Implants
PROGESTIN ONLY IMPLANT

In Jordan, the proportion of married women of reproductive age using an implant is less than half a percent\(^1\). The primary implant used in Jordan is the single rod etonogestrel (ENG) implant, commercially known as Implanon\(^\circ\). Most women can use this progestin only implant, but health professionals should be aware of the World Health Organization Medical Eligibility Criteria for Contraceptive Use\(^2\).

**Effectiveness**
Implanon\(^\circ\) is highly effective if used as directed. It is approved for three years of use and with correct placement, less than 1 percent will experience a method failure in the first year of use\(^3,4\). For women who prefer an implant, duration of use is not associated with any decrease in efficacy or safety\(^5\).

**Mode of Action**
There are several modes of action of Implanon\(^\circ\) in preventing pregnancy. It acts primarily by suppressing ovulation. Other ways Implanon\(^\circ\) may act to prevent pregnancy is to alter the endometrial structure and to impede sperm penetration by thickening cervical mucus\(^6\).

**Advantages of Implanon\(^\circ\)**
In addition to being highly effective, other advantages to using Implanon\(^\circ\) are:
- the absolute number of ectopic pregnancies are reduced\(^7-11\)
- it is reversible\(^12-14\)
- ease of use
- relief of dysmenorrhea\(^14\)
- it is an option throughout reproductive years

**Disadvantages of Implanon\(^\circ\)**
- Menstrual cycle disturbances\(^15\)
- Increased risk of ovarian cysts\(^16\)
Special Topics

- Amenorrhea

*There is an increased risk of amenorrhea*\(^{17-19}\).*

- Cancer

*No data available to appropriately assess cancer risks.*

- Postpartum Use/Effect on Breastfeeding

*Among breast feeding women using Implanon\(^\text{®}\), there is no decrease in milk volume nor is the growth of the infant affected*\(^{30}\).*
REFERENCES

Single Rod Etonogestrel (ENG) Implant


List of Critically Appraised Topics

1-Efficacy
2-Long Term Use
3-Liver Enzymes Use
4-Ectopic Pregnancy
5-Return to Fertility
6-Menstrual Blood Loss
7-Amenorrhea
8-Dysmenorrhea
9-Endometriosis
10-Weight Gain
11-Acne
12-Libido
13-Vison Changes
14-Bone Mass Density
15-Ovarian Cysts
16-Headache
17-Hypertension
18-Stroke
19-Breastfeeding

Note that the level of evidence accompanying each publication in each of the CATs refers to the study design.
The single rod etonogestrel implant is highly efficacious and comparable to other contraceptive methods containing hormone as well as intrauterine devices

Conclusion
The single rod etonogestrel implant is highly effective contraceptive for up to three years after insertion.

Clinical Question
What is the efficacy of the single rod etonogestrel implant in comparison to other methods?

Search Terms
Implanon®, single rod etonogestrel implant, contraceptive efficacy

Citations


Object of Research
Single rod etonogestrel implant

Research Outcome
Efficacy
Study Features
Darney et al
This report is based on an integrated analysis of the clinical data from 11 international studies. Studies were conducted in the United States, Chile, Europe, and Asia. A total of 923 subjects were enrolled in the clinical studies designed to assess efficacy. Failure was said to have occurred if a pregnancy occurred while the implant was in place or if it occurred within 14 days after its removal.
(Level 1 Evidence)

Power et al
This is a review of all randomized and controlled trials comparing subdermal implants with other forms of reversible contraceptives. Primary outcomes of these studies were pregnancy and continuation. All nine identified trials compared different types of contraceptive implant. Eight, involving 1578 women, compared the single rod etonogestrel implant with Norplant®, and one, involving 1198 women, compared Jadelle® with Norplant.
(Level 1 Evidence)

The Evidence
Darney P, et al
No pregnancies were reported while the ENG implants were in place. There were six pregnancies reported with a conception date within 14 days after the removal of the single rod etonogestrel implant. The cumulative Pearl Index of the implant was 0.38 (year 1 and 2 Pearl Indexes were 0.27 and 0.30, respectively).

Power et al
There was no difference between the single rod etonogestrel implant and Norplant® for contraceptive effectiveness rates or continuation over 4 years. Both were highly effective methods of contraception with no pregnancies occurring in any of the trials during 26,972 and 28,108 women months of follow up respectively. The authors failed to find any randomized clinical trials that compared subdermal implants with either IUDs, oral contraceptives, barrier-
methods or injectable contraceptives.

Note: Based on data from studies of other contraceptives, these rates are compare favorably with the efficacy of other contraceptives.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 3 March 2016
There is no decrease in the efficacy of the single rod etonogestrel implant over time

Conclusion
The single rod etonogestrel implant is a highly effective and quickly reversible sub dermal long-acting hormonal method of contraception for women. Typical use of this implant achieves a contraceptive effectiveness exceeding 99%. There is no evidence that use up to three years increases the risk of pregnancy.

Clinical question:
Is there a decrease in the efficacy of the single rod etonogestrel implant (Implanon®) over time?

Search Terms
Implanon®, single rod etonogestrel implant, increased risk of pregnancy

Citation

Object of Research
Single rod etonogestrel implant

Research outcome
Increased risk of pregnancy

Study Features:
This analysis included 11 international studies and data collected during 9 years of marketing experience (1998-2007). Seven of these studies were noncomparative; the four other studies included the 6-rod levonorgestrel
implant system or an intrauterine device as a comparator. All studies except one were of at least two years in duration, and all had contraceptive efficacy as an objective. The integrated efficacy analysis included 923 non-breastfeeding women.

(Level 1 Evidence)

The Evidence:
The 923 non-breastfeeding women were exposed to the implant for 24,100 cycles. No in-treatment or pretreatment pregnancies were reported. Fifty post treatment pregnancies were reported six of which occurred within 14 days of implant removal, indicating that fertility had quickly returned. Over 9 years of recorded experience, an overall pregnancy rate of 0.049 per 100 implants sold (estimated Pearl index =0.031 based on all pregnancies reported). When only counting contraceptive method failure the pregnancy rate was 0.010 per 100 implants sold (estimated Pearl index= 0.006). Considering the pregnancy distribution over the three-year period, the Pearl Index was 0.021 for year 1, 0.034 for year 2, and 0.054 for year 3.

Note: One Australian postmarketing study (Harrison-Woolrych and Hill Contraception 2005; 71:306-308) reports an approximate failure rate of 1 per 1000 insertions (218 pregnancies out of 204,486 insertions) though 130 of these pregnancies were either because of non-insertion or prior conception. No information was given as to the timing of these pregnancies so that a statement about long term use could not be made.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Update By: 26 February 2016
Women using the single rod etonogestrel implant may have higher rates of contraceptive method failure with concomitant use of liver enzymes inducers

Conclusion
The efficacy of the single rod etonogestrel implant may be reduced in women taking liver enzymes inducers drugs such antiepileptic. For women using this implant for contraception, the product information advises an additional barrier method when using a hepatic-enzyme inducing drug and for at least 7 days after discontinuation.

Clinical Question
Is the use of the single rod etonogestrel implant in women taking liver enzymes inducers drugs associated with increased contraception failure rate?

Search Terms
Implanon®, the single rod etonogestrel implant, liver enzymes inducers, contraception, failure rates

Citation

Object of Research
Single rod etonogestrel implant

Research Outcome
Liver enzymes inducers

Study Features
This post marketing surveillance study describes a case series of 218 unintended pregnancies associated with the etonogestrel implant, from May 1, 2001, to April 30, 2004 (the first 3 years following licensing in Australia).
These cases were reported to the Australian Adverse Drug Reactions Advisory Committee. Each case of confirmed pregnancy associated with the implant was assessed to determine possible reasons for contraceptive failure. The information taken into account included the estimated date of conception from ultrasound scans or other information (to determine if the woman was already pregnant at the time of insertion), the timing of insertion (with respect to the menstrual cycle or whether postpartum insertion), any concomitant medicine use (for possible drug interactions) and evidence that the implant was actually inserted (including blood etonogestrel levels and/or location by palpation or ultrasound scanning).

(Level 4 Evidence)

The Evidence
Of 218 cases included, 8 (4%) were determined to have resulted from interactions with concomitant medications. All drug interactions identified in this case series involved antiepileptic drugs; with 7 of these 8 women taking carbamazepine (which is liver enzymes inducer) while using the single rod etonogestrel implant.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Updates by: 2 March 2016
The use of the single rod etonogestrel implant is associated with a very rare, but possible risk of ectopic pregnancy.

**Conclusion**
The single rod etonogestrel implant is associated with very low failure rate which means the possibility of having ectopic pregnancy is very rare. However, based on reported case studies, the possibility of an ectopic pregnancy should be considered in any women using the single rod etonogestrel implant as contraception and who presents with missed period and abdominal pain.

**Clinical Question**
Is there an increased risk of ectopic pregnancy among women using the single rod etonogestrel implant?

**Search Terms**
Implanon®, single rod etonogestrel implant, ectopic pregnancy

**Citations**


**Object of Research**
Single rod etonogestrel implant
Subject of Research
Ectopic pregnancy

Study Features
All the 5 reported studies were case reports published during the period 2005 to 2012 (3 reports from UK and 2 from France). Due to the high efficacy of the single rod etonogestrel implant as contraception, a given pregnancy is very rare, so is ectopic gestation. No large scale study that deals with the incidence of ectopic pregnancy and Implanon® was found in our search. (Level 4 Evidence)

The Evidence
Mansour, Louis-Sylvestre and Paniel
The first published case report study of ectopic pregnancy occurring in a patient with Implanon® who had no obvious risk factor predisposing to a failure of technique (implant in place for less than 2 years and normal body mass index). In addition there was no risk factor for an ectopic pregnancy. This case was considered as primary failure of the contraceptive effect.

Panti, Ebdan, et al
A 27-year-old woman, who had no history of any risk factor for ectopic pregnancy. Implant in place for 6 months duration. This patient was on Rifampicin treatment for tuberculosis. This drug is known to have a reducing effect on the contraceptive efficacy of Implanon®.

Henderson and Gillespie
A 25-year-old woman, who had had a single rod etonogestrel implant inserted 28 months prior to the occurrence of ectopic pregnancy. Neither obvious risk factor predisposing to a failure of technique nor any risk factors for an ectopic pregnancy were reported in this case. This case was considered as primary failure of the contraceptive effect.

Olowu, Karunaratne and Odejinmi
A 26-year-old woman presented with an ectopic pregnancy conceived while having a single rod etonogestrel implant in situ. The only risk factor which was reported here was a previous history of treated contralateral ectopic pregnancy 2 years before this pregnancy, following which the implant was inserted.
Bouquier, Fulda, et al
A case of ruptured ectopic pregnancy reported in a patient with the single rod etonogestrel implant. The implant was in place for less than 2 years. The only factor predisposing to a failure in this case was a moderately elevated body mass index (BMI=29).

Comment
Despite the lack of any large scale studies, the results of these 5 case reports suggest that physicians should be alert to the possibility of an ectopic pregnancy among women using Implanon.

Appraised by: The Jordan Evidence Based Medicine – Reproductive Health Group

Update by: 3 March 2016
The use of the single rod etonogestrel implant is not associated with a decrease in the ability to become pregnant after removal.

Conclusion
The ability to become pregnant after removal of the single rod etonogestrel implant as determined by a return to normal menstrual cycles or ovulation is rapid. Most women who did not use another method of contraception after removal became pregnant within twelve months.

Clinical Question
Is the use of the single rod etonogestrel implant associated with a decrease in ability to become pregnant after removal?

Search Terms
Implanon®, single rod etonogestrel implant, return to fertility

Citation


Object of Research
Implanon®

Research Outcome
Return to fertility determined by return to menses
Study Features
Affandi et al
This is an open-label, non-comparative, single center study conducted in Jakarta, Indonesia. Two hundred women were enrolled in the study for a period of two years with a possible extension of three to four years. Women included in the study were 18-40 years, sexually active, with a normal menstrual cycle of 24-35 days. A post-treatment evaluation was performed on those women using no method of contraception after removal of their implant.
(Level 2 Evidence)

Croxatto et al
This is an open-label, multicenter study designed to assess the efficacy, safety, and acceptability of the single-rod contraceptive implant Implanon®. The study involved 635 healthy women who were sexually active and of childbearing potential and 21 centers in 11 counties in Europe and South America. Return to fertility was determined by a reported return to menses.
(Level 2 Evidence)

Funk et al
This is an open-label multicenter study conducted in the United States and designed to assess the safety and efficacy of Implanon®. The study involved 330 sexually active women between the ages of 18 and 4 and with apparently normal menstrual cycles. Return to fertility was determined by a reported return to menses.
(Level 2 Evidence)

The Evidence
Affandi et al
Sixty-nine women who discontinued and were found not to be using another form of contraception, all experienced a return to normal menstruation. The number of women who became pregnant during this period was not reported.
Croxatto et al
Post-treatment information three months after removal of their implant was obtained. Of those who chose a non-hormonal method of contraception 91 percent returned to normal menses within three months. This was not influenced by the length of use of their implant use. Of the post-treatment pregnancies that were reported, the estimated date of conception was within 90 days in 20 (14%) of the 145 who “no contraceptive method.”

Funk et al
Post-treatment information three months after removal of their implant was available for 282 (85%) of the 330 women in the study. Of these, 248 (88%) reported their menses had returned to normal. Forty-six of these women did not use any contraceptive after removal and 11 (24%) became pregnant between 7 and 131 days later.

Appraised by: The Jordan Evidence-Based Medicine Reproductive Health Group

Update by: 6 January 2016
The use of the single rod etonogestrel implant is associated with abnormal uterine bleeding patterns

Conclusion
The use of the single rod etonogestrel implant is associated with an unpredictable bleeding pattern, which includes infrequent, frequent, and/or prolonged bleeding. The bleeding pattern experienced during the first three months is broadly predictive of future bleeding patterns for many women. Effective pre-insertion counseling on the possible changes in bleeding patterns may improve continuation rates.

Clinical Question
Is the use of single rod etonogestrel implant associated with abnormal uterine bleeding?

Search Terms
Implanon®, single rod etonogestrel implant, abnormal uterine bleeding

Citation

Object of Research
Single rod etonogestrel implant

Research Outcome
Abnormal uterine bleeding patterns

Studies Features
Data from 11 clinical trials including 923 women were reviewed. These studies were conducted in the United States, Southeast Asia, Europe, Chile, and Russia. The women were between 18 and 40 years of age, were sexually active, and had previously reported regular menstrual cycles. Breast feeding subjects and those without post baseline efficacy data were excluded. Assess-
ments included bleeding-spotting records and patient-perceived reasons for discontinuation. In addition, to assess whether blood loss associated with the use of the implant resulted in anemia, hemoglobin blood levels were measured at baseline and at the end of treatment in several studies.

Data were analyzed by dividing each subject’s bleeding information into 90-day segments. Each segment represented one “reference period.” Reference period information was considered invalid and thus excluded if bleeding information was missing for three or more consecutive days. The authors used WHO recommended definitions. For each of the 90-day reference periods, amenorrhea was defined as no bleeding or spotting days, infrequent bleeding as less than three bleeding/spotting episodes excluding amenorrhea, frequent bleeding as 3 to 5 bleeding/spotting days, and prolonged bleeding as any uninterrupted bleeding/spotting lasting more than 14 days. (Level 1 Evidence)

The Evidence
Single rod etonogestrel implant use was found to be associated with the following bleeding irregularities; infrequent bleeding (33.6%), amenorrhea (22.2%), prolonged bleeding (17.7%), and frequent bleeding (6.7%). In 75% of the reference periods, bleeding-spotting days were fewer than or comparable to those observed during the natural cycle, but they occurred at unpredictable intervals. The bleeding pattern experienced during the initial phase predicted future patterns for the majority of women. The group of women with favorable bleeding patterns during the first three months tended to continue with this pattern throughout the first two years of use, whereas the group with unfavorable initial patterns had at least a 50% chance that the pattern would improve. Some 11.3% of patients discontinued due to bleeding irregularities, mainly because of prolonged flow and frequent irregular bleeding.

Appraised by: The Jordan Evidence-Based Medicine Reproductive Health Group

Update by: 2 March 2016
Use of the single rod etonogestrel implant is associated with an increase the risk of amenorrhea

Conclusion
The single rod etonogestrel implant is an effective contraceptive device though the risk of amenorrhea is increased.  

Clinical Question
Does the single rod etonogestrel implant increase the incidence of amenorrhea?

Search Terms
Single rod etonogestrel implant, amenorrhea

Object of Research
Implanon®, single rod etonogestrel implant

Research Outcome
Amenorrhea.

Citations


Study Features
Gezgine et al
This is a prospective cohort study of 80 patients who received the single rod etonogestrel implant as a contraceptive. The study was conducted in Konya, Turkey starting in 2004 and completed in 2006. Amenorrhea was defined as the absence of menstruation for three months. (Level 2 Evidence)

Bitzer et al
This is a multicenter, retrospective study of the single-rod etonogestrel contraceptive implant in which 1,183 women users were identified. A total of 991 (84%) women had at least one follow-up visit and 306 (26%) had two visits with a mean duration between insertion and follow-up of 224 days and 347 days, respectively. (Level 2 Evidence)

Study Features (con’t)
Bhatia et al
This is a prospective study of 200 Indian women users of the single rod etonogestrel implant enrolled over a period of one year in 2004 and 2005. The plan was for women to use the implant for up to three years. (Level 2 Evidence)

The Evidence
Gezgine et al
Amenorrhea was reported by 33 (41%) of the 80 patients. The time of these events post-insertion was not reported. None of the women in this study had their implant removed because of amenorrhea.

Bitzer et al
Amenorrhea was reported by one-third of all women. The time of these events post-insertion was not reported. Importantly, none of these women in this study had their implant removed because of amenorrhea.
Bhatia et al
Nine (4.5%) of the 200 women had their device removed because of amenorrhea. Overall, almost one-quarter of all users reported the occurrence of amenorrhea.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Update by: 3 March 2016
The use of the single rod etonogestrel is associated with relief of dysmenorrhea

Conclusion
In a sub-study of a large multicentre study in the United States, there evidence that the single rod etonogestrel implant is associated with relief of dysmenorrhea. Almost half of the women in this study reported decreased dysmenorrhea.

Clinical question:
Is the use of Implanon® associated with any changes in dysmenorrhea?

Search Terms
Implanon®, Single rod etonogestrel implants, dysmenorrhea

Object of Research
Single rod etonogestrel implant

Research Outcome
Changes in dysmenorrhea

Citations

Study Features:
This is a multicenter cohort study of 330 sexually active female volunteers in the United States. Of these 330 women, 315 (95.5%) provided baseline and post baseline information on dysmenorrhea. Single rod etonogestrel implant contraceptive acceptors were assessed over a two year period at 3 month intervals.

(Level 2 Evidence)
The Evidence
The percentage of women with dysmenorrhea at baseline was almost three times that observed at post baseline; 59 percent compared to 21 percent. The shifts from baseline to the end of the study showed that 151 (48%) women reported decreased dysmenorrhea, 139 (44%) reported no change, and 25 (8%) reported an increase. Of the 187 women who had dysmenorrhea at baseline, 151 (81%) reported decreased dysmenorrhea, 151 (81%) 26 (14%) reported no change, and 10 (5%) reported increased dysmenorrhea.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Update By: 2 March 2016
The use of the single rod etonogestrel implant is associated with an improvement of symptoms of endometriosis

Conclusion
The therapeutic effect of the single rod etonogestrel implant is similar to depot medroxyprogesterone acetate (DMPA) for the treatment of symptomatic endometriosis. Improvement in the symptoms associated with endometriosis was generally associated with the implant.

Clinical question:
Is the use of the single rod etonogestrel implant associated with an improvement in the symptoms of endometriosis?

Search Terms
Single rod etonogestrel implant, Implanon®, endometriosis

Object of Research
Single rod etonogestrel implant

Research Outcome
Improvement of endometriosis symptoms

Citations


**Study Features**

**Walsh K, et al.**

This clinical research was conducted in the university hospital, 41 patients with dysmenorrhea, non-menstrual pelvic pain and dyspareunia associated with histologically proven endometriosis were included in an open, prospective, randomized, controlled trials. Twenty-one women were assigned by computer-generated randomization to receive Implanon® and 20 to receive DMPA. Prior to inclusion in the study, women were requested to grade the severity of dysmenorrhea, non-menstrual pelvic pain, and dyspareunia on a 100-mm visual analog scale (AS).

(*Level 1 Evidence*)

**Funk et al**

This is a multicenter cohort study of 330 sexually active women in the United States. Acceptors of the single rod etonogestrel implant contraceptive method were assessed over a two year period at 3 month intervals. Dysmenorrhea, a symptom of endometriosis was assessed at the time of insertion of the device and at each of the follow-up visits. At baseline, 136 (41.2%) of the acceptors had no dysmenorrhea, 120 (36.4%) mild, 73 (22.1%) severe and 1 (0.3%) very severe.

(*Level 2 Evidence*)

**Croxatto et al**

This is a multicenter cohort study of 635 sexually active women in Europe. Acceptors of the single rod etonogestrel implant contraceptive method were to be assessed over a two year period at 3 month intervals, but the period of observation was extended to 3 years in a group of 137 women in two centres. Dysmenorrhea, a symptom of endometriosis was assessed at the time of insertion of the device and at each of the follow-up visits. At study initiation, 35 percent of the women reported a history of dysmenorrhea.

(*Level 2 Evidence*)
The Evidence

Walsh K, et al
During a follow-up period of 1 year, there were clear improvements in pain intensity for both treatment options. After 6 months, the average decrease in pain was 68% in the single rod etonogestrel implant group and 53% in the DMPA group. The side-effects profile and the overall degree of satisfaction after study termination were comparable for both treatment options.

Funk et al
Three hundred fifteen implant users provided baseline and post baseline dysmenorrhea information. Of these, 151 (48%) reported decreased dysmenorrhea, 139 (44%) reported no change and 25 (8%) an increase in dysmenorrhea.

Croxatto et al
At the end of the study, dysmenorrhea had improved in 87 percent of the women using implants and who had a history of dysmenorrhea. In 4 percent, this symptom was reported as a new occurrence or a worsening of existing dysmenorrhea.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Update By: 3 March 2016
The use of a single rod progesterone is not associated with significant weight gain

Conclusion
Weight change was variable among women using progestin-only contraceptives. However, adjusting for other weight risk factors, when compared to a copper IUD, no significant weight gain among the single rod etonogestrel implant users was observed.

Clinical Question
Is the use of a single rod etonogestrel implant associated with weight gain?

Search Terms
Single rod etonogestrel implant, Implanon®, weight gain.

Citations

Object of Research
Single rod etonogestrel implant

Research Outcome
Weight gain

Study Features
This was a sub-study of the Contraceptive CHOICE Project, a prospective cohort study of 9,256 women provided no-cost contraception. Women who had been using the single rod etonogestrel implant, LNG-IUS a three months injectable DMPA or a copper IUD continuously for at least 11 months were eligible for participation. The study obtained body weight at enrollment and at 12 months and compared the weight change for each progestin-only method to the copper IUD. A total of 427 women were enrolled: 130 ENG implant users, 130 LNG-IUS users, 67 DMPA users and 100 copper IUD users. *(Level 2 Evidence)*
The Evidence
The mean weight change (in kilograms) over 12 months was 2.1 for the single rod etonogestrel implant users; 1.0 for LNG-IUS users; 2.2 for DMPA users and 0.2 for copper IUD users. The range of weight change was broad across all contraceptive methods. When adjusting for baseline factors, compared to the copper IUD, no difference in weight gain with the single rod etonogestrel implant, LNG-IUS or DMPA was observed.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Update by: 2 March 2016
The use of the single rod etonogestrel implant does not have an overall effect on severity of acne

Conclusion
In a sub-study of a large multicentre study in the United States, there was no evidence that the single rod etonogestrel implant is associated with any negative effects on acne. However, among those with acne at the start of the study, more than half experienced an improvement of their acne condition.

Clinical question:
Is the use of the single rod etonogestrel implant associated with any changes in acne?

Search Terms
Implanon®, single rod etonogestrel, acne

Object of Research
Single rod etonogestrel implant

Research Outcome
Perceived changes in acne

Citations

Study Features:
This is a multicenter cohort study of 330 sexually active women in the United States. Of these 330 women, 315 (95.5%) provided baseline and post baseline information on their acne condition. These Implanon® contraceptive acceptors were assessed over a two year period at 3 month intervals.

(Level 2 Evidence)
The Evidence
There were no observed changes in the proportion of those with acne at baseline (26.7%) and at post baseline (23.8%). The shifts from baseline to the end of the study showed that 51 (16%) women reported decreased acne, 221 (70%) reported no change, and 43 (14%) reported increased acne. Of the 231 women who did not have acne at baseline, 195 (84%) reported no change whereas 36 (16%) reported increased incidence of acne. Of the 84 women who had acne at baseline, 51 (61%) reported a decrease, 26 (31%) reported no change and 7 (8%) reported increased acne.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Update By: 2 March 2016
Women using the single rod etonogestrel implant had a small reduction in libido after one year of use.

**Conclusion**
The single rod etonogestrel implant used as a contraceptive had little effect on women sexuality and the reduction in libido was observed in less than 10% of users. It should be noted that no large scale studies are available to assess decreases in libido.

**Clinical Question**
Is the use of the single rod etonogestrel implant associated with a decrease in libido?

**Search Terms**
Single rod etonogestrel implant, Implanon®, sexuality, libido

**Citation**


**Object of Research**
Single rod etonogestrel implant

**Research Outcome**
Libido
Study Features
Aisien et al
This study was part of an on-going prospective longitudinal study that involved 32 women out of 46 sexually active healthy volunteers aged between 24-45 years. They were recruited from a family planning clinic between February and March 2007. All the subjects received the single rod etonogestrel implant etonogestrel. The 32 women had completed records after 12 months of the single rod etonogestrel implant. Data on socio-demographic characteristics, menstrual pattern, haematological indices, weight, blood pressure, side effects and user’s satisfaction were collected and analyzed.
(Level 2 Evidence)

Gezginc et al
This is a prospective study of 80 Turkish women who used the single rod etonogestrel implant for contraception. All women were followed up at three months intervals for at least a year.
(Level 2 Evidence)

The Evidence
Aisien et al
Only 3 (7.3%) women reported a reduction in libido. There were no discontinuations were reported for this reason.

Gezginc et al
Loss of libido was reported by 2 (2.5%) women. Both of these women had the device removed.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Updates by: 3 March 2016
The use of the single rod progesterone is not associated with any vision disturbances

Conclusion
In small sub-study of a large multicenter investigation, the single rod etonogestrel implant was not found to be not associated with any negative effects on vision.

Clinical question:
Is the use of the single rod etonogestrel implant associated with any vision disturbances?

Search Terms
Single rod etonogestrel implant, Implanon®, vision disturbances

Object of Research
Single rod etonogestrel implant

Research Outcome
Changes in vision

Citation

Study Features:
This is a multicenter cohort study of 330 sexually active women in the United States. Acceptors of the single rod etonogestrel implant were assessed over a two year period at 3 month intervals. A small sub-group of 20 women were assessed for vision changes using gross external examinations, slit lamp examinations and opthalmoscopy.

(Level 2 Evidence)
The Evidence
Ophthalmologic examinations revealed no clinically significant findings in the subset of 20 women.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Update By: 2 March 2016
The use of the single rod etonogestrel implant may have an effect on loss of bone mineral density (BMD)

Conclusion
Use of the single rod etonogestrel implant for up to 3 years resulted in lower bone mass density relative to pre-insertion measurements. The clinical significance of these changes are unclear. In a comparative study with IUD users, no significant differences with single rod etonogestrel implant users were found in bone mass density changes.

Clinical Question
Is the use of a single rod etonogestrel implant associated with a significant decrease in bone mineral density?

Search Terms
Implanon®, single rod etonogestrel implant, bone mineral density

Citations


Object of Research
Single rod etonogestrel implant

Subject of Research
Bone mineral density
Study Features
Monteriro-Dantas et al.
This was a prospective study conducted in Brazil between August 2003 and July 2004. Initially it included 111 women, 19-43 years of age. Patients were randomly allocated to two groups: 56 to a single rod etonogestrel implant and 55 to a two-rod levonorgestrel contraceptive (Jadelle®) implant. Bone mineral density (BMD) was evaluated at the mid shaft of the distal radius and at the ultra-distal radius. Measurements were taken using dual-energy X-ray absorptiomerty before insertion and at 18 and 36 months of use.

(Level 2 Evidence)

Beerthuizen et al.
This was open, prospective, comparative multi-centre study (Finland, Chile, and Netherlands) for healthy women between the ages of 18 and 40 years. The study was designed to study the effect of the single rod etonogestrel implant on BMD. The control group used a non-hormone-medicated IUD. BMD measurements included the lumbar spine (L2 – L4), the proximal femur, Ward’s triangle, and distal radius. These were taken at baseline and at 6, 12 and 24 months post-insertion using dual-energy, X-ray absorptiomerty. Data was collected from 44 women using the implant and 29 using a non-hormonal IUD.

(Level 2 Evidence)

The Evidence
Monteriro-Dantas et al
At the 18 month evaluation, the BMD of the distal radius in the single rod etonogestrel group dropped from pre-insertion level of 0.475 g/cm² to 0.454 g/cm² after 18 months of usage (p < 0.0001). The ultra-distal radius dropped from 0.406 g/cm² to 0.390 g/cm² (p=0.104). The difference at the mid shaft ulna was statistically significant

At 36 months, 36 (64%) of the original 56 single rod etonogestrel patients continued to use the method. For this group, the BMD of the distal radius dropped from pre-insertion level of 0.475 g/cm² to 0.447 g/cm² at 36 months
of usage (p < 0.0001). The ultra-distal radius changed from baseline figure of 0.406 g/cm² to 0.396 g/cm² at 36 months (p=0.249).

The authors comment that though BMD was decreased relative to baseline at 18 and 36 months, it is not possible to conclude that the losses are of clinical significance.

Beerthuizen et al.  
This study did not show any significant differences in BMD between the single rod etonogestrel implant and the non-hormone IUD groups in the initial assessments nor in the follow-up measurements for all the different sites evaluated.

Appraised by: The Jordan Evidence Based Medicine-Reproductive Health Group,

Update by: 3 March 2016
The use of the single rod etonogestrel implant is associated with an increased risk of simple ovarian cysts

Conclusion
The finding of ovarian cysts or enlarged ovarian follicles during the first year of use of the single rod etonogestrel implant is common and transient. Nevertheless, close follow-up is recommended to exclude other underlying pathological causes.

Clinical Question
Is the use of the single rod etonogestrel implant associated with an increased risk of ovarian cysts?

Search Terms
Ovarian cysts, single rod etonogestrel implant, Implanon®

Citation

Object of Research
Single rod etonogestrel implant

Research Outcome
Ovarian cysts
Study Features
This is a prospective Brazilian study of the three contraceptive methods; the single rod etonogestrel implant, Jadelle® and a TCu380. Women were recruited at insertion and consecutively followed up for one year at three month intervals. In total, 116 single rod etonogestrel implant users, 123 users of Jadelle® and 105 users of the TCu380 IUD were enrolled in the study. The presence of an ovarian cyst or ovarian follicle was assessed at the three, six, and twelve month period after insertion of their implant/device.

(Level 2 Evidence)

The Evidence
Ovarian cysts were detected in 6 (5.2%), 16 (13.0%), and 2 (1.9%) users of the single rod etonogestrel implant, Jadelle® and the TCu3800, respectively at the third month of use. The differences among the groups was statistically significant (p<0.005). At six months, the presence of ovarian cysts in these three groups was detected in 8 (7.2%), 9 (8.0%) and 1 (2.1%), respectively. This difference among the three groups was not statistically significant (p=.168) while at 12 months, 27 (26.7%), 15 (14.6%) and 1 (1.2%) ovarian cysts, respectively, were detected. At this follow-up visit, ovarian cysts were detected in almost twice the number of single rod etonogestrel implant users as compared to those who were Jadelle® users. Both types of implants had a significantly higher prevalence than the IUD users. The presence of these ovarian cysts was transient with disappearance occurring 7 to 72 days for the single rod implant, 7 to 62 days for Jadelle®, and 7 to 53 days for the TCu380 IUD.

Appraised by: The Jordan Evidence Based Medicine-Reproductive Health Group

Update by: 3 March 2016
The use of the single rod etonogestrel implant appears to be associated with an increased risk of headache.

**Conclusion**
Headache as an adverse event appears to be associated with the use of the Implanon®.

**Clinical Question**
Is the use of Implanon® associated with an increased risk of headache?

**Search Terms**
Single rod etonogestrel implant, Implanon®, headache

**Citation**

**Object of Research**
Single rod etonogestrel implant

**Research Outcome**
Headache

**Study Features**
This report is based on an integrated analysis of the clinical data from 11 international Good Clinical Practice compliant studies. Studies were conducted in the U.S, Chile, Europe and Asia. Study participants were healthy, sexually active women, 18-40 years of age with normal menstrual cycles. After exclusion of women who used other hormonal contraception in the last 2-6 months, or who had recent delivery or abortion, a total of 946 subjects using Implanon® were enrolled in the clinical studies. *(Level 1 Evidence)*
The Evidence
All adverse events experienced by subjects throughout the duration of the 11 clinical trials are presented. Of those adverse events headache was observed in 15.5% and headache was the primary reason for discontinuation in 1.6 percent of the users.

Appraised by: The Jordan Evidence-Based Medicine Reproductive Health Group

Update by: 3 March 2016
The use of the single rod etonogestrel implant is not associated with increased risk of hypertension.

Conclusion
Some women using the single rod etonogestrel implant experience slight increases in blood pressure while others have a decrease. Overall, most women stay within normal limits with respect to systolic and the diastolic blood pressure.

Clinical question
Is the use of the single rod etonogestrel implant associated with an increased risk of hypertension?

Search Terms
Implanon®, the single rod etonogestrel implant, hypertension

Citations


Object of Research
Single rod etonogestrel implant

Research outcome
Hypertension

Study Features
Aisien et al
This was part of an ongoing prospective longitudinal study that involved 32 women out of 46 sexually active healthy informed volunteers recruited
from a Nigerian family planning clinic between February and March 2007. All the subjects received the single rod etonogestrel implant containing 68 mg etonogestrel. Data on socio-demographic characteristics, menstrual pattern, hematological indices, weight, blood pressure, side effects and user’s satisfaction were collected and analyzed.  
*(Level 2 Evidence)*

*Croxatto et al*
This is an open label, multicenter study to assess efficacy and safety of the single-rod etonogestrel contraceptive implant. The study drew patients from 21 centers in nine different countries and involved 635 young healthy women who were sexually active and of child bearing potential. Women were followed up every three months for three years. A systolic blood pressure reading greater than 140 mmHG with an increase of 20 mmHg and a diastolic greater than 90 mmHg with an increase greater than 10 mmHg each at two assessments or at the last assessment was considered clinically significant.  
*(Level 2 Evidence)*

**The Evidence:**
*Aisien et al*
The mean systolic and diastolic blood pressures did not show any significantly significant changes from baseline at the 6 months follow up (systolic: p=0.17; diastolic p=0.64). However at 12 months there were statistically significant changes from baseline though the changes were within normal range (systolic: p=0.003; diastolic p=0.05).

*Croxatto et al*
Ten (1.6%) had women clinically significant blood pressure readings. Overall though, the mean systolic and diastolic blood pressure showed a small decrease over time.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** 2 March 2016
There is no evidence that the use of the single rod etonogestrel is associated with an increase in stroke

Conclusion
Data on the use of the single rod etonogestrel implant with respect to stroke is sparse. But WHO Guidelines consider this progestin only method as a contraceptive option for women with a history of stroke.

Clinical Question
Does the use of the single rod etonogestrel implant increase the risk of stroke?

Search Terms
Implanon®, the single rod etonogestrel implant, stroke

Citation


Object of Research
Progestin only contraceptives, the single rod etonogestrel implant. Implanon®

Research Outcome
Stroke

Study Features
This report is based on an integrated analysis of the clinical data from 11 international studies. Studies were conducted in the United States, Chile, Europe, and Asia. A total of 923 subjects were enrolled in the clinical studies designed to assess safety. (Level 1 Evidence)
The Evidence
Fifty-six (5.9%) of 942 women using the single rod etonogestrel implant experienced a total of 77 serious adverse events. None of these women experienced an event involving deep vein thrombosis, stroke or myocardial infarction.

Appraised by: The Jordan Evidence-Based Medicine Reproductive Health Group

Update by: 3 March 2016
The use of the single rod etonogestrel implant used by breastfeeding woman does not affect breast milk production

Conclusion
When early insertion of the single rod etonogestrel implant was compared to standard insertion time, there were not significant differences in breastfeeding outcomes. That is, early postpartum insertion does not appear to affect breast milk production in breastfeeding women.

Clinical Question
Will the use of the single rod etonogestrel implant in a breastfeeding woman affect breast milk production?

Search Terms
Single rod etonogestrel implant, Implanon®, breastfeeding, breast milk production, lactogenesis.

Citation

Object of Research
Single rod etonogestrel implant

Subject of Research
Breast milk production

Study Features
This was a randomized controlled trial. Sixty-nine women who desired the etonogestrel implant for contraception were enrolled. They were healthy peripartum women with healthy, term newborns were randomly assigned to early (1–3 days) or standard (4–8 weeks) postpartum insertion. Thirty-five were randomly assigned to early insertion and 34 to standard insertion. There
were no statistically significant differences between the groups in age, race, parity, mode of delivery, use of anesthesia, or prior breastfeeding experience.

The primary outcomes, time to lactogenesis stage II and lactation failure, were documented by a validated measure. The margin for the mean difference in time to lactogenesis stage II was defined as 8 additional hours. Secondary data (device continuation and contraceptive use, breast milk analysis, supplementation rates, side effects, and bleeding patterns) were collected at periodic intervals for 6 months.

(Level 1 Evidence)

The Evidence
Early insertion was found to be similar to standard insertion in time to lactogenesis stage II [early: mean=64.3±19.6 hours; standard: 65.2±18.5 hours]. Early insertion was also found to be similar to standard insertion in incidence of lactation failure [early: 0/35; standard: 1/34]. Nor was use of formula supplementation significantly different between the two groups. Finally, analysis of milk composition at 6 weeks revealed no significant differences.

Appraised by: The Jordan Evidence Based Medicine-Reproductive Health Group

Update by: 3 March 2016