Haematological and biochemical effects of etonogestrel subdermal implant (Implanon) in Ilorin Nigeria

Olayinka R Balogun, [1] Abiodun S Adeniran, [1] Adebayo A Adewole [2]

[1] Department of Obstetrics & Gynaecology, University of Ilorin/ University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria,
[2] Department of Obstetrics & Gynaecology, Federal Medical Centre, Lokoja, Kogi State, Nigeria.

Abstract

Objectives: To evaluate the effect of etonogestrel subdermal implant (Implanon) on haematological and biochemical parameters of its users.

Methodology: A prospective observational study among healthy women using Implanon for contraception. The study site was the family planning clinic of the University of Ilorin Teaching Hospital, Ilorin, Nigeria. Informed consent was obtained and participants were followed up for three years. Follow up parameters were haematological and biochemical evaluation at insertion (baseline), first and third years post-insertion. Statistical analysis was with SPSS-version 20.0; p value <0.05 was significant.

Results: 124 participants of age 20-44years were included in the study. During the period of study, a progressive increase in the weight as well as in the level of alanine transaminase and systolic blood pressure was recorded. As compared to the baseline values, statistically significant difference in the mean values of systolic blood pressure ($p<0.01$), alanine transaminase ($p<0.01$) and weight ($p=0.001$) were recorded at the first year. Packed Cell Volume ($p=0.001$), weight ($p=0.001$), alanine transaminase ($p=0.001$) and alkaline phosphatase ($p<0.05$) were significant at the third year. Between the first and third year post-insertion, there was statistically significant difference in Packed Cell Volume ($p=0.001$), urea ($p<0.05$), aspartate ($p=0.001$) and alanine transaminase ($p=0.001$) and weight ($p=0.001$). However, there were no clinically detectable abnormalities or pregnancy during the study period.

Conclusion: Haematological and biochemical parameters change with Implanon use but they were not significant to cause clinical sequelae. Implanon remains a safe long term contraceptive.

Keywords: Contraception; Etonogestrel subdermal implant; Implanon; Haematology; Parameters; Biochemical.

Correspondence:

Abiodun S Adeniran
Department of Obstetrics & Gynecology,
University of Ilorin, PMB 1515,
Ilorin, Kwara State, Nigeria.
Tel: +23480 5753 4788;
E-mail: acrowncord@hotmail.com

Introduction

Etonogestrel subdermal implant (Implanon) is a user independent, long term contraceptive that lasts for three years. It provides respite for adherence and user dependence associated problems, encourages user independence without interfering with coitus. There has been an increasing trend in its use and acceptability [1, 2] because of its effectiveness, tolerable side effects [1-4] and negligible post-insertion complications. [1, 5] However, there are concerns about its effect on biochemical and haematological parameters of its users due to its metabolism. Reports suggest Implanon to be a good choice for women with medical disorders like hypertension or diabetes mellitus [6] and it has not been shown to increase the risk for cardiovascular disorders in healthy women. [7] However, most of such long-term follow up reports were mostly in developed countries while majority of reports in developing countries were of shorter duration. As Implanon uptake increases in black populations, there is the need for long-term follow up studies to evaluate its effects and compare with reports from other population. The aim of this study was to evaluate the haematological and biochemical effects of Implanon over a three-year period among healthy users in Ilorin, Nigeria.

Methodology

Study design/ study site

The study was a prospective observational study conducted among healthy female clients on contraception at the family planning clinic of the University of Ilorin Teaching Hospital, Ilorin, Nigeria.

Study population

The study population were women who after evaluation and counseling accepted and had etonogestrel subdermal implant (Implanon) inserted at the clinic.

Inclusion criteria

The inclusion criteria were previous normal and regular menstrual cycle, non-use of hormonal contraceptive for at least six months before presentation and decision to have Implanon inserted. In addition, consent to participate in the study, healthy pre-insertion clinical status and willingness to present for post-insertion follow up were required.

Exclusion criteria

Women on other forms of contraception, those with prior irregular menstruation, unwilling to participate or comply with the follow up protocol for the study were excluded from the study.

Study protocol

All participants had physical and gynaecological examinations to exclude gynaecological disorders prior to insertion. Thereafter, participants were followed up using haematological, biochemical and clinical parameters over a period of three years. The laboratory parameters were evaluated pre-insertion (baseline) as well as end of first and third year post-insertion. The parameters of interest were the Packed Cell Volume (PCV), white cell count, serum electrolyte, urea, urate and creatinine as well as liver function tests. The clinical evaluation was by serial weight and blood pressure measurements as well as clinical evaluation for pallor, jaundice, hepatomegaly, facial or pedal edema. Counseling was reinforced at each visit and complaints were addressed by the family planning providers.

Data analysis / ethical issues

Statistical evaluation was by SPSS-version 20.0 (IBM, USA) and p value <0.05 was significant. Confidentiality of participants was maintained by using codes instead of actual names. Institutional ethical approval was obtained for the study before commencement and its conduct was guided by guidelines on conduct of research in human subjects. No financial or material support was obtained for the study and the authors have no conflict of interest to declare.

Sample size determination

The sample size was calculated using the formula [8]

$$n = 2\frac{z^2 pq}{d^2}$$

n= desired sample size

z= standard normal deviate set as 1.96 which corresponds to 95% confidence interval

p = proportion in the target population estimated to have FGM i.e. 0.036 (i.e. 3.6%). [1]
q = 1.0-0.036 = 0.964
d= degree of accuracy desired set at 0.05

$$n = 2x1.96^2 \frac{x\ 0.036\ x\ 0.964}{(0.05)^2} = 107$$

Thus, the minimum sample size was 107 + 11 (10% for non-respondents) = 118

Results

There were 124 participants aged 20-44years (mean 31.64±5.85); generally, there was a progressive increase in the systolic blood pressure, weight, and alanine transaminase (ALT). An initial fall followed by a rise in white cell count and aspartate transaminases with a progressive fall in PCV and alkaline phosphatase (ALP) were observed during the study (table 1).

In table 2, comparison of mean values of baseline and first year parameters shows reduction in PCV (36.58±5.32 vs. 36.13±3.18; p>0.05), aspartate transaminase (AST) (20.12±10.34 vs. 18.34±3.87; p>0.05) and alkaline phosphatase (34.51±12.78 vs. 30.11±7.03; p=0.001). There was an increase in systolic blood pressure (115.82±9.37 vs. 117.74±9.18; p<0.01), serum alanine transaminase (ALT) (11.35±5.43 vs. 17.77±4.80; p<0.01) and weight gain (68.27±11.62 vs. 71.88±13.35; p=0.001).

Table 3 shows a comparison of the mean baseline and third year values with significant reduction in Packed Cell Volume (36.58±5.32 vs. 29.90±8.41; p=0.001) and alkaline phosphatase (34.51±12.78 vs. 27.97±7.72; p<0.05) with a significant weight gain (68.27±11.62 vs. 74.79±11.99; p=0.001) and alanine transaminase (ALT) (11.35±5.43 vs. 18.94±4.90; p=0.001). Changes in white blood cell count and serum electrolytes were not significant.

From table 4, comparing mean values at first and third years shows reduction in PCV (36.12±3.18 vs. 29.90±8.41; p=0.001), serum urea (6.27±2.67 vs. 4.47±1.31; p<0.05) and alkaline phosphatase (30.11±7.03 vs. 27.97±7.72; p=0.001). There were significant increases in ALT (17.77±4.80 vs. 18.94±4.90; p=0.001), AST (18.34±3.87 vs. 19.52±5.42; p=0.001) and weight gain (71.88±13.35 vs. 74.79±11.99; p=0.001).

Table 1: Variation of clinical, haematological and biochemical parameters over three years

Parameter	Insertion Mean ± SD	1st Year Mean ±SD	3rd Year Mean ±SD
Systolic BP	115.82±9.37	117.74±9.18	119.68±7.96
PCV	36.58±5.32	36.13±3.18	29.90±8.41
Sodium (Na^+)	136.17±4.03	134.77±3.79	134.79±3.38
Potassium (K^+)	3.94±0.56	4.6±1.72	4.56±1.34
Urea	5.40±4.66	6.27±2.67	4.47±1.31
Creatinine	73.68±17.98	79.17±7.47	78.76±4.79
Urate	0.17±0.05	0.28±1.33	0.16±0.04
ALT	11.35±5.43	17.77±4.80	18.94±4.90
AST	20.12±10.34	18.34±3.87	19.52±5.42
Alkaline Phosphatase	34.51±12.78	30.11±7.03	27.97±7.72

WBC	6.35±7.84	5.28±1.20	5.38±1.36
Weight	68.27±11.62	71.88±13.35	74.79±11.99

SBP: Systolic blood pressure
ALT: Alanine transaminase
AST: Aspartate transaminase
WBC: Total white cell count

Table 2: Comparison of clinical, haematological and biochemical parameters at insertion (baseline) and first year post-insertion

Variable	Insertion Mean ± SD	1st year Mean ± SD	R	P value
SBP	115.82 ± 9.37	117.74 ± 9.181	0.256	0.004
PCV	36.58 ± 5.32	36.13 ± 3.18	-0.884	0.379
Sodium	136.17 ± 4.03	134.77 ± 3.79	- 0.009	0.925
Potassium	3.94 ± 0.56	4.61 ± 1.72	0.006	0.951
Urea	5.40 ± 4.66	6.27 ± 2.67	- 0.050	0.582
Creatinine	73.68 ± 17.98	79.17 ± 7.47	0.103	0.253
Urate	0.17 ± 0.05	0.28 ± 1.33	- 0.052	0.567
ALT	11.35 ± 5.43	17.77 ± 4.80	- 0.234	0.009
AST	20.12 ± 10.34	18.34 ± 3.87	-0.653	0.515
Alkaline Phosphatase	34.51 ± 12.78	30.11 ± 7.03	0.342	0.001
WBC	6.35 ± 7.84	5.28 ± 1.20	0.074	0.413
Weight	68.27 ± 11.62	71.88 ± 13.35	0.760	0.001

SBP: Systolic blood pressure
ALT: Alanine transaminase
AST: Aspartate transaminase
WBC: Total white cell count

Table 3: Mean values of clinical, haematological and biochemical parameters at insertion (baseline) and third year

Variable	Insertion Mean ± SD	3rd year Mean ± SD	R	P value
SBP	115.82 ± 9.37	119.68 ± 7.96	0.004	0.968
PCV	36.58 ± 5.32	29.90 ± 8.41	-7.786	0.001
Sodium	136.17 ± 4.03	134.79 ± 3.38	- 0.103	0.255
Potassium	3.94 ± 0.56	4.56 ± 1.34	- 0.131	0.146
Urea	5.40 ± 4.66	4.47 ± 1.31	0.048	0.598
Creatinine	73.68 ± 17.98	78.76 ± 4.79	0.007	0.938
Urate	0.17 ± 0.05	0.16 ± 0.04	0.036	0.690
ALT	11.35 ± 5.43	18.94 ± 4.90	11.093	0.001
AST	20.12 ± 10.34	19.52 ± 5.42	-0.653	0.515
Alkaline Phosphatase	34.51 ± 12.78	27.97 ± 7.72	0.229	0.011
WBC	6.35 ± 7.84	5.38 ± 1.36	0.025	0.785
Weight	68.27 ± 11.62	74.79 ± 11.99	0.720	0.001

SBP: Systolic blood pressure
ALT: Alanine transaminase
AST: Aspartate transaminase
WBC: Total white cell count

Table 4: Comparison of mean values of parameters at first and third year post-insertion

Variable	1st year Mean ± SD	3rd year Mean ± SD	R	P value
SBP	117.74 ± 9.181	119.68 ± 7.96	0.168	0.062
PCV	36.13 ± 3.18	29.90 ± 8.41	- 0.340	0.001
Sodium	134.77 ± 3.79	134.79 ± 3.38	0.055	0.542
Potassium	4.61 ± 1.72	4.56 ± 1.34	-0.300	0.765
Urea	6.27 ± 2.67	4.47 ± 1.31	0.212	0.018
Creatinine	79.17 ± 7.47	78.76 ± 4.79	0.148	0.100
Urate	0.28 ± 1.33	0.16 ± 0.04	- 0.048	0.593
ALT	17.77 ± 4.80	18.94 ± 4.90	0.534	0.001
AST	18.34 ± 3.87	19.52 ± 5.42	0.639	0.001
Alkaline Phosphatase	30.11 ± 7.03	27.97 ± 7.72	0.657	0.001
WBC	5.28 ± 1.20	5.38 ± 1.36	0.146	0.106
Weight	71.88 ± 13.35	74.79 ± 11.99	0.736	0.001

SBP: Systolic blood pressure
ALT: Alanine transaminase
AST: Aspartate transaminase
WBC: Total white cell count

Discussion

There was a progressive increase in the weight gain, alanine transaminase, and systolic blood pressure throughout the period of the study. In the first year post-insertion, Implanon caused a significant increase in systolic blood pressure, liver function tests and weight gain while the increase in weight gain and liver function tests persisted till the third year. Between the first and third year post-insertion, the increase in systolic blood pressure was sustained with a fall in urea, urate, creatinine, alkaline phosphatase and Packed Cell Volume. In all, there was a wide variation in

haematological and biochemical parameters but there was no resultant clinical abnormality or pregnancy during the study period.

Weight gain has been documented as a complication of Implanon from previous studies [1,9] and was the reason for 13% of complications of Implanon in previous users in Ilorin Nigeria. [1] In a report from Benin-City, Nigeria, there was a reduction in weight among Implanon users by six months after insertion but with a subsequent weight gain between six months and one year post-insertion. [3] This is similar to the report of index study which reported weight gain at first and third year following insertion of Implanon. The probability of weight gain should be central in counselling of intending clients desiring Implanon while caution is advised in clients particularly opposed to weight gain.

The progressive increase in systolic blood pressure in this study did not correlate with reports of Aisien et al [3] who evaluated a study population of Nigerians in South-South Nigeria. They reported no statistical change from baseline values by six months following insertion as well as a subsequent significant reduction by twelve months post-insertion. Although these reports appear to be at variance, both showed that the range of the blood pressure measurements were within normal range. Thus, clinically significant hypertension or hypotension are not expected with Implanon use. Other authors reported that Implanon has no clinically important effect on blood pressure [10] and it is unlikely to substantially modify risk for cardiovascular events including stroke, myocardial infarction and venous thromboembolism among healthy women. [11]

Menstrual irregularity remains a common complication of Implanon [1] and about 20% may experience amenorrhea while about 50% may experience infrequent, frequent or prolonged bleeding. [12] However, previous reports has ranged between no significant change in PCV at six and twelve months following Implanon insertion in a Nigerian [3] and a significant increase in haematocrit in a Brazilian population. [13] The observed progressive reduction in PCV with Implanon use in this study may be due to participants who experienced increased and prolonged menstruation. Therefore, response of the menstrual pattern of individual clients should determine the interval of evaluation using the PCV; clients experiencing increased or prolonged menstruation will require closer monitoring.

Not many reports evaluating white cell count in Implanon users are available. However, an available report from a population similar to participants in this study reported no statistical significant changes at six and twelve months following insertion. [3] Although there was an observed fall at first year and rise at third year in white cell count from index study, the differences were not statistically significant and generally remained within normal range. Therefore, Implanon use does not increase susceptibility to infections among its users.

There has been documentation of a modification of the renal function by progesterone during the luteal phase of menstrual cycle. [14, 15] This is similar to the increases in creatinine clearance or tubular secretion of creatinine independent of its clearance observed in a previous study [16] as well as the index study. The summary is that Implanon does not cause renal impairment despite the observed changes which produced no clinical effects.

Reports of effect of Implanon on hepatic function ranged from a non-negative effect [16] to a significant reduction by one year following insertion. [13] Other reports suggest a mild hepatocellular dysfunction with no apparent clinical consequences [10] similar to report in this study. This may have contributed to the recommendation that risk of progestin-only contraceptives outweigh the benefit in women with active hepatitis, hepatic decompensation or tumours. [11] Elevation of liver function test is expected with Implanon; therefore, closer attention should be employed to prevent duplication of other medications which can exert similar effects on the liver to prevent overt clinical hepatic dysfunction. This can be achieved through adequate drug history among potential and current users of Implanon.

A previous retrospective descriptive study reported a 26.1% discontinuation rate among Implanon users with majority (35%) due to desire to get pregnant, [1] long term follow up studies have reported more favorable continuation rates. The continuation rate of 93.8% after one year follow up in Benin-City [3] was similar to a 0% discontinuation rate within

three years follow up in Sao Paolo, Brazil. [13] The 0% pearl index in this study compares favourably with same results reported from other studies on Implanon. [1, 13, 16, 17]

Conclusion

This study corroborates previous long term reports that Implanon subdermal implant is associated with changes in weight, haematological and biochemical parameters among long term users. However, these changes were not associated with clinical abnormalities thereby reinforcing its safety. Drug history is important in intending and current Implanon users while its use should be discouraged in women with active hepatic diseases or tumours. A regular follow up of the Packed Cell Volume is recommended especially with users experiencing increased or prolonged menstruation.

References:

1. Balogun OR, Olaomo N, Adeniran AS, Fawole AA. Implanon subdermal implant: an emerging method of contraception in Ilorin, Nigeria. J Med Biomed Sciences 2014; 3(1): 1-5.
2. Ojule JD, Oranu EO, Enyindah CE. Experience with Implanon in Southern Nigeria. J Med Medical Sci 2012; 3(11):710-4.
3. Aisien AO, Enosolease ME. Safety, efficacy and acceptability of Implanon a single rod implantable contraceptive (Etonogestrel) in University of Benin Teaching Hospital. Niger J Clin Pract 2010; 13(3):331-3.
4. Ladipo OA, Akinso SA. Contraceptive implants. Afr J Reprod Health 2005; 9:16-23.
5. Mutihir JT, Daru PH. Implanon sub-dermal implant: A 10 month review of acceptability in Jos, North central Nigeria. Niger J Clin Pract 2008; 11(4):320-3.
6. Meckstroth KR, Darney PD. Implant contraception. Semin Reprod Med 2001; 19(4):339-54.
7. MerkiFed GS, Imthurn B, Seifert B. Effects of the progestogen-only contraceptive implant on cardiovascular risk factors. Clin Endocrinol (Oxford) 2008; 68(3):355-60.
8. Araoye MO. Research Methodology with Statistics for Health and Social sciences. Ilorin: Nathadex Press, 2003:115-21.
9. Sergent F, Clamegeran C, Bastard AM, Verspyak E, Marpeau L. Acceptability of Etonogestrel-containing implant (Implanon). J Gynaecol Obstet Biol Reprod 2004; 3:407-15.
10. Newberry YG. Implanon: A new implantable contraceptive. Nursing Women's Health 2007; 11(6):607-11.
11. World Health Organization. Progestogen-only contraceptives, 2014. Available at http://www.who.int/reproductivehealt/publishers/me/pocs.html.
12. National Collaborating Centre for Women's and Children's Health. Long Acting Reversible Contraception: The effective and appropriate use of long-acting reversible contraception. London: RCOG Press; 2005.
13. Guazelli CA, de Queiroz FT, Barbieri M, Barreiros FA, Torloni MR, Araujo FF. Metabolic effects of contraceptive implants in adolescents. Contraception 2011; 84(4):409-12.
14. Gault MH, Chafe L, Prabkaran V. Mid-menstrual cycle decline in creatinine and urea clearances. Nephron 1994; 67:158-66.
15. Paaby P, Brochner-Mortensen J, Fjelbord P, Raffn W, Larsen CE, Moller-Petersen J. Endogenous overnight creatinine clearance compared with Cr-EDTA clearance during menstrual cycle. Acta Med Scand 1987; 222:281-4.
16. Inal MM, Yildirim Y, Ertopcu K, Avci ME, Ozelmas I, Tinar S. Effects of subdermal contraceptive Etonogestrel implant (Implanon) on biochemical and hormonal parameters (three years follow up). Eur J Contraception Reprod Health Care 2008; 13(3):238-42.
17. Funk S, Miller MM, Mishell DR Jr, Archer DF, Poindexter A, Schmidt J, et al for the Implanon US study group. Safety and efficacy of Implanon a single rod implantable contraceptive containing Etonogestrel. Contraception 2005; 71:319-26.
18. Dilbaz B, Ozdegirmenci O, Caliskan E, Dilbaz S, Haberal A. Effect of Etonogestrel implant on serum lipids, liver function tests and haemoglobin levels. Contraception 2010; 81(6):510-4.