Summary of analysis of efficacy and safety of Implantable Contraceptives (levonorgestrel and etonogestrel releasing implants).

Definition
Implantable contraceptives are progestogen-only contraceptive implants (levonorgestrel or etonogestrel releasing implants), which were introduced into clinical practice in the 1970s. These methods are known to be highly effective in preventing pregnancy, well tolerated and without serious side effects\(^1\),\(^2\),\(^3\).

Levonorgestrel releasing implants exert their contraceptive action through inhibition of sperm transport, normal endometrial development and partially ovulation, while Etonogestrel/3-keto-desogestrel releasing implants work mainly by inhibiting ovulation\(^4\).

Currently there are 5 (6 including complementary listing) items for non-barrier contraception on the WHO EML, Section 18.3 Contraceptives:

18.3.1 _Hormonal contraceptives:_
- ethinylestradiol + levonorgestrel, tablet, 30 µg + 150 µg
- ethinylestradiol + norethisterone, tablet, 30 µg + 1.0 mg
- levonorgestrel, tablet, 30 µg, 750 µg (pack of two), 1.5 mg
- norethisterone enantate, oily solution, 200 mg/ml in 1-ml ampoule
- complementary listing – medroxyprogesterone acetate, depot injection, 150 mg/ml in 1-ml vial with the footnote stating: "The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee."

18.3.2 _Intrauterine devices:_
- copper containing device

Levonorgestrel and etonogestrel are listed on the Anatomical Therapeutic Chemical (ATC) classification index with Defined Daily Doses (DDDs) (WHO Collaborating Centre for Drug Statistics Methodology), Oslo, Norway, 2004 under section G03 Sex Hormones and modulators of the genital system, subsection G03A C – Hormonal Contraceptives for systemic use, Progestogens: G03A C03 Levonorgestrel; G03A C08 – Etonogestrel.

Efficacy and safety issues

No randomized clinical trials (RCTs) were found that compared implantable contraceptives with barrier, oral or injectable contraceptive methods.

The application for inclusion of both Implantable contraceptives (levonorgestrel and etonogestrel releasing implants) is supported mainly by the results of cohort studies and by clinical evidence of equal efficacy of two types of levonorgestrel releasing implants (Norplant and Norplant-2) and of equal efficacy of levonorgestrel releasing implants to levonorgestrel releasing intrauterine devices in preventing pregnancies, summarised in a newly updated Cochrane systematic review\(^5\).
The conclusion of equal efficacy was drawn by the authors of the review on the basis of the only one randomised controlled trial (Wang 1992, 200 participants totally included, 100 participants in study groups), included into the Cochrane systematic review.

Levonorgestrel releasing device used in this study (Wang 1992) was Norplant 2, which consisted of two silastic capsules containing levonorgestrel, 70 mg with contraceptive life up to 3 years. Levonorgestrel releasing intrauterine device used in the study was LNG-20 IUS, containing 52 mg of levonorgestrel mixed with polydimethylsiloxane, allowing a steady, local release of 20µg levonorgestrel per day.

Calculated in this Cochrane systematic review rate rations for the major efficacy and safety outcomes point at the lack of significant difference between the LNG-20 IUS versus Norplant-2 as two methods of reversible contraception:

- Pregnancy - 3.01 (95% CI 0.13 to 75.56) at one year of follow up, 3.06 (95% CI 0.12 to 75.56) at two years of follow up, 3.00 (95% CI 0.12 to 73.53) at three years of follow up;
- Continuation – 0.89 (95% CI 0.66 to 1.2) at one year of follow up;
- Expulsion – 7.18 (95% CI 0.37 to 139.04) at one year of follow up;
- Ovarian cysts – 4.10 (95% CI 0.65 to 26.04) at one year of follow up;
- Breast cancer – none;
- Discontinuation (menstrual side effects) – 1.03 (95% CI .023 to 4.51) at one year of follow up;
- Discontinuation (device problem ) – 9.23 (95% CI 0.5 to 171.51) at one year of follow up;
- Discontinuation (adverse events) – 1.03 (0.11 - 9.86) at one year of follow up;

The Cochrane analysis provides the following risk ratios, documenting the difference between the two methods in indicators of menstrual disturbances:

- Amenorrhoea was significantly more likely to be experienced by LNG-20 IUS users compared to Norplant-2 users with the risk ratios of 2.27 [95% CI 1.03 to 4.99] at one year follow up, 42.46 [95% CI 2.62 to 689.20] at two years' follow up and 2.65 [95% CI 0.53 to 13.20] at three years' follow up;
- Oligomenorrhoea was significantly more likely to be experienced by LNG-20 IUS users compared to Norplant-2 users with the risk ratio of 6.17 [95% CI 2.76 to 13.78] at two years' follow up, with no significant differences at years' one and three of follow up;

On the contrary:

- Spotting was significantly less likely to be experienced by LNG-20 IUS users compared to Norplant-2 users with the risk ratios 0.33 [95% CI 0.18 to 0.60] at one year, 0.18 [95% CI 0.07 to 0.5] at two years and 0.17 [95% CI 0.05 to 0.57] at three years;
- Prolonged bleeding was significantly less likely to be experienced by LNG-20 IUS users compared to Norplant-2 users with the risk ratios 0.13 [95% CI 0.05 to 0.35] at one year, 0.17 [95% CI 0.06 to 0.46] at two years and 0.15 [95% CI 0.04 to 0.64] at three years.

The authors of the Cochrane review did not formulate any recommendations on the use of Norplant-2 in 'Implications for practice' section on the basis of these findings and emphasised the 'vital' need for the future research able ‘to answer the queries and concerns of contraceptive users’. 

Additional studies

Direct comparisons of levonorgestrel releasing implants versus etonogestrel releasing implants

One multicentre RCT compared the contraceptive efficacy and bleeding patterns of a single-rod (Implanon – etonogestrel releasing implant) and a six-capsule (Norplant – levonorgestrel releasing implant) contraceptive implant for 2 years, with an optional extension of up to 4 years, among 200 healthy female volunteers in China. Both implants demonstrated excellent contraceptive performance with no pregnancies during the study period. Compared with Norplant, there was less frequent bleeding with Implanon, whereas the incidence of infrequent bleeding and amenorrhea was higher. Implanon was significantly quicker to insert and to remove than the multiple capsule system\(^{10}\).

Another small RCT in China (100 participants totally, 75 – Implanon and 25 – Norplant users) found no difference in efficacy or overall safety between two contraceptives. The methods differed only in terms of number of times of bleeding (2.25 for Implanon and 2.99 for Norplant per reference period (P < 0.05)) and the times for insertion and removal (shorter for Implanon) documenting advantages of Implanon as a single rod design\(^{11}\).

Single small studies provided information on ovarian function\(^{12}\), endometrial histology and cervical cytology\(^{13}\), haemostatic system and liver function\(^{14}\), apo-lipoproteins profile\(^{15}\), carbohydrate metabolism\(^{16}\), selected parameters of thyroid and adrenal function\(^{17}\) with the use of Implanon compared with Norplant, that did not find major significant differences between two contraceptives. The exception was minimal but statistically significant rise in fasting glycosylated hemoglobin A(1)C levels at 24 months in the Implanon group while both implants induced mild insulin resistance with no significant change in serum glucose levels\(^{18}\).

Reformulated levonorgestrel releasing 2 rod implants versus Norplant (6 capsules) studies

A multi-center 5 year RCT compared levonorgestrel rod implant (Jadelle) with Norplant capsule (6) implants in 1198 participants (600 – Norplant capsules and 598 – Jadelle) at 7 centers in the USA, Finland, Bangkok, Chile, Egypt and Singapore. The study found high and equal contraceptive effectiveness for both implants and advantages of 2 rod implants compared to Norplant in their relative ease in removal\(^{19}\).

Another multi-center RCT in 1052 Mexican women at 8 centers followed up for 3 years with the same design found equal effectiveness, safety and acceptability of both implants\(^{20}\).

Conclusion

The advantage of 2 rod levonorgestrel releasing implant (Norplant-2/Jadelle) over the 6 capsules implant (Norplant) and its equal efficacy with LNG20-IUS is documented. At the same time high quality clinical evidence (RCTs) on efficacy and safety of levonorgestrel and etonogestrel releasing implants for reversible contraception to date is limited.


6 Wang 1992{published data only}


