

## The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study Questions and Answers

[About the ECHO Study](#)

[Background and Implications for the Field](#)

[How the Study Works](#)

[About the Products](#)

### About the ECHO Study

#### **1. What is the ECHO Study?**

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study is an open-label randomised clinical trial that aims to compare three highly effective, reversible methods of contraception—the progestogen-only injectable depot medroxyprogesterone acetate (DMPA), a progestogen implant called Jadelle and the copper IUD—to evaluate whether there is any difference in the risk of HIV acquisition among women using these methods. The study will also compare side effects, pregnancy rates and women’s patterns of use for the three contraceptive methods.

#### **2. Why is the ECHO Study needed?**

More than 150 million women worldwide use various hormonal contraceptives, including progestogen-only contraceptives such as injectables, for family planning. In sub-Saharan Africa, progestogen-only injectable contraceptives are the most commonly used method. Over the past 25 years, as the HIV epidemic took hold in many countries, a number of observational studies were undertaken to explore whether or not hormonal methods increase the risk of HIV acquisition. No association between combined hormonal contraceptive methods — which include the use of two hormones (estrogen and progestogen) to prevent pregnancy from occurring — and HIV acquisition has been shown. For women using progestogen-only injectables, the cumulative evidence from observational studies indicates a possible increased risk of HIV acquisition (particularly with DMPA), but it is uncertain whether there is a causal relationship, as opposed to just an observed association, due to the methodological limitations of these studies. Few studies have examined whether hormonal implants or intrauterine devices (IUDs) affect users’ risk of HIV acquisition. (See [Background](#) for additional information.)

Given the widespread use of DMPA in areas of high HIV incidence, the question of whether DMPA increases women's risk of HIV is a critical public health issue requiring the strongest evidence possible. Women need to know whether the use of DMPA or other highly effective alternatives to DMPA affects their risk of acquiring HIV so they can make informed choices about contraception. ECHO will provide high-quality information about contraceptive risks and benefits that women can use in making contraceptive decisions, that healthcare providers will use for contraceptive counseling, and to inform policy-makers' decisions for programmes.

### **3. What is the status of the ECHO Study?**

The ECHO Study began enrolling participants in December 2015 with a plan to enrol 7 800 women. By the end of February 2017, more than 4 500 women had been enrolled across 12 sites in South Africa, Kenya, Swaziland and Zambia. Results are expected in 2019.

The trial's independent Data and Safety Monitoring Board (DSMB) met on 2 March 2017. This planned six-monthly DSMB review focused on safety and operational issues, including performance metrics such as enrolment, retention and method refusal rate. The DSMB reviewed the rationale, design and outcomes of the study within the context of the overall field, including the revised guidance on hormonal contraception and HIV released earlier that day by the World Health Organization (WHO). Based on the DSMB's review of the ECHO Study data, the current scientific evidence and the [2 March 2017 WHO statement](#), the DSMB reaffirmed the continued need for ECHO and its ongoing equipoise, and recommended that the study continue. (See question #11 for further details.)

### **4. How do the new changes to the WHO guidelines on the use of hormonal contraception for women at high HIV risk affect the ECHO Study?**

Based on a December 2016 expert consultation to review the latest evidence on hormonal contraception and HIV, the WHO recently changed its recommendation for progestogen-only injectables for women at high risk of HIV from 'can use without restriction' (Medical Eligibility Criteria category 1) to can also use 'because the advantages of these methods generally outweigh the possible increased risk of HIV acquisition' (MEC category 2).

The ECHO team will inform current and potential study participants of this new WHO guidance, which says that women at high risk of acquiring HIV can use progestogen-only injectables should be advised about: 1) concerns that these methods may increase their risk of HIV acquisition; 2) continued uncertainty over whether the use of these methods *causes* increased risk; and 3) how to minimize their risk of acquiring HIV.

## **5. What does the WHO guidance say about the randomised clinical ECHO Study?**

The WHO recommendations reaffirm the need for randomised clinical trials, such as ECHO, to determine whether there is a causal relationship between hormonal contraception and the risk of HIV acquisition.

## **6. How will the change in the WHO guidance be communicated to ECHO Study participants?**

The ECHO team is fully committed to ensuring all study participants are kept informed about any updates in the science and guidelines. All study materials, including outreach and recruitment materials and the informed consent form, are being updated to reflect the change in the WHO guidelines on DMPA. These revisions will be reviewed by local ethics committees (institutional review boards). All women interested in joining ECHO will be informed about the new WHO guidance by trained staff as part of the recruitment and informed consent process. Current ECHO Study participants will also be informed about the new guidance, and counsellors will answer any questions they have. (See [How the Study Works](#), questions #14–15)

## **7. What data will the ECHO Study produce, and how will the data be used?**

The primary findings will be the comparative risk of HIV acquisition among the three contraceptive methods studied. This information will be published and submitted to WHO for review of its contraceptive guidelines. WHO's contraceptive guidelines are used worldwide by programme managers, policy-makers and clinicians. The study team is committed to ensuring that study participants and other women at high risk of HIV, as well as other stakeholders, have timely access to the information provided by the study. Results will also be presented to national and international policy-makers, scientists and advocates.

## **Background of the ECHO Study and Implications for the Field**

## **8. What are the origins of the ECHO Study?**

In February 2012, a World Health Organization expert group met to review all the available data on hormonal contraception and HIV risk. The group found that the information on combined oral contraceptive pills was reassuring, but the data on the safety of progestogen-only injectables were inconclusive, with some but not all studies showing an increased risk of HIV acquisition. These data came from observational studies and secondary analyses that are subject to bias and other limitations, making it difficult to interpret the data. The group concluded that there was an urgent need for further research carefully designed to show whether or not use of progestogen-only injectables increases the risk of HIV acquisition — a

conclusion that was reaffirmed in 2014 and 2017.

## 9. What are the current data available? What does the evidence say?

Research on hormonal contraceptive (HC) use and risk of HIV acquisition has yielded mixed results. The most recent data are from a systematic review<sup>1</sup> commissioned by the World Health Organization to analyse studies published from 15 January 2014 to 15 January 2016 and synthesise the results with those from a previous systematic review.<sup>2</sup>

The updated systematic review found that most of the data for oral contraceptive pills, injectable norethisterone enanthate (NET-EN) and levonorgestrel implants do not suggest an association with HIV acquisition, though data for NET-EN and especially implants are very limited. Data are also very limited on the copper intrauterine device (IUD), and no data are available on whether contraceptive rings or patches, combined injectables or levonorgestrel IUDs affect the risk of HIV acquisition.

Some studies suggest increased risk of HIV acquisition among users of DMPA. Data from recent studies included in the latest systematic review strengthen concerns about a possible increased risk of HIV acquisition associated with DMPA use (Polis, 2016). After reviewing the evidence, a WHO technical consultation concluded that the available evidence continues to indicate an association between use of progestogen injectables and an increased risk of acquiring HIV; however, it is unknown whether the associations seen in these observational studies were due to a true biological effect or the limitations of such studies.

## 10. What are the limitations of the studies on the potential link between DMPA use and HIV risk?

All of the studies have been observational studies, in which women choose which contraceptive methods they use. Women who choose to use DMPA may be different from women who do not use DMPA — particularly those who do not use contraception at all — in important ways that affect their risk of HIV and are difficult to measure. (See #12.) The WHO statement notes that ‘data from observational studies come with a high level of uncertainty’, and calls for randomised clinical trials to provide better information about possible causality.

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<sup>1</sup> Polis CB, Curtis KM, Hannaford PC, et al. Update on hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence, 2016. *AIDS* 2016; **30**: 2665-83. [Epub ahead of print]

<sup>2</sup> Polis CB, Phillips SJ, Curtis KM, et al. Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence. *Contraception* 2014; **90**: 360-90; Polis CB, Curtis KM. Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence. *Lancet Inf Dis* 2013; **13**: 797-808.

## **11. What are the implications of these findings for the ECHO Study?**

ECHO is a randomised controlled trial (RCT) designed to address the long-standing concern in the public health community of a possible association between hormonal contraception, especially DMPA, and the risk of HIV acquisition. On 2 March 2017, the ECHO Study's DSMB met and agreed that the results of the updated systematic review and the new WHO guidance underscore the need for an RCT that will yield higher-quality evidence than the available data from observational studies. The DSMB members also weighed the data and potential risk with the benefits of injectable contraception, along with the ease and acceptability of use, and concluded that the ECHO trial is in equipoise. This means there is scientific uncertainty about possible differences in risk of HIV acquisition and the benefits among the three randomised methods. Importantly, ECHO is designed to assess the relative risks and benefits of alternative contraceptive methods — the levonorgestrel implant and the copper IUD — compared to DMPA and to each other. The recent systematic review includes very little data to weigh whether implants and IUDs are better alternatives to DMPA with respect to HIV or other risks and benefits.

## **12. Why is a randomised study needed?**

Randomised clinical trials are considered the gold standard in producing reliable scientific evidence about the effect of a medical intervention. When women have an equal chance of using any of the contraceptive methods under study, sexual behaviours and other factors that might influence HIV risk are equally likely to occur across the groups of women who are randomly allocated by computer to use one of the study methods. As a result, with a randomised trial there is more certainty that a true difference in HIV acquisition is being measured and that any differences measured can be more certainly attributed to the contraceptive method used.

### How the Study Works

## **13. How many women will be enrolled in the ECHO Study? And who will be able to join?**

Approximately 7 800 sexually active HIV-negative women ages 16 to 35 years will be enrolled in the ECHO Study.

Women are eligible to join the study if they are seeking effective contraception, are willing to be randomly assigned to any of the study groups and do not want to become pregnant for the duration of the study. Women who have recently given birth must also be at least six weeks postpartum to be eligible to enrol. Participants must intend to stay in the area for the duration of their participation in the study.

Young women ages 16 and 17 years may join the study upon approval based on local and national regulations and the relevant ethics committee's guidance. Where required, as in South Africa, the study will seek the informed consent of a parent or legal guardian in addition to that of the minor participant. In other countries, such as Kenya, a previously pregnant 16- to 17-year-old is considered to be a legally 'emancipated minor'; in these instances, we will seek informed consent directly from the young woman.

#### **14. How are participants recruited for the study?**

Recruitment teams partner with local organisations and conduct community outreach events to introduce the study to potential participants. They hand out flyers, give health talks and encourage women who are interested in the study to visit the local study site for further information.

At the sites, educational sessions are held and women are given additional information that they can take home to learn more about the study before deciding whether to participate. When a woman decides that she wants to participate, she goes through an informed consent process. The potential participant sits with a counsellor, and together they go through the informed consent form and discuss why the study is being conducted, the aims of the study, study procedures, and the risks and benefits of participating. After the potential participant has understood and signed the informed consent form, screening tests and counseling are carried out. If the tests confirm that the woman is eligible and if she still wants to participate in the study, only then can she be enrolled.

#### **15. How does the ECHO Study work?**

Women interested in joining the study learn about the study procedures and the risks and benefits of participation through an informed consent process. Counsellors carefully explain how the study randomly assigns participants to receive one of three contraceptives: DMPA, a hormonal implant containing levonorgestrel or the copper IUD. They counsel women to ensure they would be happy with any of the three study methods. There are also separate screening and enrolment visits to ensure that each woman has time to consider her options and does not feel pressured to take part in the study or to start a method she does not want.

Women who are enrolled and randomly assigned to a method are asked to visit the study clinic every three months. During these regular visits, they receive counselling on contraception and HIV risk reduction and are assessed for pregnancy, HIV and other sexually transmitted infections (STIs), and side effects from the contraception. They are also asked limited questions about sexual behaviour (for example, about condom use and number of partners) and their experiences with the contraceptive method they are using. Women assigned to receive injectable contraception are given injections according to the product's dosing schedule.

At the end of the study, the researchers will compare the number of women in each group who acquired HIV, became pregnant or experienced side effects that led them to stop using the contraceptive method to which they were randomly assigned.

**16. Will the study participants benefit directly from the study?**

All study participants are volunteers, and they agree to join the study without being paid for their participation. Participants are reimbursed for their transport costs to attend regular study visits. During the study period, participants also receive health services, such as HIV counselling and testing, contraceptives, condoms, and screening and any needed treatment for STIs.

**17. Will participants have the option to receive antiretroviral pre-exposure prophylaxis (PrEP)?**

The ECHO Study is committed to providing the highest standards of HIV prevention services to participants as recommended by Good Participatory Practice guidelines. Participants who are interested in antiretroviral pre-exposure prophylaxis (PrEP) will be referred to services as programmes become available in each study community. PrEP use is permitted by the study protocol, and data on PrEP use will be collected throughout the study. The ECHO Study was designed so that investigators will be able to determine if use of any of the study contraceptives is associated with a higher risk of HIV infection compared to the other study contraceptives even if some participants are taking PrEP.

**18. Where will the study be conducted?**

The ECHO Study is being conducted at 12 trial sites in four countries: Kenya, South Africa, Swaziland and Zambia (see next question for full list of sites). These countries were selected because women in southern and East Africa continue to be among the hardest hit by HIV and maternity mortality. DMPA is also the most widely used modern method of contraception in the region. It is important to work with affected communities to ensure the study provides evidence based on the population most in need of guidance on hormonal contraceptive use and any possible link with HIV acquisition.

**19. Who is conducting the ECHO Study?**

Leading global and national institutions are collaborating on the ECHO trial. The study is jointly sponsored by FHI 360, the Wits Reproductive Health and HIV Institute (WRHI), and the University of Washington, who are coordinating to implement the trial. The World Health Organization is a partner on the study, along with investigators from the Kenya Coast Provincial Hospital/ International Centre for Reproductive Health, the Kenya Medical Research Institute, the University of Fort Hare, and the University of Zimbabwe.

Collaborating study site partners include: in South Africa, the Aurum Institute in Klerksdorp, the Desmond Tutu Foundation Emavundleni Research Centre in Cape Town, the Effective Care Research Unit in East London, the Madibeng Centre for Research in Brits, Maternal, Adolescent and Child Health (MatCH) Research in Durban and Pietermaritzburg, the Qhakaza Mbokodo Research Clinic in Ladysmith, the Setshaba Research Centre in Shoshanguve and WRHI / University of the Witwatersrand in Johannesburg; in Kenya, the KEMRI-RCTP Study Centre, Lumumba Health Centre, in Kisumu; in Swaziland, the Family Life Association of Swaziland and ICAP-Columbia in Manzini; and in Zambia, the UNC Global Projects Zambia/Kamwala Clinic in Lusaka.

## **20. When did the study begin, and when will it end?**

The study began in December 2015, when two sites in South Africa started screening and enrolling participants. Enrolment of all participants is expected to take approximately 18 months to complete, and the total duration of the study in the field will be approximately 36 months from first enrolment. However, the study could end earlier or later, because the protocol is endpoint-driven. This means that the study will run until it reaches its research goal. If the study proceeds as planned, the study team anticipates that the results will be released in 2019.

## **21. How is the study funded?**

A consortium of donors is funding the study. They include the Bill & Melinda Gates Foundation, the US Agency for International Development (USAID), the Swedish International Development Cooperation Agency (SIDA), the United Nations Population Fund (UNFPA) and the Medical Research Council of South Africa. In addition, USAID and the South African government are donating the contraceptives used in the study.

## **22. What approvals were required for this study?**

The ECHO Study has been reviewed and approved by the institutional review board (IRB) of FHI 360 and by local research ethics committees in the countries where it is being conducted. In addition, national regulatory authorities, including the South African Medicines Control Council (MCC) and Kenya's Pharmacy and Poisons Board, have been notified of the study.

## **23. Who oversees the study?**

There are a few groups that together oversee the ECHO Study. A stewardship committee composed of the funders oversees the ECHO consortium, and their main role is to assure the financial resources and operational milestones of the trial. A management committee provides overall accountability of the ECHO Study, including meeting the timelines and major trial

milestones; the management committee includes representatives from the three organisations sponsoring the study (FHI 360, WRHI and the University of Washington). Finally, the implementation team is responsible for overseeing the implementation of the protocol and has final responsibility for trial conduct, including Good Clinical Practice (GCP) quality assurance and regulatory oversight.

In addition, an independent Data and Safety Monitoring Board (DSMB), comprised of global experts in reproductive health, HIV and biostatistics, has been established to oversee the well-being of participants. The DSMB reviewed the protocol before the study began and conducts regular reviews of the study data every six months. The DSMB can recommend modifying or stopping the study if there is a safety concern, or if a reliable result is unlikely by the end of the study. This could happen in the event of low enrolment, low contraceptive continuation, poor retention or other potential operational challenges.

#### **24. How does the study monitor participants' safety and well-being?**

The study has several mechanisms for monitoring the safety of participants and implementation of the study. An independent Data and Safety Monitoring Board (see #23) is responsible for reviewing all safety study data and ensuring that participants' well-being is protected. If the DSMB members have safety concerns, they can recommend that the study be modified or stopped.

The study site investigators are responsible for continuous safety monitoring of all study participants and for alerting the safety monitor and protocol management team if unexpected concerns arise. The safety oversight committee reviews safety data from all sites monthly and is available 24-7 to the sites for clinical advice.

#### **25. What happens if a participant acquires HIV during the study?**

The well-being of the women enrolled in the study is the ECHO Consortium's highest priority. ECHO researchers do their best to reduce each participant's risk by providing condoms and HIV prevention counselling. Even so, because of the high rates of HIV in their communities, some women are likely to acquire HIV during their participation in the ECHO study.

Women who seroconvert during the study will receive counselling and will be referred to local HIV care providers for on-going care, including assessment of CD4 cell counts and antiretroviral treatment according to local guidelines. They will be asked to remain in the study until completion of the follow-up period. This will give participants the opportunity to continue receiving services at the clinical site and will allow researchers to continue collecting data relevant to the additional study questions.

**26. What happens to participants who become pregnant during the study?**

Study staff will provide care or refer for further care women who become pregnant, according to their wishes and in keeping with local laws. If a pregnancy continues, the woman will discontinue her assigned method but will remain in the study to the end of the follow-up period so that study staff can continue collecting data on HIV acquisition. Should a pregnancy end prior to completion of study follow-up, the woman will be encouraged to resume her allocated method of contraception but will be offered a choice of any method available at the study site. If a pregnancy continues beyond the end of the study, the woman will be referred for further care of her pregnancy.

**27. What happens to participants who want to switch to a different contraceptive method during the study?**

The study team pays close attention to the eligibility criteria and conducts thorough counselling before enrolling women in the study, to ensure that participants are comfortable with random assignment to a method and are willing to continue using that method throughout the study. If a woman experiences side effects or concerns regarding her assigned method, she will be advised to come to the clinic to discuss her questions and experience with the method. Trained clinicians will work closely with participants to resolve any challenges faced.

Some women may wish to switch to another contraceptive method despite receiving counselling and treatment for any side effects. Participants are free to change methods at any time during the study. If a participant prefers a non-study contraceptive method, she will receive that method either on site or by referral. All women who switch methods will remain in the study and will be seen according to the same schedule as other participants. Women who choose not to use any contraceptive method will similarly continue to be followed according to the same schedule as all other participants.

**28. What will happen to study participants' contraception when the trial is over?**

When a participant exits the ECHO Study, she will be given the option to remain on the same contraceptive to which she was randomly assigned at the beginning of the study. Any woman who wishes to switch methods can have her study-assigned method removed (if she was assigned to an IUD or implant) and have any new method provided by the site at no cost. A participant who had been assigned to an IUD or implant may also choose not to use contraception after the device is removed.

## 29. How is the operational feasibility of the study being monitored?

As with all clinical trials, the ECHO study has a set of challenges which are being monitored closely. One anticipated challenge was whether women would accept randomisation. Several studies have successfully randomised women to use either an IUD or an injectable contraceptive.<sup>3</sup> The ECHO Study team has taken great care to ensure women are properly selected and counselled appropriately, which has resulted in very few participants who have refused to start the method to which they were assigned.

Method continuation is also critical to the success of the trial, because a high percentage of women must continue their assigned methods to ensure sufficient statistical power to detect any differences in HIV acquisition among the groups. To promote and support method continuation, study staff receive intensive training in contraceptive method delivery and management, and women are carefully screened prior to study entry. The study sites are closely monitored to ensure that the study team responds quickly if retention is low or contraceptive discontinuation rates are higher than anticipated. This monitoring will allow the study leadership to intervene with sites that have difficulty in the conduct of the study, and to modify or discontinue the study if required.

### About the Products

## 30. How do the contraceptives being tested work?

**DMPA** is given by injection every three months and is slowly absorbed into the blood stream to prevent pregnancy. DMPA contains a synthetic progestogen that acts like the hormone progesterone, which occurs naturally in a woman's body. It works primarily by preventing the release of eggs from the ovaries (ovulation) and by thickening the cervical mucus, which prevents sperm from penetrating into the uterus (womb) and fallopian tubes and meeting an egg. Once women stop using DMPA, there may be a six- to nine-month delay before she is able to conceive.

**Levonorgestrel implant (Jadelle)** consists of two thin, flexible rods that are inserted just under the skin of a woman's upper arm, where they continuously release low doses of the synthetic progestogen levonorgestrel into the bloodstream. Once inserted, Jadelle protects against pregnancy for up to five years but can be removed at any time. Like DMPA, it works primarily by preventing ovulation and thickening the cervical mucus. Implants do not delay the return of a woman's fertility after they are removed. Women who stop using implants can become pregnant as quickly as women who stop non-hormonal methods.

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**The copper IUD** is a small, flexible plastic frame with copper sleeves or wire around it. Once inserted in the uterus, it provides contraceptive protection for 10 years but can be removed at any time. The copper IUD prevents pregnancy mainly by preventing fertilisation. Once the IUD is removed, fertility returns quickly.

**31. What are benefits and side effects of each of the contraceptives being tested in the study?**

All of the contraceptives being tested in the ECHO Study are highly effective, long-acting, reversible, private methods that do not interfere with sex. The specific benefits and side effects of each method are summarised in the following table.

## Contraceptives being used in the ECHO Study

Family Planning	<b>DMPA</b> 	<b>Levonorgestrel Implant (Jadelle)</b> 	<b>Copper IUD</b> 
<b>What it is</b>	DMPA (depot medroxyprogesterone acetate, also known as Depo Provera) is the most widely used progestogen-only injectable.	This implant consists of 2 thin, flexible rods filled with a progestogen (levonorgestrel) that are inserted just under the skin of a woman's upper arm.	The copper-bearing intrauterine device is shaped like a 'T' and is the size of a matchstick. It is made of soft but strong plastic with copper bands and has a 'tail' made of 2 strings. The doctor or nurse places it in the womb.
<b>Frequency</b>	Given every 3 months	Once inserted, lasts up to 5 years; can have it removed at any time	Once inserted, lasts up to 10 years; can have it removed at any time
<b>Benefits</b>	<ul style="list-style-type: none"> <li>• Long-acting and privacy of use — given by injection into the muscle</li> <li>• No interference with sex</li> <li>• Often stops monthly periods</li> <li>• Can be used during breastfeeding</li> <li>• Protects against uterine cancer &amp; uterine fibroids</li> </ul>	<ul style="list-style-type: none"> <li>• Long-acting and privacy of use—inserted underneath skin of the arm</li> <li>• No interference with sex</li> <li>• Often stops monthly periods while being used</li> </ul>	<ul style="list-style-type: none"> <li>• Long-acting and privacy of use</li> <li>• No delay in return to fertility</li> <li>• May protect against uterine and cervical cancer</li> </ul>
<b>Side Effects</b>	<ul style="list-style-type: none"> <li>• Irregular or prolonged menstrual bleeding initially, followed by infrequent or no bleeding</li> </ul> In some women: <ul style="list-style-type: none"> <li>• Reversible reductions in bone density</li> <li>• Mood changes, including depression</li> <li>• Weight gain</li> <li>• Diminished libido</li> </ul>	<ul style="list-style-type: none"> <li>• Prolonged/irregular menstrual bleeding</li> <li>• Application site reactions</li> <li>• Dizziness</li> <li>• Headache</li> <li>• Vaginal discharge</li> <li>• Breast pain</li> <li>• Nausea</li> <li>• Pelvic pain</li> <li>• Urinary tract symptoms</li> <li>• Vaginitis</li> <li>• Weight gain</li> </ul>	<ul style="list-style-type: none"> <li>• Changes in menstrual bleeding (heavier periods and more menstrual cramps) are common, especially in the first 3 to 6 months of use</li> <li>• Some women have light bleeding between periods</li> </ul>
<b>Return to Fertility</b>	<ul style="list-style-type: none"> <li>• Return of fertility is often delayed by 6–9 months after the last injection.</li> </ul>	<ul style="list-style-type: none"> <li>• Rapid return to fertility once removed</li> </ul>	<ul style="list-style-type: none"> <li>• Return to fertility can be immediate.</li> </ul>