tend to diminish with time, although these irregularities can persist for some women throughout the three or five years.

42. Is the lack of bleeding (amenorrhea) harmful?

Sometimes a woman is concerned about amenorrhea—the absence of monthly bleeding. A woman's health or future fertility will not be harmed if she does not have her period while using Jadelle; there is no blood "buildup." Pregnancy tests should be performed whenever a pregnancy is suspected. Six weeks or more of amenorrhea after a pattern of regular menses may signal pregnancy.

43. Does the use of Jadelle make women anemic?

Despite the increased frequency of menstrual bleeding in some women using Jadelle, the amount of total blood loss is usually less than occurs during normal menses. In some studies, in fact, hemoglobin values of Jadelle users have been shown to increase. A few rare cases of severe blood loss have been associated with anemia.

44. Should women be given estrogen to control bleeding and spotting?

Jadelle is estrogen-free and many women and their health care providers choose the method for this reason. Although research has been conducted to test the effectiveness of a few treatments for bleeding irregularities, there is no evidence available to promote any specific treatment.

45. Does Jadelle use affect lipid and carbohydrate metabolism?

Serum lipoprotein levels were altered in three clinical studies involving 544 women using Jadelle. Levonorgestrel rod users had mean decreases from baseline in total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol of approximately 12 percent, 14 percent, and 10 percent, respectively. Triglyceride levels decreased about 25 percent from pretreatment values. Although these decreases were statistically significant, all mean values remained within the normal ranges. The long-term clinical effects of these changes have not been determined. Women who are being treated for hyperlipidemias should be followed closely if they elect to use Jadelle. Some progestins may elevate LDL levels, thereby making the control of hyperlipidemias more difficult.

The effect of levonorgestrel-containing implants on carbohydrate metabolism appears to be minimal.

During the Norplant postmarketing surveillance study, diabetes mellitus developed in Norplant users at the rate of 0.2 per 1,000 woman-years, a rate not significantly above that of control subjects who were not using hormonal contraception. While the clinical significance of these findings is unknown, diabetic patients should be carefully observed while using Jadelle.

46. What are warning signs of possible problems?

A woman using Jadelle should return to her health care provider or clinic immediately if she has severe lower abdominal pain (possible ectopic pregnancy), heavy vaginal bleeding (masking symptoms of cervical or endometrial cancer), delayed menstrual periods after several regular cycles (possible pregnancy), pus or bleeding at the insertion site (indication of infection), or expulsion of an implant (when placement is shallow).

Of course, women also should seek immediate medical attention if they have sharp chest pain, coughing of blood, or sudden shortness of breath (possible clot in the lung); pain in the calf or arm (possible clot in the leg or arm); sudden partial or complete loss of vision (possible clot in the eye); crushing chest pain or heaviness in the chest (possible heart attack); sudden severe or persistent headache or vomiting, dizziness, or fainting, disturbances of speech or blurred vision, weakness or numbness in an arm or leg (possible stroke or other neurological problem); or sleep disorders, weakness, lack of energy, fatigue, or changes in mood (possibly indicating severe depression).

The absence of menstrual periods after several regular cycles may be a sign of pregnancy. If a woman is not bleeding at her expected time or has lower abdominal pain or symptoms of pregnancy, she should visit the clinic without delay. Lower abdominal pain may indicate an ectopic pregnancy.

A change in the frequency, pattern, severity, or persistence of headaches, or blurred vision, may be signs of papilledema, which in turn may indicate idiopathic intracranial hypertension. Women experiencing these symptoms should discuss them with their health care provider, who may screen them for papilledema and, if the condition is present, refer them to a neurologist for further diagnosis and care. This condition, which is seen most commonly in obese women of reproductive age in the general population, has been reported in postmarketing use of Norplant in the United States and the United Kingdom. However, a causal relationship is unclear. Jadelle rods should be removed from women experiencing papilledema.

Contact lens wearers who experience visual changes or changes in lens tolerance while using Jadelle should be assessed by an ophthalmologist.

Women who become significantly depressed while using Jadelle should discuss with their health care provider whether the rods should be removed.

47. Are there other health considerations with Jadelle use?

Women with certain health conditions can use Jadelle, provided they have regular checkups. If a woman has any of the following conditions, she should discuss them with her health care provider before using the rods: breast nodules, fibrocystic disease of the breast, or an abnormal breast x-ray or mammogram; diabetes; elevated cholesterol or triglycerides; high blood pressure; migraine or other headaches; epilepsy; mental depression; gallbladder, heart, or kidney disease; or a history of blood clots, heart attack, or stroke.

48. Does Jadelle cause heart or vascular problems?

There have been reports of superficial phlebitis in clinical trials of Jadelle and postmarketing reports of thrombophlebitis and superficial phlebitis coincident with Norplant use, more commonly in the arm of insertion. In such cases, the implants should be removed. Removal should also be considered in women who will be subjected to prolonged immobilization because of surgery or illness. There have also been reports of other thromboembolic disorders and cardiovascular problems (such as stroke, myocardial infarction, pulmonary embolism, and deep-vein thrombosis) coincident with Norplant use. In the Norplant postmarketing surveillance study, which observed more than 30,000 woman-years of Norplant use and comparable experience in women not using hormonal contraception, no myocardial infarctions occurred in either group. It is expected that this experience applies equally to Jadelle.

An increased risk of thromboembolic and thrombotic disease (pulmonary embolism, superficial venous thrombosis, and deep-vein thrombosis) has been associated with the use of combination oral contraceptives. Combined oral contraceptives, which contain both estrogen and progestin, have been shown to increase both the relative and attributable risks of thrombotic and hemorrhagic strokes, although the risk is greatest among women over 35 years of age who are hypertensive (have high blood pressure) and also smoke.

49. Does Jadelle use increase blood pressure?

Increased blood pressure has been reported in users of combined oral contraceptives. The prevalence of elevated blood pressure increases with long exposure. Although no clinically significant rises in mean blood pressure occurred among Jadelle users in clinical trials, physicians should be aware of the possibility of elevated blood pressure in women using this method. In the Norplant postmarketing surveillance study, the incidence of hypertension and borderline

hypertension was moderately higher in Norplant users compared with women in the control groups. Because Norplant users had more frequent blood pressure measurements than controls, the results might partially reflect a reporting bias.

50. Does Jadelle cause autoimmune diseases?

Autoimmune diseases such as scleroderma, systemic lupus, and rheumatoid arthritis occur in the general population and more frequently among women of childbearing age. There have been rare reports of various autoimmune diseases, including the ones listed above, in users of the six-capsule Norplant implants; however, the rate of reporting is significantly lower than the expected incidences for these diseases in the general population. Studies have raised the possibility of antibodies being developed against silicone-containing devices; however, the specificity and clinical relevance of these antibodies are unknown. While it is believed that the occurrence of autoimmune diseases among Norplant capsule users is coincidental, health care providers should be alert to the earliest manifestations of such diseases in Jadelle users. In the Norplant postmarketing surveillance study, no significant difference in the risk of autoimmune disease was found between Norplant users and users of nonhormonal methods.

51. Does Jadelle use increase the risk of gallbladder disease?

Some studies have reported an increased lifetime relative risk of gallbladder disease in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative increased risk of developing gallbladder disease among oral contraceptive users is minimal. These recent findings may be related to the lower doses of estrogens and progestins in current pill formulations. In the Norplant postmarketing surveillance study, the relative risk of gallbladder disease was moderately higher in Norplant users in Chile and China compared with women in the control groups.

52. Does Jadelle cause birth defects?

Extensive epidemiological studies have revealed no increased risk of birth defects in the children of women who have used oral contraceptives before pregnancy. Studies also fail to suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when oral contraceptives are used inadvertently during early pregnancy. There is no evidence suggesting that the risk associated with Jadelle or Norplant use is different from the risk associated with oral contraceptives.

There were no reports of birth defects for the live births that occurred during use of Jadelle in clinical trials. However, in postmarketing use of Norplant capsules, congenital anomalies have been reported in the offspring of women who used the method inadvertently during early pregnancy. A cause and effect relationship has not been established. If a woman becomes pregnant while using Jadelle, the rods should be removed immediately.

53. Can a smoker use Jadelle?

Cigarette smoking increases the risk of heart attacks and strokes in users of combined oral contraceptives. This risk increases with age and with heavy smoking (15 or more cigarettes a day) and is quite marked in women over 35 years old. While this is believed to be an estrogen-related effect, it is not known whether a similar risk exists with progestin-only methods such as Jadelle. A woman who chooses to use Jadelle is advised not to smoke.

54. Does Jadelle protect against sexually transmitted diseases?

No. This form of contraception does not protect against HIV/AIDS or other sexually transmitted diseases. If a woman who elects to use Jadelle thinks she might be at risk for STDs, she or her partner should use a condom in addition to the rods.

55. Does Jadelle cause cancer at the incision site?

In rare instances cancers have occurred at the site of foreign-body intrusions or old scars. None have been reported in Norplant users or in clinical trials with Jadelle. In rodents, which are highly susceptible to such cancers, the incidence decreases with decreasing size of the foreign body. Because of the resistance of humans to these cancers and because of the small size of the implants, the risk to users of Jadelle is judged to be minimal.

56. Can a woman use Jadelle if she is breastfeeding?

Hormones are not considered the most appropriate contraceptives for breastfeeding women. However, studies have shown no significant effects on the

growth or health of infants whose nursing mothers began using levonorgestrel implants five to seven weeks after childbirth. There is no experience to support the use of Jadelle earlier than six weeks after childbirth in lactating women.

57. Is sickle cell anemia a contraindication?

Sickle cell anemia is not considered a contraindication for the use of Jadelle. However, the Population Council does not have relevant data from clinical trials since women who were anemic were not included in the Council's studies with Norplant capsules or with Jadelle. One published study indicated that women with sickle cell anemia did not suffer adverse effects when using Norplant capsules.

58. Do other drugs interact with Jadelle?

Certain drugs may interact with the hormone delivered by Jadelle to make the rods less effective in preventing pregnancy. These include drugs used for epilepsy such as phenytoin (like Dilantin), carbamazepine, and oxcarbazepine. When considering Jadelle use, a woman should tell her health care provider if she is taking any of these or other medications. Rifampin is known to decrease the effectiveness of combination oral contraceptives; its effect on levonorgestrel concentrations is unknown.

59. Is there a risk of ectopic pregnancy?

The absolute risk of ectopic pregnancy (a fetus developing outside the uterus) during use of Jadelle is very low, because of the high effectiveness of the method. Ectopic pregnancies occur with Jadelle at a rate of less than 0.5 per 1,000 woman-years. Clinical and controlled postmarketing studies of Norplant users showed no increase in the rate of ectopic pregnancies per year as compared with women using IUDs, oral contraceptives, condoms, or no method at all. Physicians should be alert to the possibility of an ectopic pregnancy among women using Jadelle who become pregnant or complain of lower abdominal pain. Any patient who presents with lower abdominal pain must be evaluated to rule out ectopic pregnancy.

60. Are ovarian cysts a problem for Jadelle users?

Functional ovarian cysts or enlarged follicles occur in levonorgestrel implant users more frequently than they do in women who do not use Jadelle or Norplant. If follicles become enlarged, they may produce some discomfort in some women, although most users would not be aware of them unless they were found during a physical exam. In the majority of women affected, enlarged follicles will spontaneously disappear and do not require surgery. Rarely, they may twist or rupture, sometimes causing abdominal pain, so that surgery is required.

61. Are there known long-term side effects?

No studies of long-term health effects from either Jadelle or Norplant use have been conducted beyond five years. However, the drug contained in both types of implants—levonorgestrel—has been used in oral contraceptives for over 30 years.

62. What is known about medium-term health effects of Jadelle use?

The best evidence of medium-term health effects comes from the five-year Norplant postmarketing surveillance. The surveillance compared some 8,000 Norplant users with about 8,000 users of either IUDs or sterilization in eight developing countries. The women were followed for five years, even if they discontinued use of the method, switched to another, or became pregnant. Norplant was not associated with any material risk of major morbidity compared with the two control groups. For greater detail, see the section on the postmarketing surveillance in this monograph.

Research and development

63. Why was Jadelle developed?

The Population Council developed Jadelle to provide the same level of contraceptive protection as Norplant while using fewer implants, thereby making the method easier to insert and remove.

64. Why are additional contraceptives needed?

There is currently no reversible contraceptive that all women like and are able to use. A woman may try several methods until she finds the one that best suits her. Furthermore, a woman may switch methods several times during her reproductive lifetime because of changes in her age, health, economic security, marital status, lifestyle, and concept of ideal family size. All of these factors can have an impact on a woman's decisions about contraception: when to use or stop using it, what kind to use, and when

to switch to another method. Even with Jadelle as an option, there is a need for new contraceptives for groups of women whose needs are not met by available methods.

65. Where was Jadelle tested?

Jadelle was studied in three multicenter trials beginning in 1990. The studies enrolled 1,393 rod users in seven countries. Almost half of the women studied were in the United States; other clinics were in Chile, the Dominican Republic, Egypt, Finland, Singapore, and Thailand. The studies provided data on blood levels, safety, and efficacy.

The Council conducted clinical trials using an earlier version of the rods in five countries from 1983 to 1988. This version of the rods had to be reformulated when an ingredient in the tubing was discontinued by the manufacturer.

Much of the information regarding characteristics of levonorgestrel implants comes from extensive studies of the six-implant Norplant. In addition, many countries have conducted preintroduction studies to obtain data on local experience with the Norplant method and to train providers in insertion, removal, and counseling techniques. By 1991, when the method became available in the United States, Norplant capsules had been used in clinical trials and preintroduction studies involving over 55,000 volunteers in more than 40 countries.

66. Where has Jadelle been approved?

Regulatory agencies in the following countries have approved Jadelle: Finland, France, Iceland, Indonesia, Luxembourg, Netherlands, Norway, Spain, Sweden, Thailand, and the United States.

67. Is there a risk of Jadelle being used coercively?

There is a risk of any provider-controlled method being used coercively. The Population Council strongly advocates the voluntary use of any contraceptive and believes that women have the right to balanced and accurate information, trained and capable health care providers, aseptic conditions, and ability to discontinue the use of the contraceptive on request.

Wherever provider-dependent methods are offered, providers should obtain women's informed consent at the time the method is adopted, and users should have ready access to removal of the rods by competent health care providers.

INTERNATIONAL POSTMARKETING SURVEILLANCE OF NORPLANT

A five-year international postmarketing surveillance of some 8,000 Norplant users in eight developing countries compared with the same number of users of either intrauterine devices (IUDs) or sterilization shows the implants to be a safe and highly effective contraceptive method (Meirik, Farley, and Sivin 2001a; Meirik, Farley, Sivin et al. 2001b; Meirik, Farley, Sivin et al. 2001c). The study's purpose was to determine the safety of these methods in developing-country settings and to examine the risk of relatively rare public health events that had not been identified earlier in clinical trials. The authors concluded that Norplant was not associated with any material risk of major morbidity compared with the two control groups. This study was the first prospective postregistration surveillance of a newly introduced contraceptive in developing countries.

The study concluded that all three methods provided excellent long-term protection against unplanned pregnancy and considerably reduced the risk of ectopic pregnancy. Average annual pregnancy rates for Norplant, copper IUDs, and sterilization were less than one per 100 women. Continuation rates for both Norplant and IUDs averaged 90 per 100 women entering each year. The overall follow-up rate was 94.6 percent; 78,323 woman-years of observation were accumulated.

The study was conducted by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), the Population Council, and Family Health International.

Working with investigators at 32 family planning clinics in eight developing countries, the surveillance followed 7,977 Norplant capsule users, 6,625 users of IUDs, and 1,419 women who had been sterilized in Bangladesh, Chile, China, Colombia, Egypt, Indonesia, Sri Lanka, and Thailand. With few exceptions, women were followed for five years, even if they discontinued use of the method, switched to another contraceptive, or became pregnant. The women made regular clinic visits every six months, reported any health problems, and kept diaries of contacts with other health providers and facilities. Medical records were obtained from clinics and hospitals. Women who had missed a visit were contacted. Former Norplant users returned six weeks after implant removal to ensure recording of any removal complications.

Clients were enrolled from 1987 to 1991, with follow-up completed in 1997. Ninety-five percent of the women enrolled in the study were accounted for at the end of the five-year follow-up period.

All complaints, symptoms, and diseases were classified according to the International Classification of Diseases, 9th revision (ICD-9). All major health-related events were reported and reviewed. Major health events were potentially life-threatening problems that (a) required hospitalization, convalescence of at least one month, or medication for three months or more, (b) resulted in sequelae, or (c) led to death.

Major health events

Data were generally reassuring for major health events. The study reported no significant excess of malignant neoplastic disease or cardiovascular events, such as stroke or venous thromboembolism in Norplant users compared to women using non-hormonal methods. Furthermore, the number of such events was not greater than the expected estimate from population-based incidence rates. There was little or no association between Norplant use and diabetes or thromobocytopenia. No association was found between Norplant use and severe depression or severe connective tissue diseases, such as systemic lupus erythematosus. The rates of diagnosis of rheumatoid arthritis and polyarthropathies were low and not statistically significantly different between Norplant users and women using an IUD or those sterilized.

Twenty-two of 34 deaths during the study were due to accidents, suicides, and homicides. There were no differences in the number or patterns of deaths according to the contraceptive method chosen.

Most other major health events reported in the study were related to diseases of the digestive and

genitourinary systems, reflecting expected patterns of disease among otherwise healthy women of reproductive age in developing countries. The researchers found that the incidence of gallbladder disease was moderately higher in Norplant users compared with women in the control groups, though this occurred mainly in users in Chile and China. Use of combined oral contraceptives has been reported to be weakly associated with gallstone disease and cholecystitis in some studies (Thijs and Knipschild 1993). While the overall incidence of hypertension was low in all contraceptive groups, the combined incidence of hypertension and borderline hypertension was higher in current Norplant users compared with women in the control groups. Because Norplant users had more frequent blood pressure measurements, the results might partially reflect a reporting bias, according to the researchers. (A woman was classified as having hypertension if her systolic blood pressure was >140 mm Hg and her diastolic blood pressure was >90 mm Hg on more than one occasion; she was classified as having borderline hypertension if these results were recorded only once.)

Pregnancies

The majority of the pregnancies (1,134 out of 1,737) occurred among women who had stopped using contraception. Some 317 women using IUDs became pregnant; most of these were women in China using nonmedicated IUDs. Annual pregnancy rates during the period of use of Norplant and the copper IUD and among sterilized women were less than one per 100 women. Eighty-nine Norplant users became pregnant; ten of these pregnancies were ectopic. The low number of pregnancies reflects the method's high effectiveness.

Other reported health problems

The study confirmed a higher incidence of less serious disorders previously described in Norplant clinical trials and/or labeling, such as irregular or excessive menstrual bleeding, amenorrhea, and ovarian cystic enlargement not requiring hospitalization. A variety of symptoms and conditions, ranging from headaches and mood changes to respiratory tract and skin problems, were also more frequently reported by women using Norplant than by IUD users and sterilized women. However, the higher incidence of these complaints by Norplant users may have been partly due to the fact that the implant was a new method for both service providers and users, leading to a greater focus on health problems.

Clustering of diagnoses also occurred. For example, centers in Colombia, with 6.2 percent of the study's participants, reported over 65 percent of all migraine headaches but only 1.6 percent of other headaches. This apparent anomaly led researchers to conclude that clinicians in Colombia did not use the same diagnostic signs and symptoms as were used elsewhere. In Bangladesh, extensive reporting for sterilization participants of other health problems, such as headache or malaise, resulted in higher overall incidence rates for these conditions than found elsewhere.

The researchers concluded that the postmarketing surveillance demonstrated the feasibility of conducting large multicenter cohort studies in developing countries and confirmed the safety with respect to serious disease of Norplant, IUDs, and sterilization.

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