Jadelle®

Contraceptive Implants up to 5 years
First Implants WHO-prequalified (since September 2009)

Global HealthCare Programs
Family Planning

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Agenda

- General Information
- Impact of Jadelle®
- Facts
- Important Guideline
Jadelle® Contraceptive Implants

First Implants WHO Prequalified since September 2009

Jadelle® 2 x 75mg Implants  Disposable Trocar for insertion
Jadelle® Disposable Trocar with CE Mark

- Developed by Bayer AG and Süddeutsche Feinmechanik, Wächtersbach/Germany
- Manufacturer: Süddeutsche Feinmechanik, Wächtersbach/Germany
- Bayer logo, 2 laser marks
- Launched in December 2009
Packaging of Jadelle® Implants
Worldwide use of Jadelle® Implants

Registered in more than 50 countries worldwide
(in Regions Africa, Asia, Europe, Latin America and US)
Pharmacokinetics (1)

The daily release is about

• 100 mcg/day of LNG over the first month
• 40 mcg/day at 12 months
• 25 mcg/day at 5 years

Serum LNG concentrations

• **Rise** to 772 pg/ml within 48 hours
• **Decline** to a mean level of:
  • 355 pg/ml at 6 months
  • 277 pg/ml at 5 years

*Jadelle® provides a very high level of contraceptive efficacy for up to 5 years*

Source: Sivin et al1997b, Sivin et al.2001
Pharmacokinetics (2)
Hümpel et al. 1997

Mean serum levels of levonorgestrel (pg/ml) achieved with Jadelle®

Source: Sivin et al. 1997b, Sivin et al. 2001
Mode of contraceptive action (1)

- Thickening of cervical mucus, preventing passage of sperm into the uterus \(^1,2\)
- Suppression of endometrial maturation \(^3\)
- Decrease of natural progesterone production from the ovaries to about 52–68\% \(^4\)

*Inhibition of ovulation in 45–85\% of cycles*

1. Brache et al. 1990, Croxalto et al. 1987
No inhibition of endogenous estradiol

»Mean estradiol levels during the 5 years do not differ from those in control patients.«¹

»... is reflected in unchanged vertebral bone density at one year.«²

LNG implants do not have a negative effect on bone density

¹ Croxatto et al, Contraception 1988; Brache et al, Contraception 1990
² Cromer et al, J. of Pediatrics 1996
Contraceptive efficacy (1)

<table>
<thead>
<tr>
<th>Method</th>
<th>Typical use</th>
<th>Perfect use</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNG implants (Jadelle®)</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>LNG IUS (Mirena®)</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Combined or progestin-only pill</td>
<td>9</td>
<td>0.3</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>0.15</td>
<td>0.1</td>
</tr>
<tr>
<td>Progestin-only injectable</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Copper IUD</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Male condom</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

Percentage of women experiencing unintended pregnancy within first year of use

Modified from http://www.contraceptivetechnology.org/CTFailureTable.pdf
Contraceptive efficacy (2)

• Pearl Index during 5 years 0.17
• Contraceptive failure rate 0–0.8%
• Cumulative rate over 5 years 1.1%

• Ectopic pregnancy rate 0.04 % lower than for women not using contraceptives (1) 0.3%

• Because contraceptive efficacy decreases after 4 years of use, change of Jadelle implants should be considered after 4 years, especially with women weighing over 60 kg

Continuation rates (1)

Gross cumulative termination and continuation rates for Jadelle® use

<table>
<thead>
<tr>
<th>Rate (+SE) per 100 subjects</th>
<th>Year 1</th>
<th>Year 3</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>0.1 (0.1)</td>
<td>0.3 (0.2)</td>
<td>1.1 (0.4)</td>
</tr>
<tr>
<td>Menstrual problems</td>
<td>4.5 (0.6)</td>
<td>14.1 (1.0)</td>
<td>19.3 (1.2)</td>
</tr>
<tr>
<td>Medical problems</td>
<td>4.7 (0.6)</td>
<td>14.7 (1.0)</td>
<td>23.1 (1.3)</td>
</tr>
<tr>
<td>Planning pregnancy</td>
<td>1.1 (0.3)</td>
<td>9.7 (0.9)</td>
<td>18.6 (0.3)</td>
</tr>
<tr>
<td>Other personal</td>
<td>1.6 (0.3)</td>
<td>7.2 (0.8)</td>
<td>12.5 (0.1)</td>
</tr>
<tr>
<td>Used other method</td>
<td>0.2 (0.1)</td>
<td>0.9 (0.3)</td>
<td>3.7 (0.7)</td>
</tr>
</tbody>
</table>

| Women started year | 1393 | 1011 | 668 |
| Women completed year | 1212 | 817 | 525 |

| Continuation rate    | 88.3 (0.9) | 60.6 (1.3) | 41.5 (1.3) |

Source: adopted from Croxatto, Diaz and Pavez 1982
Continuation rates (2)

Clinical studies with LNG implants in developing countries showed high continuation rates after:

- 2 years of use: up to 95%³
- 3 years of use: 65%⁴
- 5 years of use: 41.5%⁵

In developing countries continuation rates with LNG implants were shown to be significantly higher than with

- Combined oral contraceptive pills⁶
- Injectable contraceptives and LNG IUS⁷

³ Zenger, Contraception 1995
⁴ Rizk, J. Reproduct. Med. 1995
⁵ Sivin, Population Council 2002
⁶ Rakshani, East Med. Health 2004
⁷ Chaudhury, Contraception 1988
Return of Fertility

- Prompt return of fertility after removal of LNG implants

- Pregnancy occurs within
  - 3 months  45%
  - 1 year  86%

These rates are similar to women not using contraceptives.

Clinical and metabolic effects (1)

A prospective, long-term (5 year) study in 32 clinics in 8 developing countries compared

- 7,977 LNG implant users with
- 6,625 IUD users and
- 1,419 sterilized women

The study confirmed the safety of LNG implants showing:

- No significant increase with respect to serious disease and
- No significant excess of
  - Reproductive morbidity
  - Malignant disease
  - Cardiovascular events
  - Severe depression
  - Connective tissue disease

Meirik et al, Contraception 2001
Clinical and metabolic effects (2)

- Long-term studies (5 years) on lipids and glucose tolerance showed no increase in cardiovascular risk indicators.
- Studies for liver, kidney, adrenal, thyroid and endocrine function, and hematology showed no adverse effects.
- Studies in mineral bone density showed significant increase or no change.
- The effects of Jadelle on clotting factors have varied. A causal relationship of Jadelle use to thromboembolism has not been established. An individual benefit-risk assessment should be performed in patients at risk.
- More than 3 years of use of LNG implant was not associated with abnormal Pap smear findings.

1. Population Council, 2 Dorflinger 2002

Menstrual bleeding pattern (1)

Menstrual disturbances have been the most common side effects reported during 5 years of use

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased duration of bleeding</td>
<td>27.0%</td>
</tr>
<tr>
<td>Irregular periods</td>
<td>20.9%</td>
</tr>
<tr>
<td>Spotting</td>
<td>15.8%</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>12.3%</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>11.2%</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

Source: Adapted from Sivin et al 1989
References to be found at the end of this presentation
Menstrual bleeding pattern (2)

Menstrual disturbances are most common during the first 6–9 months of use when ovulation is most often impaired. As ovulatory cycles become more re-established, the frequency of bleeding irregularities is reduced.¹⁰

<table>
<thead>
<tr>
<th>Menstrual pattern (% of users)</th>
<th>Year 1</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular cycles</td>
<td>27</td>
<td>62</td>
</tr>
<tr>
<td>Irregular cycles</td>
<td>66</td>
<td>38</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>7</td>
<td>0 ¹¹</td>
</tr>
</tbody>
</table>

¹¹ Shoupe et al, 1991
Menstrual bleeding pattern (3)

Discontinuation rates due to menstrual problems \(^{12}\)

- Annual rate \(0.9−7.1\%\)
- 5-year cumulative rate \(12.1−24.2\%
- Anemia does not occur, instead statistically significant increases in mean hemoglobin levels were reported after reductions in menstrual blood loss. \(^{13}\)

\(^{12}\) Sivin, Studies in Family Planning 1988

\(^{13}\) Huupponen 1999 Clinical Expert Report Table 16 on page 18
Non-menstrual side effects

Over 5 years of use, 14% of women discontinued due to non-menstrual adverse effects

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Incidence (% of subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>30.5</td>
</tr>
<tr>
<td>Leucorrhea</td>
<td>30.3</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>24.4</td>
</tr>
<tr>
<td>Weight increase</td>
<td>22.4</td>
</tr>
<tr>
<td>Genital pruritus</td>
<td>16.3</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>14.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14.5</td>
</tr>
<tr>
<td>Breast pain</td>
<td>12.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>11.6</td>
</tr>
<tr>
<td>Acne</td>
<td>10.9</td>
</tr>
<tr>
<td>Dysuria</td>
<td>9.0</td>
</tr>
<tr>
<td>Nervousness</td>
<td>8.6</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>8.2</td>
</tr>
<tr>
<td>Cervical lesion</td>
<td>7.6</td>
</tr>
<tr>
<td>Cervicitis</td>
<td>7.1</td>
</tr>
<tr>
<td>Pain at implant site</td>
<td>6.9</td>
</tr>
<tr>
<td>Implant site reaction</td>
<td>6.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Source: Clinical Expert Report Leiras 1999
The role of counseling on continuation rates

- Counseling on side effects and bleeding irregularities was shown to be essential for high continuation rates.

- Studies in developing countries found high continuation rates of up to 95% after 2 years, 65% after 3 years, and 41.5% after 5 years.

Contraceptive benefits

- Highly effective reversible contraceptive
- Contraceptive effectiveness begins 24 hours after insertion, when inserted during the menses and stops after removal
- Long-term method (up to 5 years)
- Pelvic examination not required prior to use
- No interference with intercourse
- Does not affect breastfeeding
- Immediate return of fertility after removal
- Return to clinic required only for removal or if problems occur
- Contains no estrogen
Non-contraceptive benefits

- Trend to increased hemoglobin concentration
- Reduction in dysmenorrhea
- Significantly lower rate of PID compared to copper IUD users
- Decrease in ectopic pregnancies
- May protect against endometrial cancer and benign breast disease

Sivin, Studies in Family Planning 1988; Affandi, Contraception 1988; Farley, Contraception 2001

Lower rate compared to copper IUD described in the Norplant PMS (Meirik Contraception 2001). This was reproduced in the WHO study comparing Implanon and Jadelle with (non-randomized) copper IUD users. (Bahamondes Human Reproduction 2015). PID associated with insertion of an IUD is acknowledged as class effect, so it is not a benefit per se, but a benefit compared to copper IUD use.
Women who can use Jadelle® (1)

- Any reproductive age
- Any parity including nulliparous
- Wanting highly effective, long-term contraception
- Breastfeeding (6 weeks or more postpartum)
- Postpartum and not breastfeeding
- Post abortum
Women who can use Jadelle® (2)

- With desired family size who do not want sterilization
- With history of ectopic pregnancy
- With menstrual cramping
- Who smoke (any age)
- Who should not use estrogen
- Who experience difficulties in compliance for daily pill intake
Jadelle® in breastfeeding women

Jadelle® can be used by breastfeeding women six weeks post partum

• May increase quantity of breast milk

• Has no effect on
  • Initiation or duration of breastfeeding
  • Long-term growth and development of infants

Source WHO1988, WHO 1994a, 1994 b
Women who should not use Jadelle®

Contraindications:

• Known or suspected pregnancy
• Undiagnosed vaginal bleeding
• Breast cancer or other hormone dependent cancer
• Presence or history of severe liver disease or liver tumor
• Active thromboembolic disease
• Hypersensitivity to LNG or any other component
Conditions requiring precautions

In the following cases, Jadelle is only recommended upon individual risk benefit analyses if other methods are not available or acceptable:

- Significant risk factors for arterial or venous disease
- Ischemic heart disease or stroke
- Jaundice (active, symptomatic)
- Patient develops migraine headaches with aura or benign intracranial hypertension during use
- Sustained arterial hypertension
- Patient becomes significantly depressed during use
- “Chronic treatment with drugs that may affect contraceptive efficacy of Jadelle, including treatment for epilepsy (...), tuberculosis (...) and certain anti-retroviral regimen (in particular ART including efavirenz)” (SmPC Jadelle)
Conditions no longer requiring precautions for use due to change in WHO MEC (1)

WHO class 1 (use without restrictions) or 2 (generally use the method) in cases of

- Diabetes (incl. complicated and > 20 years’ duration)
- Viral hepatitis
- Elevated blood pressure (incl. history of hypertension during pregnancy)
- Smoking (any amount, any age)
- Surgery (incl. major surgery with immobilization)
- Valvular heart disease (including symptomatic)
- Known thrombogenic mutations or hyperlipidaemias

1. WHO Medical Eligibility Criteria for Contraceptive use 5th Edition 2015
Limitations of LNG implants

- Changes in menstrual bleeding pattern in most women
- Require well-trained provider for insertion and removal
- Women must return to trained provider for removal or new insertion
- Women cannot stop whenever they want (provider-dependent)
- Effectiveness lowered by drugs for epilepsy (phenytoin, barbiturates) and tuberculosis (rifampin) and certain ART regimen (including efavirenz)
- Cost-effectiveness dependent on length of use
- No protection against STDs (e.g. HBV, HIV/AIDS)
When to insert? (1)

Optimal times for insertion are

- Within 7 days from onset of menstrual bleeding
- Immediately or within 7 days after abortion
- Immediately or within 3 weeks postpartum if not breastfeeding
- From 6 weeks postpartum if breastfeeding
When to insert? (2)

Recommended times for insertion when changing from another contraceptive

- **Natural family planning or barrier method:** before day 7 of menstrual cycle
- **Combined oral contraceptive:** within 7 days of last active pill
- **Progestogen-only pill, implant or intrauterine system:** on the day the last pill is taken, or the implant or intrauterine system removed
- **Combined or progestogen-only injectables:** any time before next injection
- **IUD:** any time, after insertion leave IUD for 7 days
Recommendations for infection prevention

- Wash patient’s entire arm and hand before antiseptic preparation
- Use sterile or high-level disinfected instruments and surgical gloves
- After use, decontaminate all items
- Place disposable needle and syringe and other waste in puncture-proof container
- Cleaning and sterilization (or high-level disinfection) of reusable items
Client instructions

- Keep incision area dry for 48 hours
- Keep pressure bandage on for 48 hours, leave band-aid until healing (3–5 days)
- Temporary bruising, swelling, and tenderness are common
- Routine work can be done immediately
- Avoid bumping of the area, carrying heavy loads, or unusual pressure to the insertion area
General information

- Contraceptive effectiveness begins 24 hours after insertion when inserted during the menses and stops after removal
- Changes in menstrual bleeding patterns are common
- Certain drugs may reduce effectiveness
- Removal necessary after 5 years
- Fibrous tissue may be felt after removal
- Use condom if at risk of STDs (e.g. HBV, HIV/AIDS)
## Insertion site problems

<table>
<thead>
<tr>
<th></th>
<th>% of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Expulsions</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>&lt; 0.5</td>
</tr>
</tbody>
</table>

*Source: Population Council 1990*
When to return to a clinic?

Women should return to a clinic in case of

- Delayed period after several months of regular cycles (pregnancy?)
- Severe lower abdominal pain (ectopic pregnancy?)
- Heavy bleeding
- Pus, bleeding, or infection at insertion site
- Expulsion
- Migraine headache
Use of LNG implants in developing countries (1)

- Long-acting alternative to short-term acting contraceptives
- Substitute for sterilization, IUDs, or injectable
- High efficacy comparing favorably to other reversible methods
- Suitable for women with low compliance with other methods
- No estrogenic side effects, suitable for women with contraindications to estrogens
- Favorable pharmaco-economic cost-benefit analysis
Use of LNG implants in developing countries (2)

- Breastfeeding not affected
- Users need to return to clinic only for follow-up or removal of implants, suitable for areas with weak healthcare infrastructure
- Suitable for women who have completed a family and who do not want permanent sterilization
- Suitable for women with anemia
- Ideal for birth spacing because of quick reversibility
- Suitable for long-acting and reversible contraception after abortion or childbirth
Use of LNG implants in developing countries (3)

- Few serious side effects, low dose of hormone (about 30 mcg LNG daily), no estrogen
- May be started immediately postpartum, (if not breastfeeding) or post abortum
- Reduction of dysmenorrhea (menstrual cramping)
- Suitable also for nulliparous women
- Reduction of PID compared to copper IUD users

1 Lower rate compared to copper IUD described in the Norplant PMS (Meirik Contraception 2001). This was reproduced in the WHO study comparing implanon and Jadelle with (non-randomized) copper IUD users. (Bahamondes Human Reproduction 2015). PID associated with insertion of an IUD is acknowledged as class effect, so it is not a benefit per se, but a benefit compared to copper IUD use.
Requirements for provision of implants

• Attention to counseling and information
• Access to trained providers
• Assurance of provider competence
• Adherence to aseptic procedures
• Well-functioning logistic system
• Management information system (MIS) to locate clients
• System to monitor quality of care
• Commitment by national programs or donors to sustain provision of implants
• Private location for insertion, removal, and counseling
• Community participation

Sivin et al, Population Council 2002
Clinical expert Report by Huupponen, references 16 and 17


Singh K and Ratnam SS. A study on the effects of Norplant implantable contraceptive on lipid, lipoprotein, and apolipoprotein metabolism in Singaporean women. Contraception 1997;56:77-83

Clinical expert report references 18 and 19


Huupponen R. Jadelle Clinical Expert Report 1999

Huupponen 1999 Clinical Expert Report Table 16 on page 18
Thank you!

www.jadelle.com