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POPULATION COUNCIL AWARD NO. I87.14A

to

The XI Asian and Oceanic Federation of
Obstetricians and Gynecologists Congress

held in Bangkok, Thailand
on December 1-4, 1987

THE POPULATION COUNCIL
One Dag Hammarskjold Plaza
New York, New York 10017

January 1988

Pre-Congress Seminar of the XI AFOG Congress

Bangkok, December 1-4, 1987

Theme of Seminar - Practical Aspects of Fertility Management -

See attached program.

The pre-congress seminar was well attended, with approximately 300 participants from Thailand and other countries in the region. Many of the participants went on to Hong Kong to the Congress which started December 6, 1987.

NORPLANT® Symposium. The meeting was extremely well attended and first class presentations were given which provided the participants with an excellent overview of the development of the NORPLANT® method, its performance internationally, regionally, and at the country level. Side effects and those related to bleeding were adequately dealt with and endocrine and haematological factors were also presented and discussed.

Outside the seminar, information about the method was presented by video tape and information materials were available.

All the participants supported by the PopCouncil attended the Pre-Congress Seminar.

Attached are the abstracts of the papers presented at the Pre-Congress Seminar.

ABSTRACT

Endocrinologic changes in Swedish Norplant^R users.

Sven-Eric Olsson*

Two methods for release of levonorgestrel from polydimethylsiloxane (Silastic^R) subdermal implants for contraception were studied. The first system consists of six 3 cm long Silastic^R capsules filled with levonorgestrel (NORPLANT^R). The second one consists of two 4 cm long rods made from Silastic^R and levonorgestrel, covered with thin Silastic^R tubing (NORPLANT^R-2). The contraceptive efficacy of NORPLANT^R implants was excellent during the four years of observation. That of NORPLANT^R-2 implants was very good during the first three years, but not acceptable during the fourth year.

Both types of implants were well tolerated and the most common side effect experienced was bleeding disturbances such as irregular bleeding and periods of prolonged bleeding. The frequency of such disturbances decreased considerably after the first year of use.

The plasma levels of levonorgestrel decreased throughout the study, and did not show any statistically significant difference between users of the two types of implants.

The plasma levels of levonorgestrel in women who became pregnant did not differ from those in women who did not become pregnant. Levonorgestrel binds to sex hormone binding globulin (SHBG) with high affinity, and in the bound form is not biologically active. A "free levonorgestrel index" (FLI), i.e. the ratio of plasma level of levonorgestrel to SHBG capacity was calculated. Women with NORPLANT^R had higher FLI than those with NORPLANT^R-2 and women who became pregnant had lower FLI than those who did not. It is suggested that NORPLANT^R-2 implants have a lower rate of release of levonorgestrel than NORPLANT^R implants.

SHBG capacity, thyroid binding proteins and corticosteroid binding globulin decreased during treatment.

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* Dept of Obstetrics and Gynecology, Uppsala University, Akademiska Sjukhuset, S-751 05 Uppsala

Plasma total testosterone decreased during treatment, whereas free testosterone was unaltered. Thyroid function and plasma cortisol levels did not change during treatment.

Treatment with phenytoin decreased the contraceptive effect.

In a group of regularly menstruating women who had used NORPLANT^R-2 implants for more than three years, 40% showed anovulation, 20% luteinization of unruptured follicles and 40% apparent ovulation.

ABSTRACT

Thai experience with Norplant^R six capsules and Norplant^R two covered rods

Suporn	Koetsawang*
Orawan	Kiriwat*
Manee	Piya-anant*
Pansri	Darakorn*
Pacharee	Naewpanich*

Clinical study of Norplant^R six capsules has initiated in Thailand by the National Family Planning Program (NFPP), Ministry of Public Health (MOPH) since mid 1980. Findings from over 1,000 cases in five study centers were satisfactory. Most acceptors were under 30 years old with low parity and used Norplant^R for spacing. The convenience of the method and its long-term effectiveness were the major reasons for high acceptability. The common side effects was irregular bleeding and amenorrhoea which with good counseling will be considerably accepted by many Thai women. Though, approximately 40% of the users perceived normal menstruation. Cumulative pregnancy rate at 2 years of use was 0.1% or 1 in 1,000 users. Two years continuation rate was 75% which was higher than the NFPP rates of the pill (49%), injectable (32%) and IUD (47%). Because of these satisfactory findings, Norplant^R 6 was approved by the Thai FDA in 1985 and was included in NFPP in 1986 after the physicians' training course has completed.

Norplant^R two covered rod system, the second generation of Norplant^R has been studied in Siriraj Hospital, Bangkok since October 1983. The first 3-year results in 240 users were similar to those of Norplant^R. Further follow-up is still going to confirm its efficacy in the last two years of use.

* Siriraj Family Planning Research Center, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital. Mahidol University, Bangkok 10700, THAILAND.

Abstract

Introduction of the Norplant^R Subdermal Contraceptive System into a Family Planning Program Indonesia

Drs. Hermini Sutedi, Biran Affandi, Joedo Prihartono, Firman Lubis

In May 1981 Indonesia implemented a 2 center Norplant^R capsules study including 1,000 acceptors. This was reviewed in late 1982 and owing to the favourable continuation rates of over 90 per 100 acceptors in the first year of use, a large field trial of 10,000 acceptors was started involving 11 teaching hospitals. Two years later following a review of the field trial which had recruited over 8,000 acceptors an extended field trial was proposed to introduce Norplant^R services to subcenters around the 11 teaching hospitals. These reviews were carried by a steering committee comprising of representatives from the Badan Koordinasi Keluarga Berencana Nasional (BKKBN), MOH, and the Medical School, University of Indonesia.

In May 1986, the BKKBN included the Norplant^R capsules into the ongoing national family planning programme.

Training of physicians and other health personnel in the insertion/removal technique of the Norplant^R method has been an important part of the introduction program and studies in user acceptance have also been carried out. In training, counselling of acceptors on the side-effects and how to cope with them has been emphasised. Preparation and testing of information material for providers and acceptors has also been carried out.

Inclusion of the Norplant^R contraceptive system into ongoing training at BKKBN provincial training institutes is underway. Steps are also being taken to include training and lectures in the method into the curriculum of undergraduates in medicine and nurse training courses.

Presentations of results of Norplant^R studies have been made at various meetings and seminars held in Indonesia and internationally over the past 4 years to inform health personnel about the method. Logistics of supplies and funding required to purchase the implants was also examined.

Registration of the Norplant^R capsules was approved by the FDA of the Ministry of Health, Indonesia in January 1986.

Abstract

Evaluation of the Norplant Subdermal

Contraceptive System - China

The clinical trial in China has been conducted in two phases. Phase I commenced in the last quarter of 1984 in four centers. It involved both Norplant^{R6} capsules and Norplant^{R2} covered rods. The expansion to phase II to another 8 centers began in February 1986. Till May 1987, 10710, acceptors of Norplant^{R6} capsules and 1,208 acceptors of Norplant^{R2} covered rods have been recruited to the study. The presentation will include the results from this entire recruitment to the study and will examine the characteristics in more detail of the first 1,000 Norplant^{R6} capsules and 200 Norplant^{R2} covered rods.

Average age of acceptors was about 30 years, and 90% of women had only one living child. Pregnancy rate was less than 0.1 per 100 acceptors. There was one ectopic pregnancy given a rate for the Norplant^{R6} capsules of 1 per 10,300 women years of use. Bleeding problems accounted for over 70% cases of removals and the continuation rate varied from 77.1 - 83.6 per 100 acceptors at 2 years of use.

Principal investigators:

1. Shanghai Medical University, Obst. & Gyn. Hospital, Department of Family Planning, Dr. Yuan Dao Yuan.
2. Laoning Province, Family Planning Research Institute, Shenyang, Dr. Zhang Ling De.
3. Second Hospital, Tianjin Medical College, Dr. Xu Mei Fang.
4. Beijing Municipal Research Institute of Family Planning, Dr. Wang Su Hua.
5. Wuhan Province, Regional Institute of Family Planning, Dr Wu Song-Ling.
6. 2nd Hospital of Hubei Medical College, Dr. Wang Pei-Zhu.
7. Jilin Province, Regional Institute of Family Planning, Dr. He Xin
8. First Hospital of Lanzhou Medical College, Dr. Gao Yun-Li.
9. Shandong Province, Regional Institute of Family Planning, Dr. Qi Li-Fang.
10. People's Hospital of Shanxi Province, Dr. Chen Chang-Rong.
11. Guizhou Province, Regional Institute of Family Planning, Dr. Mo Ping
12. Fujian Province, Regional Institute of Family Planning. Dr. Bao Su-Zhen.
13. Dr. Gu Sujuan, Director, RDFP Beijing, Beijing Municipal Research, Beijing.

Recent International Experience
with Implant Contraception

Irving Sivin
Center for Biomedical Research
The Population Council

Extensive experience with implant contraception now permits more refined analyses of subpopulations of implant users. Negative correlations between plasma levels of levonorgestrel and body weight have proved to be statistically significant. These correlations have translated into higher pregnancy rates among women weighing 75 or more kilograms at placement. Rates of method failure in various settings may be related to the underlying weight distributions, but do not exhibit these correlations with NORPLANT 2 until the fourth year of use.

Rates of adverse reactions and of removal complications with NORPLANT and NORPLANT 2 are also reviewed.

ABSTRACT

Contraceptive Implant NORPLANT^(R)
Two-Year Evaluation of its Safety,
Efficacy and Acceptability in Sri Lanka

24 Months Experience with NORPLANT^(R) Implants
in Sri Lanka

Dr. Sriani Basnayake, MBBS (Ceylon) Medical Director
Family Planning Association of Sri Lanka,
Colombo, Sri Lanka

This paper presents findings based on a 2-Year Phase III clinical study concerning the safety and efficacy as well as acceptability of the contraceptive implant Norplant^(R) in Sri Lanka. The study is based on 200 acceptors of the implant at the Family Planning Association's Headquarters Clinic in Colombo. The mean age of the acceptors was 25 years, and they had on an average 2 children. About 1/3rd of the acceptors did not want to have another child. The acceptors were followed up at 1, 3 and 6 months after insertion, and every 6 months thereafter. Annual termination rate on account of medical problems were very low, and no pregnancies were observed. Disruption of menstrual cycle was the main side effect observed. Amenorrhea increased to a maximum during the first 3 months of use, and decreased progressively with time. Inter-menstrual bleeding increased progressively with continued use. In spite of these menstrual disturbances the degree of satisfaction with the implants was very high. The two most important features of the implant liked by the majority of the acceptors were the long duration of action and convenience of use. The results of this study suggest that the NORPLANT^(R) implant system is a safe, effective, highly acceptable contraceptive for Sri Lankan women. The introduction of the implant on a larger scale will most likely enhance the role of reversible contraception in the Family planning programme of Sri Lanka.

THE EFFECTS OF LEVONORGESTREL CONTRACEPTIVE IMPLANTS, NORPLANT
ON BLOOD CHEMISTRY IN SINGAPOREAN ACCEPTORS

O A C VIEGAS
KULDIP SINGH
S KOH
D LIEW
S S RATNAM

Department of Obstetrics & Gynaecology
National University Hospital
National University of Singapore
Lower Kent Ridge Road
Singapore 0511

A longitudinal study of coagulation parameters, liver function, glucose and lipid metabolism was conducted on 100 Singaporean women using the levonorgestrel subdermal implants, NORPLANT.

The measurements undertaken were:

- A: Blood coagulation Studies: Haemoglobin, haematocrit, prothrombin time, Activated Partial Thromboplastin Time, Thromboelastograph (Screening Tests), Fibrinogen, Factors II, V, VII, VIII C, VIII R: Ag and X (Coagulation Factors); Plasminogen activator on fibrin plate, FDP (Fibrinolytic activity) Antithrombin III, Protein C, Plasmin inhibitors (coagulation inhibitors), platelet count, platelet aggregation (platelet function).
- B: Liver Function Tests: Serum Albumin, Total protein, alkaline phosphatase, bilirubin.
- C: Lipid Metabolism: Total cholesterol, HDL and triglycerides
- D: Glucose Metabolism: Glucose tolerance at one year

The tests were done at admission and after 6 months and one year of NORPLANT use.

With respect to coagulation parameters, significant changes were observed in platelet function at the end of 1 year. Mean platelet count rose from $207 \times 10^9/L \pm 52.1$ to $278 \times 10^9/L$ ($p < 0.001$) and in vitro studies showed significantly enhanced platelet aggregation. There was also a significant shortening of prothrombin time and activated partial thromboplastin time whilst there was a significant rise in antithrombin III (antigen) activity.

No clinically significant impairment of glucose tolerance was observed during the 1 year period of Norplant use.

With regard to liver function, there was a slight fall in total protein, a significant increase in mean bilirubin levels but no change in mean levels of alkaline phosphatase.

Total cholesterol and Triglycerides showed a reduction at the end of one year with only minor change in HDL levels.

The results of this ongoing study indicate that the use of levonorgestrel implants (NORPLANT) is associated with changes in the coagulation system in Singaporean acceptors. These are related mainly to platelet count and function. There is also some evidence to suggest liver dysfunction as indicated by the rise in mean bilirubin level. Therefore it is imperative to continue longer term surveillance in patients using this contraceptive delivery system.

Participants - name and address - USAID.

India

Dr. Badri Saxena
Senior Deputy Director General
Indian Council of Medical Research
Ansari Nagar
New Delhi 110029
India Telex 3163067 ICMR IN

Telephone 669374
667136 Home 606676

Indonesia

Dr. Finnan Lubis
Executive Director
YKB Foundation
P.O. Box 25/KBYTT
Asem Baris Raya
Block A/3
Gudang Peluru Phone 826337
Tebet Jakarta Selatan
Indonesia Telex 61571 USAHA IA
61488 USAHA IA

Dr. Hermini Sutedi
Chief Bureau of Contraceptive
Service
Jalan Let Jen. M.T. Haryono
P.O. Box 186 JKT Phone 811308
Jakarta
Indonesia Telex 48181 BKKBN IA

Singapore

Dr. Osborn A.C. Viegas
University Dept. of Obst. & Gyn.
Kandang Kerbau Hospital
Hampshire Road
Singapore 0821

Telegram UNIVSPORE
Telephone: 779555
Telex UNISPO RS 33943

Bangladesh

Dr. H. Akhter
Bangladesh Fertility Research Program
3/7, Asad Avenue
Mohammadpur
Dhaka 7
G.P.O. Box 279
Bangladesh

Phone 327588, 310792, 313034.
Cable: BAFEREP DHAKA

SRI LANKA

Dr. Sriani Basnayake
Medical Director
Family Planning Association
of Sri Lanka
37/27 Bullers Lane
Colombo 7
Sri Lanka

Telegram: FAMPLAN

Telephone Office: 84153, 84157
Clinic: 588131

Telex 22238 TRUST CE

U.S.A.

Dr. Irving Sivin
The Population Council
One Dag Hammarskjold Plaza
New York, N.Y. 10017
U.S.A.

Telex 238274 POBI UR

Participants - name and address - USAID.

India

Dr. Badri Saxena
Senior Deputy Director General
Indian Council of Medical Research Telephone 669374
Ansari Nagar 667136 Home 606676
New Delhi 110029
India Telex 3163067 ICMR IN

Indonesia

Dr. Finman Lubis
Executive Director
YKB Foundation
P.O. Box 25/KBYIT
Asem Baris Raya
Block A/3
Gudang Peluru Phone 825337
Tebet Jakarta Selatan
Indonesia Telex 61571 USAHA IA
61488 USAHA IA

Dr. Hermini Sutedi
Chief Bureau of Contraceptive
Service
Jalan Let Jen. M.T. Haryono
P.O. Box 186 JKT Phone 811308
Jakarta
Indonesia Telex 48181 BKKBN IA

Singapore

Dr. Osborn A.C. Viegas
University Dept. of Obst. & Gyn. Telegram UNIVSPORE
Kandang Kerbau Hospital Telephone: 779555
Hampshire Road Telex UNISPO RS 33943
Singapore 0821

Bangladesh

Dr. H. Akhter
Bangladesh Fertility Research Program Phone 327588, 310792, 313034
3/7, Asad Avenue Cable: BAFEREIP DIIAKA
Mohammadpur
Dhaka 7
G.P.O. Box 279
Bangladesh

SRI LANKA

Dr. Sriani Basnayake
Medical Director
Family Planning Association
of Sri Lanka
37/27 Bulliers Lane
Colombo 7
Sri Lanka

Telegram: FAMPLAN

Telephone Office: 84153, 84157
Clinic: 588131

Telex 22238 TRUST CE

U.S.A.

Dr. Irving Sivin
The Population Council
One Dag Hammarskjold Plaza
New York, N.Y. 10017
U.S.A.

Telex 238274 POBI UR