

A STUDY OF EFFICACY AND SAFETY PROFILE WITH SUB DERMAL SINGLE ROD CONTRACEPTIVE IMPLANT IMPLANONSapna Singh¹, Suman Gupta², Nitu Nigam³, Sanjay Kumar Nigam⁴**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: INTRODUCTION: The development of sub dermal contraceptive implant has been an important improvement in current contraceptive technology and to a good alternative to offer well established contraceptive method. Hormonal implant must show high efficacy, high acceptability and rapid return of fertility after removal by maintaining a sustained release of progesterone, the contraceptive effect of the implant can be obtained with a much smaller daily dose than when administering the same steroid by an oral or intramuscular route. Sub dermal implants are also independent of user compliance which remains a determinant factor in the efficacy of most contraceptive methods. In addition after removal of the hormonal implant, fertility returns almost immediately. They contain only progestogen, these implant may also be used by women who cannot tolerate oestrogen or by women for whom oestrogen is contraindicated. The availability of new innovative contraceptive implant system such as implanon is very important to offer couples alternative methods to plan size of their family more efficiently. **OBJECTIVES:** To study efficacy and safety profile of single rod sub dermal contraceptive device implant implanon. To evaluate the vaginal bleeding patterns observed during the use of implanon. To assess the acceptability of the contraceptive device as indicated by discontinuation rates. **MATERIAL AND METHODS:** Study was carried in OBG department of RMC Kanpur on healthy female volunteers having regular menstruation & at least one living child. **RESULT:** The result of this study was excellent in terms of contraception with pearl index of 0, almost one third cases were having in frequent bleeding episode. **CONCLUSION:** The study was conducted on 110 women of age 20-35 years with at least one living child and having regular menstrual period, in present study half of cases discontinued implant due to no fix pattern of bleeding and failure was 0%, efficacy of this implant is excellent with a pearl index of 0%.

KEYWORDS: Contraceptive Technology, Subdermal Implant, Implanon, Progesterone.

INTRODUCTION: Implanon was developed with the aim of introducing a long term contraceptive device that was effective independent of the user's compliance and that had efficacy comparable to other long term methods. The present study was designed to show that the mechanism of action is ovulation inhibition with possible additional non contraceptive benefits. Because of the continuous progesterone administration, they may be associated with irregular menstrual bleeding as is commonly found with other progestogen only methods of contraception, and is the main reason why women stop using such contraceptives.⁽¹⁾ It is therefore important to assess carefully how bleeding patterns are altered by new contraceptive methods such as implanon, to provide a sound basis for patient counselling. To allow comparison of menstrual bleeding patterns from different studies, a standardized approach known as reference period analysis is used. Data from daily menstrual diaries are analysed on the basis of reference period, usually 90 days long. Bleeding pattern indices are

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defined by the WHO, indicate the extent of deviation from a normal pattern as observed in a normal menstrual cycle. Bleeding pattern include amenorrhea, infrequent bleeding, frequent bleeding, prolonged bleeding and normal bleeding.

In vitro release profile of the implant is characterized by initial in vitro release of 60-70 μ gm/day followed by gradual decline to about 40, 34 & 25-30 μ gm/day, At the end of the first, second, third year respectively. Mean in vitro release over the 3 year period amounts to approximately 40 μ gm /day. After implanon insertion serum concentration increase within 8 hrs to concentration associated with ovulation inhibition. Maximum Means serum concentration amounted to 813pg/ml (Hubar et-al1998) and time to reach was 4 days. After reaching Cmax ENG serum concentration decline gradually by the end of third year. After removal of implanon. Serum ENG concentration declined to level less than detection limit of the assay within 1 week.

Implanon is a single rod contraceptive implant (NV Organon, OSS et-al1998) made of ethylene vinyl acetate co-polymer (EVA) with a core containing 68mg etonogestrel. The implant has a length of 40mm and a diameter of 2mm and is provided in a disposable sterile inserter for sub dermal application contraceptive action is achieved mainly by inhibition of ovulation and lasts for 3 years (Makarainen et-al 1998)^(2,3,4)Efficacy of this implant is excellent with pearl index of 0.

MATERIAL & METHOD: The study was carried out in the department of Obstetrics & Gynecology in Rama Medical College Hospital and research centre Kanpur.

STUDY GROUP: Healthy female volunteers having regular menstruation and at least One living child(age between 20-35 years) and requiring spacing method or postponing permanent method of contraception will form the study population⁽⁵⁾ after screening and counseling the women will be offered the contraceptive device. The implanon will be inserted after 5 days of LMP or concurrent with MTP.

EXCLUSIVE CRITERIA:

- Suspected pregnancy.
- H/O menstrual disorder.
- H/O ectopic pregnancy.
- PID.
- Ac/Ch liver diseases, Heart diseases & D. M.
- Family H/O of breast CA.
- Hb% < 8gm%.

DETAILS OF THE DEVICE: Implanon has been developed by NV organon in1998. It is the only single rod non-biodegradable contraceptive implant available. Implanon is presented as single rod in a pre-load sterile disposable applicator. The applicator facilitates easy and rapid insertion.

APPLICATOR: Preload with single rod, sterile package and disposable.

DESIGN OF IMPLANON ROD: (a) The core containing 68mg of crystalline⁽⁶⁾ etonogestrel dispersed in a matrix of ethylene vinyl acetate co-polymer, single rod of 4cm*2mm in dimension, and non-biodegradable.

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DESIGN OF THE APPLICATOR: A special applicator has been designed in which the implant is pre-loaded. The tip of the needle has two cutting edges with different slopes. The extreme tip has the greater angle and is sharpened to allow penetration through the skin. The second needle is smaller and unsharpened to reduce the risk of inserting the rod too deeply.

DETAILS HISTORY AND EXAMINATION:

- History of menstrual disorder.
- Ectopic pregnancy.
- PID.
- Any type of allergy.
- H/o any Contraceptive uses.

PERSONAL HISTORY:

- Her and husband's occupation.
- Rural or urban dweller.

Obst H/O: Parity and duration of last delivery.

Menstrual H/O: Cycle length and bleeding day amount.

Exam: Body wt, General and systemic examination was done f/b Gynecological examination.

Gynecological Exam: In full dorsal position.

1. P/S was done to examine the condition of Vaginal & CX to look for signs of inflammation, erosion & discharge.
2. Bimanual pelvic examination was done for position size, shape, consistency, mobility and tenderness of Uterus and CX and rule any adnexal mass.

INV: Hb%

Urine <r/m.

Implanon Insertion Procedure: Insertion of implanon should be performed under antiseptic condition and only by physician who is familiar with the procedure.

Stretch the skin around the insertion site with thumb and index finger. Introduce the needle in the space between the biceps and triceps (sulcus bicipitalis malialis), directly under the skin as superficially as possible, slightly angled and parallel to the skin surface, while lifting the skin with the tip of needle. Insert the needle to its full length.

Follow up procedure: Each subjects will be followed up at 7 days and at 1, 3, 6 and 12months after insertion. Subsequently follow up will be done at an interval of 6 month for three years.

At each follow up visit details should be obtained on the subject's menstrual history since her last visit and should be recorded on the follow up form.

The site of implant will be observed for local irritation, expulsion, inflammation and infection. If there is partial expulsion of the rod it will be removed.

Hemoglobin should be estimated at 6 monthly intervals or earlier if indicated.

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Each subject should have systemic examination and breast examination done, B. P and weight should be recorded at 3, 6 months and 6 monthly follow up visit thereafter.

RESULT & DISCUSSION: Effects of sub dermal single rod progesterone containing contra ceptive device. Implanon was assessed on 110 women attending OPD of RMC and Hospital Kanpur during the period of 1 Year.

Cases selected in study group were all sexually active women between the age of 20-35 yrs, parity between 1 to 3 and willing to participate in the trial.

Sl. No.	Age Group(Years)	Number of cases	Percentage
1.	15-20	14	12.72%
2.	21-25	56	50.90%
3.	26-30	33	30%
4.	31-35	7	6.36%
	Mean \pm SD	25.7 \pm 2.1	100%

Table 1: Age distribution

Out of 110 female, maximum 93.62% of cases were below the age of 30 years as in developing country like India the girls are married at young age, a family is usually completed between 18-30 yrs. Age. Mean age of cases in study group using implanon was 25.7 \pm 2.1 yrs (Table no. 1). Similar to our study D. Reinprayoon et al (2000) also found the mean age of 25.2 yrs, in his study. Horacio B et (1999) observed the average age of women to be 29 yrs. Reenc Wenzl et al (1998),⁽⁷⁾ reported mean age of 33.5 yrs. in study group which is contrast to present study. Shu-Rong Zheng et al (1999) found the mean age of their cases was 29.4 \pm 3.1 yrs. which was close to our study.

Sl. No.	Parity	Number of cases	Percentage
1	1	35	31.8%
2	2-3	68	61.84%
3	\geq 4	7	6.36%
	Mean \pm SD	2.25 \pm 0.56	100%

Table 2: Parity

Maximum number of cases 68(61.8%) were para two and three. It denotes that in developing countries like India most of women came for contraception after completion of family and least for spacing of child births. Mean parity in study group was 2.25 \pm .56 (Table 2) Similar to present study Horacio et al (1999) noticed in his study has maximum women (31.2%) were para two. Saxena (1993) reported in his study maximum women (63.8%) were para two.

Sl.No.	Menstrual Cycle(Days)	Number of cases	Percentage
1	1-2	7	6.36%
2	2.1-3	10	9.09%

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3	3.1-4	47	42.72%
4	4.1-5	22	20%
5	5.1-6	24	21.8%
	Mean \pm SD	4.02 \pm 1.12	100%

Table 3: Menstrual Cycle

Present study revealed duration of bleeding in menstrual cycle in majority of cases 47(42.72%) was 3-4 days, Loo Makarainen et al (1998) also evaluated that all women before implant use have had regular menstrual cycle 28.2 \pm 1.3 days with a mean duration of living of 5 \pm 1 day. This observation is very important as majority of women did not opted implanon as a contraceptive method of choice because of associated heavy menstrual cycles.

At first visit observation site was normal in 100% cases. There was no irritation, inflammation or expulsion of rod after 7 days of observation at site of implant. Similar to this study Horacio Croxatlo et -al.

Sl. No.		Number of cases	Percentage
1.	Normal	110	-
2.	Irritation	-	-
3.	Inflammation	-	-
4.	Explosion	-	-
		110	100%

Table 4: At first visit 7th day observation of site of implant

(1999) reported that maximum no. 96. 2% of cases were having no abnormalities. Only few no. of cases were having swelling (.6%), redness (.5%), pain (3.5 %), hematoma (0.6%) at the site of implant implanon.

Sl.No.		Number of cases	Percentage
1	Amenorrhea	13	11.83%
2	Infrequent Bleeding	42	38.18%
3	Frequent bleeding	40	36.36%
4	Prolonged Bleeding	15	13.63%
	Total	110	100%

Table 5: Bleeding pattern after implantation in reference period

References Period: Period of 90 consecutive days. Starting on the day of implant placement.

Amenorrhea: No Bleeding or spotting throughout a reference period.

Infrequent bleeding: less than three bleeding- spotting episode starting within a reference period, excluding amenorrhea.

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Frequent bleeding: More than five bleeding- spotting episode starting within a reference period.

Prolonged bleeding: At least one bleeding or spotting episode starting within a reference period and lasting more than 14 days.

In present study majority of cases 42(38.18%) were having in frequent bleeding pattern minimum no. 13(11.8%) of cases were having amenorrhea. 15(13.63%) of cases were having prolonged bleeding pattern, 40 (36.36%) cases out of total cases were having frequent bleeding pattern. (Table no. 5)^(8, 9) Loe Makarinan et al (1998) reported maximum no. of cases having amenorrhea infrequent bleeding. Similarly Haracio and Craxatto et al (1999)⁽¹⁰⁾ showed that maximum no. (17.2%) of cases were having bleeding irregularities same cases were having amenorrhea in reference period.

Sl. No.	Causes	No. of Cases	Percentage
1.	Backache	3	2.72
2.	Heavy bleeding	7	6.36
3.	Prolonged bleeding	7	6.36
4.	No fix pattern of bleeding	11	10
5.	Taking ATT	1	0.90
6.	Want of Conceive	1	0.90
	Total	30	27.24

Table 6: Cause of removal

In the present study maximum no. 11(10%) of cases discontinued implant due to no fix pattern of bleeding 7(6.63%) due to prolonged bleeding, 7(6.63%) due to heavy bleeding, One case (0.90%) discontinued for next conception. Croxatto et al (1999) reported maximum reasons (17.2%) were discontinuation bleeding irregularities. Buckshee et al (1993)⁽¹¹⁾ noted in their study maximum no. (8.2%) cases discontinued this implant due to menstrual disturbances. Affandi et al (1998)⁽¹²⁾ noticed bleeding irregularities constituted the main reason for early discontinuation. One case discontinued for next conception and conceived after 4 months of removal acceptability of implanon is excellent.⁽¹³⁾

Sl. No.	Total no. of users	Number of cases	Failure Rate Percentage
1	110	0	0%

Table 7: Failure rate

In present study none of the cases conceived during implanon treatment, failure rate was 0. This study showed efficacy of sub dermal contraceptive implant implanon is 100%. Similar to present study Horacio croxatto et al (1999) noticed no pregnancy occurred during treatment with implanon, resulting in a pearl index of 0. Rene Wanzl et al (1998) concluded efficacy of this implant is excellent, with a pearl index of 0.⁽¹⁴⁾

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CONCLUSION: The study was conducted on 110 women of age group 20-35 years, each of them having at least one living child and having regular menstrual period (28 ± 7) day.

The study was done with an objective to study efficacy and safety profile of sub dermal single rod contraceptive implant implanon.

CONCLUSION DRAWN FROM THE STUDY WERE AS FOLLOWS:

- Most of cases i. e. 93.62% were below the age of 30 year. Mean age of cases was 25.7 ± 2.1 .
- More than half of cases (61.8%) were second and third Para. Mean parity was 2.25 ± 0.56 .
- All cases in study group showed no adverse reaction like irritation, pain, expulsion, migration from the site.
- Almost one third (31.18%) cases were having infrequent bleeding (more than five bleeding spotting episodes starting within a reference period).
- In present study half of cases (10%) of cases discontinued implant due to no fix pattern of bleeding. Bleeding irregularities were the main reason for discontinuation of implant implanon.
- In this study failure rate was 0% Efficacy of this implant is excellent, with a pearl index of 0%.

ASSIGNMENT 2: How you would monitor & manage a 24 yrs old primigravida with GDM, who has failed to reach glycemic goal after 2 wks. Of life style modification.

A pt. of GDM, 24yrs old primigravida is put on life style modification.

- Full fill minimum nutritional recommendations for pregnancy.
- Achieve glycemic goals without wt. loss or undue wt. gain.

MEDICAL NUTRITION THERAPY:

- Meal plan should be tailor made and easy to understand and follow.
- Small frequent meals are ideal to avoid hypoglycemia.
- Avoid prolonged fasting.
- Bedtime snack is advisable to prevent development of ketosis at night.
- Ensure adequate hydration avoid fruit juice.
- Planned physical activity of 30-45 min/day.
- Complement dietary recommendations.
- Activities that increase blood pressure should be avoided like lifting heavy wt. pushing heavy objects.
- Upper body resistance training has been shown to reduce glucose levels in the 3rd trimester.
- If MNT fails to achieve euglycemia by 2 wks (i. e. if fasting glucose remains < 95 mg/dl and 2 hr. postprandial glucose < 120 mg/dl – consider insulin therapy.

INSULIN THERAPY: Has to be individualized.

- Post prandial glucose values need special attention in a pregnant diabetic women.
- Many women with GDM have elevation of single post- meal glucose levels, in such cases, a single dose of regular insulin before the meal may suffice.

INSULIN THERAPY:

1. Regular human insulin.
2. NPH insulin.
3. Rapid acting insulin analogs (lispro aspart).
4. Premix insulin.
5. Long acting insulin analogs (determin).

INSULIN DOSAGE:

- Is trimester specific.
- Start with low dose depending on blood glucose level.
- Titrate frequently till target levels are achieved.

2nd type -1 D. M- with pregnancy:

1ⁿ 1st trimester -.7u/kg.

At 18thwks - .8u/kg.

At 26 wks - .9u/kg.

At 36 wks - .1u/kg.

Type – 2nd D. M – with pregnancy- need much higher doses of insulin during each trimester.

- If fasting glucose levels are high, -woman may need to be put as based insulin at bedtime.
- After lunch or after dinner glucose levels are high, short acting insulin may need to be added before their meals as well.
- Insulin as part and insulin lispro in pregnancy is safe and minimally transfer across placenta. So no teratogenesis.
- Rapid acting analogues may be a useful alternative to regular insulin particularly in cases where the post prandial glucose values are high and where late post absorptive hypoglycemia is an issue.
- Insulin determin is now approved for use in pregnancy.
- Insulin glargine and degludec not recommended in pregnancy.

REFERENCES:

1. Progestogen-only implants; Faculty of Sexual and Reproductive Healthcare (Feb 2014).
2. Mommers E, Blum G-F, Gent TG, et al; Nexplanon, a radiopaque etonogestrel implant in combination with a next-generation applicator: 3-year results of a noncomparative multicenter trial. *Am J Obstet Gynecol* 2012; 207: 388. e1-6.
3. Agrawal A, Robinson C; An assessment of the first 3 years' use of Implanon in Luton. *J Fam Plann Reprod Health Care*. 2005 Oct; 31(4): 310-2.
4. Makarainen L, van Beek A, Tuomivarra L, et al. Ovarian function during the use of a single contraceptive implant; Implanon compared with Norplant. *Fertil Steril* 1998; 69: 714-21.
5. Faculty of Sexual and Reproductive Healthcare. Clinical Effectiveness Unit. UK Medical Eligibility Criteria for Contraceptive Use (UKMEC 2005/06). ([www. ffprch. org. uk](http://www.ffprch.org.uk); accessed 8 January 2010).
6. Summary of Product Characteristics (SPC) - Nexplanon® 68 mg implant for subdermal use; Merck Sharp & Dohme Limited, electronic Medicines Compendium, August 2013.

ORIGINAL ARTICLE

7. Wenzl R, van Beek A, Schnabel P, Huber J. Pharmacokinetics of etonogestrel released from the contraceptive implant Implanon. *Contraception* 1998; 58: 283-8.
8. Weisberg E, Hickey M, Palmer D, et al. A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users. *Hum Reprod*. 2009; 24(8): 852-1861.
9. Sulak PJ, Smith V, Coffee A, Witt I, Kuehl AL, Kuehl TJ. Frequency and management of breakthrough bleeding with continuous use of the transvaginal contraceptive ring: a randomized controlled trial. *Obstet Gynecol*. 2008; 112(3): 563-571.
10. Croxatto HB, Urbancsek J, Massai R, Bennink HC, van Beek A, the implanon Study Group. A multicentre efficacy and safety study of single contraceptive implant Implanon. *Hum Reprod* 1999; 14: 976-81.
11. Buckshee K (1993), Chatterjee P, Dahl G, Hazra MN, Koakany BS, Lalitha K, et al. return of fertility following discontinuation of Norplant-II Subdermal implants *Contraception* 1995; 51: 237-42.
12. Affandi B. An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon. *Contraception* 1998; 58 (6 suppl): 109s-15S.
13. Sergeant F, Clamageran C, Bastard AM, et al; Acceptability of the etonogestrel-containing contraceptive implant (Implanon). *J Gynecol Obstet Biol Reprod (Paris)*. 2004 Sep; 33(5): 407-15.
14. Power J, French R, Cowan F; Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods of preventing pregnancy. *Cochrane Database Syst Rev*. 2007 Jul 18; (3): CD001326.

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