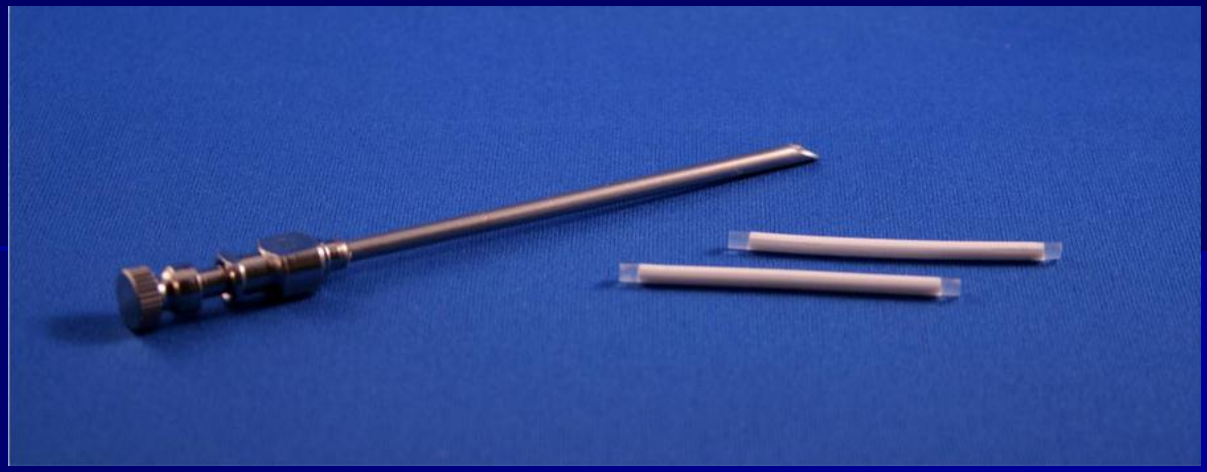
JADELLE ®



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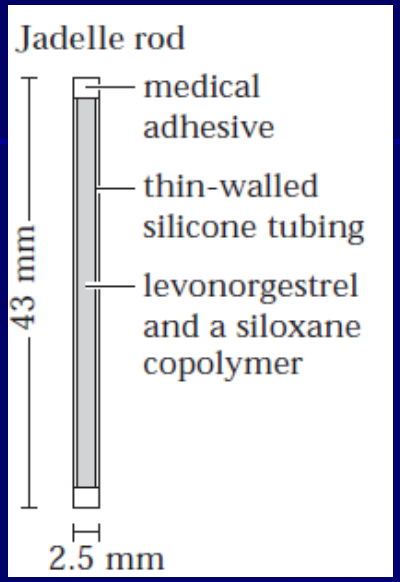
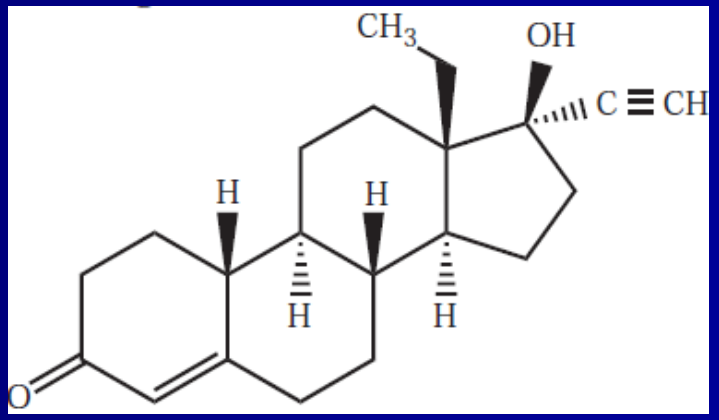
Composition of Jadelle





Implants in general worldwide

Common Trade Name	Formulation	Labeled Length of Use	Average Insertion Time[1]	Average Removal Time[1]	Registration	Bulk Public Sector Price[2]
Implanon®, manufactured by Organon	1 rod containing 68 mg etonogestrel	Up to 3 years	1.5 minutes	2.7 minutes	Registered in more than 40 countries.	US$19–$25
Norplant®, manufactured by Bayer Schering Pharma	6 capsules, each containing 36 mg levonorgestrel	Up to 5 years	4.8 minutes	10 to 15 minutes	Registered in more than 60 countries, but unavailable after 2008.	US$23
***Jadelle*®, manufactured by Bayer Schering Pharma**	**2 rods, each containing 75 mg levonor-gestrel**	**Up to 5 years**	**2.5 minutes**	**5 to 7.5 minutes**	**Registered in more than 50 countries**	**US$21–$27**
Sino-Implant (II)®, manufactured by Shanghai Dahua Pharmaceutical	2 rods, each containing 75 mg levonorgestrel	Up to 4 years	Data not available	Data not available	Registered in China and Indonesia. Registration underway in Egypt and other African countries.	US$4.50–$7.50

[1]As measured in clinical trials [2]As of September 2007

Table 2. Continuation Rates for New Implants

Percentage of Women Keeping Their New Implants for One to Five Years, Selected Studies

Authors, Date	Type of Study	Implant	Country	Number of Women Starting Implants	% Continuing to Use at…				
					1Year	2Years	3Years	4 Years	5 Years
Kiriwat et al., 1998	Pilot project/ observational study	*Implanon*	Thailand	100		87	75	72	
Flores et al., 2005	Clinical trial	*Implanon*	Mexico	417	78	67	61		
Chaovisitsaree et al., 2005	Prospective observational study	*Implanon*	Thailand	92	92				
Sivin et al., 1997 & Sivin et al., 1998	Randomized clinical trial	***Jadelle***	***6 countries***	***600***	***94***	***82***	***71***	***63***	***55***
Sivin et al., 1998	Clinical trial	***Jadelle***	***Dominican Republic & United States****	***594***	***83***	***66***	***50***	***37***	***27***
Liu et al., 1999	Prospective observational study	*Sino-Implant (II)*	China	315			80		
Fan et al., 2004	Randomized clinical trial	*Sino-Implant (II)*	China	1,000	96		86		68
Fang et al., 1998	Clinical trial	*Sino-Implant (II)*	China	9,934		90			

* Some women in this study may also be represented in the six-country *Jadelle* study in the row above *(96, 100)*

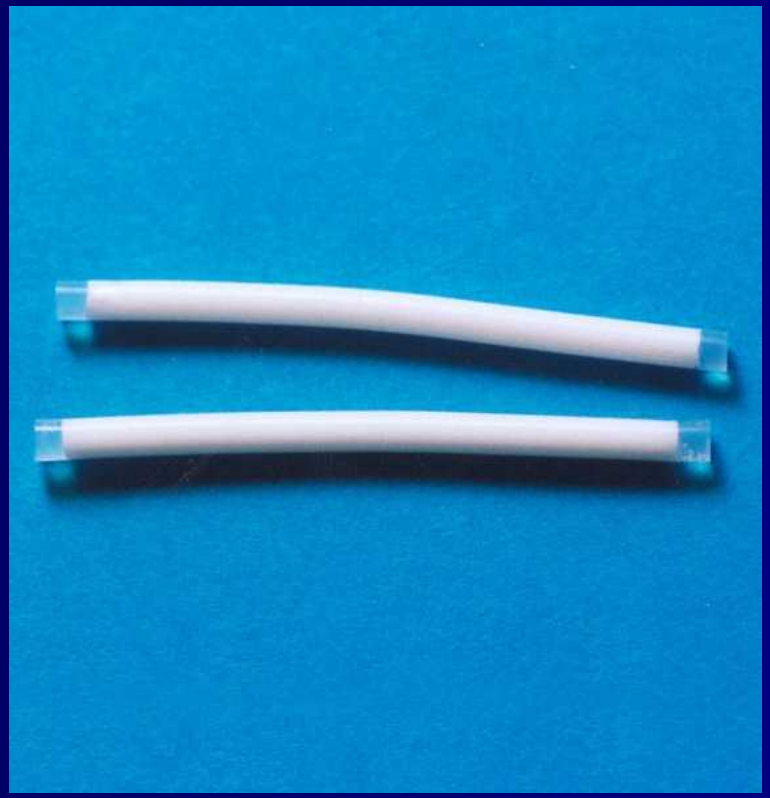
Jadelle (Dis-) Continuation Rates

	year 1	year 2	year 3	year 4	year 5	**Cumulative**
Pregnancy	0.2	0.5	1.2	1.6	0.4	**3.9**
Bleeding Irregularities	9.1	7.9	4.9	3.3	2.9	**25.1**
Medical (excl. bleeding irreg.)	6.0	5.6	4.1	4.0	5.1	**22.4**
Personal	4.6	7.7	11.7	10.7	11.7	**38.7**
Continuation	81.0	77.4	79.2	76.7	77.6	**29.5**

Conflict of interest

- Financial – none
- Bias
  - Contraception: Pill > Implant
    (Opt in_out >> procedure)
  - LNg: Mirena >> Jadelle
    (topical > systemic)
  - Implant: Implanon > Jadelle
    JADELLE >> Depot Provera

The two rod contraceptive implant



JADELLE®

Second generation contraceptive implant

Mechanism of action

only partly understood

- LH suppression = ↓ ovulation;

  high incidence of luteal insufficiency
  - 1/3 of all cycles anovulatory
  - 10% first 2 y, >50% at 5 y
- Cervical mucus thickened: sperm barrier
- Oestradiol-induced endometrial maturation is suppressed → eventual atrophy

Mechanism of action
in the obese

- Body weight (>BMI): ↑kg ⇔ ↓LNg
  - > 70 kg only 4 years use
  - LNg high affinity for SHBG = individual variations
- "Fat gobbles progestins"
- Mirena with predominantly endometrial action (x 1.000!) less affected by weight

Indication

- Delay pregnancy > 2-3 y
- Avoid oestrogen side effects in other combinations
- Compliance issues with PoP > CoC
- IUD/IUS aversion
- Breastfeeding for 1-2 years
- Chronic illness
- Little/no effect on clotting factors

Absolute Contraindication

- ACTIVE thrombo-phlebitis/embolism
- Undiagnosed genital bleeding
- ACUTE liver disease
- Any type of liver tumours
- Known/suspected breast cancer

Relative contraindication

may be used, but other methods preferable

- Severe acne
- Severe vascular or migraine headaches
- Severe depression
- Medication inducing liver enzymes
  - Carbamazepine, phenobarbital, phenytoin
  - Rifampicin, griseofulvin
  - St/ John's Wort
  - Roaccutane!!

Advantages

- Safe, highly effective, continuous
- Little user effort
- Rapidly reversible
- Option A if oestrogen contrainidicated
- Postpartum (6/52) +/- breastfeeding
- Safe and reliable for co-morbid patients
- Higher efficiency than sterilisation (x5 Implanon)

Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Use of a Contraceptive Method

Method	Typical Use	Perfect Use
Chance	85	85
Periodic Abstinence	25	
Calendar		9
Symptothermal		2
Diaphragm	20	6
Withdrawal	19	4
Condom	14	3
Pill	5	
Progestin only		0.5
Combined		0.1
IUD		
Progesterone	**2**	1.5
Copper T 380A	0.8	0.6
Depo-Provera	0.3	0.3
NORPLANT	**0.05**	**0.05**
Female sterilization	**0.5**	0.5
Male sterilization	0.15	0.1

From Hatcher RA et al., *Contraceptive Technology,* 17th Revised Edition. New York, NY: Irvington Publishers, 1998. Table 9-2

Pearl Indices (Pregnancies per 100 woman-years) by Year for Jadelle (levonorgestrel implants (unavailable in us))

	Year 1	Year 2	Year 3	Year 4	Year 5
Annual Pearl Index	0.08	0.09	0.11	0.00	0.84
95% CI	(0.00,0.43)	(0.00, 0.50)	(0.00, 0.61)	(0.00, 0.50)	(0.27, 1.95)
Cumulative Pearl Index	0.08	0.08	0.09	0.07	0.17
95% CI	(0.00, 0.43)	(0.01, 0.30)	(0.02, 0.26)	(0.01, 0.22)	(0.07, 0.34)

Jadelle Failure ↑ ⇔ weight↑ + duration↑

Weight class	year 1	year 2	year 3	year 4	year 5	Cumulative
< 50kg	0.2	0	0	0	0	0.2
50-59 kg	0.2	0.5	0.4	2.0	0.4	3.4
60-69 kg	0.4	0.5	1.6	1.7	0.8	5.0
≥ 70 kg	0	1.1	**5.1**	2.5	0	8.5
All	**0.2**	**0.5**	**1.2**	**1.6**	**0.4**	**3.9**

Annual and Five-Year Cumulative Pregnancy Rates Per 100 Users by Weight Class

Not only for the overweight patient: MIRENA is preferable

Table 3. Estimated Worldwide Use of Implants
Among Women Ages 15–49 (Married or In Union), 2005

Region	% Currently Using		
	Any Method	Any Modern Method	Implants
DEVELOPING AREAS	**58**	**52**	**0.4**
Sub-Saharan Africa	21	15	0.2
Near East & North Africa	52	40	0.1
Asia	63	59	0.5
Latin America & Caribbean	71	62	0.1
DEVELOPED AREAS	**68**	**56**	**0.2**
Europe	**74**	64	0.0
Eastern Europe & Central Asia	63	42	0.0
North America	**75**	71	**0.9**
Other Developed*	***59***	***54***	***<0.10***
WORLD	**59**	**53**	**0.3**

* Includes Australia, Israel, Japan, and **New Zealand** *Methodology and data sources:* Country usage rates from United Nations, 2005 (115) are weighted by the size of the population of women ages 15–49, obtained from population projections for 2005 by the World Bank (120).

A simple exercise estimated that, if 100,000 users of oral contraceptives switched to implants, an estimated 26,000 unintended pregnancies would be prevented over a five-year period

Disadvantages

- Disruption of bleeding pattern esp 1st y
  Endogenous estrogen levels near normal
  Implant's hormone not cyclic withdrawn
  → unpredictable endometrial shedding
- Insertion and removal
  - In surgical procedure
  - By trained personnel
- No self-directed opt-in/out
- 5% complicated removals
- Cultural/ethnic acceptability of metrorrhagia
- [1/3 of pregnancies are ectopic (3/10.000, usu 30)]

Menstrual Effects

- Highly variable
- pattern change: duration, interval, volume
  - 80% year 1
  - 40% year 2-3
  - 33% year 5
- Oligo/amenorrhea
  - 10% year 1, later less
  - Implanon: 20% y1, increasing to 30-40%
- Prolonged bleeding usually only first year
- "Respite Rx":
  - 2 x 625 mcg Premarin or 2 mg Progynova for 7/7
  - COC 1-3/12

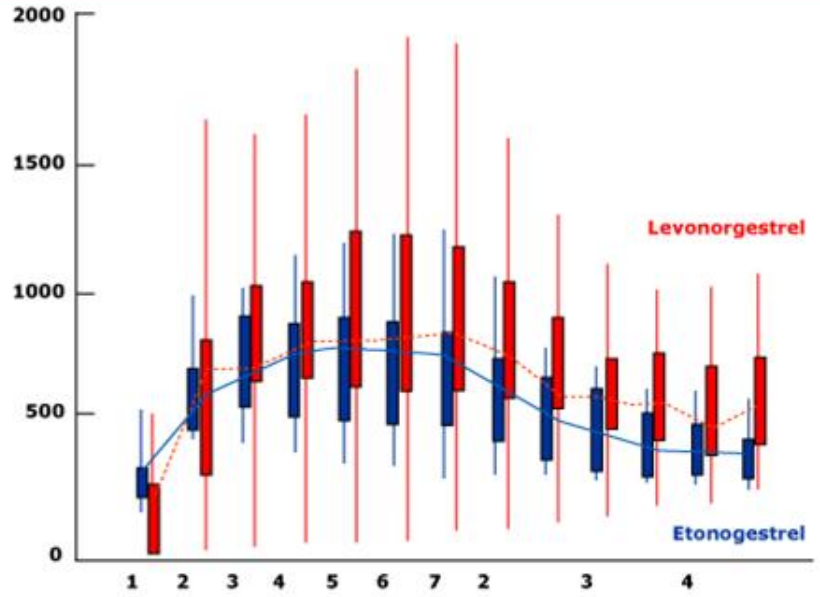
Levonorgestrel is released from the implants directly into tissue fluid.

Serum concentrations

- 772 pg/mL at 48 hours
- 435 pg/mL within one month
- 355 pg/mL within six months
- 277 pg/mL within five years.

Serum levonorgestrel concentrations are inversely related to body weight. The difference is approximately 2-fold between women weighing 50 and 70 kg

Mean serum progestin concentrations in Norplant and Implanon



Eight hours after implant insertion, etonogestrel (MW 324.44) showed a rapid rise to a mean serum concentration of 265.9 + 80.89 pg/ml. This serum concentration is higher than the mean concentration measured after 1 year (196 pg/ml) when not a single ovulation was observed. Maximum concentrations were observed between days 1 and 13, but generally on day 4. Serum concentrations of levonorgestrel (MW 312.46) showed a much larger variability among individuals over time. Maximum serum concentrations were attained between days 1 and 203 with the maximum concentrations on day 20. SHBG concentrations were suppressed with both implants but to a greater degree with Norplant, indicating that levonorgestrel has higher intrinsic androgenic activity.

Data From: Makarainen, L, van Beek, A, Tuomivaara, L, Asplund, B, et al. Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. Fertil Steril 1998; 69:714.

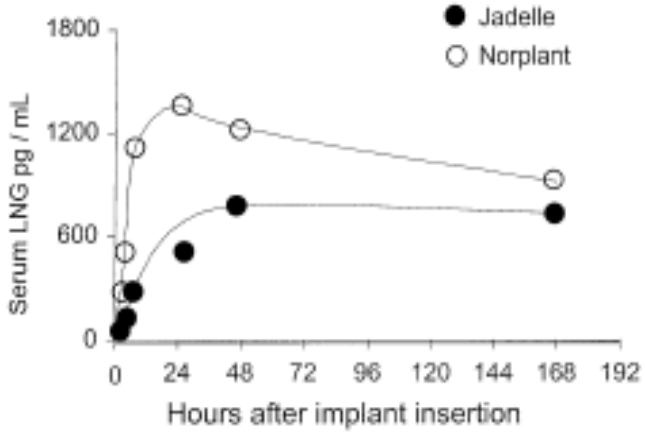


Fig. 3. Serum levels of LNG within the first week following insertion of Norplant or Jadelle.

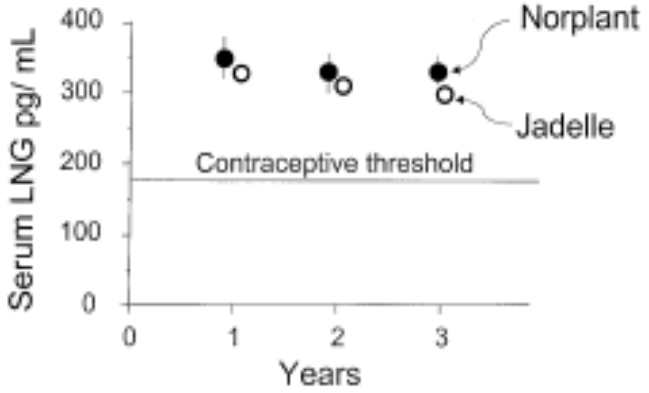


Fig. 5. Serum levels of LNG during the first 3 years of use of Norplant or Jadelle.

Mirena:

The endometrial concentration of LNg from Mirena is 1000 times higher than that observed with Jadelle

into uterine cavity levonorgestrel is released at a rate of approximately 20 mcg/day, decreasing over 5 years to 14 mcg/d .

Serum levels of Mirena– generally half of subdermal implants (DMPA 1-7 ng/ml; Noriday NETA 350mcg = 1-3 ng/ml)

- 166 +/-75 pg/ml – first 4 months
- 131 +/- 32 – 1 y
- 101 pg – 2y
- 74 at 5y

Metabolic effects

- Lipoprotein profile - minor + transient
- Carbohydrate metabolism: minor
- DM, depression, SLE, cardiovascular: nil long term
- Liver function, clotting tests: nil
- SHGB ↓ Jadelle (Implanon unchanged)
- Caution with gallbladder disease: slight ↑

Undesired effects

- Headache – 20% of quitters
- Androgenic effect
  - Acne
  - Weight change
  - Depression and mood swings
  - Hirsutism, hyperpigmentation over rods
  - Galactorrhea, mastalgia
  - Ovarian cysts 8 x more frequent (FSH =)

Non-menstrual side effects

Over 5 years of use, 17% of women discontinued due to non-menstrual adverse effects

Incidence of non-menstrual adverse effects reported during 5 years of use

Adverse effect *Incidence (% of subjects)*

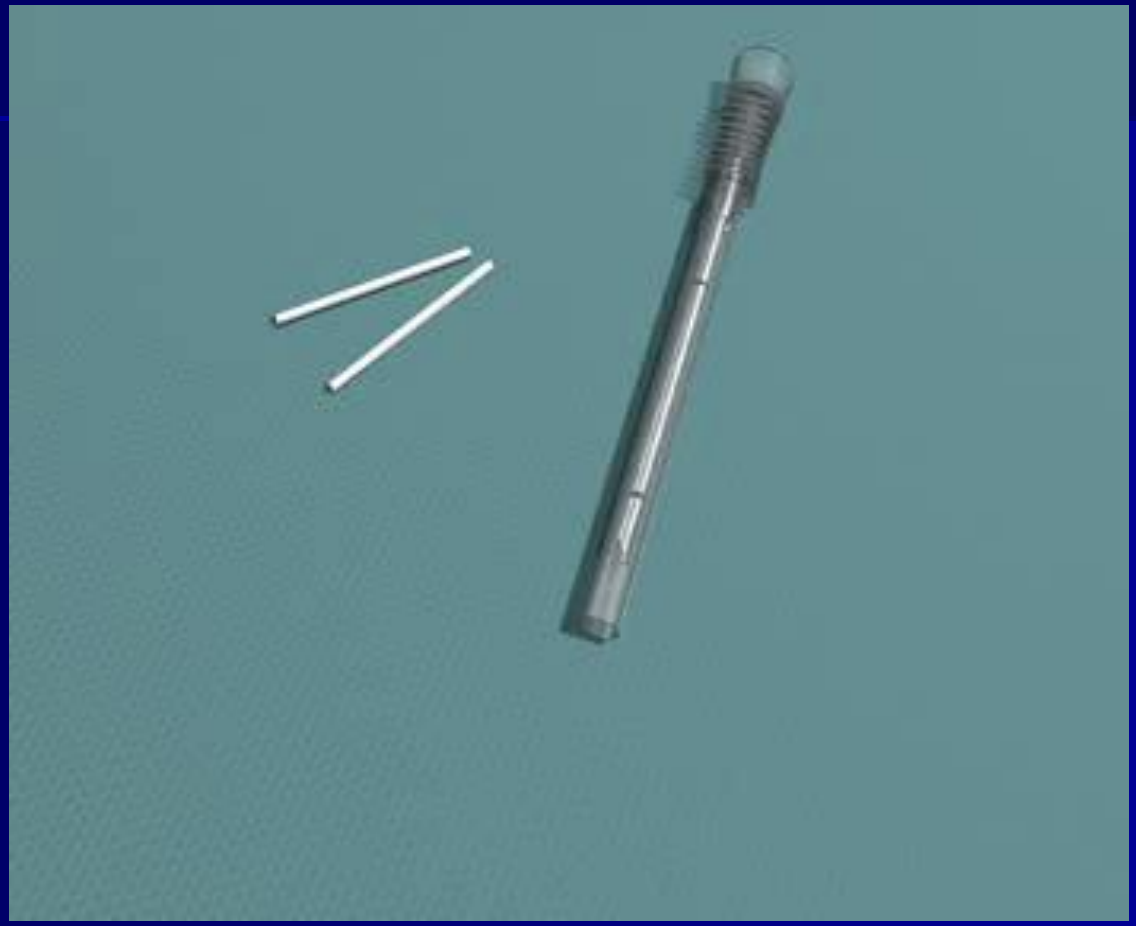
	Jadelle (n=1243)
Headache	30.5
Leucorrhea	30.3
Pelvic pain	24.4
Weight increase	22.4
Genital pruritus	16.3
Fungal infection	14.8
Dizziness	14.5
Breast pain	12.6
Nausea	11.6

	Jadelle (n=1243)
Acne	10.9
Dysuria	9.0
Nervousness	8.6
Contact dermatitis	8.2
Cervical lesion	7.6
Cervicitis	7.1
Pain at implant site	6.9
Implant site reaction	6.7
Fatigue	5.7

Duration of use

- continuation only 30% at 5 y
- 10-15% ↓ - per year:
  - higher as IUD
  - lower as COC
  - Metrorrhagia – 1st year
  - Conception – at 3rd and 4th year
  - Headache Jadelle >> Implanon
  - **Metrorrhagia**

    Jadelle >> Implanon, but still leading



Patient Q&A

- Is it effective?
- How is it inserted and removed?
  - How long does it take to do so?
  - Does it hurt?
  - Will it leave scars?
- Are the implants visible under the skin?

Q & A - 2

- Will the implants restrict movement of the arm?
- Will the implants move through the body?
- Will the implants be damaged if touched?
- Will sexual drive change?

Q & A - 3

- What are the short term side effects?
- What are the long term side effects?
- Are there any effects for future fertility?
- What do the implants look and feel like?
- What happens if pregnancy occurs during use?

Q & A - 4

- How long will it be effective?
- How much does it cost?
- When should I come for insertion?
- Does it work straightaway?